AD A20-630

AP Ltr

SBA memo

MOR

Clin. Pharm/Bio

Pharm/Tox

STAT

Chem

Micro

EA + Fonsi

AP Ltr
SBA memo

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

NDA 20-630

Food and Drug Administration
Rockville MD 20857

JUL 12 1996

Glaxo-Wellcome Inc.
Five Moore Drive
P.O. Box 13398
Research Triangle Park, North Carolina 27709

Attention: Craig A. Metz, Ph.D.
Director, Regulatory Affairs

Dear Dr. Metz:

Please refer to your September 15, 1995 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ultiva (remifentanil HCl) for Injection.

We acknowledge receipt of your amendments dated December 13 (2), 14, and 21, 1995; and January 10, 15, and 26; February 9, 16, 23 (2), 27, and 29; March 1, 4, 6, 13, 15, 19; April 16, and 23, May 3, 7; and 21, and June 6, 1996.

This new drug application provides for the induction and maintenance of general anesthesia for inpatient and outpatient procedures, and for continuation as an analgesic into the immediate postoperative period under the direct supervision of an anesthesia practitioner in a postoperative anesthesia care unit or intensive care setting. It also provides an analgesic component of monitored anesthesia care.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-630. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your Phase 4 commitments specified in your submission dated May 28, 1996. These commitments, along with any completion dates agreed upon, are listed below.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitments, please submit protocols, data, and final reports to this NDA as correspondence. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

We also remind you of your commitment specified in your submission dated July 1, 1996 to provide a product educational program prior to product availability. The program will emphasize safety issues to anesthesia practitioners and other related health care providers. For each institution that will use Ultiva, department heads for anesthesiologists, nurse anesthetists, and post-anesthesia care units will be contacted and provided educational materials. A database of the institutions contacted will be maintained and reported to the Agency for 2 years. Ongoing education will be provided to the institutions as needed. Notification about the educational program will be included in all launch advertisements.

In addition, please submit three copies of the introductory promotional and educational material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Anesthetics, Critical Care, and Addiction Drug Products, HFD-170 and two copies of both the promotional and educational materials and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and
Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

David Morgan
Consumer Safety Officer
(301) 443-3741

Sincerely yours,

Paula Botstein MD 7/12/96

Paula Botstein, M.D.
Acting Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Draft Labeling

cc:
Original NDA 20-630
HFD-170/Div. files
HFD-170/CSO/D.Morgan
HFD-170/Palmisano/Ross/Permutt/Geyer/Bashaw/Hayes/Moody
HFD-2/M.Lumpkin
HFD-103/P.Botstein
HFD-101/L.Carter
HFD-820/Yuan Yuan Chiu
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-80 (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613 (with labeling)
HFD-735/(with labeling) - for all NDAs and supplements for adverse reaction changes.
HFD-021/J.Treacy (with labeling)

drafted: DM/June 5, 1996/20630.ap
r/d Initials: MLambert/7-10-96/CPMoody/7/12/96
final: PO'Connor/7-10-96

APPROVAL [with Phase 4 Commitments]

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

Memorandum for the Record

Date: June 17, 1996
NDA 20-630 Remifentanil HCl for Injection
Sponsor : Glaxo-Wellcome, Inc.

Group Leaders Memo

I concur with the reviews and recommendations submitted by this review team (internal disciplines and external consultants).

These reviews will serve as the summary basis of approval for NDA 20-630 (remifentanil HCl) Injection.

Barbara Palmisano, M.D. 6/17/96
date

Barbara Palmisano, M.D.
Anesthesia Group Leader

MOR

MEDICAL OFFICER REVIEW

NDA #: 20-630
PRODUCT TRADE NAME: Remifentanil
SPONSOR: Glaxo-Wellcome
STUDY #214: "Intracranial Pressure (ICP) effects of Remifentanil and Alfentanil"
LETTER/SUBMISSION DATE: Nov 1, 1995
REVIEWER: Robert F. Bedford, M.D., Medical Officer
CSO: Morgan

Background:

Remifentanil is a rapid onset/rapid offset mu-opioid agonist currently under evaluation as an intravenous analgesic/anesthetic agent. This was a single-center, randomized, double-blind, controlled study performed during craniotomy for tumor resection. Initially, four patients were enrolled in an open-label, dose-escalation pilot phase - their data are included only for safety analysis.

The purpose of this study was to: (1) Determine whether administration of ropivacaine or alfentanil changed intracranial pressure (ICP) during general anesthesia, (2) determine whether ropivacaine or alfentanil change cerebral perfusion pressure (CPP, defined as mean arterial pressure [MAP] minus ICP), (3) determine the dose and/or peak plasma concentration response relationships if ropivacaine or alfentanil change ICP or CPP, and (4) obtain safety information.

METHODS:

Twenty-six patients received a one-minute bolus infusion of placebo (N=6), remifentanil (N=10), or alfentanil (N=10) in a double-blind manner. These are the Intent-To-Treat (ITT) patients. Four additional patients received a one-minute bolus infusion of remifentanil in the open-label phase and are included in the Safety Population (all subjects) from which the safety results of this study are reported. Gender: 13 male, 17 female; Age range: 21-73;

After establishing intraarterial and intravenous cannulae and non-invasive monitors, anesthesia was induced with thiopental (4-6mg/kg) and N_2O/O_2 (2:1). Isoflurane was adjusted to 0.3-0.8% and ventilation was controlled to maintain PaCO2 at approximately 30 mm Hg. The surgeon placed an epidural ICP transducer and positioned it to ensure high-fidelity wave form monitoring. <u>The head of the bed was elevated to 15 degrees from horizontal</u>.

Study drug was administered at a rate of 5mL/min over 1 minute (see table 1) and arterial blood was sampled for analysis of remifentanil or alfentanil concentration at the end of study drug infusion and again 1 minute later. Intracranial pressure was recorded at preinfusion and every minute thereafter until 10 minutes post infusion. Arterial blood was collected for analysis of P_aCO_2 10 minutes after the study drug infusion had stopped.

Table 1. Treatment Groups, Randomized, Double-Blind Phase, Intent-to-Treat patients (N = 26)

Group	N	Treatment
Placebo	6	Normal saline infused over 1 minute
Remifentanil	5	0.5mcg/kg infused over 1 minute
Remifentanil	5	1mcg/kg infused over 1 minute
Alfentanil	5	10mcg/kg infused over 1 minute
Alfentanil	5	20mcg/kg infused over 1 minute

After the last ICP measurement was made and the last arterial blood sample had been obtained, safety variables were recorded every 10 minutes until the end of surgery. Anesthesia was maintained with isoflurane, N_2O/O_2 and addtional fentanyl, as needed.

Exclusion from Analysis: Thirty patients were enrolled in this study and one patient was withdrawn because no study drug was given. The first four patients recruited in the study received open-label remifentanil in a pilot study and are not included in the Intent-To-Treat (ITT) Population.

A total of 26 patients are included in the ITT Population and 30 patients are included in the Safety Population.

Protocol Deviations: Two protocol violations (patient , were noted in this study. Both patients are included in all analyses.

- Patient (alfentanil 10mcg/kg) had a major violation because the patient did not have a mass lesion; biopsies of the tissue removed during surgery were diagnosed as fibrotic inflammatory tissue.

- Patient (placebo) received an incorrect dose, i.e., less than 50% of the fixed active treatment dose was given prior to the time of the primary endpoint assessment. This patient had originally been randomized to receive remifentanil 0.5mcg/kg, but received no study drug because the syringe had not been placed in the infusion pump correctly. This patient was subsequently added to the placebo group of both safety and ITT Populations.

Concentration-response relationship:
Linear regression was performed to assess the relationship between 1) maximum arterial remifentanil concentrations (C_{max}) and baseline-corrected maximal ICP increase (ICP_{max}), 2) remifentanil C_{max} and baseline-corrected maximum CPP decrease (CPP_{min}) or baseline-corrected maximum MAP decrease (MAP_{min}). A secondary analysis was conducted on absolute maximum change (increase or decrease) in each of those hemodynamic measures, i.e. maximum arterial remifentanil concentrations (C_{max}) and baseline-corrected maximum change (increase or decrease) in ICP (d-ICP), CPP (d-CPP), and MAP (d-MAP). The concentration-response data were also fitted to a sigmoid E_{max} model (PCNONLIN v04.2).

A similar concentration-response relationship were developed for alfentanil. The slope-ratio (remifentanil and alfentanil) from the linear regression was used to determine relative potency if the slopes of the concentration-response relationship were significant.

Follow Up: After surgery was completed (completion of the head dressing), evaluations of emergence and recovery were made, and vital signs were recorded at specified intervals until a normal recovery score was obtained or for a maximum of 90 minutes. All patients were interviewed by the investigator or study coordinator on the first postoperative day to assess adverse events and medication use since surgery. The following evaluations were made on the first postoperative day:

- clinical laboratory tests (blood sample only)
- electrocardiography (12-lead ECG)
- neurological examination
- clinical adverse events
- physical examination

RESULTS:

Overall, the patients were reasonably well-distributed with regard to extent of intracranial pathology (Table 2). The low-dose Alfentanil patients tended to have smaller lesions, whereas the remifentanil high-dose patients tended to have more mass-effect as reflected in shift of midline structures.

Table 2. Summary of Scan Report, All Patients (N = 30)
Values are N (% Total), Mean (± SEM), Median, or Range

			Remifentanil		Alfentanil	
		Placebo	0.5	1	10	20
Number of Patients		6	7	7	5	5
Maximum Tumor Diameter (cm)	Mean	5.08 (±0.8)	4.26 (±0.7)	4.79 (±0.5)	2.92 (±0.8)	3.9 (±0.5)
	Median	5.5	4.5	5	3	4.5
	Range	2-7	1.5-6.5	2.5-6	1.3-5.5	2.5-5
Maximum Midline Shift (mm)	Mean	7.58 (±2.8)	5.71 (±2.5)	9.29 (±2.7)	3 (±3)	5.5 (±2)
	Median	5.25	5	10	0	5
	Range	2.5-20	0-15	0-20	1-15	0-10
General Assessment of Tumor Mass Effect						
	None	0	1 (14%)	0	1 (20%)	0
	Mild	2 (33%)	2 (28%)	3 (42%)	3 (60%)	1 (20%)
	Moderate	2 (33%)	3 (42%)	3 (42%)	0	3 (60%)
	Severe	2 (33%)	1 (14%)	1 (14%)	1 (20%)	1 (20%)

Administration of study opioid did not change ICP significantly as compared to placebo (see Table 3), and there was no significant difference between groups with regard to maximal ICP increases (Figures 1, 2 and 3).

Table 3. Intracranial Pressure (mmHg), Intent-to-Treat Patients (N = 26)
Mean Values are Mean (± SD), Median, or Range

		Remifentanil		Alfentanil		
	Placebo	0.5	1	10	20	p-value [1]
Number of Patients	6	5	5	5	5	
Baseline ICP Mean Range	21.7 (±12) 11-44	12.8 (±7.4) 1-20	14.2 (±3.8) 9-19	16.8 (±5) 11-23	21.4 (±15) -1-40	0.488
Maximum ICP Mean Range	23.8 (±8.4) 15-38	17 (±9) 4-27	16.4 (±3.2) 11-19	17.4 (±5.5) 10-24	24 (±15) 0-40	0.753
Maximum ICP increase Mean Range	2.2 (±4.2) -6-6	4.2 (±4.1) 0-9	2.2 (±1.5) 0-4	0.6 (±4.9) -4-9	2.6 (±5.3) -3-11	0.753
Time (min) to maximum increase Median: Range:	2 1-5	5 1-22	3 2-5	4 1-9	4 1-10	0.625

[1] p-value is to detect an among treatment difference using GLM controlling for baseline and body weight.
p-value for time to max increase is based on Cox Proportional Hazards model to detect an among treatment difference.

Figure 1. Mean (± SEM) Maximal ICP Increase From Baseline, Intent-to-Treat Patients (N = 26)

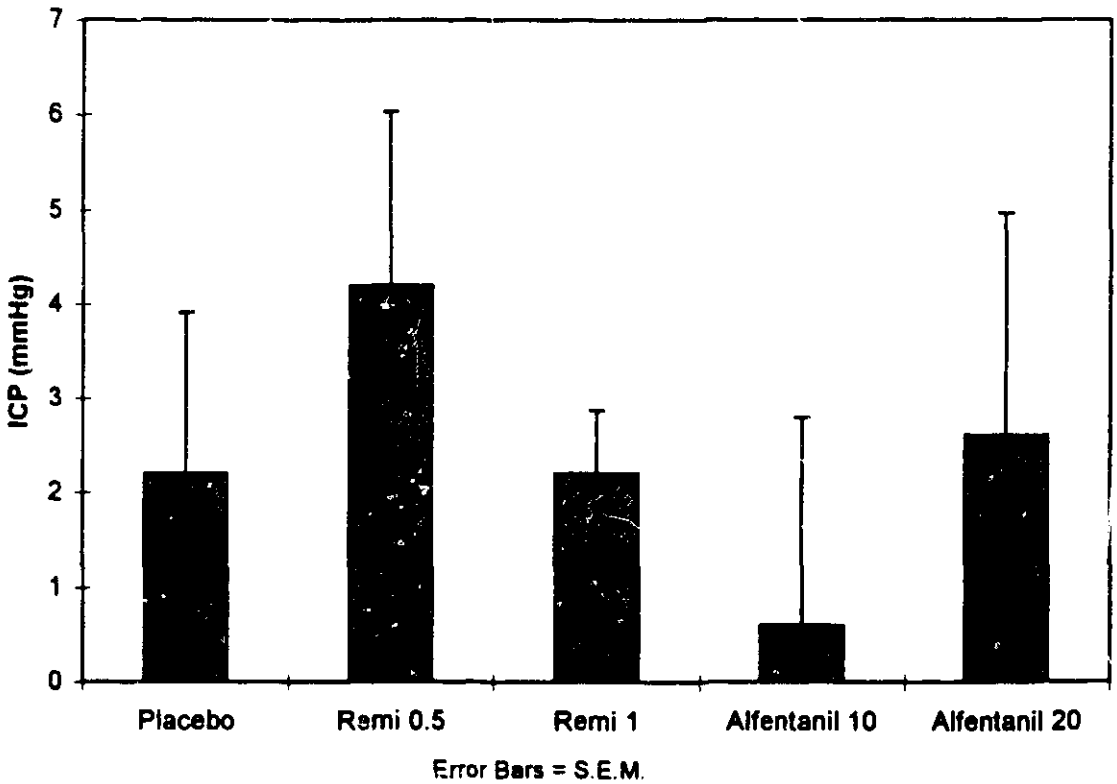


Figure 2. Alfentanil: Mean (±1.5 SEM) ICP Change Over Time

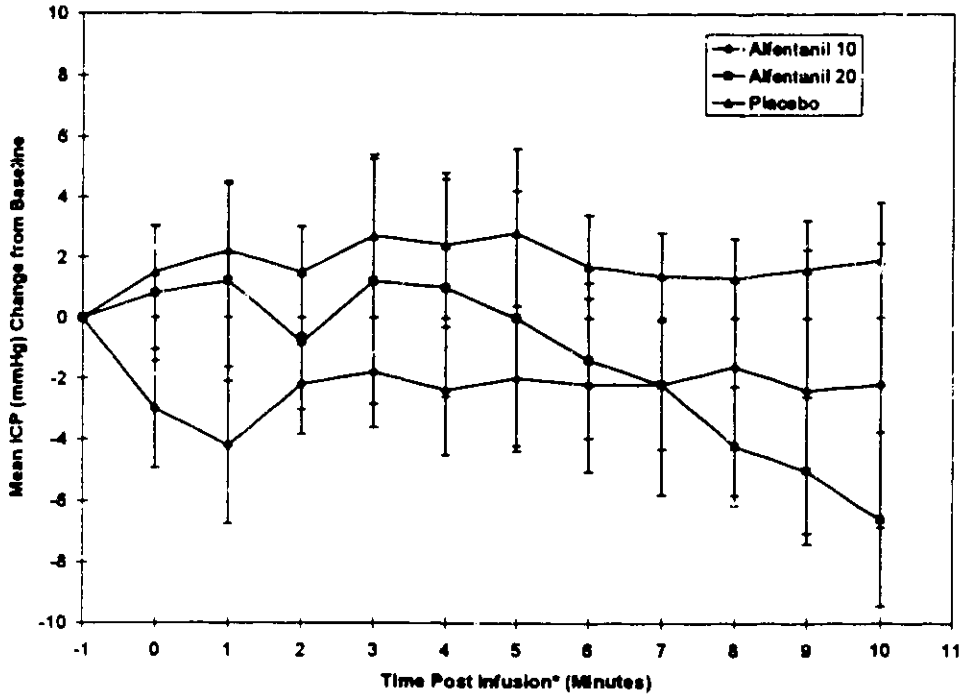
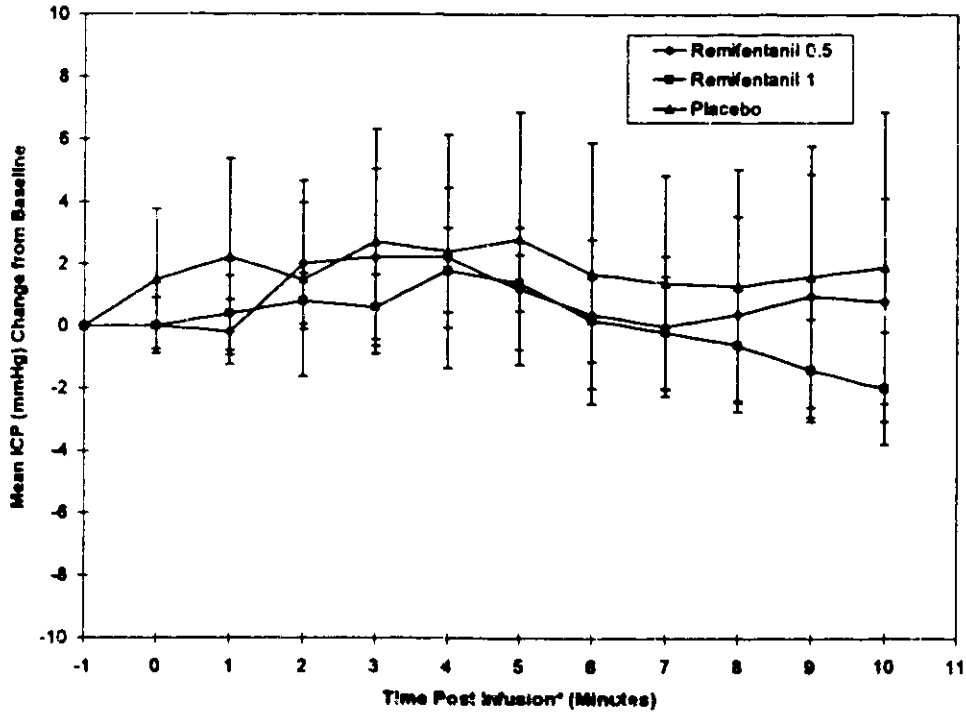


Figure 3. Remifentanil: Mean (±1.5 SEM) ICP Change Over Time



* Time (-1) is beginning of 1 minute infusion, Time 0 is end of infusion

Patients receiving higher doses of study drug experienced significant decreases in MAP and, accordingly, in CPP. The changes in MAP over time are summarized in Figures 4 and 5. The mean maximal MAP decreases were greatest for the higher dose remifentanil and alfentanil groups. One patient (006) that received remifentanil 1.0mcg/kg required an intervention (ephedrine) to increase blood pressure. The median time to a maximum MAP decrease ranged from 3 minutes (remifentanil 0.5 and 1.0mcg/kg) to 8.5 minutes (placebo) after the end of the infusion.

Figure 4. Alfentanil: Mean (±1.5 SEM) Arterial Pressure (MAP) Change Over Time

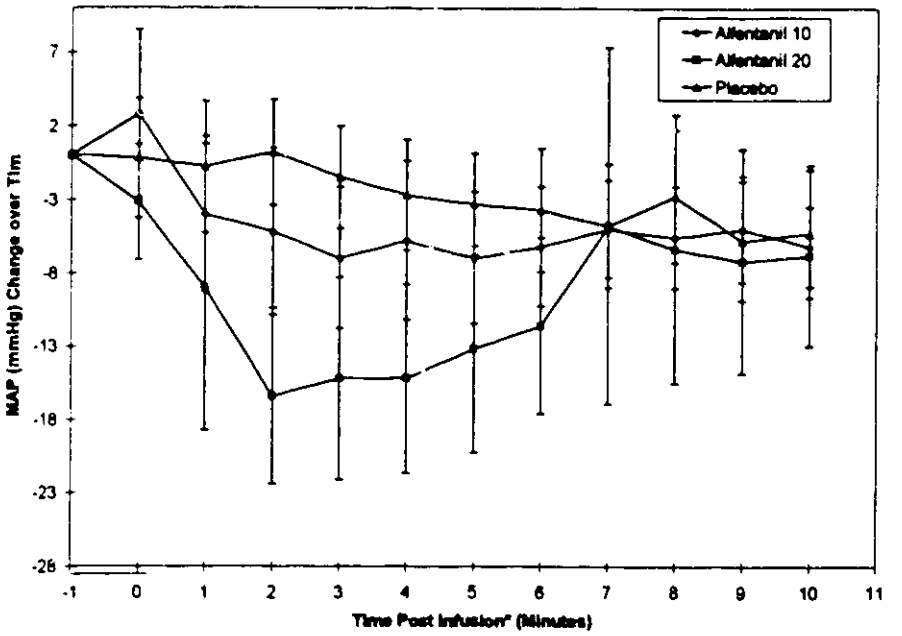
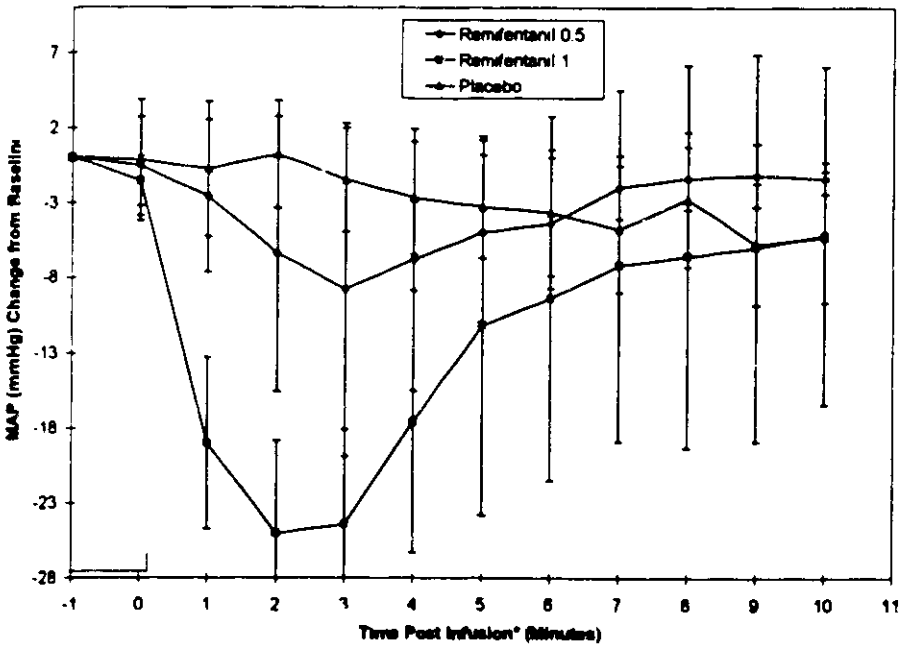


Figure 5. Remifentanil: Mean (±1.5 SEM) Arterial Pressure (MAP) Change Over Time



* Time (-1) is beginning of 1 minute infusion, Time 0 is end of infusion

The maximum ICP increases and MAP and CPP decreases from baseline occuring over the 10 minutes following drug infusion, and the most common AE results are summarized in Table 4: No treatment group had a mean maximal ICP increase >5mmHg from baseline and no patient required an intervention for ICP increases deemed clinically unsafe. The median time to a maximum ICP increase from the end of infusion ranged from 2 minutes (placebo) to 5 minutes (remifentanil 0.5mcg/kg).

Table 4. Summary of Drug Effects on ICP, MAP, CPP, Intent to Treat (N=26)
Values are Mean (±SD)

	Placebo	Remifentanil 0.5mcg/kg	Remifentanil 1.0mcg/kg	Alfentanil 10mcg/kg	Alfentanil 20mcg/kg	p-value*
	N=6	N=5	N=5	N=5	N=5	
Max ICP Increase:	2.2 ± 4.2	4.2 ± 4.1	2.2± 1.5	0.6± 4.9	2.6± 5.3	0.753
Max MAP Decrease	-7.7±6.2	-13.2± 11	-25.4± 9.2	-9.2±4.4	-17.4 ±8.8	0.018
Max CPP Decrease	-5± 5.6	-13.8± 9.7	-26± 9.6	-8± 5.8	-18.6± 14	0.014

*p-value is to detect an among-treatment difference using GLM controlling for baseline.

There was a trend for more patients in the higher dose remifentanil and alfentanil treatment groups to have clinically relevant decreases in MAP and CPP. The same patients experiencing a clinically relevant decrease in MAP also had clinically relevant decreases in CPP.

Concentration-Response Relationship (Primary Analysis)

The relationship between Cmax of remifentanil and alfentanil and changes in ICP, CPP and MAP were examined by linear regression. There was no relationship between ICP and remifentanil levels. By contrast, the following figures (E and F) demonstrate a close negative correlation between remifentanil levels and MAP. The regression slope ratio (remifentanil to alfentanil) for MAP suggests that remifentanil is approximately 33 times more potent than alfentanil.

Figure E

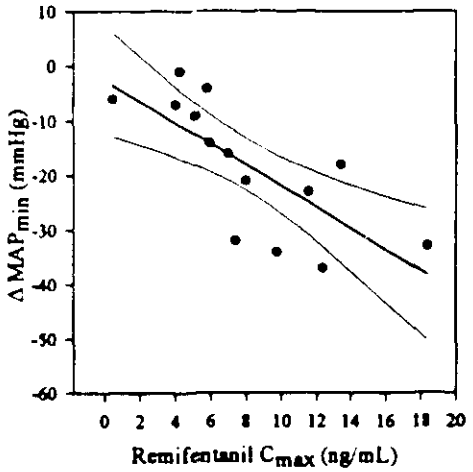
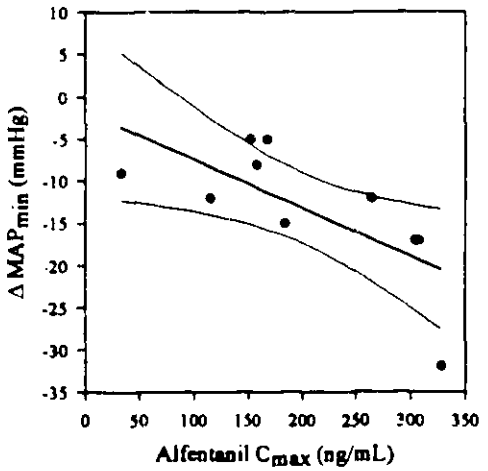
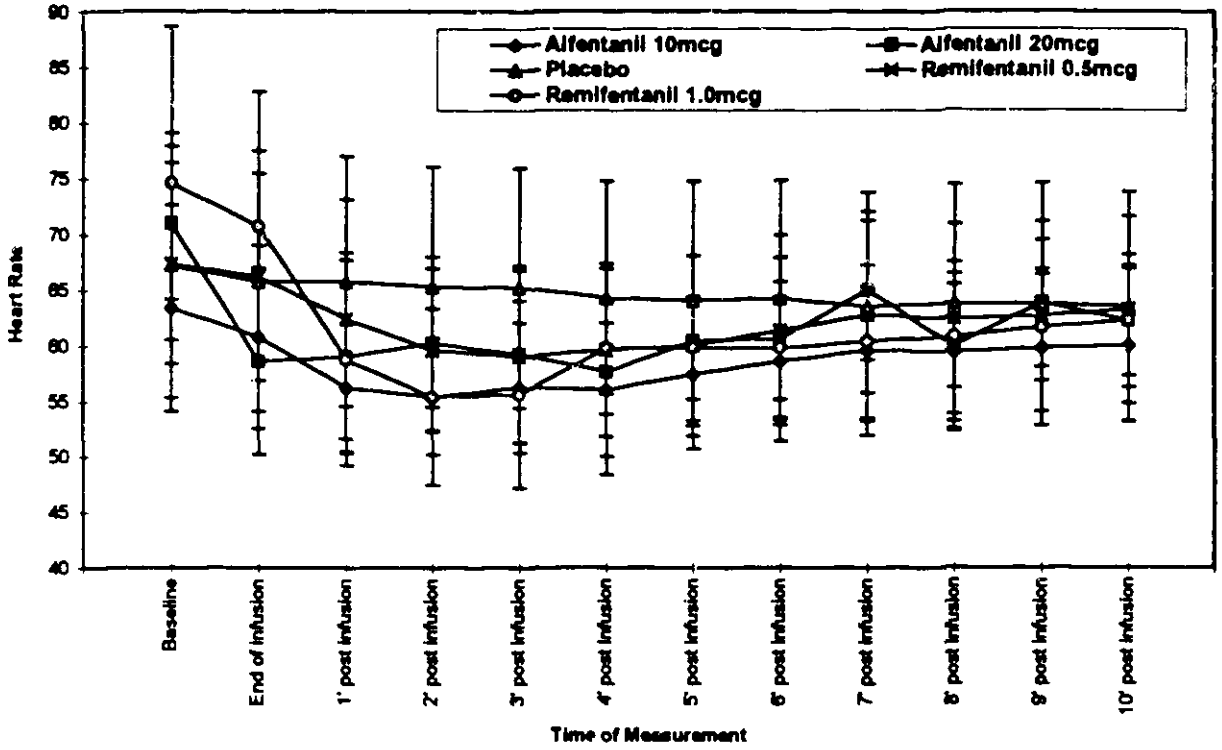


Figure F



Changes in heart rate are summarized in Figure 6. As expected, opioid infusion resulted in decreases in heart rate, with higher doses resulting in greater reductions in the first few minutes following drug administration.

Figure 6. Comparison of Heart Rate, All Patients. Values are Mean ± 1.5 SE



Safety:

Adverse Events:

The proportion of patients who reported adverse events were similar in each treatment group. The most frequently reported adverse events were of the digestive system, nausea and vomiting (Table 5). There was a tendency for more bradycardia occurring in the remifentanil-treated patents as compared with the alfentanil or placebo groups.

Table 5. Most Common Adverse Events, All Patients (N=30)

Values are N (% Total)

		Remifentanil		Alfentanil	
	Placebo	0.5mcg/kg	1.0mcg/kg	10mcg/kg	20mcg/kg
	N=6	N=7	N=7	N=5	N=5
Nausea	3 (50%)	2 (29%)	1 (14%)	2 (40%)	3 (60%)
Vomiting	0	2 (29%)	1 (14%)	1 (20%)	3 (60%)
Hypotension	0	1 (14%)	3 (43%)	1 (20%)	0

Data Listings of Important Adverse Events:

There were no deaths. No patient died during the study and no patient was withdrawn from the study due to an adverse event. Two patients had serious adverse events related to surgery during the study:

Patient Number	Sex/ Age	Treatment	Description of Event
019	F/70	Remifentanil 0.5mcg/kg	After prolonged surgery (12hrs), patient showed no sign of awakening. Next morning CT Scan revealed bifrontal cerebral contusion and cerebral edema.
021	M/55	Alfentanil 10 mcg/kg/min	Convulsions five hours post-operatively and left hemiparesis believed due to seizure. Treated with phenobarbital and phenytoin. CT scan revealed bifrontal cerebral contusion and substantial cerebral edema.

2. OVERALL CONCLUSIONS:

This study shows that brief remifentanil infusion during isoflurane-N_2O anesthesia has negligible impact on ICP in patients with small intracranial mass lesions, as long as they are maintained in a hypocapnic state with their heads elevated approximately 15° above neutral. The effects of long-term remifentanil infusion are unanswered by this study.

Drug-induced reductions in blood pressure were clearly dose-dependent in this study. Given current thinking that increases in ICP during opioid infusion reflect autoregulatory cerebral vasodilation resulting from induced hypotension, it is not surprising that there was no meaningful dose-response correlation between opoid dose and ICP or CCP changes.

3. CONCLUSIONS REGARDING LABELING:

1) This study clearly demonstrates a dose-dependent reduction in blood pressure caused by 0.5 and 1.0 ug/kg/min infusions. This is reflected in the labeling as "...bolus doses < 2ug/kg..are associated with a dose-dependent bradycardia and hypotension. This effect may have been augmented by the fact that patients were placed in a 15° head-up position at the time of remifentanil infusion.

2) This study is supportive of the claim that remifentanil has no significant impact on ICP during isoflurane/N2O anesthesia ("Cerebrodynamics" portion of the Clinical Pharmacology Section).

3) Under the "neurosurgery" and "cerebrodynamics" sections, it seems appropriate to add a statement to the label that cerebral perfusion pressure may be adversely affected during remifentanil infusion due to decreases in arterial pressure.

Robert F. Bedford

Robert F. Bedford, MD 1/19/96

MEDICAL OFFICER REVIEW

NDA #: 20-630
PRODUCT TRADE NAME: Remifentanil
SPONSOR: Glaxo
STUDY #222 "Effect of Remifentanil on Evoked Potentials"
LETTER/SUBMISSION DATE: Nov 1, 1995
REVIEWER: Robert F. Bedford, M.D., Medical Officer
CSO: Morgan

Background

Remifentanil is a rapid onset/rapid offset mu-opioid agonist currently under evaluation as an intravenous analgesic/anesthetic agent. This study was designed to investigate whether there is a dose-response relationship for the effect of remifentanil on auditory and somatosensory evoked potentials in patients undergoing general anaesthesia. The study was conducted in two parts; an ascending dose pilot open phase, followed by a randomized, parallel-group, double-blind study.

Investigators:

Protocol: In the preliminary phase of this study, 9 patients (8 ASA I and 1 ASA II, 8 male, 1 female)) took part in an open-label phase. Their data is included in the safety analysis. The subjects of the pharmacokinetic/pharmacodynamic study were 60 ASA 1 patients (32 male, 28 female) ranging in age from 18 to 62 years. After premedication with temazepam, 5-10 mg, anesthesia was induced with propofol and maintained with low-dose isoflurane (0.3-0.4 MAC). Prior to endotracheal intubation and for the remainder of the study period, remifentanil was administered by one of 3 regimens:

Low Dose = Remifentanil, 1μg/kg bolus, followed by 0.2mg/kg/min infusion (low dose)

Medium Dose = Remifentanil, 2.5μg/kg bolus, followed by 0.5μg/kg/min infusion(medium dose)

High Dose = Remifentanil, 5μg/kg bolus, followed by 1.0μg/kg/min infusion(high dose).

Monitoring:
Standard non-invasive cardiovascular monitors, scalp electroencephalographic (EEG) recordings and venous cannulae were placed for blood sampling to determine remifentanil levels. Venous remifentanil concentrations were determined before and after tracheal intubation, and before and after skin incision. Cardiovascular and evoked potential data were recorded at the following times:

a) immediately pre remifentanil infusion (baseline)

b) Immediately pre intubation (nominally 3 minutes before)

c) Immediately post intubation (nominally 3 minutes after)

d) Immediately pre incision (nominally 3 minutes before)

e) Immediately after incision (nominally 3 minutes after)

Auditory evoked responses (AERs) were generated with binaural click stimulus (6Hz), delivered by earphones, applied prior to loss of consciousness and continued throughout the surgical period. The AERs were obtained from 1024 consecutive click stimuli (taking 2.8 minutes) and signal-averaged in the usual fashion, with appropriate latency and voltage amplitude analyses. Primary variables for AER response were Pa amplitude and Nb latency. Secondary variables for AER were Pa latency, Nb amplitude and AER index.

Somatosensory evoked potentials (SER's) were produced with electrical stimuli applied to the median nerve at a frequency of 2.2 Hz throughout the procedure after loss of consciousness. Somatosensory responses were derived from a approximately 375 stimuli over a 2.8 minute period. The SER was derived by averaging the EEG (SER) over the time course of the 1024 stimuli required to produce the AER. The primary variables measured for SER were P15-N20 amplitude and N20-P25 amplitude. Secondary variables for SER were P15, N20, P25 and P45 latencies, and P25-N35 and N35-P45 amplitude.

Clinical observations

The following were recorded immediately prior to low dose remifentanil administration and at 3-minute intervals until 30 minutes after termination of remifentanil infusion:

- Non invasive blood pressure by automated oscillotonometry (systolic/diastolic)
- Heart rate (beats per minute)
- Pupil size (scored 0-2)
  - 0= Pinpoint, no reaction to light
  - 1= Dilated, no reaction to light
  - 2= Dilated, reaction to light
- Sweating (scored 0-2)
  - 0= No sweating
  - 1= Slight sweating
  - 2= Heavy sweat
- Movement (present/ absent)
- Coughing (present/ absent)
- Swallowing (present/ absent)

Blood pressure and heart rate were also recorded at thirty minute intervals until the end of the surgical procedure.

Statistical Evaluation: All analyses were performed on the intent-to-treat population.

For each study parameter separate analyses were performed comparing the pre-intubation and post-intubation values. Additional analyses were undertaken comparing the evoked responses pre-incision, post-incision and the difference between the post-incision and pre-incision values. In each case treatments were compared using analysis of covariance with baseline as the covariate. Pairwise comparisons were made between each pair of treatments, with an estimate of the comparison, along with an associated 95% confidence interval.

The values pre-intubation, post-intubation, pre-incision and post-incision were summarized by unadjusted geometric means and ranges. The values for the differences between pre- and post-intubation and incision were summarized by unadjusted arithmetic means.

For blood pressure and heart rate the data were additionally summarized by weighted mean in each of the periods. The weighted mean was calculated as the area under the parameter/time curve divided by the duration of measurement.

Results:

The study groups were well-balanced with regard to age, sex and ethnic origin. The resultant blood levels of remifentanil are shown in the table below. As expected, the blood levels tended to increase with time at endotracheal intubation, since drug infusion was still relatively early. Blood remifentanil levels had pretty well stabilized by the time of surgical incision.

Table 1. Remifentanil Blood Concentrations (ng/mL), All Subjects (N = 60)

Remifentanil		Mean Concentration (ng/mL)	Standard Deviation
Low Dose	Before intubation	3.38	1.31
	After intubation	4.11	1.11
	Before Incision	4.79	1.56
	After Incision	4.59	1.43
Medium Dose	Before Intubation	11.06	4.64
	After Intubation	13.22	4.79
	Before Incision	15.65	5.54
	After Incision	14.86	3.90
High Dose	Before Intubation	17.82	6.61
	After Intubation	24.70	6.81
	Before Incision	27.13	8.15
	After incision	27.11	7.62

Auditory Evoked Responses: Pa wave Amplitude.

At both intubation and incision, the amplitude of the Pa wave increased for low dose remifentanil, remained fairly constant for medium dose remifentanil and decreased for high dose remifentanil. (See Table 2). In all cases the pairwise comparisons between medium and low dose was statistically significant ($p<0.05$), with the comparison between high and low dose being highly statistically significant ($p=0.020$ post intubation, $p<0.001$ in all other cases). Comparing pre- and post-stimulus values, there was no significant difference between remifentanil doses.

Somatosensory Evoked Responses: P15-N20 Amplitude.

Comparing high and low-dose remifentanil, there was a statistically significant difference in P15-N20 amplitude at the post-intubation time-point ($p=0.002$). In addition, there were significant differences between post and pre-intubation ($p<0.001$), pre-incision ($p=0.005$) and post-incision ($p=0.019$). The pairwise comparisons of medium and low dose, and, high and medium dose were also significant with respect to the difference between post and pre-intubation ($p=0.044$ and $p=0.014$, respectively).

In the case of both Auditory and Somatosensory evoked potential latencies and amplitudes described in the methods section, there were a variety of statistically significant changes in response to the different remifentanil infusions. The clinical significance of these changes is unknown to this reviewer.

Table 2.

	Low Dose	Medium Dose	High Dose
Pharmacokinetics	N = 20	N = 20	N = 20
Remifentanil Conc Range (ng/mL)			
Pharmacodynamics			
Auditory Evoked Potentials	N =20	N = 20	N = 20
Pa Amplitude (uV)			
Baseline	0.43	0.32	0.38
Pre-intubation	0.51	0.33	0.29
Post-Intubation	0.49	0.32	0.28
Pre-incision	0.46	0.27	0.25
Post-Incision	0.46	0.30	0.25
Somatosensory Evoked Potentials			
P15-N20 amp. (uV)			
Baseline	1.7	2.3	2.2
Pre-Intubation	1.2	1.8	1.8
Post-Intubation	1.4	1.8	1.5
Pre-Incision	1.2	1.4	1.1
Post-Incision	1.2	1.3	1.2

Hemodynamic Results:

Following bolus administration of remifentanil, blood pressure and heart rate decreased significantly as compared with baseline isoflurane anesthesia. As indicated in Table 3, the incidence of hypotension below 80 mm Hg was somewhat lower in the low-dose group. The overall data observed before and after remifentanil infusion are shown in Figures 1 & 2.

Table 3. Systolic Blood Pressure < 80 mmHg, All Patients (N = 63)

	Treatment Group					
Time	N	Low Dose	N	Medium Dose	N	High Dose
Pre-Study Drug	20	0	20	0	20	0
During Study Drug Admin.	20	4 (20%)	20	7 (35%)	20	3 (15%)
Post Termination of Study Drug	20	0	20	4 (20%)	20	4 (20%)
Post Termination of Anaesthesia	20	0	20	0	20	0

Figure 1. Systolic Blood Pressure, All Subjects (N=60)
Mean±1.5SEM

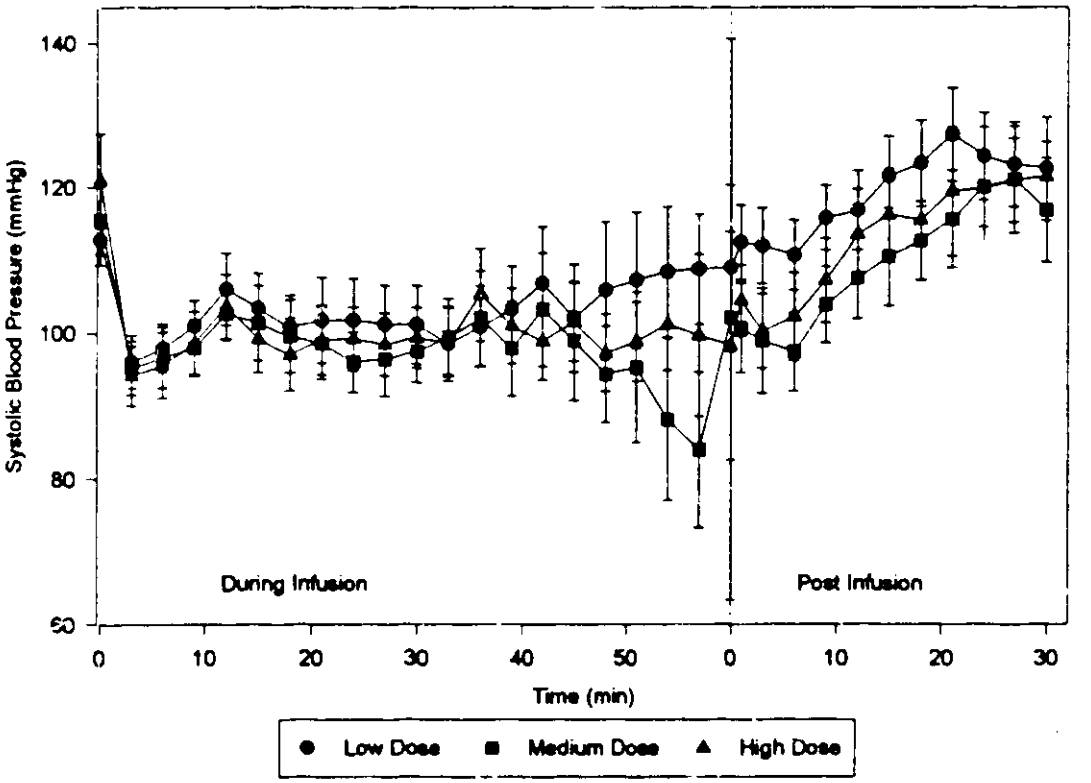
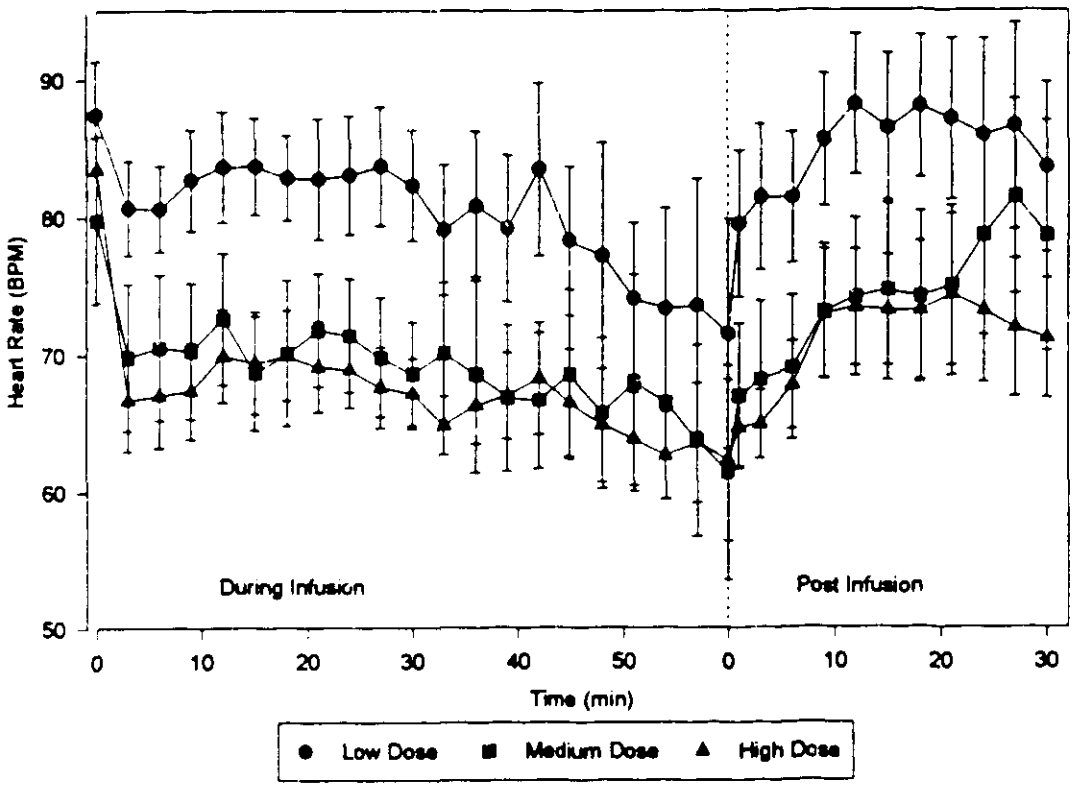


Figure 2. Heart Rate Changes, All Subjects (N=60) Mean±1.5SEM



Adverse Events:
The adverse event incidence tended to increase in the three dose groups, as shown in table 4 below.

Table 4:

Remifentanil Dose:	Low Dose	Medium Dose	High Dose
Safety	N = 23	N = 23	N = 23
Any adverse event	5	7	10
During Treatment	0	1	2
After Treatment	5	6	8

There was no evidence of awareness during remifentanil administration. During treatment in the open phase of the study (9 patients), one patient who received high dose remifentanil developed hypotension. The only events assessed as possibly drug related were: 1) muscle stiffness and xerostomia, reported in a patient who received medium dose remifentanil and 2) nausea and vomiting in a patient who received high dose remifentanil.

Among the 60 patients in the double-blind phase of the study, one patient who received medium dose remifentanil and one patient who received high dose remifentanil had hypotension. During the post treatment period adverse events were reported in four patients with low dose remifentanil, five patients with medium dose remifentanil and six patients with high dose remifentanil. The most commonly reported adverse events were nausea and vomiting (reported with all doses of remifentanil) and

shivering (reported in two patients) with high dose remifentanil. One event of urinary urgency in a patient who received medium dose remifentanil and one event of vomiting in a patient who received high dose remifentanil were assessed as drug related. No adverse reaction was severe.

Laboratory measurements:

During the double-blind phase of the study four patients with low dose remifentanil, eight patients with medium dose remifentanil and nine patients with high dose remifentanil developed a laboratory value outside the threshold range. The majority of these were hematological parameters, in particular a low lymphocyte count, which was reported with a higher incidence in patients who received high dose remifentanil. One patient who received medium dose remifentanil developed a low platelet count and four patients who received high dose remifentanil developed a low lymphocyte count. Three patients who received medium dose remifentanil and one patient who received high dose remifentanil developed a low potassium level below the PSSL.

No patient developed a change in a laboratory parameter that was reported as an adverse event.

Conclusions: During propofol-isoflurane-O_2 anesthesia, remifentanil infusion caused a dose-dependent change in some auditory and somatosensory evoked potential parameters consistent with μ opioid activity. The effect on auditory evoked potentials suggests that addition of remifentanil contributed to the hypnotic effect of isoflurane. The magnitude of the changes seen with somatosensory evoked potentials were less than those seen with auditory evoked potentials. Whether this indicates the top of the dose-response curve for this parameter or whether a no-effect dose was given is debatable and probably inconsequential given the lack of clinical correlation with evoked potential monitoring. Doses used in this study were well tolerated, with typical opioid effects on heart rate and blood pressure seen and rapid offset of effect noted at the termination of remifentanil infusion.

Conclusions Regarding Labeling:

1) Hemodynamic changes described in the draft package insert (hypotension at bolus doses < 2 μg/kg) and peak changes occurring with in 3-5 min are supported by the findings in this study.

2) The electrophysiologic findings are supportive of the labeling claim for an interaction with the effects of inhaled anesthetics, at least isoflurane. The label states "synergistic" effect, but whether this is actually addititive or synergistic cannot be determined from this study.

3) Offset of hemodynamic effects as described in the labeling are compatible with the data obtained in this study at the termination of remifentanil infusion.

4) Adverse reactions reported in this study are compatible with the current draft labeling.

RF Bedford

Robert F. Bedford, MD 1/18/96

MEDICAL OFFICER REVIEW

NDA #: 20-630
PRODUCT TRADE NAME: Remifentanil
SPONSOR: Glaxo-Wellcome
STUDY # 304P - "Pilot Study: Remifentanil in Neuroanesthesia"
LETTER/SUBMISSION DATE: Oct 27, 1995
REVIEWER: Robert F. Bedford, M.D., Medical Officer
CSO: David Morgan

Background

Remifentanil is a rapid onset/rapid offset mu-opioid agonist currently under evaluation as an intravenous analgesic/anesthetic agent. Some of drugs of the same class have been associated with marked increases in intracranial pressure and cerebral blood flow during neurosurgical operations. This is described by the sponsor as a preliminary, open-label study examining the effects of remifentanil in patients undergoing craniotomy.

Investigators:

Anesthesia Protocol: Subjects of the study were thirty patients scheduled for elective surgical removal of a supratentorial mass lesion. Gender: 14 female, 16 male; Age range: 22-74. Chronic medications such as dexamethasone, anticonvulsants and antihypertensives, were administered on the day of study. No premedicants, except ranitidine or midazolam (up to 0.07mg/kg), were administered.

Induction: Anesthesia was induced with thiopental (4-6mg/kg) followed by vecuronium (up to 0.2mg/kg). Mask ventilation then was begun with oxygen. Remifentanil infusion was started at a rate of 1mcg/kg/min and administered continuously at this rate until the investigator determined a clinically appropriate level of anesthesia required for intubation had been achieved (target 5 minutes), or until a maximum of 10 minutes had elapsed (total dose=10mcg/kg from Syringe "A"; see Table 1). A supplementary dose of thiopental (50-150mg) could be given both at the time of intubation or during placement of the pin holder, as needed.

Table 1. Remifentanil Treatment Protocol.

Study drug treatment	Study Drug Syringes			
	Induction Period	Maintenance Period		
	Infusion syringe "A"	Infusion syringe "B"	Infusion syringe "C"	Response bolus syringe (per 10mL)
Remifentanil Syringe Concentration	25mcg/mL	96mcg/mL	96mcg/mL	1mcg/kg
Infusion Rate	0.25mL/kg/hr (0.4mcg/kg/min)	Initial Rate: 0.25mL/kg/hr (0.4mcg/kg/min)	Same as final Syringe "B" rate	10mL over 1 minute

Maintenance: After intubation, anesthesia was maintained with N_2O/O_2 (2:1) and remifentanil from infusion syringe B was started at 0.25mL/kg/hr (0.4mcg/kg/min). Paralysis was maintained with vecuronium, as needed. Ventilation was controlled to maintain P_aCO_2 at approximately 28mmHg throughout the treatment period, except during cerebral blood flow measurements as noted below, when it was deliberately increased by adding CO_2 to the anesthetic circut.

If deemed necessary by the investigator, hemodynamic responses occuring during the maintenance period could be treated with additional remifentanil boluses, 1mcg/kg, administered over approximately 1 minute from the response bolus syringe. Up to three remifentanil boluses could be administered. If the response was still not controlled, an additional remifentanil bolus was given followed by a rate increase of 0.2mcg/kg/min from remifentanil infusion syringe B. A minimum of 1 minute was allowed to elapse between boluses and at least 2 minutes elapsed between infusion rate increases.A maximum of five remifentanil boluses and/or a maximum infusion rate of 0.5mL/kg/hr (0.8mcg/kg/min) was allowed.

If the maximum number of boluses or infusion rate had been administered, then 0.2% isoflurane could be added to the inspired inhalational gas mixture and increased in 0.2% increments, as needed. The remifentanil infusion syringe B rate was decreased by 0.125mL/kg/hr if the hemodynamic safety criteria were met. Isoflurane administration was discontinued before decreasing infusion syringe B. The hemodynamic safety criteria were defined as:

- SBP <80% of baseline for ≥1 minute
- HR <45bpm for ≥1 minute

The surgeon could request intentional, intentional hypertension, or to control the patient's blood pressure. For unacceptable hemodynamic events, ephedrine, phenylephrine, atropine, labetalol, or esmolol could be administered at any time, if deemed necessary by the investigator. Each center, except also collected an arterial blood sample for analysis of remifentanil, or GR90291 concentration at baseline and every 2 hours after remifentanil infusion syringe B had started.

ICP and CBF Measurement: After the first burr hole was drilled, an epidural ICP transducer was placed at 2 of the 3 centers. After the ICP waveform had stabilized (1-3 minutes) the mean ICP was recorded. After the mean ICP was recorded, an arterial blood sample was collected for measurement

of P_aCO_2 ? [illegible] craniotomy proceeded. Patient position was recorded, ie, degrees of head tilt and neck ro[illegible]

At [illegible] center, after the bone flap was removed, a CBF measurement was made and an arterial blood sample was collected for measurement of P_aCO_2. The predicted P_aCO_2 was then increased to approximately 38mmHg by the addition of CO_2 to the fresh gas mixture. Five minutes after a predicted P_aCO_2 of approximately 38mmHg had been achieved, a second CBF (normocapnic) was measured and an arterial blood sample was collected for measurement of P_aCO_2..

After the bone flap had been removed and the dura opened, the surgeon was asked to assess the condition of the brain. Brain relaxation was scored by the neurosurgeon using a 4-point scale (1=excellent, no swelling, 2=minimal swelling, but acceptable, 3=serious swelling, but no specific change in treatment required, and 4=severe brain swelling requiring some intervention). Standard treatment was given if deemed necessary (eg, additional mannitol, furosemide, further decrease in P_aCO_2, change in head position, etc.).

During bone flap replacement at the end of craniotomy, remifentanil infusion syringe B was replaced with the remifentanil infusion syringe C and the same infusion rate was maintained. Before the end of surgery, labetalol and/or hydralazine could be given prophylactically for emergent hypertension. At the end of surgery, residual neuromuscular blockade was reversed. When reversal was deemed adequate, both N_2O and remifentanil infusion syringe C were discontinued.

Recovery period: Postoperatively, SBP, DBP, MAP, HR, RR and recovery scores were recorded every 5 minutes for 30 minutes, then every 15 minutes for a maximum of 60 minutes or until a normal score (which was defined as first time when patient was oriented, no agitation, followed verbal commands, had an LOC score of 1 or 2, and a motor function of 1, and a modified Aldrete score of 9 or 10) was obtained. Quality of emergence was assessed by the neurosurgeon (except for the [illegible]) and anesthesiologist after surgery.

A standard order for codeine 30-60mg every 3 hours or ketorolac 30-60mg every 6 hours as needed for headache was written. Headache occurrence as noted from analgesic use was recorded for the first 8 hours after surgery.

Follow-up phase: All patients were interviewed by the investigator or study coordinator on the first postoperative day to assess adverse events and medication use since surgery. Patients were also given a neurological examination and questioned about recall of operative events. On the seventh postoperative day or immediately before discharge from the hospital, adverse events and medication use since surgery were assessed again, and the neurological examination was repeated.

<u>Monitors/Vascular Access:</u> Subjects had two peripheral intravenous lines, one for administration of study drug and one for intravenous fluids and other intraoperative medications. A catheter was placed in the radial artery for continuous measurement of arterial blood pressure and intermittent collection of blood samples for measurement of arterial carbon dioxide pressure (P_aCO_2) and/or remifentanil levels. Instrumentation included lead II ECG, pulse oximeter, ICP transducer (Gaeltec®) and recording device, and CBF measurement equipment

Exclusion from Analysis: No patients were excluded from either the efficacy or safety analysis.

Protocol Deviations: Protocol violations were identified for two patients: one was operated on in the prone position, the other received an opioid during a preoperative carotid arteriogram. All patients were included in the efficacy and safety analyses.

RESULTS:

Remifentanil dosages are summarized in the following 2 tables. The final mean infusion rate of remifentanil that was used in this pilot study was 0.297mcg/kg/min, as opposed to the initial maintenance rate of 0.4mcg/kg/min.

Table 2. Summary of Remifentanil Continuous Infusion Rate, All Patients (N=30)

Values = Mean ± SD (Range) and Range (min, max)

	Remifentanil Infusion Rate (mcg/kg/min)			
	Rate Immediately Prior to Intubation	Weighted Mean Rate During Maintenance	Rate immediately Prior to Skin Incision	Rate Immediately Prior to End of Infusion
Mean (±SD) Range	0.965 (±0.183) 0-1.005	0.361 (±0.11) 0.181-0.628	0.357 (±0.128) 0.131-0.607	0.297 (±0.163) 0.05-0.797

Table 3. Total Remifentanil Exposure for all patients (N=30)

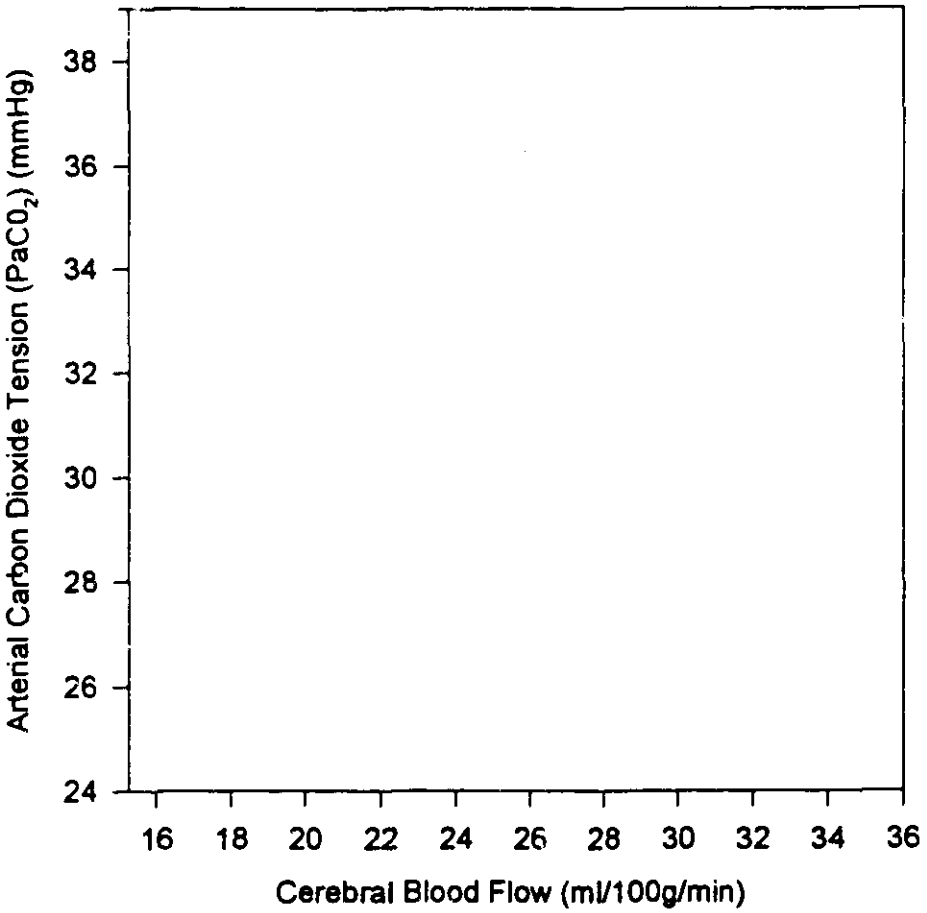
Values = N or Mean ± SD

Total Bolus Exposure (mcg/kg)	
Mean ± SD	146.9 ± 83.1
Range	51.3 - 408.6
Duration of Infusion (minutes)	
Median	334
Range	157 - 737

Preoperative head scans indicated that the patients had small, well-compensated intracranial space-occupying lesions: mean tumor diameter = 3.7 mm ±2.1 SD, mean midline shift = 2.8mm±5.3 SD. The mean ICP was 10.7 mmHg ± 7.4 SD with a $PaCO_2$ of 29.2mm Hg ± 3.8 SD; brain relaxation scores were judged excellent to minimal swelling in 97% of patients.

The relative CBF reactivity was 3.6 ml/100gm/min/mmHg (Normal range 2-4%). CBF and P_aCO_2 values are presented below. CBF results are presented in Figure 1.

Figure 1. Correlation of Cerebral Blood Flow (CBF) with Arterial Carbon Dioxide Tension (PaC02), N=9 Patients



Error Bars = S.E.M

The mean P_aCO_2 during the hypocapnic CBF measurement was 26.7mmHg and 35.9mmHg during the normocapnic CBF measurement. The mean CBF during hypocapnia was 21.2mL/100g/min and during normocapnia the mean CBF was 31.2mL/100g/min. The protocol allowed mannitol to be administered per surgeon request for excessive brain swelling during the cerebral blood flow measurement periods; however, no patient required use of mannitol.

Overall hemodyanamic responses to induction and perioperative stimuli are summarized in Tables 4 and 5. As expected, there was a statistically significant reduction in blood pressure with induction of anesthesia which returned to control levels during the recovery period.

Table 4. Comparison Of Systolic Blood Pressure At Selected Time Points All Patients (N=30)
Values are Weighted Mean ± SD (Range)

Baseline	Induction Period	During Intubation	During Skin Incision	Maintenance Period	At End of Surgery	Recovery Period	Intraop* Mean Min/Max
150.3±22 (108-195)	131.4±21.2 (95-168)	129.4±30.8 (97-245)	113.8±20.1 (87-157)	113.6±10.5 (96-134)	123.7±21.7 (90-169)	144.5±17.8 (122-189)	91.4/150.9

* Mean minimum and maximum from beginning of infusion to end of surgery

Table 5. Comparison Of Heart Rate At Selected Time Points All Patients (N=30)
Values are Mean ± SD (Range)

Baseline	Induction Period	During Intubation	During Skin Incision	Maintenance Period	At End of Surgery	Recovery Period	Intraop* Mean Min/Max
74.9±15 (55-108)	73.6±15.4 (55-126)	69±14.8 (49-99)	58±10.1 (42-84)	61.9±10.6 (47-83)	82.3±13 (59-112)	85.3±17.9 (58-120)	50.3/ 90.7

* Mean minimum and maximum from beginning of infusion to end of surgery

Eleven patients had the infusion rate increased for hypertension. The most common reason for increasing the remifentanil infusion rate, however, was not for signs of light anesthesia, but for other reasons (19 patients); eg, blood pressure control requests or intentional inducement of hypotension. Nineteen patients received at least one bolus of remifentanil.

Twenty patients had the infusion rate decreased for hypotension. The most common reason for decreasing the rate, however, was not for signs of excessive anesthesia, but for other reasons (24 patients); eg, blood pressure control requests or intentional inducement of hypertension.

Table 6. Summary of Response to Intubation, Head Pin Placement, Skin Incision, and Skin Closure[1], All Patients: Values are N (% total)

	Remifentanil 1mcg/kg/min + 0.4mcg/kg/min			
	Intubation (N=30)	Head Pin Placement (N=24)	Skin Incision (N=30)	Skin Closure (N=30)
Number of Patients With At Least One Response	9 (30%)	1 (4%)	3 (10%)	2 (7%)
Number (%) of Patients with:				
Hemodynamic Response:				
Hypertensive	8 (27%)	1 (4%)	3 (10%)	0
Tachycardic	3 (10%)	0	0	1 (3%)
Somatic Response	0	0	0	1 (3%)
Autonomic Response	0	0	0	0

[1] From remifentanil beginning to remifentanil end.

Pharmacokinetic Results:

Principal pharmacokinetic results are presented in Figures 2 and 3. The values for remifentanil (0-0.95ng/mL) are consistent with the rapid elimination half-life (5-8min) of this compound and the time between termination of the infusion and sampling time. The scheduled 30 minute blood sample was actually collected at a median time of 24 minutes after remifentanil was discontinued.

Figure 2. Individual Remifentanil (N=18) and GR90291 (N=20) at a mean of 24 min Post Infusion

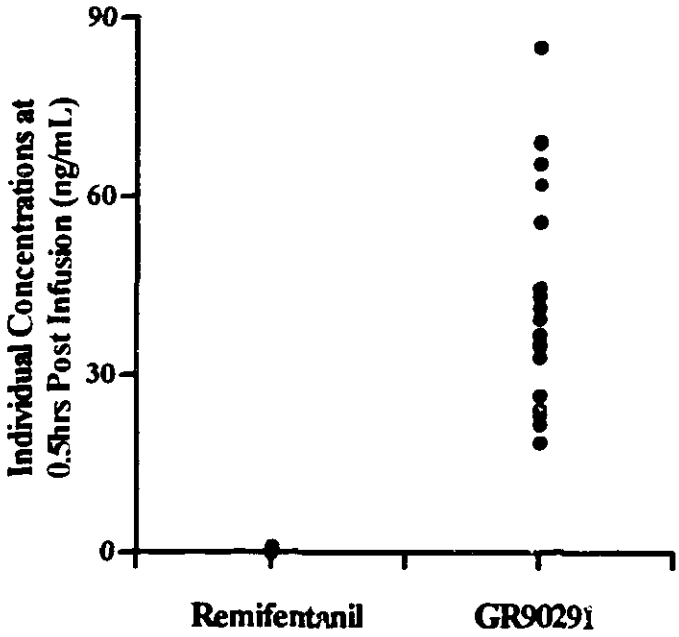
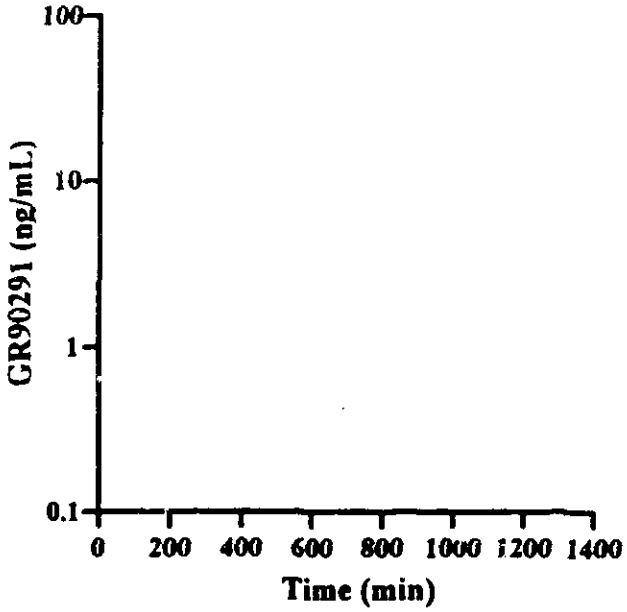


Figure 3. Individual Post Infusion GR90291 (N=20)



Observations made during emergence and recovery from remifentanil/N20/O2 anesthesia are summarized in Table 7. While most patients awoke and had satisfactory scores in a mean time of 5 minutes, the ranges indicate that many had extended periods required for full awakening. Whether this is related to the anesthetic or to the neurosurgical procedure is subject to conjecture, although some of the delayed awakening episodes are explained in the adverse event records. No patient required naloxone for delayed emergence.

Table 7. Summary of Emergence and Recovery, All Patients (N=30)
Values = N (% Total), or Median (Range)

Time (min) from end of remi infusion to: [1]	
Spontaneous Respiration	
N	28
Median, (Range)	3 (-1-10)
Adequate Respiration	
N	10
Median, (Range)	4.5 (1,8)
Extubation	
N	30
Median, (Range)	5 (-1-14)
Open Eyes on Command	
N	25
Median, (Range)	3 (0-9)
Respond to Verbal Commands [2]	
N	29
Median, (Range)	5 (0-19)
Number of Patients, N(%), Who Remember Any Aspect of the Operation:	0 (0%)

Time (min) from end of remi infusion to: [1]	
Normal Score [3]	
N	23
Median, (Range)	10 (1-45)
Aldrete Score ≥ 9	
N	26
Median, (Range)	10 (1-45)
Normal Neuro Score [4]	
N	22
Median, (Range)	5 (0-45)
Level of Consciousness (LOC)	
N	29
Median, (Range)	5 (0-20)
Orientation	
N	24
Median, (Range)	5 (0,-45)
Normal Motor Function	
N	30
Median, (Range)	5 (0-45)

[1] Time is measured from remifentanil infusion end to point of each emergence/recovery profile variable.
[2] First time patient followed commands when aroused.
[3] Normal score = LOC score of 1 or 2, patient is oriented, responds to commands, motor function is normal or no change from pre-study, no agitation, and Aldrete score ≥ 9.
[4] Normal neuro score = LOC score of 1 or 2, patient is oriented, responds to commands, motor function is normal or no change from pre-study, and no agitation.

Adverse Events:

Arterial hypotension was the most common adverse event related to remifentanil infusion, occurring in 47% of patients. The timing of these episodes is summarized in Table 8.

Table 8. Systolic Blood Pressure < 80mmHg
Values = N/N Total, (% Total)

Treatment Group	Induction	Intubation	Maintenance
Remifentanil (N=30)	2/30 (7%)	1/30 (3%)	5/30 (17%)

Five patients experienced SBP<80mmHg during these specified time periods.

During induction, cardiovascular adverse events (ie, bradycardia, hypotension, bigeminy, and hypertension) were reported in 17% of patients. Cardiovascular adverse events were also most frequent during the maintenance phase (63% of patients), with hypotension being reported for 43% of patients. Treatments for hypotension included phenylephrine (five patients) and ephedrine (eleven patients). Atropine was used to treat bradycardia in five patients.

All reported episodes of nausea (53% incidence) were considered related to study drug. One episode each of drug-related involuntary movements and bronchospasm occurred in the same patient during maintenance. Twenty-three patients required post-surgical use of analgesics for headache. The median time to first analgesic use was 41 minutes (range 10-283). No patient reported remembering any aspect of the operation.

Data Listings of Important Adverse Events:
One patient had a serious adverse event during the study (Table 9). No patient died during the study period. One patient died from progressive central nervous system impairment 83 days after remifentanil treatment and the other patient died from a massive pulmonary embolism 19 days after receiving remifentanil.

Table 9. Serious Adverse Events, All Patients (N=30),

Patient Number	Sex/ Age	Description of Event
111	F/59	One minute after initiation of remifentanil, the patient developed hypotension (78/42 mmHg) probably related to remifentanil. The hypotension was treated with phenylephrine; however, a dilutional error resulting in overdose. Two minutes later, the patient's blood pressure increased to a peak of 283/167mmHg which was considered serious and life-threatening. The hypotension, but not the hypertension, was related to remifentanil.

2. CONCLUSIONS:

This study, considered by the Sponsor to be a "pilot," demonstrates that cerebral blood flow (CBF) reactivity to CO_2 remains intact during remifentanil - N_2O/O_2/Isoflurane anesthesia.

Only limited conclusions can be drawn regarding the impact of remifentanil on ICP because: 1) all patients were receiving a constant infusion at the time of ICP measurement and, 2) most of the patients had small, inconsequential intracranial lesions.

The mean infusion rate of remifentanil used for maintenance of anesthesia with nitrous oxide/isoflurane in this pilot study was 0.297 mcg/kg/min.

Emergence and recovery occurred rapidly (5-10 min) following discontinuation of remifentanil.

The mean half-life of GR90291 was 111 minutes, indicating no disproportionate accumulation of this metabolite during prolonged neurosurgical procedures.

3. RECOMMENDATIONS REGARDING LABELING:

1) The label quotes the maintenance infusion rate for neurosurgery as 0.4 ug/kg/min. This study had a final maintenance infusion rate close to 0.3 ug/kg/min, and the final study #304 (where the remifentanil was titrated to effect in a blinded trial), actually wound up with a dose of 0.22 ug/kg/min. This reviewer suggests that the latter infusion rate is probably more appropriate guidance for practitioners.

2) The label statement that cerebrovascular reactivity to CO_2 remains intact during remifentanil infusion is supported by this study.

Robert F Bedford

Robert F. Bedford, MD

1/22/96

MEDICAL OFFICER REVIEW

NDA #: 20-630
PRODUCT TRADE NAME: Remifentanil
SPONSOR: Glaxo
Study 304 - Remifentanil vs. Fentanyl in Neuroanesthesia
LETTER/SUBMISSION DATE: Nov 1, 1995
REVIEWER: Robert F. Bedford, M.D., Medical Officer
CSO: David Morgan

Remifentanil is a rapid onset/rapid offset mu-opioid agonist currently under evaluation as an intravenous analgesic/anesthetic agent. This was a 3-site, randomized, double blind, parallel, controlled study performed in sixty-three patients scheduled for elective surgical removal of a supratentorial mass lesion

Goals of the study were: 1) Compare efficacy of remifentanil and fentanyl for the treatment of perioperative hemodynamic responses; 2) Compare emergence/recovery profiles of remifentanil and fentanyl following craniotomy, 3) compare cerebrovascular effects (ICP, CBF, and CPP) and clinical event profile of remifentanil and fentanyl.

Investigators:

Study Protocol: Patients were permitted their usual neurological medications, including dexamethasone and anticonvulsants up to the time of surgery. Specific preoperative medications could include midazolam and/or ranitidine. Intravenous and intraarterial cannulae and standard non-invasive monitors were placed. General anesthesia was induced with thiopental, 4 mg/kg, and pancuronium; oxygen was administered by face mask and an induction infusion of remifentanil 1.0mcg/kg/min or fentanyl 2.0mcg/kg/min was begun. Study drug infusion syringe A then was started at a rate of 2.4ml/kg/hr (1mcg/kg/min remifentanil or 2mcg/kg/min fentanyl) and continued until level of anesthesia required for intubation had been achieved (target 5 minutes), or a maximum of 10 minutes elapsed (10mcg/kg remifentanil or 20mcg/kg/min fentanyl; see Table 1). After intubation, mechanical ventilation began with a 2:1 mixture of nitrous oxide and oxygen (N_2O/O_2). A supplementary dose of thiopental (50-150mg) could be given at the time of intubation and/or during placement of the pin holder, as needed. Following intubation, a maintenance infusion of 0.2mcg/kg/min and 0.03mcg/kg/min of remifentanil and fentanyl, respectively was administered.

Table 1. Study Drug Treatment

Study drug treatment	Study Drug Syringes			
	Induction Period [1]	Maintenance Period [2]		
	Infusion syringe "A"	Infusion syringe "B"	Infusion syringe "C" [3]	Response bolus syringe (per 10ml)
Remifentanil Concentration: Initial Rate:	25mcg/ml 2mcg/kg/min	48mcg/ml 0.2mcg/kg/min	48mcg/ml	1mcg/kg
Fentanyl Concentration: Initial Rate:	50mcg/ml 1mcg/kg/min	8mcg/ml 0.03mcg/kg/min	Normal Saline	2mcg/kg

[1] Infusion of syringe A from induction beginning until intubation or maximum of 10 minute infusion.
[2] Infusion of syringe B from intubation to time of bone flap replacement. Infusion of syringe C from time of bone flap replacement to end of nitrous oxide.
[3] Initial rate of infusion syringe C equals final infusion rate of infusion syringe B.

During maintenance of anesthesia, hemodynamic responses were treated with study drug boluses and/or infusion rate increases, if deemed necessary by the investigator. Each bolus consisted of 10ml of study drug (fentanyl 2mcg/kg or remifentanil 1mcg/kg) administered over approximately 1 minute from the response bolus syringe. If three study drug boluses had been administered for a particular response and a fourth bolus was required, then the fourth bolus had to be followed by a study drug infusion syringe B rate increase. The study drug infusion syringe B rate increase was in increments of 0.125ml/kg/hr [fentanyl (0.016mcg/kg/min) or remifentanil (0.2mcg/kg/min)]. A minimum of 1 minute was to have elapsed between boluses and at least 2 minutes between infusion rate increases.

A maximum of five remifentanil boluses and/or a maximum infusion rate of 0.5ml/kg/hr [fentanyl (0.06mcg/kg/min) or remifentanil (0.4mcg/kg/min)] was allowed. If the maximum number of boluses and/or infusion rate had been administered, then 0.2% isoflurane could be added to the inspired inhalational gas mixture and increased in 0.2% increments as needed.

The study drug infusion syringe B rate was decreased by 0.125ml/kg/hr if the hemodynamic safety criteria were met. Isoflurane administration was to be discontinued before decreasing study drug infusion syringe B as SBP <80% of baseline for ≥1 minute or HR <45bpm for ≥1 minute

Additionally, the surgeon could request intentional hypotension (blood pressure below hypotensive criteria, i.e., SBP <80% baseline for ≥1 minute), intentional hypertension (blood pressure above hypertensive criteria), or to control the patient's blood pressure (adjustment of blood pressure within the hypotensive and hypertensive criteria).

At the time of bone flap replacement, isoflurane was discontinued and the study drug infusion syringe B was replaced with the study drug infusion syringe C (placebo or remifentanil). The same infusion rate was maintained. At the end of surgery residual neuromuscular blockade was reversed. When reversal was deemed adequate, both N_2O and study drug infusion syringe C were discontinued.

Table 2. Total Study Drug Exposure, All Subjects (N=63)
Values = N or Mean ± SD

	Remifentanil	Fentanyl
Number of Patients	31	32
Induction Dose (mcg/kg)		
Mean (±SD)	6.9 (±1.5)	13.7 (±3.3)
Range	5-10	10-20
Total Dose Exposure (mcg/kg)		
Mean (±SD)	73.2 (±29.1)	34.2 (±10)
Range	24.8-148.7	17.1-53.9
Duration of Infusion (minutes)		
Median	297	293.5
Range	143-587	159-813

Hemodynamic responses during surgery could be controlled using ephedrine, phenylephrine, atropine, labetalol, or if deemed necessary by the investigator, for unacceptable hemodynamic events. Before the end of surgery, labetalol and/or hydralazine could be given as prophylactic measures against emergent hypertension.

ICP and CBF Measurement: CBF measurements were conducted at Columbia University and ICP was measured at the other two centers. After the first burr hole was drilled, an ICP transducer was placed in the epidural space for measurement of intracranial pressure. After the ICP waveform had stabilized (1-3 minutes) the mean ICP was recorded. After the mean ICP was recorded, an arterial blood sample was collected for measurement of $PaCO_2$. After the ICP measurement was made, the craniotomy proceeded.

At Columbia University, as the bone flap was being removed, the predicted $PaCO_2$ was increased to approximately 38mmHg by the addition of CO_2 to the fresh gas mixture. After the bone flap was removed and five minutes after a predicted $PaCO_2$ of approximately 38mmHg had been achieved, a CBF measurement was made. At the end of this measurement, an arterial blood sample was collected for measurement of $PaCO_2$. The CO_2 was then discontinued and, when the predicted $PaCO_2$ had returned to the previous baseline, a second CBF measurement was made and an arterial blood sample was collected for measurement of $PaCO_2$.

After the bone flap had been removed and the dura opened, the surgeon was asked to assess the condition of the brain using a 1-4 scale. Standard treatment was given if deemed necessary (e.g., additional mannitol, furosemide, further decrease in $PaCO_2$, change in head position, etc.).

At the end of operation, N_2O/O_2 was discontinued, neuromuscular blockade was reversed and evaluations of emergence and recovery were made. Cardiovascular parameters and recovery scores were recorded every 5 minutes for 30 minutes, then every 15 minutes for a maximum of 60 minutes or until a normal score was obtained. Quality of emergence was assessed by the neurosurgeon (except for the Columbia University center) and anesthesiologist after surgery. Any complications of surgery were recorded. Quality of recovery was assessed by the nurse primarily responsible for the patient's care during the first 8 hours after surgery.

All patients were interviewed by the investigator or study coordinator on the first postoperative day to assess adverse events and medication use since surgery. Patients were also given a neurological examination, assessed for mental clarity, and questioned about recall of operative events. On the seventh postoperative day or immediately before discharge from the hospital, adverse events and

medication use since surgery were assessed again, and the neurological examination and mental clarity evaluation was repeated.

Exclusion from Analysis: No patients were excluded from either the efficacy or safety analysis.

Protocol Deviations: No major protocol violations occurred. All patients were included in the efficacy and safety analyses.

Efficacy: The following variables were summarized:

- Response to major stress events
- Light anesthesia responses
- Excessive anesthesia responses (bradycardia and hypotension)
- Study drug adjustment: increases, decreases, and bolus use
- Elapsed time from end of study drug syringe C to emergence (spontaneous respiration, adequate respiration, extubation), time to respond to command, and time to recovery
- Incidence of nausea/emesis after surgery, and by follow-up interview
- Patients remembering any aspects of the operation
- Frequency of intentional hypertension, hypotension, or blood pressure control requests

RESULTS:

Patient Characteristics: As seen in the following 2 tables, the randomization schedule resulted in satisfactory distribution of patients among the 2 study groups.

Table 3. Patient Characteristics by Treatment Group, All Patients (N=63)
Values are N (% Total) or Mean (±SD) or Range

	Remifentanil	Fentanyl
Number of Patients	31	32
Sex: Male	18 (58%)	23 (72%)
Female	13 (42%)	9 (32%)
Age (yr) Mean (±SD)	50.8 (±13.5)	49.4 (±13.5)
Weight (kg) Mean (±SD)	80.7 (±16.3)	81.9 (±17.8)
Ethnic Origin		
Caucasian/White	31 (100%)	31 (97%)
Hispanic	0 (0%)	1 (3%)
ASA Status II	18 (58%)	17 (53%)
III	13 (42%)	15 (47%)
Common Preop Medications[1]		
Dexamethasone	25 (81%)	24 (75%)
Ranitidine	19 (61%)	17 (53%)
Phenytoin	17 (55%)	17 (53%)

[1] Pre-operative medications primarily included prophylactic antibiotics, anti-seizure, neuroprotectant, and anti-stress ulcer drugs

Table 4. Summary Of Preop CT or MRI Scan Reports
Values= Mean (±SD) and Range or N (% total)

	Remifentanil	Fentanyl
Number of Patients	31	32
Maximum Tumor Diameter (cm): Mean (±SD)	4 (±1.5)	3.8 (±1.7)
Maximum Midline Shift (mm): Mean (±SD)	3.9 (±6.7)	3.9 (±5.7)
General Assessment of Tumor Mass Effect:		
None	5 (16%)	7 (22%)
Mild	11 (35%)	8 (25%)
Moderate	11 (35%)	11(34%)
Severe	4 (13%)	6 (19%)

Primary Efficacy Endpoints:

CBF reactivity was 2.6% (remifentanil) and 4.0% (fentanyl). The mean ICP during remifentanil infusion was 13.2 mmHg±10.1; range=0-36 and 14mmHg±13.1, range=0-38 during fentanyl infusion. Brain relaxation scores were judged excellent to minimal swelling in most patients (90% remifentanil, 75% fentanyl). Three of the fentanyl patients, but none of the remifentanil patients were judged to have excessive brain swelling requiring additional treatment. ICP and CBF results are presented in Table 5 and Figure 1.

Figure 1. Responsiveness of Cerebral Blood Flow (CBF) to Arterial Carbon Dioxide Tension (PaC02), (N=11 Remifentanil, N=10 Fentanyl Patients)

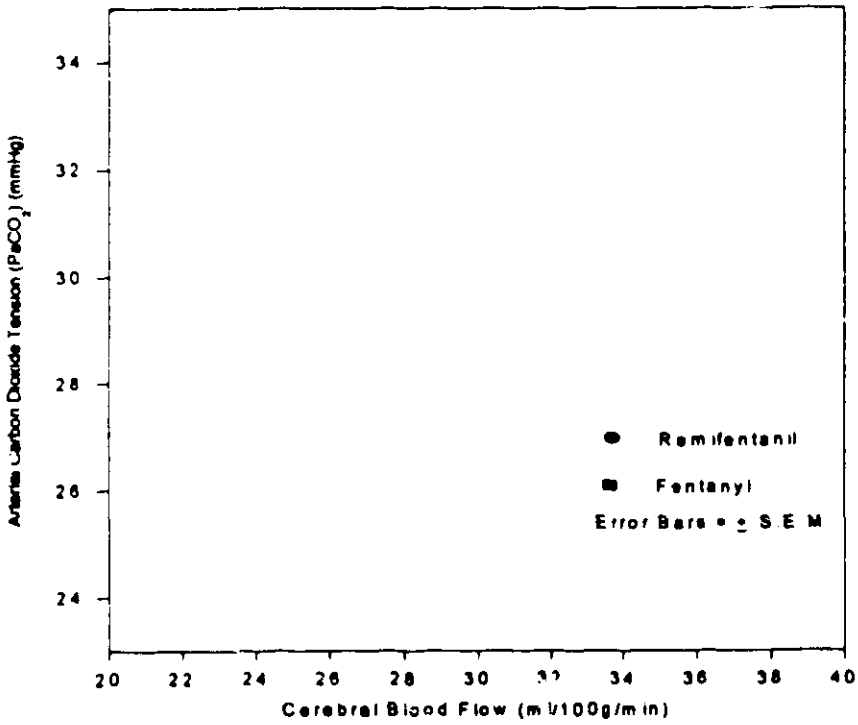


Table 5. Primary Efficacy Results: Cerebrovascular Effects
Values=N, Median (Range)

	Remifentanil	Fentanyl	p-value[1]
Intracranial Pressure (mmHg)			
N	17	16	
Median (±SD)	13.2 (±10.1)	14 (±13.1)	0.650
Range	0-36	0-38	
Relative CBF reactivity (%)			
N	10	9	0.288
Median (±SD)	2.6 (±3.5)	4.0 (±2.1)	
Range	-5-7	2-9	

[1] p-values are based on ANOVA controlling for investigator

Study Drug Dosage Adjustments and Intraoperative Responses:

Patients experienced signs of light anesthesia most frequently during placement of head pins and at skin incision (Table 6). The most common response during these periods was an increase in systolic blood pressure. There was no clinically or statistically significant difference between the two anesthetic regimens. There was a tendency for the fentanyl-treated patients to require more isoflurane for control of signs of light anesthesia. (Table 7).

Table 6. Summary of Response [1] to Intubation, Head Pin Placement, Skin Incision, Burr Hole Placement, Bone Flap Elevation, Bone Flap Replacement, and Skin Closure [2], All Patients (N=63)
Values are N and (% Total)

	Remifentanil						
	Intubation	Head Pinning	Skin Incision	Burr Hole	Bone Flap Off	Bone Flap On	Skin Closure
Number of Patients	31	31	31	31	31	31	31
Number of Patients With At Least One Response	1 (3%)	7 (25%)	7 (23%)	0	4 (13%)	1 (3%)	2 (6%)
Number (%) of Patients with:							
Hemodynamic Response:							
Hypertensive	1 (3%)	7 (28%)	6 (19%)	0	2 (6%)	1 (3%)	2 (6%)
Tachycardic	0	1 (4%)	2 (6%)	0	2 (6%)	0	0
Somatic Response	0	0	0	0	0	0	0
	Fentanyl						
	Intubation	Head Pinning	Skin Incision	Burr Hole	Bone Flap Off	Bone Flap On	Skin Closure
Number of Patients	32	32	32	32	32	32	32
Number of Patients With At Least One Response	5 (16%)	6 (20%)	10 (31%)	1 (4%)	1 (3%)	3 (9%)	4 (13%)
Number (%) of Patients with:							
Hemodynamic Response:							
Hypertensive	3 (9%)	5 (17%)	10 (31%)	1 (4%)	1 (3%)	2 (6%)	2 (6%)
Tachycardic	2 (6%)	3 (10%)	0	0	0	0	2 (6%)
Somatic Response	0	0	0	0	0	1 (3%)	1 (3%)
p-value [3]	0.196	0.522	0.572	0.491	0.187	0.613	0.672

[1] Response was defined as having at least one of the following within 5 minutes after intubation, head pin placement, burr hole placement, skin incision, and skin closure: Hypertension, tachycardia, somatic, or autonomic
[2] From study drug beginning to skin closure.
[3] p-value is based on exact test to detect a treatment difference, except for head pin placement and bone flap elevation, which is based on logistic regression to detect a difference between treatments and is adjusted for investigator.

Table 7. Summary of Isoflurane Use, All Patients (N=63)
Values=N (% Total) or Mean

	Remifentanil	Fentanyl	p-value
Patients receiving isoflurane:	8 (26%)	13 (41%)	0.210 [1]
Mean dose (MAC hours)	0.07	0.644	0.039 [2]
Patients receiving isoflurane meeting rescue criteria:	5 (16%)	7 (22%)	0.572 [1]
Mean dose (MAC hours)	0.081	0.295	0.136 [2]

[1] p-value is based on logistic regression adjusted for investigator
[2] p-value is based on ANOVA and is adjusted for investigator

Excessive depth of anesthesia occurred with equal frequency in both groups of patients. There was no difference between the groups in the incidence of excessive heart rate and blood pressure decreases requiring opioid dosage adjustment. However, there were more patients with systolic blood pressure below 80 mm Hg in the remifentanil group than in the fentanyl group (Table 9).

Table 8. Intraoperative Responses to Excessive Anesthesia, All Patients (N=63)

	Remifentanil	Fentanyl	p-value
Number of patients	31	32	
Number of patients (%) with excessive anesthesia response: [1]	26 (84%)	24 (75%)	0.361

[1] p-value is based on logistic regression to detect a difference between treatments and is adjusted for investigator

Table 9. Systolic Blood Pressure < 80mmHg, All Patients (N=63)
Values = N/N Total, (% Total)

Treatment	Baseline	Induction Period	During Intubation	Maintenance Period	Skin Incision	End of Surgery	Recovery Period
Remifentanil	0	1 (3%)	3 (10%)	2 (6%)	0	0	0
Fentanyl	0	0	0	1 (3%)	0	0	0

Hemodynamic data (Tables 10 and 11) suggest that remifentanil, at the doses used in this study, produced significantly better blockade of cardiovascular response to endotracheal intubation than fentanyl. On the other hand, there was also higher mean systolic blood pressure observed in the recovery period in the remifentanil patients, probably indicating inadequate postoperative analgesia and/or postoperative excitation.

Table 10. Comparison Of Systolic Blood Pressure At Selected Time Points All Patients (N=63)

Values are Mean or Weighted Mean ± SD (Range) [1]

Treatment	Baseline	Induction Period	During Intubation	Maintenance Period	Skin Incision	End of Surgery	Recovery Period
Remifentanil	147.5 ± 21.4 (120-220)	129.9 ± 19.3 (82-167)	113.3 ± 18.4 (71-153)	120.3 ± 10.1 (105-139)	123.2 ± 18.9 (92-164)	106.1 ± 15.3 (82-137)	146.9 ± 15.1 (107-173)
Fentanyl	145.8 ± 17.4 (123-178)	133.7 ± 21.5 (97-176)	127.1 ± 23.1 (90-190)	124.9 ± 12.2 (104-155)	126.8 ± 24.1 (86-184)	120.9 ± 20 (85-156)	134.3 ± 16.4 (93-173)
p-value [2]	0.732	0.231	0.004	0.054	0.208	0.004	0.001

[1] Baseline and end of surgery values are mean values. Induction, intubation, maintenance, skin incision, and recovery values are based on weighted means

[2] p-value is based on ANOVA on least square means to detect a treatment difference and is adjusted for investigator and baseline.

Table 11. Comparison Of Heart Rate At Selected Time Points All Patients (N=63)

Values are Mean ± SD (Range) [1]

Treatment	Baseline	Induction Period	During Intubation	Maintenance Period	Skin Incision	End of Surgery	Recovery Period
Remifentanil	74 ± 13.2 (48-110)	74.1 ± 10.6 (54-101)	69 ± 8.5 (50-87)	68.3 ± 11 (51-92)	68.4 ± 10.1 (52-90)	71.5 ± 15.4 (41-103)	79.8 ± 13.1 (59-107)
Fentanyl	82.5 ± 16.9 (49-113)	83 ± 15.7 (50-111)	83.1 ± 16.8 (47-113)	72.4 ± 11.1 (50-96)	73.6 ± 12.9 (46-103)	75.7 ± 13.4 (55-98)	77.1 ± 14.5 (56-112)
p-value [2]	0.034	0.183	0.001	0.969	0.636	0.558	0.246

[1] Baseline and end of surgery values are mean values. Induction, intubation, maintenance, skin incision, and recovery values are based on weighted means

[2] p-value is based on ANOVA on least square means to detect a treatment difference and is adjusted for investigator and baseline.

Recovery:

Because of the longer duration of action of fentanyl compared to remifentanil, the fentanyl infusion was scheduled to end at the time of bone flap closure, (replacement of infusion syringe B with syringe C containing normal saline) with nitrous oxide being continued up to the end of surgery. The median time from the end of the fentanyl infusion until the discontinuation of nitrous oxide was 44 minutes (range: 25 to 95 minutes). By contrast, patients receiving remifentanil were maintained on nitrous oxide up to within a few minutes of ending the remifentanil infusion (range: 0 to 3 minutes). In general, there was no clinically meaningful difference between the 2 opioids with regard to time patients acheived various emergence criteria, the incidence of nausea and emesis or the quality of their awakening. As expected, postoperative analgesics were required sooner after remifentanil than after fentanyl-based anesthesia. No remifentanil patient required naloxone reversal whereas 7 fentanyl patients did. Pertinent emergence data are summarized in the following 2 tables:

Table 12. Summary of Emergence and Command Response, All Patients (N=63) Values = N (% Total), or Median (Range)

	Remifentanil	Fentanyl	p-value [1]
Number of Patients	31	32	
Time (minutes) to: [2]			
Spontaneous Respiration Median, (Range)	3 (-2-15)	2 (-7-10)	0.346
Adequate Respiration Median, (Range)	6 (0-15)	4 (0-22)	0.318
Extubation Median, (Range)	5 (1-15)	3.5 (-1-40)	0.521
Open Eyes on Command [3] Median, (Range)	3 (-2-12)	2 (-8-21)	0.518
Respond to Verbal Commands [3] Median, (Range)	5 (2-60)	5 (-3-20)	0.083

[1] p-value is based on Cox's proportional hazards model adjusted for investigator. Patients are censored if their time is missing or they received naloxone before their response time.
[2] Time is measured from end of opioid infusion or end of nitrous oxide, whichever is latest.
[3] First time patient followed commands when aroused.

Table 13. Summary of Time to First Analgesic Use, and Naloxone Use. All Patients (N=63) Values = N (% Total), or Median (Range)

	Remifentanil	Fentanyl	p-value
Time to First Analgesic Use (minutes) [1] N (%) Median, (Range)	20 (64%) 34.5 (7-403)	16 (50%) 136 (6-416)	0.043 [2]
Number of Patients Who Required Naloxone	0	7 (22%)	0.011 [3]

[1] Time is measured from end of opioid infusion or end of nitrous oxide, whichever is latest. Patients are censored if they had no headache after infusion stop.
[2] p-value is based on Cox's proportional hazards model adjusted for investigator. Patients are censored if their time is missing or they received naloxone before their response time.
[3] p-value is based on exact test.

Adverse Events:

No deaths were reported. Four serious adverse events occurred, one considered related to study drug: emergence delerium (remifentanil). Among the other adverse events recorded, there was no suggestion of a difference between remifentanil and fentanyl.

Data Listings of Important Adverse Events:

No patient died during the study period. Two fentanyl patients and two remifentanil patients experienced serious adverse events during the study period (Table 14). The emergence delirium observed in subject 128, described below, was probably related to remifentanil. All other serious adverse events were considered unrelated to study drug.

Table 14. Serious Adverse Events, All Patients (N=63),

Patient Number	Sex/ Age	Treatment Group	Description of Event
124	F/60	Fentanyl	After removal of the bone flap the patient developed severe hemorrhage from an abnormal configuration of the epidural venous system.
128	M/55	Remifentanil	Ten minutes after remifentanil was discontinued the patient became extremely agitated and pulled out his intravenous catheters and other monitoring devices. This combative behavior persisted for approximately 90 minutes during which he was intermittently hypertensive, hypotensive, tachycardic and unresponsive. Hypoxia and hypercarbia was ruled out and his neurological examination was non-focal. The patient was sedated with midazolam, morphine, thiopental and fentanyl. His hypertension was treated with propanolol, labetalol and hydralazine. The investigator felt that the event was life-threatening because the patient discontinued monitoring devices and intravenous support immediately postoperatively. The patient had no history of psychiatric disorder or alcohol abuse. The investigator reported that the emergence delirium (agitation) was probably related to remifentanil. This reviewer agrees.
163	M/71	Remifentanil	Approximately one hour after the patient was extubated the patient was given labetalol 5mg for treatment of systolic hypertension of 160mmHg. The patient's systolic BP decreased to 70mmHg and subendocardial infarction was confirmed by a cardiologist.
164	M/44	Fentanyl	The surgical procedure lasted fourteen hours. The following morning the patient remained unconscious. It was noted that the patient's intracranial pressure was increasing and CT scan of the brain showed right frontal edema with mass effect.

Conclusions:

- Cerebral blood flow (CBF) reactivity to hypocapnia is preserved during anesthesia with both remifentanil and fentanyl with N_2O/O_2.
- Remifentanil and fentanyl provided similar efficacy in treating hemodynamic responses, except that remifentanil, at the doses used, was somewhat superior to fentanyl in preventing hypertension/tachycardia following endotracheal intubation.
- The fentanyl group required greater increases in initial opioid infusion rate (67%) and using significantly more isoflurane than occurred in the remifentanil group. The mean final infusion rate of remifentanil (0.22mcg/kg/min) used for maintenance of anesthesia with nitrous oxide/oxygen in this study was only 10% higher than the initial maintenance rate.
- Emergence and recovery occurred rapidly following discontinuation of remifentanil.
- There was no evidence for an increased incidence of adverse events associated with remifentanil-nitrous oxide anesthesia as used in this protocol. Postoperative excitement does seem to be a complication following remifentanil anesthesia, and this is not well-described in the draft package insert.

Conclusions regarding labeling:

1) Under "Neurosurgery" in the Clinical Trials section, the remifentanil maintenance infusion rate is described as "0.4 μg/kg/min" (Line 279). This was actually the maximum allowed maintenance dose allowed by the protocol. The actual average infusion rate during this trial was 0.22 μg/kg/min.

2) The single case of postoperative agitation following remifentanil was truly life-threatening. This is not the only such case in the clincal trials. This reviewer believes greater attention should be drawn to this complication in the labeling.

3) Hemodynamic changes described in the labeling regarding onset and severity of hypotension and bradycardia from doses of remifentanil <2 ug/kg are supported by the findings in this study.

4) Awakening following neurosurgical procedures was no different with remifentanil versus fentanyl. The awakening times in this study are compatible with the labeling. No comparative claims are made regarding the effects of remifentanil versus fentanyl on ICP, CPP or cerebrovascular responsiveness to hypocapnia.

5) Since all the patients were paralyzed at the time of opioid administration, it is not possible to estimate the incidence of perioperative rigidity. Did the other clinical trials tend to minimize this complication by use of neuromuscular blockade prior to administration of remifentanil?

Robert F. Bedford

Robert F. Bedford, MD 1/18/96

NDA#: 20-630
Generic name and form: Remifentanil
Route of Administration: IV
Sponsor: Glaxo, Inc.
Letter Date: 10/12/95
Date Completed: 1/22/96

MEDICAL OFFICER REVIEW
NDA Report
Remifentanil
IV

"Ultiva"

Type of Submission: NDA Report
Date Received: 10/15/95
Reviewer: I. L. Tyler, Ph.D., M.D.

1 Material Reviewed

Volumes: 129-134, 186, 187, 198, 199, 200-206, 220.

1.1 Human Pharmacology, Pharmacokinetics, Pharmacodynamics

Remifentanil pharmacokinetics fit a two-compartment model. It has a distribution half-life of about 30 sec, a volume of distribution of 300-500 ml and a clearance rate of 60-65 ml/min. ($\tau_{1/2}$ for clearance min.). These parameters make it seem nearly an ideal drug for use during short procedures requiring sedation. The rapid distribution permits bolus loading because plasma levels in clinically significant excesses of the target level persist for only about a minute — a time so short that hypoxemia in a pre-oxygenated patient is unlikely. The rapid clearance permits maintenance of a relatively deep level of sedation during the procedure followed by complete recovery from sedation about 15 minutes after stopping drug delivery. The excessive pain response sometimes observed following general anesthesia with remifentanil would be less likely for

Important questions to be answered in remifentanil sedation trials are whether side effects — muscle rigidity, hypotension, pruritis, nausea, and

Important questions to be answered in remifentanil sedation trials are whether side effects — muscle rigidity, hypotension, pruritis, nausea, and vomiting — together with remifentanil's lack of anxiolysis overbalance its desirable features.

2 Description of Clinical Data Sources

Two European studies are included in this review. Both involved small numbers of patients in each of many study sites. Neither was sufficiently well standardized to provide valid efficacy data. The remaining studies were performed in the U.S. with IND protocols submitted prior to completion of the studies.

3 Results

Overview of Efficacy of Remifentanil as an Anesthetic Adjunct

Remifentanil in the wide range 25 μg/kg/min. provided satisfactory sedation for regional and local anesthetic blocks and for the subsequent surgical period. Generally, about half of the dose required during the stimulation of the anesthetic injection was needed to provide subsequent sedation. However, there was a high incidence of nausea — higher than the incidence with alfentanil in one double-blind, phase 3 study. Pruritis was also a frequent side effect. Because controls frequently included remifentanil in lower doses along with either propofol or alfentanil, it is not possible to generate composite statistics regarding the incidence of side effects of remifentanil vs. propofol or alfentanil.

Overview of Safety of Remifentanil as an Anesthetic Adjunct

Two study drug overdoses occurred. One was a ten-fold overdose. This patient developed apnea with muscle rigidity so severe that paralysis and intubation were necessary. The other was a three-fold overdose. While apnea and bilateral upper extremity muscle rigidity ensued, all returned to normal in less than a minute. The patient, who was receiving nasal cannula oxygen, 3 L/min., did not even become hypoxemic.

Muscle rigidity, even moderate to severe muscle rigidity, did occur at sedation-dose levels but did not seem to compromise patient safety and was quickly reversible with discontinuation of the remifentanil infusion.

Two patients — one after spinal anesthesia and one after regional anesthesia for hand surgery experienced sudden apnea resulting in oxygen saturation percentages

in the 70s. One of these also developed concurrent profound hypotension (SBP=60 mmHg). These events occurred during surgery and well after any changes in infusion rates or boluses of any sedative drugs. A third patient became apneic during placement of an opthalmic nerve block and the S_aO_2 dropped to 70%. However, there was no CRF evidence that the protocol-prescribed nasal cannula oxygen was being supplied at the time.

Two patients, without histories of liver problems, developed transient ten-fold elevations in liver enzymes on the first postoperative day of Study 209. LFT's were obtained postoperatively only in Study 208 (n=73) and Study 209 (n=30) so the possibility exists that there is an approximately 1% incidence of liver enzyme elevation after remifentanil use.

There was also a higher incidence of neonatal jaundice when IV remifentanil rather than epidural fentanyl or placebo was used for sedation/pain relief during c-section (26% vs. 11%). However, in this small study, the difference was not statistically significant.

Study 3006: Sedation for local injection for breast biopsy.

Patients were randomized to IV placebo or midazolam (2, 4, or 8mg) as a premedicant. Approximately 5 minutes later, a continuous infusion of remifentanil was started at 100 ng/kg/min. Five minutes later still, the local anesthetic was administered. Remifentanil was titrated for the remainder of surgery according to patient responses, primarily discomfort and respiratory depression.

During the procedure, the mean remifentanil infusion rate was <u>increased</u> slightly from baseline for patients receiving placebo (no midazolam) and was <u>decreased</u> for all midazolam dosed groups. Only the remifentanil decrease (45%) for the highest dosed midazolam group, however, was statistically significant.

No complaints of muscle rigidity were recorded and only one patient experienced an episode of SBP<80 mmHg.

Respiratory depression (RR< 8 BPM) accompanied by S_aO_2 < 90 mmHg was the only significant AE. There was a trend toward a higher number of patients with hypoxemia as the midazolam dose increased — only one patient (5%) in the placebo group (getting only remifentanil) versus 6 patients (32%) in the 8 mg midazolam group.

In the following studies remifentanil was given as an infusion, bolus, or bolus plus infusion. Additional boluses were given and/or infusion rates were changed by the investigator depending on his/her assessment of sedation, anxiety, and pain. Infusion rates were usually halved after the local/regional anesthetic injection procedure.

Study 3009: Sedation for local injection for cataract surgery.

A remifentanil bolus, remifentanil bolus plus infusion, and alfentanil bolus were compared in a double-blind fashion. There was a greater percentage of patients in the remifentanil groups than in the alfentanil group reporting no pain at injection. However, this was at the expense of a considerably higher incidence of nausea, respiratory depression, and muscle rigidity.

Studies 3010 and 3011: Sedation for regional or peripheral nerve block and surgery — remifentanil vs. propofol.

These were necessarily open-label studies.

Not surprisingly, remifentanil was found to provide more consistent pain relief with less sedation during the block. However, even with that significantly lower sedation score, only patients in the remifentanil group (11%) experienced episodes of respiratory depression with $S_aO_2 < 90\%$. In addition, 60% of the remifentanil group eventually experienced nausea. In contrast, only 17% of the propofol group experienced nausea even after postoperative pain medication.

Study 3011 was a European multi-center study (11 centers, 66 remifentanil patients). Comparison of rates of hypoxemia — were obscured by choosing an unusual definition of normoxemia ($S_aO_2 \geq 95\%$).

Study 2018: Remifentanil IV vs. Fentanyl EA vs. Placebo as an Adjunct to Epidural Anesthesia for Non-Emergent C-Section.

This was a phase 2, open label, randomized study. Protocol deviations, an unconventional definition of hypoxemia ($S_aO_2 < 95\%$), and uncontrolled premedication with narcotics render the study inappropriate for assessment of efficacy or of side effects.

A statistically significant increased rate of SBP<100mmHg prior to umbilical cord clamping occurred in the remifentanil group. All patients had received 1-2 liters of glucose-free crystalloid "prior to entrance into the obstetrical suite".

Maternal artery, umbilical artery, and umbilical vein samples were obtained from some of the remifentanil group. PK parameters were estimated:

Estimated Maternal/Neonatal PK Parameters

	Estimates ± SD
Remifentanil	
CL (ml/kg/min.)	100±80 (N=20)
Maternal to Neonatal Ratio (MA/UV)	1.8±0.9 (N=15)
Umbilical Arterial to Venous Ratio (UA/UV)	0.3±0.1 (N=10)
GR90291*	
Maternal to Neonatal Ratio (MA/UV)	2.0±0.9 (N=10)
Umbilical Arterial to Venous Ratio	1.2±0.8 (N=7)
GR90291 to Remif Ratio (MA_G/MA_R)	3.4±4.2 (N=10)

MA, UA, and UV are maternal arterial, umbilical arterial, and umbilical venous drug, respectively.
*Patients with measurable concentrations of this primary metabolite of remifentanil.

There was a increased incidence of neonatal jaundice in the remifentanil group (26% vs. 11%) but the increase did not reach statistical significance.

Study 208: Adjunct to Regional Anesthesia: Hip Replacement, Hand Surgery.

This was a European multi-center phase 2 study attempting to determine a dose-response curve for deep sedation by comparing three starting infusion doses of remifentanil — 0.04, 0.07, and 0.10 μg/kg/min. Eventual supplementation with midazolam was permitted. Unusual definitions of and safeguards against hypoxemia were employed; muscle rigidity was not strictly defined.

Midazolam plus a remifentanil infusion rate of 0.1-0.6 μg/kg/min. in the preoperative period and 0.01-0.24 μg/kg/min. in the operative period rendered the patients deeply sedated but arousable.

Respiratory depression as an adverse event — defined as RR<6 or S_aO_2 < 90% — occurred in 17% of the remifentanil patients but in none of the placebo patients even though the placebo patients received enough midazolam to render them deeply sedated.

Study 3012: Evaluation of Remifentanil vs. Remifentanil/midazolam During Monitored Anesthesia Care.

This was a U.S. 6-center, double-blind, parallel group study comparing 78 adults the receiving a remifentanil infusion (initial rate 0.100 μg/kg/min.) plus placebo with 81 adults receiving remifentanil (0.05 μg/kg/min.) plus midazolam, 2 mg IV in divided doses. Remifentanil titration for appropriate reasons and at appropriate intervals was permitted and the remifentanil alone group could receive supplemental midazolam, 0.5 mg IV either prn or because the maximum allowable group remifentanil dose had been failed to achieve adequate sedation/anxiolysis in either group.

Final mean remifentanil infusion rates ± 1.5 × SEM were 0.123 ± 0.009 μg/kg/min. for the remifentanil/placebo group and 0.065 ± 0.005 μg/kg/min. for the remifentanil/midazolam group. Eleven (14%) of patients — *(requested from sponsor)* in the remifentanil alone group, *(requested from sponsor)* in the remifentanil midazolam group — received supplemental midazolam.

Pain during local anesthetic injection was the primary efficacy endpoint but there was no statistically significant difference in this parameter between groups. There was a statistically significant increase in the amount of nausea intra-operatively and in the amount of nausea and of vomiting postoperatively in the remifentanil/placebo group. Unresolved headache and nausea was also the cause of an extended (6 hr.) hospital recovery stay for one remifentanil/placebo patient. In addition, pruritis was more frequent (23% vs. 12%) in the remifentanil/placebo group.

The incidence of respiratory depression with $S_aO_2 < 90\%$ was low in both groups (4% remifentanil/placebo vs. 2% remifentanil/midazolam) and no other significant safety issues occurred.

These results invite extrapolation to placebo + midazolam, 4 mg. as an even better choice for MAC than remifentanil + midazolam, 2 mg.

Pages 7-8
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Labeling Review

1 Conclusions

Remifentanil appears to be safe for MAC and as an adjunct to regional anesthesia. Rapid recovery from accidental overdose or from excess sedation due to overestimation of a required dose is an important property. Unfortunately, the high incidence of nausea and vomiting associated even with low-dose remifentanil will probably limit its usefulness in these settings.

Remifentanil in low doses given to parturients increased the incidence of neonatal jaundice (unconjugated). However, the relevant study was too small to rule out a statistical fluctuation.

2 Recommendations

Remifentanil should be approved for use in MAC and as an adjunct to regional/local anesthesia. Both bolus injection and infusion should be approved. However, *neither bolus nor infusion should be approved without one-to-one surveillance by practitioners experienced in airway management.* Bolus doses are more susceptible to major error but even infusions can result in serious adverse events. The rapidly-developing effects of accidental remifentanil overdose during a continuing infusion would not be ameliorated by the rapid recovery seen after bolus doses.

Because of the potential for respiratory depression, patients should receive supplemental oxygen during remifentnail administration. Because of the potential of inadvertent infusion of remifentanil in IV lines, remifentanil should be infused into T-piece connections attached directly to the intravenous cannula.

Additional studies in parturients are needed to assess the association between remifentanil and neonatal jaundice.

I. L. Tyler, Ph.D., M.D. — 1/22/96 date

Orig IND#
Orig NDA# 20-630
HFD-170/Div File
HFD-170/ITyler
HFD-170/D Morgan

Division of Anesthetics, Critical Care, and Addiction Drug Products

Clinical Safety Review

NDA 20-630

Sponsor: Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

Product: Ultiva (remifentanil hydrochloride) for injection

Date: This Review: 14 June 96

Medical Officer: Dan Spyker

Peer Medical Officer: Barbara Palmisano

CSO: David Morgan

Material Reviewed included all clinical laboratory standard reports, case report forms X 8 chosen based on the review of the standard reports, product labeling, and clinical summaries as needed.

Executive Summary

Three types of safety issues were considered during the remifentanil safety review: an apparent change in acute lethality in the dog studies, microhemorrhages in dog brain histology, and review of laboratory data in the clinical studies.

The apparent change in acute toxicity occurred in animal studies performed concurrently with the early clinical trials. The sponsor suspended clinical trials while further investigations were completed. From this experience the sponsor and review team became familiar with the problems of using animals without concurrent respiratory suppor in acute toxicity evaluation of opioidst.

The microhemorrhages in dog brain histology, well described in the pharmacologists review, appear to represent a similar problem, that is, difficulties in acute toxicity studies without concurrent respiratory support. In this case, a follow-up animal study with respiratory support was conducted to demonstrate the absence of the histological microhemorrhages.

For the clinical laboratory data, a standard change display/analysis approach was developed with the sponsor, the results of clinical studies displayed, and individual patients reviewed as appropriate. No untoward laboratory he clinical laboratory data (hematology and chemistry) were found.

Recommendations: This reviewers believe that the safety data so far gathered and reported adequately support this application and pose no safety problems not adequately covered by the product labeling.

Clinical Laboratory Data Review

Standard Change Analysis & Display: The review team developed a four part analysis & display system for chemistry and hematology data including:

- Each data set included all patients where we have both a baseline and a post-dose observation. In patients with more than one post-dose lab value, the largest post-dose value was used. The same dataset was used in each of the five analyses described below. The title identified this subset, e.g.,

  Figure A-12. Summary of Changes in AST (SGOT)
  All patients with baseline and post-dose results (N=799)
  from among all patients exposed in clinical studies (N=822)

  and an appropriate footnote, e.g., *Clinical studies included: 203, 204, 212, 213, 226, 221, 301, 313, 405, 415.*

Graphical Shift Display

The heart of the standard change analysis is a lab value scatter plot of post-dose (ordinate) *vs.* pre-dose (on the abscissa) observations. Each patient for which we have a pre and post-dose observation contributes one point. Different symbols are used to represent the treatment (remi *vs.* other anesthetics). We chose the graph scales to best spread the data and used a scaling for the graphic which at least includes the normal range.

Shift Table

- A shift table counts the number of patients whose laboratory value category (Low, Normal, High) changes. The Shift table used a descriptive title, e.g.

  Shifts (baseline to post-dose)

  and sorted the categories in a sort of best -> worst, e.g.,

  HL HN HH NL NN NH LL LN LH

Mean Shift Analysis

- The Mean change used a one-line format and included ranges and 95% confidence intervals (CI's) on the difference, viz:

		Baseline		Post-dose		Difference	
	N	Mean	Range	Mean	Range	Mean	95% CI*
Remifentanil	524	22.3	(5-189)	29.3	(5-189)	7.0	[-1.1, 14]
Hi dose remi	133	21.2	(5-189)	34.2	(5-189)	13.0	[1.1, 39]
Opioids	104	24.3	(10-116)	27.3	(10-116)	3.0	[-6.6, 13]
Hi dose opioids	38	19.9	(10-99)	26.6	(10-99)	6.7	[-4.4, 13]

* 95% *Confidence Intervals calculated by ANOVA*

Exceed Threshold Limits

- The exceed threshold limits table counts and the number of patients who exceed the "clinically significant" value for that laboratory measure and are changing in that direction from baseline. Footnote identifies the criterion used for this measure, e.g., *Exceeds threshold defined as post-dose value > 2 X upper limit of normal (UNL) and post-dose value > 1.3 X baseline value.*

Change Listing

- The Change Listings comprise a line listing of the patients for whom Exceed threshold limits as described above. The listing, was sorted by: 1) treatment, and 2) difference (greatest to least)

Treatment	Difference	Baseline	Post-dose	Age	Sex	Procedure	Study	Pat #
Remifentanil	98	16	114	63	M	hemorroidectomy	204	
Hi dose remi	30	21	51	65	M	hemorroidectomy	204	
Opioids	95	10	105	29	F	C-section	203	
Hi dose opioids	118	14	132	55	F	C-section	213	

Review of individual patient data

The review team examined the standard change displays for six clinical subsets, viz:

A - Volunteers (N=297)

B - Clinical Pharmacology Pts (N=267)

C - General Anesthesia Patients (N=2332)

D - General Anesthesia Uncontrolled (N=286)

E - MAC Randomized Clinical Trials (N=644)

F - MAC Uncontrolled Studies (N=30)

The table below lists patients whose laboratory and other clinical data were selected for further evaluation. Case report forms (CRFs) were requested 5/20/96 and received in volumes dated June 6 received 6/10/96 and dated June 7 received 6/11/96. The following table lists the patients evaluated

Patient ID	Parameter	Baseline	Post Dose	Comment / Resolution
	AST (SGOT)	10	337	72 y/o W F for regional anesthesia, levels resolved
	AST (SGOT)	22	1492	MI & death post-CABG, AST due to low CO
	AST (SGOT)	16	215	67 y/o W M for CABG, rise minor considering surgery
	Phosphorus	4.6	9.1	35 y/o volunteer, minor elevation in K+ and Phos @ 1 day post dose
	ALT (SGPT)	22	299	48 y/o B F with chronic renal failure on hemodialysis, minor change for illness
	AST (SGOT)	21	94	Levels resolve by 5th post-op day
	AST (SGOT)	17	106	Levels resolve by 5th post-op day
	AST (SGOT)	14	147	50 y/o W F, 118 kg, surgery, minor change for illness

Resolution and/or an adequate explanation were found in each case.

Recommendations

This reviewers believe that the safety data so far gathered and reported adequately support this application and pose no safety problems not adequately covered by the product labeling.

Respectfully submitted,

D. A. Spyker, MD
Medical Reviewer

6/17/96
Date

Barbara Palmisano, MD
Peer Medical Reviewer

6/17/96
Date

cc: Original NDA 20-630
HFD-170/Division File
HFZ-450/Spyker
HFD-170/Palmisano
HFD-170/Morgan

MacDan\glaxo\remi safety review, 6/96 Sunday, June 16, 1996

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-630 Trade (generic) names Ultiva (remifentanil HCl)

Check any of the following that apply and explain, as necessary, on the next page:

✓ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim. 1 STUDY

___ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

___ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

___ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

✓ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is ~~no~~ reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).
because all new anesthetics are used in pediatric patients

✓ a. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing.
___ (2) Protocols have been submitted and approved.
___ (3) Protocols have been submitted and are under review.
✓ (4) If no protocol has been submitted, on the next page explain the status of discussions.
Company has agreed to study to 1 # pediatric patients.

___ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

Signature of Preparer

Date 6/5/96

cc: Orig NDA
HFD /Div File
Action Package

Ultiva (Remifentanil for Injection)
NDA 20-630

DEBARMENT CERTIFICATION

In accordance with the certification provision of the Generic Drug Enforcement Act of 1992 as outlined in correspondence dated July 29, 1992, from Daniel L. Michels, Office of Compliance, Glaxo hereby certifies that to the best of its knowledge and belief, it did not and will not use in any capacity the services of any person debarred under section 306(a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this application.

Richard Kiernan
Worldwide Director, GLP and GCP Compliance

24 Aug 95
Date

Integrated Review of Efficacy and Safety

NDA 20-630
Remifentanil HCl for Injection
Glaxo-Wellcome, Inc.

Background Pharmacology

Remifentanil is a fentanyl analog (4-anilidopiperidine) with a propionic acid methyl ester linkage that renders the molecule susceptible to ester hydrolysis by blood and tissue esterases. This hydrolysis results in the production of a carboxylic acid metabolite which essentially lacks opioid activity and is excreted in the urine. The only other identified metabolite accounts for less than 2% of the dose. Remifentanil is approximately 72% bound to human plasma proteins, mostly to α-1-acid glycoprotein. It has been shown in animal studies to be selective for μ-opioid receptors. Although it binds to γ- and κ- opioid receptors it lacks intrinsic efficacy to produce significant activation of these receptors. Remifentanil has no significant binding affinity for any of multiple receptors or ion channels tested other than opioid receptors.

Non-organ dependent metabolism is unique among the currently marketed fentanyl analogs (fentanyl, sufentanil, and alfentanil) which undergo hepatic metabolism. Because of rapid hydrolysis, the biologic half-life of remifentanil is 3-10 minutes. The short duration of effect make remifentanil best suited to administration by continuous intravenous infusion. Steady-state concentration is reached within 10-15 minutes after initiation of or adjustment of an infusion. While opioid effects are qualitatively similar to other fentanyl analogs, because of lack of accumulation, duration of effect should be independent of duration of administration.

Overview of NDA Clinical Studies

The remifentanil NDA contains 50 clinical studies (including 4 pilots). Remifentanil was administered to 2879 patients in 40 studies and to 267 volunteers in 10 studies (*see Appendix B* for complete study listings).

In Phase I studies (study # 100's) remifentanil was administered to healthy adult volunteers. These studies provided preliminary pharmacodynamic and pharmacokinetic data.

Phase II (study # 200's) clinical studies examined dose ranging and pharmacodynamics/kinetics in general patient populations as well as special populations. Remifentanil was evaluated for induction and maintenance of general anesthesia alone and with other agents (benzodiazepines, propofol, thiopental, isoflurane, nitrous oxide), as a post-operative analgesic while transitioning to longer-duration analgesics, and as an adjunct to local/regional anesthesia. Alfentanil was the most common comparator agent, but comparisons were also made to fentanyl and propofol. In pharmacodynamic studies during

general anesthesia, hemodynamic effects and effects on spontaneous ventilation, intracranial pressure and somatosensory evoked potentials were evaluated. In pharmacodynamic studies during local anesthesia, effects on intraocular pressure were evaluated. Pharmacokinetics/dynamics were also evaluated in special populations: pediatrics, elderly, renal impaired, hepatic impaired and during hepatic transplant, obese, cardiac and neurosurgical patients. Special populations were also evaluated during anesthesia: pediatrics, cardiac, and obstetrical (operative delivery)

Phase III (study # 300's) clinical studies generally examined use of remifentanil during induction and maintenance of general anesthesia in combination with other agents, as a post-operative analgesic while transitioning to longer-duration analgesics, and as an adjunct to local/regional anesthesia. These studies are intended to support dosing guidelines in the package insert and to obtain a safety profile with this dosing.

Brief Overview of Efficacy and Safety. The efficacy of remifentanil is as a potent opioid analgesic with effects similar to those of the other fentanyl analogs. In anesthesia practice it is a potent analgesic and blunts physiologic responses to noxious stimuli. The sponsor proposes that remifentanil allows intense, titratable analgesia without prolongation of recovery. Remifentanil has typical opioid-class side effects: respiratory depression, muscle rigidity, nausea, vomiting, pruritis, bradycardia, and hypotension under general anesthesia. As with other fentanyl analogs, hypoxia from respiratory depression and/or muscle rigidity is the most likely cause of potentially serious adverse effect. The rapidity of offset of effect with remifentanil is both a safety factor and a safety concern.

Pharmacodynamics/kinetics in volunteer subjects:

Offset of respiratory depression was compared between remifentanil and alfentanil in volunteers (Study 103, N=30). Both drugs were titrated to an endpoint of decrease in CO_2-stimulated minute ventilation by approximately 55%. Following termination of 3-hour infusion the time to offset of effect was significantly shorter for remifentanil (median 9 min, range min) than for alfentanil (median 73 min, range min).

Blood-brain equilibration was modeled for remifentanil and alfentanil in volunteers using EEG effect (spectral edge) (Study 104, N=35). Half-time for equilibration was short for both drugs (1±1min, mean±sd). Previous work by the same investigators showed a longer equilibration time for fentanyl and sufentanil (5-6±2-3min, *from Anesthesiology 74:34, 1991).*

Histamine release was not associated with remifentanil infusions in surgical patients (Study 202) or volunteers (Study 101).

Renal Impairment was not associated with altered pharmacokinetics of remifentanil (Study 210, N=15). The kinetics of the renally excreted primary metabolite were altered: AUC, Cmax and half-time of elimination were significantly increased. The significance of delayed elimination of the metabolite were not addressed. A pharmacodynamic measure of respiratory depression (EC_{50} minute ventilation in response to hypercarbic challenge) was not changed. Protein binding of remifentanil was not measured in these patients

Hepatic Impairment did not alter pharmacokinetic parameters of remifentanil or of the major metabolite (Study 211, N=10) The pharmacodynamic measure of respiratory depression, EC_{50} minute ventilation in response to hypercarbic challenge, was lower than control for subjects with hepatic impairment receiving remifentanil 0.025µg/kg/min for 1 hour followed by 0.05µg/kg/min for 3 hours because the control group had an unusually high EC_{50}. With a lower dose of remfentanil, subjects with hepatic impairment were not different from controls Protein binding of remifentanil was not measured in these patients.

Gender differences in pharmacokinetics and pharmacodynamics of EEG effect (spectral edge) were examined in studies 104 and 216 (N, female=31, male=39). A smaller central compartment volume for remifentanil and increased AUC and Cmax with reduced terminal half-life of the primary metabolite was noted in females. No gender differences were noted in EEG effects.

Age differences between elderly (>65 years, N=24) and younger adults were identified in pharmacokinetic parameters and in pharmacodynamic EEG effect (spectral edge) in studies 216 and 104. In elderly, EEG recovery was slower and EC_{50} lower for elderly subjects. Remifentanil clearance decreased and volume of distribution increased with advancing age. The major metabolite had increased AUC, Cmax, and AUC ratio (metabolite:remifentanil) in the elderly. Based on these findings the sponsor recommends that both loading and maintenance infusions of remifentanil be reduced in elderly subjects.

Indications

The sponsor has proposed 2 indications for remifentanil:

1. as an analgesic agent for use during the induction and maintenance of general anesthesia for inpatient and outpatient procedures and for continuation as an analgesic into the immediate postoperative period under the direct supervision of an anesthesia practitioner in a post anesthesia care unit or intensive care setting.
2. as an analgesic component of monitored anesthesia care.

Indication 1: Remifentanil for Use in General Anesthesia

Efficacy

1. Blunting of response to intubation and surgical stimulation - General Population

Remifentanil was used in conjunction with other agents (benzodiazepines, nitrous oxide, propofol, and isoflurane) to provide general anesthesia in a variety of surgical procedures in general populations (17 studies). For most studies ventilation was controlled, but in 3 studies patients breathed spontaneously (*see Respiratory Depression below*). Efficacy was measured as absence of hemodynamic, somatic and autonomic responses to intubation and various surgical stimuli. Comparisons were made to alfentanil (6 studies) and fentanyl (1 study) (*see Table 1*). (One additional study, #203, compared remifentanil and alfentanil for induction only). In general, doses of remifentanil that showed better efficacy than the comparator opioid were associated with a higher incidence of side-effects, in particular hypotension and muscle rigidity.

One of the sponsor's aims in these studies was to demonstrate that remifentanil can be dosed to a higher level of opioid effect without delaying recovery. Comparisons of recovery were made to alfentanil (4 studies) and fentanyl (1 study) (*see Table 2*). Differences in recovery times as measured by time to spontaneous or adequate ventilation, eye opening, extubation and response to verbal command were generally less than 5 and always less than 10 minutes between comparators. In addition, psychometric testing and times to discharge from PACU and discharge to home did not demonstrate prolongation of recovery with remifentanil.

2. Loss of Consciousness

Remifentanil even at high doses does not reliably induce loss of consciousness and therefore, is unsuitable as a sole agent for induction or maintenance of general anesthesia. This was demonstrated in Studies 203 and 205 in which single doses up to 20 μg/kg and infusions up to 1μg/kg/min for 5 minutes failed to produce loss of consciousness in all patients. In addition, awareness or recall under general anesthesia was reported in several studies. Ten patients (5%) reported recall in Study 314 which was judged by the sponsor to be due to inadequate doses of the concurrent maintenance agent, propofol. The sponsor recommends a minimum dose of 75μg/kg/min propofol for total intravenous anesthesia with remifentanil and propofol.

Table 1. General Anesthesia - Selected Efficacy Parameters and Adverse Events

Study treatment (N)	Intubation Dose Initial (µg/kg)	Intubation Dose Infusion (µg/kg/min)	Initial Maintenance Infusion (µg/kg/min)	Concurrent Induction/ Maintenance Anesthetic	Response to Intubation (%)	Response to Skin Incision (%)	Signs of Light Anesthesia (%)	Response to Skin Closure (%)	Muscle Rigidity (%) all/mild†	Hypotension (%)	Bradycardia (%)	Nausea/ Vomiting (%)
204												
remifentanil (18)	1	0.04	0.04	Propofol / N_2O	not reported	72	100	not reported	relaxant prior to opioid	8	0	64/42
remifentanil (9)	1	0.1	0.1			56	100			4	14	61/36
remifentanil (18)	1	0.4	0.4			22	72			14	6	78/50
alfentanil (16)	40	0.75	0.75			75	100			0	0	68/45
212												
remifentanil (35)	1	0.1	0.1	Propofol / N_2O	77	57	94	17	3/0	0	9	77/57
remifentanil (35)	1	0.4	0.4		31	9	34	6	9/6	3	6	71/46
alfentanil (35)	20	1.0	1.0		74	69	94	34	6/0	3	0	71/49
213												
remifentanil (54)	2‡	0.25	0.25	Thiopental / N_2O	76	2	23	—	52/17	20	7	63/26
remifentanil (55)	2‡	0.25	0.5		63	2	8	—	44/16	20	11	69/25
alfentanil (59)	50	0.5	0.5		44	19	36	—	55/20	6	8	55/18
301												
remifentanil (116)	1	0.5	0.25	Propofol / N_2O Isoflurane	15	8	57	16	8/3	53†	7	47/10
alfentanil (118)	25	1.0	0.5		28	17	72	21	5/3	39†	15	47/16
303												
remifentanil (102)	1	0.25	0.25	Propofol Isoflurane/ Isoflurane	not reported	25	53	11	1/0	15*	4*	19/8
alfentanil (99)	25	0.5	0.5			23	66	22	0	2*	7*	21/6
307												
remifentanil (81)	1	0.5	0.25	Propofol/ Propofol	25	16	68	2	2/2	42	7	52/18
remifentanil (80)	1	1.0	0.5		6	11	54	10	7/2	50	14	53/53
308												
remifentanil (134)	1	0.5	0.5→0.25	Propofol/ Propofol	19	11	53	19	relaxant prior to opioid	9	7	52/52
alfentanil (66)	20	2.0	2.0		29	32	71	20		15	8	61/38
313												
remifentanil (98)	1	0.2	0.2	Propofol/ Isoflurane	36	12	68	7	11/7	52*	5*	46/23
remifentanil (91)	2‡	0.4	0.4		13	4	48	3	12/4	48*	3*	51/23
fentanyl (97)	3	—	1.5-3 prn		30	33	87	11	1/1	30*	3*	58/26
314												
remifentanil (135)	1	0.5	0.25	Propofol/ Propofol	10	11	64	—	15/6	20	3	1/1

‡ dose higher than recommended in package insert * glycopyrrolate or atropine given during induction ** maintenance phase only † mild rigidity does not impair respiration

Notable Adverse Reactions

204 - remifentanil - 63 yo male receiving 0.3µg/kg/min remifentanil experienced life-threatening but intermittent bradycardia and hypotension 1 min after starting infusion

212- remifentanil - one patient in the remi 0.4 group received atropine to treat sinus arrest

303 - alfentanil - life-threatening respiratory depression and apnea 37 minutes after stopping infusion

Table 2. General Anesthesia - Selected Recovery Parameters and Adverse Events Time values are median (range)

Study treatment (N)	Intubation Dose Initial (μg/kg)	Intubation Dose Infusion (μg/kg/min)	Initial Maintenance Infusion (μg/kg/min)	Concurrent Induction/ Maintenance Anesthetic	Duration of Anesthesia (min)**	Time to Adequate Respiration (min)	Time to Extubation (min)	Time to Aldrete score ≥9 (min)	Time to qualify for discharge from PACU (min)	Time to discharge home (min)	Time to first Anangesic (min)
204						spontaneous					
remifentanil (18)	1	0.04	0.04	Propofol	180	0 (0-4)	3 (1-11)	—	16 (10-61)	94 (71-160)	29 (15-43)
remifentanil (9)	1	0.1	0.1	/ N_2O	180	4 (2-6)	4 (3-8)	—	20 (12-51)	98 (75-128)	28 (16-55)
remifentanil (18)	1	0.4	0.4		180	6 (0-15)	7 (2-18)	—	20 (13-45)	85 (71-197)	42 (21-59)
alfentanil (16) †	40	0.75	0.75		180	3 (0-15)	4 (1-16)	—	22 (12,163)	100 (68-173)	50 (12-81)
212											
remifentanil (35)	1	0.1	0.1	Propofol	38(20-114)	4 (1-7)	4 (1-8)	—	10 (2-107)	164 (121-248)	10 (4-191
remifentanil (35)	1	0.4	0.4	/ N_2O	29(17-46)	4 (1-9)	4 (2-9)	—	5 (2-50)	161 (121-257)	13 (6-51)
alfentanil (35)	20	1.0	1.0		32(19-66)	3 (1-7)	3 (1-7)	—	7 (2-34)	157 (124-340)	17 (4-132)
213						spontaneous					
remifentanil (54)	2‡	0.25	0.25	Thiopental	[2-5 hrs	3-5 (0-65)	6-9(4-130)	—	—	—	—
remifentnail (55)	2‡	0.25	0.5	/ N_2O	across	2-3 (0-18)	7-8(1-23)	—	—	—	—
alfentanil (59) †	50	0.5	0.5		groups]	2-14 (0-24)	5-15(3-37)	—	—	—	—
301				Propofol							
remifentanil (116)*	1	0.5	0.25	/ N_2O	176(46-391)	10 (0-56)	12 (1-42)	24 (6-91)	101 (18-1218)	—	—
alfentanil (118) †	25	1.0	0.5	Isoflurane	169(57-526)	11 (0-80)	12 (0-225)	25 (3-114)	87 (13-975)	—	—
303				Propofol							
remifentanil (102)	1	0.25	0.25	Isoflurane/	42(17-95)	9 (0-25)	9 (0-25)	10 (0-50)	14 (0-97)	206(115-1025)	—
alfentanil (99)	25	0.5	0.5	Isoflurane	43(14-149)	6 (0-23)	6 (0-24)	9 (1-74)	13 (1-88)	210 (62-1602)	—
308									(phase 2)	(qualify)	
remifentanil (134)	1	0.5	0.5→0.25	Propofol/	39(13-252)	3 (0-22)	4 (0-24)	—	100 (37-291)	90 (37-243)	23 (5-197)
alfentanil (66) †	20	2.0	2.0	Propofol	34(17-150)	3 (0-20)	4 (0-19)	—	117 (14-293)	96 (14-293)	39 (2-168)
313											
remifentanil (98)*	1	0.2	0.2	Propofol/	133(49-383)	16 (2-33)	16 (3-34)	28 (3-372)	96 (9-387)	—	—
remifentanil (91)*	2‡	0.4	0.4	Isoflurane	131(45-370)	15 (0-193)	15(1-193)	27 (5 -245)	88 (13-308)	—	—
fentanyl (97)	3	—	1.5-3 prn		144(49-428)	9 (0-41)	11 (0-527)	24 (1-123)	64 (14-303)		

* remifentanil infusion continued at reduced rate for 30-45 min after surgery ‡ dose higher than recommended in package insert

† alfentanil discontinued 10-20 minutes before the end of surgery; remifentanil discontinued at the end.

** mean or median (range)

Safety

1. Respiratory Depression

Two non-US, non-IND studies (228,229) and one pilot (225) used remifentanil in general anesthesia in spontaneously breathing subjects concomitantly with isoflurane or propofol The rationale for this was the popularity of spontaneous ventilation general anesthesia techniques in Europe Although this technique can be successfully used with doses of remifentanil of 0 025 and 0 05 µg/kg/min, the incidence respiratory depression is considerable (17-90%) In all US-conducted studies general anesthesia included controlled ventilation

Recurrent Respiratory Depression. Two safety reports of recurrent respiratory depression have been filled to the IND In one case a 60 yr old male received diazepam 10 mg for premedication and remifentanil and isoflurane for a 4-hour laparoscopic repair of hiatal hernia The patient was slow to breathe at the end of surgery but maintained adequate respiration until 22 minutes after the discontinuation of remifentanil when he became apneic and lost consciousness Treatment consisted of manual ventilation and naloxone after 5 minutes which resulted in rapid recovery The investigator attributed the event to of lack of stimulation in the PACU after remifentanil and diazepam We agree that this case may represent ongoing opioid effect with varying levels of stimulation rather than recurrent respiratory depression

The second case is a 54 yr old female who received remifentanil and propofol for laparoscopic vaginal hysterectomy The patient's initial recovery was unremarkable Thirty minutes after remifentanil discontinuation she became apneic, unconscious and was noted to have muscle rigidity She was manually ventilated and began to breathe spontaneously within 5 minutes without other interventions The presence of muscle rigidity and spontaneous reversal within 5 minutes may indicate that an inadvertent remifentanil bolus had been administered although there is no record of such "Recurrent" muscle rigidity is not a known entity and suggests that this case may not represent recurrent respiratory depression

2. Muscle Rigidity

Muscle rigidity occurred with a notable incidence in the NDA studies when remifentanil was administered prior to muscle relaxation *(see Table 1)* At recommended induction doses (1µg/kg followed by 0 5-1µg/kg/min) the incidence of muscle rigidity was 1-11% excluding cases classified as "mild" which were not associated with impairment of ventilation Most studies used propofol as the concomitant induction agent In Study 213, thiopental and 2 µg/kg remifentanil (twice the recommended initial bolus dose) produced an extremely high incidence of muscle rigidity that was not different from the incidence with the comparator, alfentanil

The occurrence of muscle rigidity in cardiac studies 215 and 221 (see below - Cardiac Anesthesia) was particularly notable In study 215, remifentanil was infused at doses of 1-2 µg/kg/min after benzodiazepine premedication but prior to other agents The occurrence of life-threatening muscle rigidity in 3 patients prompted amendment of the protocol to induction with propofol and paralysis prior to remifentanil administration In study 221 remifentanil (1-3µg/kg/min) was also infused after benzodiazepine and morphine

premedication. The incidence of muscle rigidity was high, 36-65%, of which 8-20% was classified as mild.

The sponsor's label (package insert) states that chest wall rigidity may occur after remifentanil bolus doses ≥1 μg/kg administered over 30-60 sec or infusion rates >0.1 μg/kg/min. Administration of supplemental dose(s) <1 μg/kg may cause chest wall rigidity when given concurrently with a continuous infusion of Ultiva. Prior or concurrent adminstration of a hypnotic (propofol or thiopental) or a neuromuscular blocking agent may attenuate the effect, or decreases the incidence to <1%.

3. Hemodynamic Effects - Hypotension and Bradycardia

Two studies systematically examined the hemodynamic effects of remifentanil. In study 201 (N=31) it was determined that with isoflurane, there was a high incidence of hypotension and bradycardia with remifentanil doses greater than 1.5 μg/kg unless there was pretreatment with glycopyrrolate. With glycopyrrolate pretreatment doses as high as 20 μg/kg were tolerated. It was also demonstrated that the hemodynamic effects of remifentanil were short-lived and can be rapidly treated with adrenergic agents.

In study 206 (N=43) hemodynamic effects of relatively high does of remifentanil (2-20 μg/kg) were compared in combination with either N_2O or isoflurane. With N_2O there were no cases of bradycardia and 2 of 15 patients had SBP <80 mm Hg. With isoflurane the first 3 patients (who by chance also happened to be older than the rest of the group, mean age 58 vs. <37 years) had SBP <80 mm Hg with 2 μg/kg of remifentanil, therefore all subsequent patients received pretreatment with glycopyrrolate. With glycopyrrolate pretreatment (0.4-0.5 mg) patients had baseline tachycardia and 3 of 15 patients had SBP <80 mm Hg but none had bradycardia. This study also demonstrated that escalating dose of remifentanil did not appear to produce increasing hypotension.

Clinical Studies. When used in general anesthesia, remifentanil produces an incidence of hypotension that is apparently related to presence of concomitant anesthetic and vagolytic agents (*see Table 1)*. In clinical studies patients were generally loaded with 5-10 ml/kg of isotonic fluid prior to induction. Glycopyrrolate or atropine pretreatment was given in some clinical studies that used isoflurane for concomitant maintenance anesthesia (studies 228, 303, 313). In volunteer studies, hypertension and tachycardia were common especially during emergence.

4. Nausea and Vomiting

There is a high incidence of nausea and vomiting after use of opioids in general anesthesia. In the NDA studies this was true for remifentanil as well as for comparator opioids (*see Table 2)*

5. Deaths

Seven patient deaths were reported from 5 clinical studies (221, 313, 207, 215, 224). Five deaths were in studies of cardiac anesthesia (0.9% mortality rate). All were judged by the investigator to be unrelated to remifentanil:

- 2 deaths secondary to aortic rupture in patients undergoing coronary artery bypass grafting
- 2 deaths secondary to myocardial infarction in patients undergoing coronary artery bypass grafting
- 1 death secondary to cardiac failure in a patient undergoing coronary artery bypass grafting
- 1 death secondary to cerebral ischemia and respiratory arrest 10 days postoperatively in an 84- year old patient undergoing general surgery for eventration
- 1 death secondary to sepsis following liver transplantation

6. Rapid Offset of Effect - Analgesia

The analgesic effects of remifentanil are short-lived after discontinuation of an infusion (*see Table 2*). Patients with post-operative pain require analgesic agents after discontinuation of remifentanil in general anesthesia. In one study (#314) administration of morphine (0.15 mg/kg) 20 minutes before the end of surgery did not delay recovery compared to continuing a remifentanil infusion at reduced rate into the post-operative period. The sponsor proposes that remifentanil can be continued at a reduced rate (0.1μg/kg/min) for post-operative analgesia for the initial 30-45 minutes post-operatively while patients remain in a monitored care setting.

Remifentanil Use for Short-term Post-Operative Analgesia with Transition to Morphine

In 6 general population studies remifentanil was used for post-operative analgesia in the Post-Anesthesia Care Unit with transition to morphine after 30-45 minutes (*see Table 3*). These were 2 phase II dose finding studies (213, 226) and 4 Phase III studies (301,307,313,314). The sponsor believed that the early studies showed that bolus dosing and large rate increases lead to respiratory depression and muscle rigidity so a regimen using a slightly higher starting rate, smaller incremental rate increases, and no bolus doses was incorporated into the 2 final studies, 313 and 314.

Safety

Table 3. Remifentanil for Post-Operative Analgesia

Study	Design	N (analgesia)	Dose bolus (µg/kg)	Dose infusion (µg/kg/min)	Analgesia and RR>8 bpm N (%total	RR<8bpm N (%total)	Muscle Rigidity N (%total)
213	open label	54	1	0.1-0.8	29 (54%)	17 (31%)	4 (7%) (1 mild†)
226	open label	44	0.5	0.05 titrated by 0.05-0.1 increments	43 (97%)	0	0
301	open label	107-116	0.5	*0.05-0.1 with titration	60 (56%)	4 (4%)	9 (8%) (1 mild†)
307	open label	157-178	none	*0.05-0.1 with titration	75 (48%)	52 (33%)	3 (2%)
313	open label	178-189	none	0.1 with titration by 0.025 increments	109 (61%)	6 (3%)	6 (3%) (3 mild†)
314	double blind vs morphine	62-66	none	0.1 with titration by 0.025 increments	42 (68%)	7 (11%)	1 (1%)

* When 0.05 mcg/kg/min failed to provide adequate analgesia, the protocol was amended so that the starting rate was 0.1 mcg/kg/min

† mild rigidity does not interfere with respiration

Notable adverse events related to remifentanil during the analgesia phase of these studies:

226 - one patient inadvertently received 0.15 instead of 0.05 µg/kg/min and had apnea without hypoxemia

301 - During the analgesia phase, ten patients given remifentanil had severe adverse events — including hypoventilation, apnea, and hypoxemia — attributable to remifentanil. For example, during remifentanil, 0.05 µg/kg/min, a 57 year old male developed chest wall rigidity and apnea. A 49 year old male received remifentanil at 0.05 µg/kg/min. Because of severe pain, he was given a bolus dose of 0.5 µg/kg, and the infusion was increased to 0.1 µg/kg/min. One minute later he became apneic. Six of 11 patients who received remifentanil and developed severe adverse effects during the analgesia period had received either an overdose of remifentanil or an incorrect dosing regimen.

307 - During the analgesia period, two patients demonstrated severe adverse effects. One was found unresponsive and cyanotic after transport from the recovery room; this event was attributed to administration of residual remifentanil in the intravenous tubing. A second patient experienced apnea after a bolus dose of remifentanil, 0.4 µg/kg. Of 49 episodes of respiratory depression during the analgesia period of the study, 16 were reported as apnea; only 1 of 16 of these apneic episodes followed a bolus dose of remifentanil

314 - Two severe adverse events related to remifentanil occurred. One patient developed progressive hypoventilation to a respiratory rate of 4 during remifentanil infusion. One patient inadvertently received a bolus of remifentanil (400 µg) during a remifentanil infusion. She lost consciousness and developed muscle rigidity and apnea. Ventilatory support was required for 10 minutes. An additional three remifentanil patients were withdrawn from the study because of respiratory depression. Respiratory depression was more common with remifentanil (13%) than with morphine (4%).

Safety issues with use of remifentanil in conscious patients relate to the effects of the drug as well as to its administration. Several severe adverse effects occurred due to dosing errors or inadvertent administration of the drug. In the NDA studies (3146 patients) there were 8 reported cases of remifentanil overdose. In all instances subjects were in a monitored

care setting and symptoms were rapidly recognized and treated with no serious sequelae. The reasons for inappropriate dosing were investigator error (2), dilutional error (1), pump failure (1) and inappropriate flushing of the IV line containing remifentanil when a second medication was given (5).

The sponsor's recommendations for use of remifentanil for postoperative analgesia include *direct supervision of an anesthesia practitioner*. When used as an IV analgesic in the immediate postoperative period, remifentanil should be initially administered by continuous infusion at a rate of 0.1μg/kg/min. The infusion rate may be adjusted every 5 minutes in 0.025μg/kg/min increments. Infusion rates greater than 0.2μg/kg/min are generally associated with respiratory depression (respiratory rate less than 8 breaths/min). The use of bolus injections to treat pain during the postoperative period is not recommended.

The primary medical reviewer (D. Fisher) concludes that remifentanil can provide effective analgesia during the initial recovery period. Whether its efficacy exceeds that of other opioids remains to be demonstrated. However, severe life-threatening adverse events have been associated with remifentanil administration during the recovery period. Although some of these episodes have been attributed to dosing errors, others have occurred during routine administration of remifentanil per protocol. In addition, these adverse effects have been observed despite supplemental monitoring available during a clinical trial.

In clinical practice, patients are monitored less intensively than during clinical trials. This suggests that severe adverse events will occur with greater frequency than in clinical trials and might lead to adverse outcomes. Therefore, it is questionable whether it is appropriate to recommend administration of remifentanil during the recovery period. Alternatively, a controlled roll-out with an educational program might limit the occurrence of these adverse effects.

General Anesthesia - Special Populations

Cardiac Anesthesia and Post-Operative Intensive Care. Three phase II studies and one pilot (N=252) were conducted in patients undergoing cardiac surgery with cardiopulmonary bypass. Study 207 (N=17) demonstrated that remifentanil clearance is decreased by approximately 20% during hypothermic bypass. Studies 215 and 221 provide experience using remifentanil with benzodiazepines, propofol and isoflurane in patients undergoing coronary artery bypass surgery. There were no comparative studies.

A dose-response relationship was not demonstrated between remifentanil dose (1-2 or 1-3μg/kg/min starting infusion rates) and responses to surgical stimuli. The incidence of muscle rigidity was high (up to 46%) when remifentanil was infused after benzodiazepine and morphine premedication but before administration of propofol and neuromuscular relaxant (*see Muscle Rigidity above*).

Remifentanil infusion (1μg/kg/min) was continued during intensive care for up to 5 hours after surgery. Transition was made to morphine, midazolam and/or propofol (215) or morphine (221). Initially in study 215 patients received 0.05-0.1 mg/kg morphine then remifentanil was weaned over 1 hour. This was associated with patient anxiety and agitation, so the protocol was amended to include higher doses of morphine plus midazolam and propofol. In study 221 patients were given 0.1 mg/kg morphine and after 1 hour remifentanil wean began. Early extubation (within 6 hours post-operatively) occurred in some patients.

Notable severe adverse events occurred: (study 215) one patient had an explosive wake-up leading to sternal dehiscence, 2 had respiratory arrest after extubation due definitely (1) and possibly (1) to accidental infusion of remifentanil associated with flushing the IV line. In study 221 apnea was reported as a severe adverse event in a patient who also received an inadvertent bolus of remifentanil when other medication was administered through the IV line.

The recommendation of the primary medical reviewer (R. Merin) is that further studies are needed with remifentanil use in cardiac anesthesia. In particular, further assessment is needed of early extubation protocols and hemodynamic and ischemia profiles vs. comparators.

Neuroanesthesia. Seventy-one patients received remifentanil during general anesthesia for neurosurgical procedures in three studies including one pilot. Study 214A demonstrated that remifentanil 0.5-1 μg infused over 1 minute during N_2O/isoflurane anesthesia had negligible effect on intracranial pressure in patients with small intracranial mass lesions (N=10) who were maintained hypocapnic with head elevation. Although not demonstrated in this study, **the primary medical reviewer (R. Bedford)** notes that remifentanil may have potentially deleterious effects on cerebral perfusion pressure by lowering mean arterial pressure. Studies 304P and 304 demonstrated that in patients with supratentorial masses (N=61) cerebral blood flow reactivity ($\Delta Q/\Delta Pco_2$) remained intact during general anesthesia with remifentanil/N_2O/isoflurane. Remifentanil and fentanyl provided satisfactory conditions with rapid emergence and recovery. Duration of remifentanil anesthesia was 297 minutes median, with range 143-587 minutes. Pharmacokinetic parameters in these patients (N=20) were similar to the general population.

A severe adverse event occurred in one patient who became severely agitated 10 minutes after discontinuation of remifentanil.

Pediatric Anesthesia. Remifentanil was administered to 91 pediatric patients between 2 and 12 years of age in 2 studies (219P, 2019). Pharmacokinetic parameters determined in a small number of patients (N=8, 2-6 yrs old and N=5, 7-12 yrs old) did not appear different from adult values. Sixty-eight pediatric patients received remifentanil plus N_2O for general anesthesia during strabismus surgery and were compared to 61 patients receiving N_2O and either alfentanil, propofol or isoflurane. All patients received an anticholinergic during induction. All regimens provided satisfactory intraoperative anesthesia and recovery parameters were similar between groups. **The primary medical reviewer (B. Palmisano) recommends** that additional studies in pediatric patients are needed, especially pharmacokinetics/dynamic studies in patients under 2 years of age.

Hepatic Transplant. In study 224 (N=6) remifentanil pharmacokinetics were similar in anhepatic patients as in other patients, however the small number of patients precludes definitive analysis.

Obese Patients. In study 227 remifentanil pharmacokinetics were compared between obese patients (>80% ideal body weight, N=12) and controls (N=12). Pharmacokinetic parameters showed better correlation with ideal body weight than with total body weight suggesting that dosing based on IBW may be more appropriate in obese patients. **The primary medical reviewer (M. Wood)** recommends that a study of respiratory pharmacodynamics in these patients would be of interest.

Indication 2: Remifentanil for Use as an Adjunct to Local / Regional Anesthesia

In 7 general population studies and 1 obstetrical population remifentanil was used as an adjunct to local or regional anesthesia. These were 2 phase II dose finding studies (208, 209) and 5 Phase III studies (306, 309, 310, 311, 312). One phase II study was also conducted in the obstetrical population. The sponsor believed that early studies showed that titration of remifentanil to a sedative endpoint led to respiratory depression, apnea, and muscle rigidity. Therefore, sedation was replaced with a discomfort endpoint. The primary endpoint was the attenuation of pain associated with placement of block.

Efficacy

1. Blunting of response to nerve block

Five studies (306, 309, 310, 311, 312) examined the efficacy of remifentanil to provide analgesia during placement of central or peripheral nerve block (N=423). Pain at injection of local anesthesia with remifentanil alone or in conjunction with midazolam (2 studies) occurred in 0-20% of patients. The incidence of pain on injection of local anesthesia was lower in patients receiving remifentanil than in those receiving alfentanil (1 study) or propofol (2 studies). The incidence of side effects including nausea, respiratory depression and muscle rigidity was also greater in the remifentanil groups. These studies demonstrate that remifentanil can be used to provide effective analgesia during placement of nerve block.

2. Maintenance of comfort during procedure

These studies also demonstrated that remifentanil can be used to provide comfort during surgical procedures with regional or local anesthesia. The incidence of patients with at least one discomfort response or requiring at least one infusion rate adjustment was 3%-47%.

Safety

Incidences of respiratory depression, muscle rigidity, nausea, vomiting and pruritis with remifentanil used as an adjunct to local and regional anesthesia are listed in Table 4.

Table 4. Remifentanil with Local Regional Anesthesia

Study	Design	N remi	Block	Dose (µg/kg)	single infusion (µg/kg/min)	RR <8bpm N(%total)	Muscle Rigidity N(%total)	Nausea/ Vomiting /Pruritis %total
208	double blind ± midazolam	123	orthopedic regional	none	0, 0.04, 0.07 or 0.1	SpO_2<90% 24 (20%)	none reported	n: 36-562% v: 10-21% p:17-212%
209	double blind vs alfentanil	25	ophthalmic block	none initially 0.5 for titration	0.05	?	18(72%) (10 mild‡)	n: 16% v: 8% p:122%
218	open label	24	epidural for C-section (local & narcotic)	none initially 33 µg for titration	0.1 titration 0.05	RR <12 or SpO_2<95% 4(17%)	0	
306	double bli ± 2-8 mg midazolam	81	local for breast biopsy	none	0.1 titration 0.025 -0.05	39 (81%) +SpO_2<90% 16 (20%)	0	n: 18-32% v: 9-21% p:0-32%
309	double blind vs alfentanil	57	ophthalmic block	1	0 or 0.2 then optional 0.1 post-block	9 (17%) +SpO_2<90% 3 (6%)	3 (5%) (1 mild‡)	n: 10-14% v: 0-1% p: 3-7%
310	open label vs propofol	78	unspecified regional central & peripheral	none initially 0.5 for titration	0.2 then 0.1 post-block titration 0.05	27 (38%) +SpO_2<90% 8 (11%)	4 (5%)	n: 60% v: 21% p: 13%
311	single blind vs propofol	61	unspecified regional	0.5	0.1	or SpO2 <95% 28(46%)†	4 (6%) (1 mild‡)	n: 53% v: 37% p: —
312	double blind ± midazolam	159	local superficial	0.5 -1	0.1 or 0.05+2mg midazolam titration 0.025-0.05	59 (37%)* +SpO_2<90% 6 (4%)	0	n: 19-49% v: 4-10% p: 12-23%

* RR<8 bpm for ≥1 min, or investigator's opinion.
‡ mild rigidity does not intefere with respiration

Notes:

306 - duration of respiratory depression was 3-28 minutes (median 15 minutes for 4 and 8 mg midazolam groups, median 9 and 4 minutes for 0 and 2 mg midazolam groups, respectively)
309 - duration of respiratory depression was 1-9 minutes. One patient received an overdose (amount unspecified) which resulted in apnea and muscle rigidity.
310 - investigators recorded respiratory depression as an adverse event in 6 (8%) subjects. Duration of respiratory depression in these patients was 2-8 minutes.
311 - one patient received a 100-fold overdose (50µg/kg in place of 0.05 µg/kg) due to dilution error. Severe muscle rigidity prevented manual ventilation. The patient was anesthetized, paralyzed and manually ventilated with endotracheal intubation.
312 - duration of respiratory depression was 1-6 minutes.

Sponsor's Recommendations: A single dose of remifentanil 0.5-1 μg/kg can be given over 30-60 sec approximately 90 sec prior to placement of local or regional anesthetic block to attenuate pain associated with placement of the block. Alternatively, a continuous infusion of 0.1 μg/kg/min can be started 5 minutes prior to placement of block with a decrease to 0.05 μg/kg/min at the end of the block. It is recommended to titrate the infusion rate by 0.025 μg/kg/min increments at 5 minute intervals. Rates greater than 0.2 μg/kg/min are generally associated with respiratory rates less than 8 breaths per minute.

Primary Medical Reviewer Assessment (T. Tyler): Respiratory depression and muscle rigidity with remifentanil resolve relatively rapidly so that remifentanil can safely be used as an adjunct to local or regional anesthesia with one-to-one monitoring by anesthesia practitioner. The occurrence of nausea, vomiting and pruritis may limit its usefulness

Adjunct to Regional or Local Anesthesia - Special Populations

Patients undergoing ophthalmic surgery - intraocular pressure. Intraocular pressure in the non-surgical eye was not affected by remifentanil infusion in patients undergoing ophthalmic surgery (N=25).

Obstetrical patients undergoing Cesarean section. In an phase II study 24 patients received remifentanil during cesarean section with epidural anesthesia. Placental transfer of the drug was approximately 50% of the concentration observed in the mother and the fetal arterio-venous ratio was approximately 30% indicating metabolism in the neonate. Neonatal effects as measured by APGAR and NAV Scores were similar to comparators however, 25% of neonates in the remifentanil group developed hyperbilirubunemia compared to 11% of comparators. The **primary reviewer (T. Tyler)** recommends that further studies in this population are needed prior to labeling, in particular to determine if there is an association between remifentanil and hyperbilirubinemia in neonates.

Other Issues

Abuse Potential

The sponsor recommends that remifentanil be classified as a Schedule II narcotic Animal and human drug abuse liability testing indicate that remifentanil has an abuse potential greater than placebo and equal to fentanyl (*see Abuse Liability Review*)

Maximum Drug Exposure in NDA Studies

The highest infusion rate of remifentanil was 8μg/kg/min for 20 minutes (maximum dose 15000μg) in two volunteer subjects in Study 104. The highest protocol-specified single dose was 30μg/kg over 1 minute in 6 patients in study 202. In Study 201 and 206, 13 patients received 20 μg/kg over 1 minute. The longest duration of remifentanil anesthesia was in cardiac study 221 in which mean remifentanil infusion times were 8-9 hours with mean total exposure of 700-1200 μg/kg, maximum 2000μg/kg.

Patient in study 304P received the largest amount of drug - 33.7 mg over 10 hours 42 minutes. Subject in the same study received remifentanil for the longest period of time - 12 hours and 17 min, 21.5 mg. Both patients recovered within 10 min.

Drug Interaction

Remifentanil, like other fentanyl analogs, is synergistic with other anesthetic agents. This was evident in several studies. For example, in study 220 (N=173) it was demonstrated that remifentanil produces a dose-related decrease in MAC of isoflurane. At remifentanil plasma concentration of 1.4 ng/ml (estimated infusion rate 0.05 μg/kg/min) MAC of isoflurane was reduced approximately 50%. In study 203 (N=45) it was demonstrated that remifentanil reduces thiopental dose requirements during induction. Synergism with midazolam was demonstrated in study 312 (N=159) and with propofol in study 226 (N=44)

The sponsor reports that a study with succinylcholine in dogs demonstrated no interaction with remifentanil. *In vitro* studies (in human blood) but no *in vivo* studies have been conducted with remifentanil and atracurium, mivacurium, esmolol, ecthiophate, neostigmine and physostigmine

Clinical Laboratory Data

No safety issues were identified in review of clinical laboratory data. This is consistent with expectations form short term use of an opioid

Conclusions and Recommendations

Remifentanil is a potent opioid analgesic similar in effect and side-effect to the other approved fentanyl analogs: fentanyl, sufentanil, alfentanil. Its metabolism by tissue and plasma esterases results in a unique pharmacokinetic profile with short duration and rapid offset of effect independent of the duration of administration.

There are unique safety issues for remifentanil that relate to this rapid offset and the new clinical practices that will be required for anesthesia practitioners who use the drug. For example, infusions of remifentanil will be administered until the very end of the surgical procedure, whereas the other fentanyl drugs are frequently discontinued 30* minutes prior to the end. With this new practice, as the patient emerges and is taken to the post-anesthesia care unit there is potential for residual remifentanil to remain in the IV tubing where it can be inadvertently flushed into the patient with administration of another medication. Unlike the other fentanyl drugs, the practitioner will need to make a conscious effort to clear remifentanil from the tubing prior to patient emergence.

In addition, because of the short duration of action, interruption of a remifentanil infusion will leave the the patient without analgesia in a relatively short period of time. This may occur inadvertently, such as with an occluded IV line or may be planned. When remifentanil is discontinued in patients with ongoing analgesia requirements, another agent must be supplied, either before or very shortly thereafter. These safety issues related to discontinuing a remifentanil infusion and clearing tubing are clearly stated in the package insert under *WARNINGS, PRECAUTIONS, and DOSAGE and ADMINISTRATION.*

Lastly, and perhaps most importantly, the drug will be delivered by continuous infusion, even when given to conscious, non-intubated patients for postoperative analgesia. There is potential for inadvertent flushing of remifentanil into such a patient which could result in apnea and hypoxia. This is unique among the fentanyl drugs, which are generally not delivered by continuous infusion for postoperative analgesia. It is similar to use of potent vasoactive drugs, such as nitroprusside, epinephrine, etc., which are delivered by continuous infusion and have rapid onset and offset. The indication for postoperative analgesia states that remifentanil must be used *under the direct supervision of an anesthesia practitioner*. This is in the package insert under *INDICATIONS* and *DOSAGE and ADMINISTRATION*.

We have particular concern about the safety of remifentanil when used in the out-of-OR setting in non-intubated patients. Although the NDA studies demonstrate safety in this situation under well-controlled, protocol conditions, our concern is that initially, when this drug is relatively "unknown" to the practicing community, there will be much greater potential for serious adverse effects (apnea, respiratory depression, muscle rigidity, hypoxia) than was demonstrated in the studies. There does not exist, we believe, a general familiarity in the practicing community with using potent opioids for postoperative analgesia in the manner prescribed for remifentanil. Use of remifentanil for postoperative analgesia will be different than use of fentanyl because of the unique pharmacokinetics and administration by continuous infusion. The other fentanyl products, alfentanil and sufentanil, do not have

indications for post-operative analgesia and, we believe, are not widely used off-label for that purpose, especially not by continuous infusion

Practitioners must be fully knowledgeable regarding the potential risks of using remifentanil for this indication prior to use of the drug We believe this can be accomplished by a comprehensive in-service educational program provided by the sponsor to the practing community prior to product introduction. The sponsor's plan for this program is contained in APPENDIX A.

Barbara Palmisano MD 5/21/96

Barbara Palmisano, M.D date
Primary Reviewer

Robert F Bedford May 21, 1996

Robert Bedford, M.D. date
Secondary Reviewer

Glaxo Wellcome Inc.
5 Moore Drive
Research Triangle Park, North Carolina 27709

September 15, 1995

Food and Drug Administration
P.O. Box 7777-W7745
Philadelphia, PA 19175-7745

RE: Initial Application Fee
Ultiva (remifentanil HCl) for Injection; NDA 20-630
User Fee ID No. 2801

Please find enclosed check number This initial payment is 50% of the application fee for the New Drug Application NDA 20-630 for Ultiva™ (remifentanil Hcl) for Injection that is being submitted as of this date to the Center for Drug Evaluation and Research, FDA.

Please find below requested information regarding this application:

Type of Application:	New Drug Application with Clinical Data	X
	New Drug Application without Clinical Data	
	Supplemental New Drug Application with Clinical Data	

Should you have any questions, please contact me at (919) 941-3640.

Sincerely,

Craig Metz

Craig Metz, Ph. D.
Director
Regulatory Affairs

Four Month Safety Update

This update includes (1) all safety data from patients enrolled in three clinical trials (#2019, 304, 312) which were completed after the NDA submission (September 15, 1995) and, (2) serious adverse events received from ongoing studies through December 31, 1995. Data from the three completed studies were incorporated into the NDA database and have been reviewed with the original submission. They will not be reviewed here.

The following five studies are ongoing: USAA3101 (head trauma), USAA3114 (depth of anesthesia), USAB3117 (outpatient general anesthesia), USAB3123 (outpatient anesthesia), USAB3200 (remifentanil plus propofol vs. remifentnail plus isoflurane). Five serious adverse events were reported during the safety update period:

- two patients developed non-drug-related postoperative hematomas.
- two patients experienced potentially drug-related intraoperative hypotension.
  One patient received remifentanil (at the recommended dose) for 5 minutes and developed severe, life-threatening hypotension (BP 68/25 mm Hg) and bradycardia (HR 48 bpm). He was treated with ephedrine and atropine and adjustment of anesthetic agents (isoflurane and remifentanil). The episode resolved in 6 minutes. Another patient received an inadvertent overdose of 5-times the recommended dose of remifentnail during induction due to miscalculation. The patient developed "mild" hypotension treated with ephedrine.
- a 39 year old female patient experienced an "epileptic type fit" 6 hours post-operatively. There was no prior history of seizures.

Conclusion: The occurrence of hypotension/bradycardia is consistent with known side-effects of remifentanil. The package insert lists the incidence of hypotension during induction at 19% and the incidence of bradycardia at 7%. The incidence of seizure is listed as <1%. It is not clear that the occurrence of seizure 6 hours postoperatively is drug related. The occurrence of hematoma is likely related to surgical factors.

This safety report is consistent with the safety database presented in the NDA. There are no new safety issues identified.

Barbara Palmer MD — 5/24/96

Primary Medical Reviewer — date

Concur:

RF Bedford — 5/24/96

Secondary Medical Reviewer — date

Dennis M. Fisher, M.D.
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University of California, San Francisco ... A Health Sciences Campus

July 2, 1996

David Morgan
Advisor and Consultants Staff (HFD-9)
Food and Drug Administration
5600 Fishers Lane, Room 8B45
Rockville, MD 20857

Dear Mr. Morgan,

As an external reviewer for NDA 20-630; Ultiva (remifentanil hydrochloride), I reviewed the following studies: 213, 226, 301 (3001), 307 (3007), 313 (3013), 314 (3014). Attached you will find my completed reviews.

Sincerely yours,

Dennis M. Fisher, M.D.
Professor
Anesthesia and Pediatrics

DMF:il

General Anesthesia and Post-Operative Analgesia

FDA Consultant Review

NDA #:	**20-630**
Name:	**Remifentanil for injection**
Sponsor:	**Glaxo-Wellcome**
Reviewer:	**Dennis M. Fisher, M.D.**
Review Date:	**November-December 1995**
Study #:	**213, 226, 301 (3001), 307 (3007), 313 (3013), 314 (3014)**

Background: Each of these studies has two components. All studies were designed to determine a regimen by which remifentanil could provide analgesia during the period immediately after surgery. Patient received infusions of remifentanil for 30-45 minutes; these infusions were adjusted to provide appropriate analgesia without adverse effects (typically, respiratory depression). Safety and efficacy were determined.

Each of the studies determined additional characteristics of remifentanil during anesthesia. Several studies compared remifentanil to another opioid (fentanyl or alfentanil). Other studies compared different doses of remifentanil.

Conclusions From Studies: Remifentanil can provide effective analgesia during the initial recovery period. Whether its efficacy exceeds that of other opioids remains to be demonstrated. However, severe life-threatening adverse events have been associated with remifentanil administration during the recovery period. Although some of these episodes have been attributed to dosing errors, others have occurred during routine administration of remifentanil per protocol. In addition, these adverse effects have been observed despite supplemental monitoring available during a clinical trial.

In clinical practice, patients are monitored less intensively than during clinical trials. This suggests that severe adverse events will occur with greater frequency than in clinical trials and might lead to adverse outcomes. Therefore, I question whether it is appropriate to recommend administration of remifentanil during the recovery period. Alternatively, a controlled roll-out with an educational program might limit the occurrence of these adverse effects.

FDA Consultant Review — Dennis M. Fisher, M.D.

Study #314: Remifentanil vs. Morphine Sulfate Analgesia Following Total Intravenous Anesthesia

This is a multicenter study (12 sites in the United States) of 200 patients undergoing urogenital, orthopedic, and other surgical procedures. The study has two components.

Intraoperative Anesthesia: A standardized regimen of propofol and remifentanil was used to induce and maintain anesthesia.

Postoperative Analgesia: A complicated regimen of morphine and remifentanil was used to provide analgesia during the emergence and initial recovery period. The complexity of the regimen resulted from two factors, first, the goal of blinding the investigators, and, second, dissatisfaction with the results of initial studies lead to a number of revisions (amendments) to the protocol. Briefly, 20 minutes before the anticipated end of surgery, the morphine group received morphine, 0.15 mg/kg. At the end of surgery, a placebo infusion was started and pain was treated with bolus doses of morphine. Bolus doses of placebo were administered at 25 and 30 minutes after extubation. In the remifentanil group, each of the morphine doses was replaced with placebo, the placebo infusion replaced with remifentanil, and the placebo bolus doses replaced with morphine. The intent of this regimen was to provide analgesia during the initial 30 minutes after surgery with morphine in the morphine group and remifentanil in the remifentanil group, then to use only morphine in the "post-analgesia" period.

Efficacy Assessment: Anesthetic conditions were generally satisfactory. Hypotension occurred in 20% of patients and muscle rigidity in 15%; both these events responded to appropriate treatments. Awareness was reported in a number of subjects. Most reported a dreamlike state or a feeling of pressure without pain. Some of these occurrences were related to protocol violations (*e.g.*, inadequate treatment of hypertension, failure of remifentanil administration).

The primary endpoint for postoperative analgesia was the percentage of patients with pain control (pain absent or mild) at 25 minutes after extubation. Remifentanil provided better control than morphine (70% *vs.* 38%, respectively). During the post-analgesia period, 82% of the remifentanil patients had moderate-to-severe pain; this is similar to the percentage of moderate-to-severe pain in morphine patients *during* the analgesic phase.

Safety Assessment: Two severe adverse events related to remifentanil occurred during the analgesia period. One patient developed progressive hypoventilation to a respiratory rate of 4 during remifentanil infusion. One patient inadvertently received a bolus of remifentanil (400 mcg) during a remifentanil infusion. She lost consciousness and developed muscle rigidity and apnea. Ventilatory support was required for 10 minutes. An additional three remifentanil patients were withdrawn from the study because of respiratory depression. Respiratory depression was more common with remifentanil (13%) than with morphine (4%).

Conclusions: Remifentanil provided analgesia during the 30 minutes after extubation. However, shortly after its discontinuation, the incidence of pain exceeded that in the morphine group during the *post-treatment* phase and was similar to that for morphine during the *analgesic* phase. This suggests that remifentanil delayed the onset of pain and its post-operative administration did not provide a smooth transition to comfort during the recovery period. In addition, severe adverse events related to administration of remifentanil occurred during the recovery period.

FDA Consultant Review -- Dennis M. Fisher, M.D.

Study #313: Remifentanil *vs.* Fentanyl

This is a multicenter study (36 sites in seven countries) of 280 patients undergoing major abdominal surgery. The study has two components.

Intraoperative Anesthesia: Patients were randomized to receive low dose remifentanil (bolus of 1 mcg/kg plus initial infusion at 0.2 mcg/kg/min), high dose remifentanil (bolus of 2 mcg/kg plus initial infusion at 0.4 mcg/kg/min), or fentanyl (bolus of 3 mcg/kg plus intermittent bolus doses of 1-3 mcg/kg). All patients received isoflurane for maintenance of anesthesia; remifentanil infusion could be adjusted as needed during maintenance. Primary endpoints were the response to intubation and surgical stimulation; incidence of hypotension was recorded.

Postoperative Analgesia: Patients given remifentanil intraoperatively received remifentanil, 0.1 mcg/kg/min, for 30 minutes after extubation; the remifentanil infusion could be adjusted based on the presence of pain and/or hypoventilation.

Efficacy Assessment: During tracheal intubation and during surgery, remifentanil was associated with fewer increases in blood pressure. Isoflurane requirements were smaller in the remifentanil groups. Time to spontaneous respiration at the end of surgery was more rapid with fentanyl. During the interval between the start of the analgesic infusion and morphine administration, 68% of patients given remifentanil had moderate or severe pain at some time. During the same time interval, 47% of patients in the fentanyl group had moderate or severe pain at some time. Eighteen percent of patients in the remifentanil group required morphine "rescue" before completion of the analgesic phase. Six of 177 remifentanil patients had a respiratory rate < 8 breaths per minute at morphine administration. Respiratory depression was recorded as an adverse event for 13 remifentanil patients during the analgesic phase; muscle rigidity for 6 patients.

Safety Assessment: Rigidity with induction of anesthesia was more common with remifentanil than with fentanyl. The incidence of hypotension during maintenance of anesthesia was greater with remifentanil. One patient given remifentanil hypoventilated at the end of surgery, recovered spontaneous ventilation, then became apneic and hypoxemic. Two patients in whom remifentanil was infused after surgery developed severe pain, initially refractory to treatment with morphine; the investigators attributed the magnitude of response to lack of efficacy of remifentanil.

Conclusions: Fewer cardiovascular responses were seen with remifentanil than with fentanyl. However, the incidence of hypotension was greater with remifentanil. In combination, these findings suggest a deeper plane of anesthesia in the remifentanil group; in turn, it is possible that larger fentanyl doses would have depressed cardiovascular responsiveness to the same degree as remifentanil. The more rapid recovery with fentanyl is probably an artifact of study design — patients given remifentanil continued to receive remifentanil during the emergence period; those in the fentanyl group received their final bolus dose of fentanyl approximately 45 minutes before extubation. During the analgesia period, remifentanil did not provide better pain control than conventional therapy.

Recommendations Regarding Labeling: The sponsor notes "these data support the use of a higher remifentanil rate (ca. 0.5 g/kg/min) pre-intubation" (Volume 207, page v). Although this recommendation is probably reasonable, no data are presented in its support. Despite the large numbers of investigators involved in the study (thereby limiting the "learning curve" at each site), the incidence of severe adverse reactions during the analgesia period was small.

Study 313 - Remifentanil *vs* Fentanyl

Conclusions: Significantly more fentanyl patients (64%) experienced at least 1 response (hypertension, bradycardia, somatic, or autonomic) than patients receiving remifentanil infusion of 0.4mcg/kg/min (27%; p<0.001) but not 0.2mcg/kg/min (51%; p=0.069). Compared to fentanyl patients, response to intubation was significantly less frequent for higher dose remifentanil patients, and response to skin incision was significantly less frequent for both remifentanil groups. Time to response to verbal command and recovery of respiratory functions was, however, significantly shorter for fentanyl patients. Remifentanil continued post-operatively at 0.1mcg/kg/min was effective in controlling pain. The majority of adverse events were those typically associated with mu-opioid agonists or for patients undergoing major abdominal surgery.

Investigators: European multicenter in seven countries: Belgium (2 centers); France (14 centers); Germany (5 centers); Holland (2 centers); Norway (3 centers); Sweden (5 centers); United Kingdom (5 centers).

Purpose: (1) To compare the intraoperative efficacy and safety of remifentanil and fentanyl, (11) to assess remifentanil's analgesic efficacy to control immediate post-operative pain prior to transfer to morphine.

Study Design: An open, multicenter, multinational, randomized, parallel group comparison of remifentanil at 2 infusion rates of 0.2mcg/kg/min and 0.4mcg/kg/min versus fentanyl for the maintenance of anesthesia with 0.8% (end-tidal) isoflurane in patients undergoing major elective abdominal surgery of 90 minutes or longer duration.

Demographics: 286 patients were entered with 90 male and 196 female patients, aged 19-85 years, ASA status I-III randomized and receiving treatment with remifentanil at 0.2 (N=35 male, 63 female) or 0.4mcg/kg/min (N=26 male, 65 female) or fentanyl (N=29 male, 68 female). The majority of subjects were Caucasian, (97%, 98%, and 95% in the remifentanil 0.2, remifentanil 0.4, and fentanyl treatment groups, respectively).

Anesthesia Protocol: All patients were premedicated with oral diazepam (10mg) and glycopyrrolate (0.1-0.2mg) or atropine (0.4-1.0mg) followed by oxygenation for 3 minutes. Induction was begun with either a continuous infusion of remifentanil at 0.2mcg/kg/min or 0.4mcg/kg/min with simultaneous bolus dose at 1mcg/kg or 2mcg/kg over 30-60 seconds, respectively. Patients randomized to fentanyl received 3mcg/kg. Propofol was administered at 0.5mg/kg followed by 10mg every 10 seconds until loss of consciousness (LOC) was attained. Vecuronium (0.08-0.1mcg/kg) was given to facilitate intubation. Anesthesia was maintained with 0.8% end-tidal isoflurane in an oxygen/air mixture. Fentanyl patients received 1-3 mcg/kg as needed. Remifentanil was maintained as a continuous infusion. Remifentanil treated patients continued to receive an analgesic infusion at 0.1mcg/kg/min for 30 minutes after extubation prior to transfer to morphine. Remifentanil infusion was titrated between 0 to 0.25mcg/kg/min in 0.025mcg/kg/min increment/decrements to manage pain.

Responses to surgical stimuli (primarily hemodynamic responses) were treated with boluses or study drug rate titrations.

Table 1. Principal Efficacy and Safety Results, All Patients (N=288)
Values are N (% total) or Odds Ratio, 95% Confidence Interval, and p-value

	Remifentanil Dose Group mcg/kg/min		Fentanyl
	0.2 (N=98)	0.4 (N=91)	(N=97)
Efficacy			
No. (%) of patients with >1 response	50/98 (51%)	25/91 (27%)	62/97 (64%)
Odds ratio to Fentanyl (95% CI ; p-value)	0.59 (0.33, 1.04;p=0.069)	0.21 (0.12, 0.40;p<0.001)	
Safety			
Most Common Adverse Events:			
Nausea	50 (51%)	53 (58%)	45 (46%)
Vomiting	23 (23%)	24 (26%)	22 (23%)
Hypotension	14 (14%)	17 (19%)	8 (8%)
Bradycardia	4 (4%)	4 (4%)	3 (3%)
Muscle rigidity	13 (13%)	14 (15%)	2 (2%)
Respiratory depression	4 (4%)	5 (5%)	2 (2%)

Serious adverse events occurred in 15 patients: 6 receiving remifentanil 0.2mcg/kg/min; 8 receiving 0.4mcg/kg/min; 1 receiving fentanyl. The adverse events observed were typical of mu-opioid agonists or of intra and post-operative complications. No deaths occurred during the study period; however, two deaths occurred after the study period. Neither death was considered related to remifentanil.

Study #307: A Double-Blind, Randomized Study of Remifentanil with Propofol In Patients Undergoing Elective Inpatient Surgery

This is a multicenter study (7 centers in the United States) of 178 patients undergoing a variety of surgical procedures. The study has two components.

Intraoperative Anesthesia: After midazolam premedication and a remifentanil bolus of 1 mcg/kg, patients were randomized to a low dose infusion (0.5 mcg/kg/min until tracheal intubation, then 0.25 mcg/kg/min) or a high dose infusion (1 mcg/kg/min until tracheal intubation, then 0.5 mcg/kg/min). All patients received propofol, 75 mcg/kg/min, and vecuronium, as needed. During maintenance, remifentanil infusion rate was adjusted as indicated by clinical signs.

Postoperative Analgesia: Approximately 15 minutes before surgery ended, propofol infusion rate was decreased 50%, then discontinued at the end of surgery. The remifentanil infusion rate was then adjusted to 0.05 mcg/kg/min (before amendment 4) or 0.1 mcg/kg/min (after amendment 4).

Efficacy Assessment: The high dose infusion was associated with fewer responses to tracheal intubation and skin incision. Emergence from anesthesia was rapid and did not differ between groups.

During the analgesia period, most patients achieved pain scores of mild or better and had respiratory rates > 8 breaths per minute.

Safety Assessment: The incidence of hypotension was greater in the high dose group. Muscle rigidity was observed in 11 patients including three during the analgesia period.

During the analgesia period, two patients demonstrated severe adverse effects. One was found unresponsive and cyanotic after transport from the recovery room; this event was attributed to administration of residual remifentanil in the intravenous tubing. A second patient experienced apnea after a bolus dose of remifentanil, 0.4 mcg/kg. Of 49 episodes of respiratory depression during the analgesia period of the study, 16 were reported as apnea; only one of 16 of these apneic episodes followed a bolus dose of remifentanil.

Conclusions: Remifentanil, 0.25-2 mcg/kg/min or 0.5-4 mcg/kg/min, with propofol and vecuronium provided safe and effective anesthesia and blunted most hemodynamic responses to surgical stimulation. During the analgesia period, remifentanil provided effective analgesia for most patients without inducing respiratory depression. However, some subjects developed respiratory depression (including apnea) and two subjects had severe, life-threatening adverse events.

FDA Consultant Review — Dennis M. Fisher, M.D.

Study #301: Remifentanil vs. Alfentanil for the Maintenance of Anesthesia using a Balanced Anesthetic Technique

This is a multicenter study (21 sites in 6 countries) of 234 patients undergoing various major surgical procedures. The study has two components.

Intraoperative Anesthesia: After premedication with a benzodiazepine, patients were randomized to receive remifentanil (bolus of 1 mcg/kg plus a continuous infusion of 0.5 mcg/kg/min) or alfentanil (bolus of 25 mcg/kg plus a continuous infusion of 1 mcg/kg/min). After tracheal intubation, infusion rates were decreased 50%; isoflurane (0.5%), N_2O (66%), and vecuronium were administered. The incidence of responses (increases in systolic blood pressure or heart rate, other autonomic or somatic responses) was assessed.

Postoperative Analgesia: Patients given remifentanil during anesthesia continued to receive remifentanil, 0.05 mcg/kg/min for 45 minutes after the end of surgery; morphine was administered 30 minutes into this infusion. When this regimen failed to provide adequate analgesia, the protocol was amended so that the starting rate for the remifentanil infusion was 0.1 mcg/kg/min.

Efficacy Assessment: Patients given remifentanil had fewer responses to tracheal intubation and to surgical stimulation compared to those given alfentanil.
During the analgesia period, 34% and 19% of patients in the two remifentanil groups (initial analgesia infusion rate of 0.05 and 0.1 mcg/kg/min) and 45% of patients in the remifentanil group experienced a maximum of mild pain.

Safety Assessment: Patients given remifentanil had a greater incidence of hypotension during anesthesia.

During the analgesia phase, several patients given remifentanil had severe adverse events — including hypoventilation, apnea, and hypoxemia — attributable to remifentanil. For example, during remifentanil, 0.05 mcg/kg/min, a 57 year old male developed chest wall rigidity and apnea. A 49 year old male received remifentanil at 0.05 mcg/kg/min. Because of severe pain, he was given a bolus dose of 0.5 mcg/kg, and the infusion was increased to 0.1 mcg/kg/min. One minute later he became apneic. There were several less serious adverse events related to alfentanil.
Six of 11 patients who received remifentanil and developed severe adverse effects during the analgesia period had received either an overdose of remifentanil or an incorrect dosing regimen.

Conclusions: Remifentanil blunted cardiovascular, autonomic, and somatic responses better than alfentanil; however, remifentanil was associated with more hypotension than alfentanil. These combined findings suggest that anesthesia was maintained at a deeper plane in the remifentanil groups. In turn, it is possible or likely that a similar blunting of responsiveness could have been achieved with alfentanil, albeit with a similar increase in the occurrence of hypotension.
During the analgesia phase, several patients developed profound adverse effects that could be attributed directly to remifentanil. These patients were receiving remifentanil infusions of 0.05-0.1 mcg/kg/min and several had received bolus doses of 0.5 mcg/kg. These findings lead to serious question as to the safety of remifentanil administration in the postoperative period, particularly outside of a research context.

Other Comments and Issues: The sponsor notes (Volume 174, page 188) note "that maintenance remifentanil dose chosen for the present study was based on provisional information from protocols .... Whilst these are not equipotent doses, the altentanil dose of 0.5 mcg/kg/min chosen was based upon data sheet recommendations. If an equipotent dose of alfentanil has been used in this study, alfentanil treated patients would have had to receive significantly higher doses than those used in this study, would be likely to be outside the manufacturer's recommended

dosing range, and may well have compromised recovery in favor of remifentanil due to the much longer halflife of alfentanil after prolonged administration." Although this statement is true, it does not obviate the observation of a more frequent incidence of intraoperative adverse effects with remifentanil.

Study #213: Remifentanil vs. Alfentanil for the Management of Intraoperative Stress Responses in A Balanced Anesthetic Technique

This study had two components:

Intraoperative Anesthesia: Comparison of three regimens for the treatment of intraoperative "stress" (*i.e.*, hemodynamic or other response to an increase in surgical stimulus). In group 1 (remifentanil/placebo), remifentanil was infused at 0.25 mcg/kg/min; additional boluses of remifentanil or an increase in the remifentanil infusion rate was permitted in response to signs of inadequate anesthesia. Five minutes before the major stress event (surgical incision), a placebo infusion was started. In group 2 (remifentanil/remifentanil), initial remifentanil infusion was identical to group 1; the placebo infusion was replaced with a second remifentanil infusion at a rate identical to the first (*i.e.*, doubling the remifentanil infusion). In group 3 (alfentanil/placebo), the initial infusion was alfentanil, 0.5 mcg/kg/min; the second infusion was placebo.

Postoperative Analgesia: Determination of appropriate doses of remifentanil for infusion during the immediate postoperative period. Patients with no or mild pain did not receive remifentanil. Those with moderate or severe pain received remifentanil, 1 mcg/kg/min, followed by an infusion. The first patient at each site had remifentanil infused at 0.1 mcg/kg/min. If the patient continued to experience moderate or severe pain, a bolus dose of remifentanil (1 mcg/kg) was followed by a 0.1 mcg/kg/min increase in the infusion rate (not to exceed 0.8 mcg/kg/min). The initial infusion rate for each subsequent patient was determined by the previous patient's response to their initial infusion rate: If that initial infusion rate was ineffective, the next patient's initial infusion rate was doubled (to a maximum of 0.8 mcg/kg/min). If the previous patient's initial infusion rate was effective, the next patient received the next lowest infusion rate.

Efficacy Assessment: In patients undergoing hysterectomy, blood pressure increases to the major stress event were more common with remifentanil/placebo (67%) and alfentanil/placebo (60%) than with remifentanil/remifentanil (8%). In patients undergoing laminectomy, only 1/55 patients demonstrated a blood pressure increase with the major stress event, providing limited information on efficacy. In patients undergoing prostatectomy, blood pressure increases to the major stress event were more common with alfentanil/placebo (55%) than with remifentanil/placebo (19%) and remifentanil/remifentanil (10%).

Post-operative analgesia was provided with remifentanil in only 54 patients (40% of those given remifentanil intraoperatively; 10% of those given alfentanil intraoperatively). Of these, the initial infusion rate was "low" (0.1 mcg/kg/min) in 27, "medium" (0.2 mcg/kg/min) in 17, and "high" (0.4 or 0.8 mcg/kg/min) in 10. Eighteen of these 54 patients required no increase in infusion rate or supplemental doses. The remaining patients received 0-5 bolus doses and 0-2 increases in the infusion rate. Of the 54, 18 required 1-4 decreases in the infusion rate. Fewer patients (10%) with a "high" initial infusion rate required increases in the infusion rate compared to those in whom the initial infusion rate was "low" (44%) or "medium" (47%). Similarly, fewer patients in the "high" group (10%) required bolus doses compared to the "low" (67%) and "medium" (53%) groups. 80% of patients achieved a pain score < moderate and 68% maintained a respiratory rate > 8 breaths/min; 54% maintained both a pain score < moderate and a respiratory rate> 8 breaths/min.

A third efficacy measure (not a primary or secondary measure according to the sponsor) is the response to tracheal intubation. In patients given remifentanil, 70% responded to tracheal intubation with hemodynamic, autonomic, or somatic responses; these response were less common with alfentanil (44%).

Safety Assessment: Adverse events were common in all groups; however, many of these adverse events were not related to opioid administration. Nausea was common in all groups and

with all procedures. Less common adverse events were vomiting, bradycardia, and hypotension; the incidence of these events did not differ between groups. Muscle rigidity during induction of anesthesia was common in the three groups (44%-55%); muscle rigidity occurred in 4/59 patients during the analgesia phase.

Severe adverse events related to opioid administration were uncommon. During the analgesic phase, one patient developed severe rigidity.

Conclusions: Although remifentanil/remifentanil was associated with fewer blood pressure responses to major stress events, the comparison group (alfentanil/placebo) is probably inappropriate: the alfentanil infusion rate was only 0.5 mcg/kg/min, the low end of the range recommended in the package insert. The demonstration that remifentanil/remifentanil is more effective than remifentanil/placebo suggests that the doses provided in the remifentanil/placebo group are inadequate to prevent stress responses.

Remifentanil was demonstrated to provide effective postoperative analgesia to many subjects; however, as expected, some patients developed respiratory depression.

Study #226: Interaction of Remifentanil and Propofol During Intubation and Skin Incision/Arthroscope Insertion for Orthopedic Outpatient Surgery

This study had two components:

Intraoperative Anesthesia: Determination of the potency of remifentanil at tracheal intubation, trochar insertion, and during maintenance of anesthesia with propofol and remifentanil. Propofol was administered by bolus followed by computer-assisted continuous infusion (CACI) to maintain target plasma concentrations of 4 mcg/ml for 5 minutes, then 1, 2, or 4 mcg/ml. Remifentanil was administered by CACI for a minimum of 15 minutes before intubation, then 8 minutes before trochar insertion. An increase in systolic blood pressure (to >115% of control value), heart rate (to >115% of control), or other somatic or autonomic signs of inadequate anesthesia were assessed. Logistic regression was used to determine potency (ED50/ED80/EC50/EC80).

Postoperative Analgesia: Determination of appropriate doses of remifentanil for infusion during the immediate postoperative period. At the end of surgery, remifentanil infusion rate was decreased to 0.05 mcg/kg/minute for 30 minutes. Pain was assessed as mild, moderate, or severe and the remifentanil infusion was adjusted accordingly. Moderate or severe pain resulted in a bolus dose of 0.5 mcg/kg and an increase in the infusion rate by 0.05-0.1 mcg/kg/min (not more frequently than every 3 minutes). Respiratory rate < 8 breaths/minute or SpO2 < 94% resulted in a decrease in the infusion rate by 0.05-0.1 mcg/kg/min.

Efficacy Assessment: Propofol plasma samples were mishandled resulting in no propofol plasma concentration data being available. As a result, the analysis was performed assuming that the target propofol concentrations were achieved. For the response to tracheal intubation, ED50 for remifentanil was 0.441, 0.176, and 0.070 mcg/kg/min during propofol, 1, 2, and 4 mcg/ml, respectively; EC50 values were 14 34, 4.46, and 1.38 ng/ml. For the response to trochar insertion, ED50 for remifentanil was 0.193, 0.105, and 0 057 mcg/kg/min; EC50 values were 8.79, 4.22, and 2.03 ng/ml. During surgery, EC50 values were 10.89, 5.73, and 2.28 ng/ml. For both the response to tracheal intubation and the response to trochar insertion, confidence bands were broad.

During the analgesia trials, 27/44 (61%) of patients required no bolus doses or change in the remifentanil infusion rate. Increases in the infusion rate were necessary in 17/44 (39%); decreases in none. No patient developed severe pain during the analgesia period and moderate pain was rare (<10%).

Safety Assessment: The incidence of vomiting was less with propofol, 2 and 4 mcg/ml, compared to propofol, 1 mcg/ml; the incidence of hypotension was less than propofol, 1 and 2 mcg/ml, compared to propofol, 4 mcg/ml. Although adverse effects were common during the trial, few severe events were related to remifentanil. One patient inadvertently received remifentanil at 0.15, rather than 0.05, mcg/kg/min during the recovery period; that patient had a brief period of apnea but no hypotension or hypoxemia.

Conclusions: The marked decrease in remifentanil requirements with propofol, 2 mcg/ml, compared to propofol, 1 mcg/ml, suggests synergy between propofol and remifentanil. The adverse event profile with propofol and remifentanil suggests that, when administered with remifentanil, the optimal target concentration of propofol is 2 mcg/ml. However, the results of this study must be interpreted with caution because propofol plasma concentration data are absent. Specifically, the sponsor is unable to claim that the target plasma concentrations of propofol were achieved. The best supportive evidence is an abstract (Vuyk *et al.* Anesth Analg 74:S338, 1992) that demonstrates that the Shafer *et al.*'s propofol pharmacokinetic parameters (Anesthesiology 69:348, 1988) provided a better fit than other parameter sets in nine young female subjects. However, subjects in the present study were predominantly male. In addition, the initial propofol

target concentration was 4 mcg/ml for 5 minutes for all subjects; whether the target propofol concentrations were achieved in the next 15 minutes cannot be determined.

Data from the analgesia portion of this study are promising: most patients achieved adequate analgesia with no or few adjustments in the remifentanil infusion rate and adverse effects were rare. The presence of adequate analgesia and rare adverse events with low infusion rates in this study contrasts with the findings of other investigators.

School of Medicine
Department of Anesthesiology

July 1, 1996

David Morgan
Center for Drug Evaluation and Research
Division of Anesthesia, Critical Care
Addiction Drugs (DACCAD)
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Dear David,

As an external reviewer for NDA 20-630; Ultiva (remifentanil hydrochloride), I reviewed the following: Study 201, Pilot Study of the Hemodynamic Effect of Escalating Doses of Remifentanil; Study 206, Hemodynamic Safety Evaluation of Intravenous Doses of Remifentanil or Alfentanil in Patients Undergoing Anesthesia with Nitrous Oxide or Isoflurane; Study 207, Pharmacokinetics of Single Doses of Remifentanil in Cardiac Anesthesia; Study 215, Remifentanil in Patients Undergoing Coronary Artery Bypass Graft Surgery; Study 221P, Pilot Study: Remifentanil in Patients Undergoing Coronary Artery Bypass Surgery; Study 221, Safety and Efficacy of Intravenous Remifentanil in Patients Undergoing Coronary Artery Bypass Surgery. In addition, I reviewed and suggested the changes in the proposed labeling for Ultiva (remifentanil hydrochloride). My completed reviews dated January 30, 1996 and February 23, 1996 should be in the FDA files.

Robert G. Merin, M.D.
Professor of Anesthesiology

sfg

Cardiac Anesthesia

FDA Consultant Review

NDA #:	**20-630**
Name:	**Remifentanil for injection**
Sponsor:	**Glaxo-Wellcome**
Reviewer:	**Robert G. Merin, M.D.**
Review Date:	**January 1996**
Study #:	**215 (P15), 221P, 221 (2021)**

Study 221: Safety and Efficacy of Intravenous Remifentanil in Patients Undergoing Coronary Artery Bypass Surgery

3 sites in the US with 76 Patients (72 randomized).

Premedication
40-80 mic/kg lorazepam; .05 mg/kg morphine.

Again, after catheter placement, pre-load to 10-15 mm/Hg PAOP; estimate of cardiac output stroke volume less than 50 ml excluded patient.

Induction
Vecuronium prime 10 mic/kg, remifentanil either 1,2,3 mic/kg/min to LOC; 150 mic/kg vecuronium; 15 minutes later ETI.

Maintenance
Remifentanil titrated to 2 mic/kg/min over original rate if necessary. Vecuronium 2 mic/kg/min; supplemental isoflurane and vaso-active drugs if necessary for hypertension and vaso-active drugs and decrease remifentanil infusion for hypotension

ICU
Remifentanil 1 mic/kg/min for 2-3 hours; assess for early extubation; if suitable 0.1 mg/kg morphine, another hour of remifentanil; if still eligible remifentanil infusion decreased 50% q 10 minutes until adequate ventilation; then extubation.

Monitors
PA, CV, arterial pressures, temperature, pulse oximeter, leads 2 and V5 ECG.

Results

There were 25 patients at 1 and 2 and 26 patients at 3 mic/kg/min remifentanil for the safety evaluation and 23 patients at 1, 24 at 2 and 25 at 3 mic/kg/min for the efficacy end points.

Demographics were comparable.

Supplemental medications: There was a very high incidence of phenylephrine, sodium nitroprusside and isoflurane none of which appeared dose related.

Most patients did not respond to IMA dissection (Table 1).

All remifentanil rates were greater than planned! The actual rates at 1 μg/kg/min varied from 1.8-2.2; at 2 μg/kg/min varied from 2.5-2.9; and at 3 μg/kg/min varied from 3.6-3.7. Loss of consciousness occurred between 1-8 minutes and did not appear dose related. 78% of 1 μg/kg, 83% of 2 μg/kg, and 88% of 3 μg/kg /min remifentanil did not respond to ETI. 61-64% of the intraoperative time for all 3 doses was spent with no hemodynamic responses out of range.

However, 71 (2 mic)-96 (1mic)% had hypertension at some time (Table 9).

73-83% had hypotension at some time (Table 10).

91% of 1μg/kg/min remifentanil; 63% of 2μg/kg/min remifentanil; and 56% of 3μg/kg/min remifentanil required enflurane/isoflurane rescue.

76-83% met intent-to-treat criteria for hypotension pre-bypass; 28-46% during bypass; and 58-65% post-bypass without a dose effect.

30/72 were extubated early, a median of 4 hours after entry to ICU. 42/72 were extubated late, a mean of 17 hours after entry to ICU. However, there were huge center differences.

Again 100% incidence of adverse events.

Hypertension (92-96%), hypotension (77-88%), muscle rigidity (36-65%), the latter with 3μg/kg/min dose, tachycardia (46-56%); shivering (56-65%).

Muscle rigidity on induction 28% with both 1 and 2μg/kg/min and 46% with 3μg/kg/min were rated moderate to severe.

INCIDENCE OF CV EVENT (%)

	Remifentanil (μg/kg/min)		
	1	2	3
(MAP less than 60)			
Pre-bypass	39	67	44
Post-bypass	100	83	84
(MAP greater than 120)			
Pre-bypass	26	25	12
Post-bypass	13	13	20
(% with CI less than 2)			
Pre-bypass	33	67	63
Post-bypass	5	11	5
(% with PAOP greater than 20)			
Pre-bypass	27	20	20
Post-bypass	8	15	11
(% with Significant ST Elevation/Depression)	24	16	16
(% with Other Signs of Ischemia)	12	0	8

Limitation of Study

Again, open label, small number of patients, no comparative group.

The ischemia monitoring was not Holter and had no cardiology review so that it is certainly incomplete and inaccurate.

The hemodynamic observations especially PAOP and cardiac output derivatives were not recorded at the planned times in a large number of cases. Consequently this aspect of the efficacy study was incomplete and probably not sufficient for analysis.

The early extubation study is obviously inadequate since there were major differences in the ability of investigators to implement early extubation in the face of institution opposition regardless of patient eligibility under study criteria. As indicated for Study 215 there needs to be more and better controlled studies of early extubation with remifentanil protocols.

It would appear that supplemental propofol (midazolam) or inhaled anesthetics are necessary for adequate cardiac anesthesia.

Study 221P-Pilot Study: Remifentanil in Patients Undergoing Coronary Artery Bypass Graft Surgery

This study was presumably the pilot for 221. I suppose that 215 was ongoing but the results were not known.

There were 8 patients, all male and interesting enough from patients 1-8 duration of anesthesia and surgery progressively increased. There is no mention of exclusion or inclusion criteria.

Premedication
By the time of anesthetic induction 40-80 mic/kg lorazepam were given.

Again as in 215 after catheterization patients were pre-loaded to 10-15 mm/Hg PAOP, cardiac output and stroke volume were estimated, and patients with a stroke volume less that 50 ml were excluded.

Induction
10 mic/kg vecuronium, 1 mic/kg/min remifentanil, after LOC 0.15 mg/log vecuronium ETI 15 minutes after remifentanil start.

Maintenance
Remifentanil 1 mic/kg/min supplemented as necessary with sufentanil, thiopental, isoflurane or appropriate cardiotonic drug, also vecuronium 2 mic/kg/min.

Limits for treating hypotension and tachycardia were quite restrictive.

ICU
First 3 patients 0.2 mic/kg/min remifentanil, last 5 patients 1 mic/kg/min remifentanil

Extubation
IV morphine 1-2 hour pre-extubation and remifentanil titrated down 50% q 20-30 minutes

Monitors
PA, CV and arterial pressure, temperature, pulse oximeter, lead 2 and V5 electrocardiogram results

Results

The great majority of patients had to be supplemented with the sufentanil, isoflurane or both. In addition, 100% needed nitroglycerin, 88% phenylephrine, 63% metoprolol and 38% SNP.

Of note (Figure 1, Page 8) in spite of the same dosing, blood levels were quite varied

88% had hypertension pre- and on bypass

75% had hypotension pre-bypass

7 of 8 were eligible for early extubation, 4 of 8 were actually extubated in less than 6 hours

There was 100% incidence of adverse events.

Hypertension (75%), tachycardia (75%), hypotension (63%), myocardial ischemia (38%), vomiting (38%), muscle rigidity (38%), AF (25%)

However, there were very few significant hemodynamic alterations.

Limitations of the Study

This was a pilot study so the expectations were small. However, it was not possible to characterize pharmacokinetics during hypothermic bypass so that one of the main objectives of the study was not achieved.

Study 215: Remifentanil in Patients Undergoing Coronary Artery Bypass Graft Surgery

This was a 10 center study in 5 European countries. This study was a randomized and a double blind parallel group dose comparison in patients undergoing elective first time coronary artery bypass surgery. However, there was no comparator group for another anesthetic technique other than remifentanil. Other than first time coronary artery bypass grafting, the pre-enlistment inclusions and exclusions were not detailed.

Premedication and Preparation

10 mg of diazepam 2 hours prior to anesthesia; 50 mic/kg midazolam intravenously before placement of arterial and PA catheters; IV infusion of crystalloid to a PAP 10-15 mmHg; measurement of cardiac index and stroke volume; if stroke volume less than 50 ml patient excluded.

Anesthetic Induction

Initially only remifentanil at one of the preset doses (1.0, 1.5, 2.0 mic/kg/min), then a prime of pancuronium 0.015 mg/kg was added, then propofol bolus (0.5 mg/kg) and continuous infusion (3 mg/kg/H) followed by propofol 10 mg boluses q 10 sec until LOC; then pancuronium 0.04-0.1 mg, kg. However, the induction sequence was modified to begin with propofol 10 mg 10 sec until LOC; then the paralyzing dose of pancuronium followed by the IV infusions of remifentanil and propofol.

Maintenance

Appropriate remifentanil infusion and propofol 3 mg/kg/hr. Signs of light anesthesia could be treated with 2 sequential bolus doses of remifentanil (2 mic/kg); followed by bolus doses of propofol and a 50% increase of infusion rate up to 2 sequential rate increases, then vasoactive drugs could be used. Hypotension was initial treated by fluid replacement, vasopressors and then decreases in propofol, and finally remifentanil. During CPB, propofol infusion was reduced by 50% but could be titrated upwards in 50% increments if the patient showed signs of light anesthesia during cooling. After start of rewarming propofol was titrated up to the original infusion rate and both infusions maintained until the end of surgery.

ICU

Remifentanil was reset to 1 mic/kg/min to be maintained until assessment for early extubation was made 3-5 hours later. Extubation eligible patients received a morphine bolus and in some IV midazolam 30 minutes after the morphine bolus before the remifentanil infusion was discontinued.

Monitoring

Arterial and pulmonary artery pressure; lead 2 and V5 of electrocardiogram and pulse oximeter.

However, it is notable that no ST segment ischemia results nor cardiac output results were reported. In addition, the statistical evaluation for the ST segment ischemia was inadequate.

Results

54 patients were reported at 1 mic, 44 at 1.5 mic and 43 at 2 mic/kglmin remifentanil. It is of note, however is that 2/3 to 3/4 of these patients were before the induction change with propofol.

Of particular note:

1. The groups were comparable.
2. There was good stability (heart rate and blood pressure) at sternotomy and at endotracheal intubation but less so after propofol change.

Light anesthesia did not appear to be dose related and was most common during bypass. The maximal incidence was 35% at the remifentanil 2 mic level during bypass.

Hypotension was common again with no dose relationship. Incidence was highest in the pre-bypass period (80-91% versus 68-74% during bypass and 67-78% post-bypass).

70-73% of patients were eligible for early extubation, again with no dose effect. The time from cessation of remifentanil maintenance infusion to extubation was 6-7 hours median with a range from 3.2-188 hours! But this is all patients, not only those eligible for early extubation.

89-100% patients had an adverse event.

There was a huge incidence of hypotension (less than 60 mmHg) on CPB (95-100%). As noted in the limitations of this study this is probably too conservative although many teams recently have aimed for this sort of blood pressure during bypass. And this is certainly a MAP to be desired pre- and post-bypass and the incidence of hypotension was 60-75% on those periods especially with the higher remifentanil doses.

There were 3 serious adverse events that should be noted:

1. AO830-"explosive wake up leading to sternal dehiscence."
2. AO947-respiratory arrest after extubation, accidental infusion of remifentanil when morphine given through same catheter
3. AO854-sudden respiratory arrest and LOC and hypotension 1 hour 47 minutes after extubation-? Flushing of remifentanil catheter?

Limitations of study

As mentioned previously, the lack of a comparator group with another standard type of cardiac anesthesia is a major problem

Myocardial ischemia and cardiac output results were not reported

This was really a study of propofol/remifentanil anesthesia rather that remifentanil. It may well be that not all groups are interested in using propofol.

Finally, this is one of the first studies of early extubation so that further studies are needed.

Study 207 - Pharmacokinetics of Single Doses of Remifentanil in Cardiac Anesthesia

This was a two center open label dose escalation study which patients for coronary bypass surgery received bolus doses of remifentanil of either 2 mic/kg or 5 mic/kg before bypass and during hypothermic bypass. The drug doses were also administered during either the re-warming phase of the bypass or after re-warming had been accomplished while still on bypass but because of the short time allowed for sampling, the results are not interpretable

The study suffers from lack of standardization of the anesthetic regimen and small numbers of patients. The original study included higher doses of remifentanil, but because of a high incidence of severe hypotension after the 5 mic/kg dose especially pre-bypass, the study was terminated at the 5 mic/kg dose.

The only conclusion is that the clearance of remifentanil is decreased by about 20% during hypothermic bypass compared to the pre-bypass period and that 5 mic/kg given during a cardiac anesthetic results in undesirable hypotension so that the dose of remifentanil should be limited to less than 5 mic/kg.

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MEMORANDUM

TO: David Morgan and Barbara Palmisano

FROM: Margaret Wood, M.D.

DATE: December 8, 1995

SUBJECT: NDA #20 - 630, Remifentanil

****

Please find enclosed my reviews for geriatrics, renal impairment and hepatic impairment. The review on pharmacokinetics in obese patients will follow. I do not have any edited changes for the study summaries; the pharmacokinetic studies are relatively self-explanatory, and were well-written. My only concern is that not too much is made of the pharmacokinetic study in hepatic transplant patients (please see my review) -- in this clinical setting with the protocol that they used it is difficult to make definitive conclusions.

dhc

Special Populations - Geriatrics, Obesity, Liver and Renal Impairment

FDA Consultant Review

NDA #:	**20-630**
Name:	**Remifentanil for injection**
Sponsor:	**Glaxo-Wellcome**
Reviewer:	**Margaret Wood, M.D.**
Review Date:	**December, 1995**
Study #:	**210, 211, 216, 224 (P24), 227**

Study #227. Pharmacokinetics in Obese Patients

Background

Remifentanil was evaluated in a study comparing the pharmacokinetics of remifentanil in obese and non-obese patients undergoing elective inpatient surgery. In addition, the safety of remifentanil in this patient group was evaluated

Clinical Study 227

Twenty-four patients (12 obese and 12 non-obese control subjects) aged 29-54 years were studied Three obese patients received a dose of 10 mcg/kg remifentanil Since they experienced episodes of bradycardia/hypotension, the dose was decreased to 7 5 mcg/kg for the remaining patients Arterial blood samples were collected for measurement of remifentanil and its metabolite, GR 90291, and kinetic parameters calculated Distribution and elimination half-lives were similar between obese and control patients, but when corrected for total body weight, significant differences for volume of distribution (V_1 and Vdss) were obtained V_1 for obese patients was 146 ml/kg and 217 ml/kg in matched controls A smaller V_1 by definition will result in a higher remifentanil concentration, leading to increased effect It was of interest that $_1$ acid glycoprotein levels were higher in obese patients, resulting in a lower free fraction of remifentanil The mean clearance when corrected for total body weight was 27 7 ml/min/kg in obese patients and 42 4 ml/min/Kg in matched controls Dose-normalized AUC and Cmax for GR90291 were higher in obese patients than controls These data would suggest that grossly obese patients should receive a remifentanil dose calculated on the basis of ideal body weight

Efficacy Assessment

No attempt was made to evaluate efficacy

Safety Assessment

Three patients who received 10 mcg/kg remifentanil developed bradycardia/hypotension, this was considered a severe adverse event 83% of patients (10/12) in the obese group experienced adverse events and 100% (12/12) of the control patients experienced an adverse event 50% of the patients in the obese treatment group and 25% in the control group experienced a systolic blood pressure of less than 80 mmHg, that occurred 1 to 2 mins post infusion This was probably related to higher remifentanil levels in the obese group of patients immediately post-infusion

Conclusions

Obese patients should receive remifentanil dosage calculated on the basis of ideal body weight, rather than total body weight to avoid higher remifentanil concentrations Morbidly obese patients have altered respiratory and cardiovascular physiology, and a pharmacodynamic respiratory study in this group would have been of interest

Recommendations Regarding Labeling

Should a warning be given that as for all opioids, caution is required for morbidly obese patients?

Study #210. Remifentanil PK/PD Trial in Renal Impairment

Background

Remifentanil was evaluated in a pharmacokinetic/pharmacodynamic study in patients with end-stage renal disease These patients were not studied during the perioperative period

Clinical Study #210

Twenty-three subjects (15 with severe renal disease and 8 healthy subjects) aged 28-62 years received remifentanil infusions for a period of four hours Two infusion regimens were administered low dose (0 0125 mcg/kg/min for one hour followed by 0.025 mcg/kg/min for three hours) and high dose (0 025 mcg/kg/min for one hour followed by a 3-hour infusion of 0 05 mcg/kg/min The pharmacokinetics of remifentanil were not altered in patients with severe renal disease compared with healthy volunteers However, the metabolite GR 90291, exhibited significantly different pharmacokinetic parameters The AUC of GR90291 was 35150 ± 13800 ng/min/ml in patients with renal disease compared with 993 ± 254 in healthy subjects The Cmax was higher in patients with end-stage renal disease, 12 7 ± 2 8 ng/ml versus 4 2 ± 0 6 The pharmacodynamic relevance of the increased concentrations of the metabolite GR90291 in renal disease was not assessed in this study

The EC_{50} values for remifentanil in response to a hypercarbic challenge (measurement of minute ventilation was used as a pharmacodynamic end point) were not significantly different between the two groups (2 3 ng/ml healthy versus 3 7 ng/ml renal impairment)

Mean percent change from baseline for minute ventilation in the two groups was measured for the high dose remifentanil infusion regimen (significant differences? Figure 8, page 9) End tidal CO_2 increased during of the infusion

Efficacy Assessment

No attempt was made to evaluate efficacy in this study

Safety Assessment

Mean percent change from baseline for minute ventilation and respiratory drive during a hypercarbic challenge was assessed There was no difference in sensitivity between the two groups for remifentanil EC_{50} MV ($p = 0\ 239$)

Patients with renal disease are likely to develop hypertension, a trend toward higher than baseline SBP and DBP was noted by the investigators following cessation of infusion This may require further evaluation in a perioperative setting than described in Study #210 Peripheral Oxygen Saturation was measured, and no adverse events in this respect were reported Arterial blood gases were not reported, although an arterial line was placed Adverse events were similar between groups

Conclusions

The pharmacokinetics of the parent drug remifentanil are not different in healthy conscious subjects and patients with severe renal impairment. Pharmacodynamic studies (EC_{50}:MV) are not different between groups. However, the kinetics of the renally excreted primary metabolite do differ. The pharmacokinetics/dynamics of remifentanil were not reported for patients with renal disease in a perioperative setting. Remifentanil is 70% bound to plasma proteins, in particular to AAG. Is protein binding altered in renal disease?

FDA Consultant Review — Margaret Wood, M.D.

Study #211. Remifentanil PK/PD Trial in Hepatic Impairment

Background
Remifentanil administration was evaluated in a pharmacokinetic/pharmacodynamic study in patients with severe hepatic impairment These patients were not evaluated in a perioperative clinical setting

Clinical Study #211
Twenty subjects (10 with liver disease and 10 healthy) aged 31-65 years were studied Remifentanil infusions were for four hours, low and high dose infusions were administered as described in the study protocol to five patients in each group Standard pharmacokinetic parameters were calculated for remifentanil and no significant differences were found between the two study groups Volume of distribution tended to be lower in healthy subjects compared to subjects with hepatic impairment Was protein binding of remifentanil measured, and has remifentanil binding been studied in other situations where AAG might be variable? For the primary metabolite of remifentanil, no differences in pharmacokinetics were observed between the two study groups

The pharmacodynamic arm of the study assessed respiratory drive (minute ventilation % change from baseline), psychomotor tests and VAS. It was of interest that the percent decrease in minute ventilation for the high dose remifentanil regimen was increased two-fold in the subjects with hepatic impairment There were no significant differences noted for the other pharmacodynamic measures between the two study groups

Efficacy Assessment
No attempt was made to evaluate efficacy in this study

Safety Assessment
Adverse events were similar between the two groups of subjects studied Peripheral oxygen saturation was monitored during the study period, and minor decreases were noted Mean respiratory rate in the high dose-hepatic impairment group decreased during infusion to approximately 6 bpm Mean Pet CO_2 increased to about 60 in these patients In view of the respiratory changes noted in the high-dose hepatic group, this may be a group that requires special evaluation in a clinical surgical setting

Recommendations Regarding Labeling
The product information label suggests that these patients may be more sensitive to the pharmacodynamic effects (Page 13) However, on Page 4, there is a statement that suggests that the pharmacodynamics are unaltered I wonder if some data on Et CO_2, respiratory rate, minute ventilation, ventilatory response to hypercarbia should be given in this group of patients Abstract A377, *Anesthesiology* 81, September, 1994, in a smaller group of patients suggests that the EC_{50} may be lower in hepatically impaired subjects and thus these patients may be more sensitive to the ventilatory depressant effects of remifentanil

Study #224. Remifentanil in Hepatic Transplant Patients.

Background
Remifentanil pharmacokinetics were evaluated in patients undergoing hepatic transplantation, during specific phases of the operation.

Clinical Study #224
Remifentanil pharmacokinetics were described prior to and during the anhepatic phase of transplantation. An attempt was also made to assess the contribution of the lung to remifentanil metabolism and finally *in vitro* hydrolysis of remifentanil in whole blood was determined. Six patients aged 31 - 57 years were studied. Remifentanil kinetics were calculated following an IV bolus of 10 mcg/Kg given prior to and during the anhepatic phase of transplantation. Remifentanil and GR90291 concentrations were higher during the anhepatic phase of the procedure. However, as the investigators point out, remifentanil kinetics were difficult to interpret due to the rapidly changing physiological clinical setting.

Efficacy Assessment
No attempt was made to evaluate efficacy.

Safety Assessment
Of the six patients who receive remifentanil, two had adverse events of hypotension.

Conclusions
It is difficult to ascribe pharmacokinetic parameters to such a small number of patients in this clinical setting. However, remifentanil kinetics during the anhepatic phase appear to be similar to kinetics obtained in other situations.

Study #216. Pharmacokinetic and Pharmacodynamic Study in Middle Age and Elderly Volunteers.

Background

Remifentanil was evaluated in middle age and elderly subjects. In addition, the effect of gender on remifentanil pharmacokinetics/dynamics was investigated. The data was also analyzed using data from another identical study in young healthy volunteers to show the effect of advancing age on remifentanil pharmacokinetics/dynamics

Study 216

Fifty subjects: 26 middle-aged (40 - 65 years, 18 male/8female) and 24 elderly subjects aged above 65 years (11 male/13 female) received remifentanil (3 mcg/Kg/min) for up to 15 minutes, according to EEG and hemodynamic criteria. Pharmacokinetic and pharmacodynamic methodology was standard, and used an inhibitory Emax model to describe the EEG effect as it related to remifentanil concentration

The pharmacokinetic parameters and pharmacodynamic effect as assessed by the EEG for remifentanil and its metabolite were shown to change with advancing age when all three groups were subject to analysis. The primarily metabolite, GR90291exhibited altered kinetics in the elderly; an increased AUC and Cmax and an age-related increase in AUC ratio (GR90291 remifentanil) were noted

Remifentanil produced typical μ-opioid effects on the EEG, and spectral edge was used to measure pharmacodynamic effect. The mean time to onset of effect was rapid and similar for all groups (0.8 - 1.1 min). Recovery was slower in the elderly, mean time to baseline for middle-aged subjects was 21.7 - 23.7 min compared to 29.2 - 36.3 mins for the elderly group. Spectral edge EC_{50} (a standard measure of pharmacodynamic effect) was significantly lower for elderly than middle-aged subjects (e.g., 11.7 ± 4.4 versus 8.4 ± 2.7 ng/ml for male volunteers). When the data was combined with an identical study in healthy subjects 18-40 years, linear regression analysis showed that clearance decreased with advancing age, $p<0.0001$. Similarly, Vdss and Vc decreased with increasing age ($p<0.0001$). EC_{50} and t_keo also exhibited a significant age-related decrease

Efficacy Assessment

No attempt was made to evaluate efficacy assessment in this study

Safety Assessment

No serious adverse events occurred, but severe events, such as hypotension, nausea, laryngospasm and tachycardia did occur and required treatment, for example with ephedrine, metoclopramide. 17% of the middle-aged and 18% of the elderly male subjects experienced a severe adverse event. None of the adverse events for middle-aged females were severe, but 8% of adverse events in elderly females were thought to be severe. Four of the six severe adverse events were considered drug-related, such as hypotension, nausea, laryngospasm, and

hypertension/tachycardia Four subjects had clinically significant abnormal ECG recordings during remifentanil infusion Thus, in some patients the rapid onset of effect of remifentanil may produce hypotension In addition, the awakening from remifentanil may be associated with hypertension/tachycardia Peripheral oxygen saturation was measured and appeared to be in an acceptable range

Conclusions

Pharmacokinetic and pharmacodynamic differences do exist for elderly subjects, and it is recommended that both the loading and maintenance infusion doses of remifentanil be reduced, and titrated to individual clinical effect Elderly subjects showed an increased AUC and Cmax for GR90291, and also females compared to males GR90291 is reported to have only 1/4600 the activity of remifentanil in animals, but the significance of delayed elimination of GR90291 was not addressed in this study

General Anesthesia for Inpatients

FDA Consultant Review

NDA #:	**20-630**
Name:	**Remifentanil for injection**
Sponsor:	**Glaxo-Wellcome**
Reviewer:	**Walter L. Way, MD**
Review Date:	**November-January 1995**
Study #:	**203, 204, 205P (P05P), 205 (P05), 220**

Study # 220 *Minimum alveolar concentration (MAC) reduction of isoflurane with remifentanil (R)*

Background

Remifentanil is a potent opioid analgesic of the phenyl-piperidine class which is rapidly metabolized by blood and tissue nonspecific esterases so that drug clearance is rapid with little or no drug accumulation. Onset of action and steady-state concentrations are rapidly achieved. It is reported to have a very short duration of action and is not cumulative over a wide range of infusion doses and times.

Clinical Study

Investigators:

Patient Eligibility:

220 Elective (ASA I-III) surgical patients scheduled for inpatient/outpatient procedures requiring 1-2 inch incision.

Study Objectives:

- Using steady-state (R) blood concentrations (0–32 ng/mL) MAC for isoflurane will be determined.
- To determine maximum isoflurane MAC reduction by (R)

Study Design:

Two-Center, open-label, randomized study. Anesthesia was induced by ventilation of patients with isoflurane in oxygen and a computer-assisted continuous infusion (CACI) of (R) was used to get a target blood concentration. The trachea was intubated aided by succinyl choline. This study was designed to demonstrate the contribution of (R) to the anesthetic state as measured by MAC reduction.

The influence of age on MAC was included and the Dixon up/down method used to adjust end-tidal concentrations of isoflurane. (R) CACI was stopped 2 minutes after skin incision.

Safety Assessments:

- The study drug and intravenous (IV) fluids were administered via one IV site while a second IV site provided access for administration of other medications. Lead II ECG, pulse oximeter, and a radial artery catheter were used in all patients. The arterial line was also used for blood sampling to measure (R) concentrations.

  Protocol Deviations: Nineteen patients had major protocol violations. Five patients were enrolled after receiving a benzodiazepine or alpha agonist prior to surgery. Two patients' surgery was actually a vaginal hysterectomy instead of abdominal hysterectomy, therefore, no true skin incision was made. Steady state isoflurane concentrations were not attained at the time of movement for three patients. The arterial line for collecting blood samples was not inserted in six patients. No blood samples were collected for one patient because the anesthesiologist was unable to intubate the patient with isoflurane alone. **(Don't understand this statement)** Also, no samples were collected for two patients who were withdrawn due to adverse events.

Statistical Analyses:

A logistic regression model was used with log concentrations of (R) and isoflurane as the major independent variables. (SAS 6.07). (R) CACI infusion was assessed using linear regression analysis of the CACI predicted concentration and the observed concentrations which were made from 5 mL. arterial blood samples taken 5 minutes after attaining stable end-tidal isoflurane concentrations, just prior to skin incision, and 2 minutes after skin incision. (R) was analyzed by a GS-MS method.

Summary of Results:

- 173 patients demonstrated that increasing doses of (R) would cause a dose-related decrease of the MAC for isoflurane.
- At a (R) plasma concentration of 1.37 ng/mL (estimated infusion rate – 0.05 mcg/kg/min) MAC of isoflurane was reduced about 50%.
- When (R) plasma concentrations were greater than 4–5 ng/mL, further reduction in MAC was limited.
- Clearance of (R) is not altered by isoflurane.

CONCLUSIONS:

- Initial impact of (R) on isoflurane MAC is quite marked, (Table I) but with increasing concentrations little further reduction is seen. This supports a conclusion that (R) is not a complete anesthetic.

Results: Table 1. Principal Efficacy Results, All Patients (N=173)
Values are %

MAC Reduction for Response to Skin Incision		
Remifentanil Concentration (ng/mL)	MAC of Isoflurane (%)	Isoflurane MAC Reduction (%)
0.0	1.30	–
0.5	1.14	12
1	0.78	40
1.15	0.62	52
2	0.53	59
4	0.36	72
8	0.24	81
16	0.17	87
32	0.11	91

- Clearance of (R) is not altered by isoflurane.

- Muscle rigidity was not a problem with this protocol because anesthesia was being induced as the opioid infusion was being started.

- Although nausea occurred in well over 40% of the patients receiving (R) it also was noted in 42% of patients getting a placebo!!

Study 205 (Double Blind) Effects of a benzodiazepine premedication on the dose-response of remifentanil (R) during anesthesia: induction, maintenance, and recovery

Background

Remifentanil is a potent opioid analgesic of the phenyl-piperidine class which is rapidly metabolized by blood and tissue nonspecific esterases so that drug clearance is rapid with little or no drug accumulation. Onset of action and steady-static concentrations are rapidly achieved. It is reported to have a very short duration of action and is not cumulative over a wide range of infusion doses and times.

Clinical Study

Investigators:

Eligibility: Of the 125 male and female patients (ASA I and II, male and female) selected, 120 were actually studied.

Study Objectives:

- A Pilot Study (205 P) was used to ascertain clinically acceptable doses of remifentanil (R). From these data various bolus and infusion doses of (R) were selected to be used in conjunction with a single dose of a benzodiazepine (temazepam) or a placebo given orally 1 hour prior to surgery. The investigators hoped to determine the impact of temazepam on achieving loss of consciousness (LOC) when used as premedication prior to various bolus and infusion doses of (R).
- Other specific objectives were responses to skin incision, hemodynamic stability, recovery times (time to adequate respiration), and incidence of adverse events.
- Pharmacokinetic data (CL, V, V_{ss}) were generated for both drug and placebo groups. An attempt was made to statistically relate venous (R) concentrations to LOC (response) thus possibly getting the probability of relating drug concentration to response and to determine the LOC - ED_{50}.

Study Design:

120 patients (ASA I and II) were divided into 5 treatment groups as shown in Table 5.

Table 5. Remifentanil Treatment Regimens

Dose Group	Remifentanil Infusion Rate
Group A	2mcg/kg bolus plus 0.05mcf/kg/min infusion
Group B	4mcg/kg bolus plus 0.1mcf/kg/min infusion
Group C	6mcg/kg bolus plus 0.25mcf/kg/min infusion
Group D	8mcg/kg bolus plus 0.5mcf/kg/min infusion
Group E	10mcg/kg bolus plus 1.0mcf/kg/min infusion

Approximately half of each treatment group received either 20 mg temazepam or placebo per OS one hour prior to surgery. Investigators and patients were blinded to receiving or not receiving active premedication. After preoxygenation, the selected iv bolus of (R) was administered over 1 minute and concurrently the continuous iv infusion of (R) was begun. Response to verbal command was evaluated for the next 5 minutes to determine LOC. Administration of propofol was then used to produce LOC in those patients not exhibiting LOC or in those in whom LOC was "fleeting". The trachea was intubated after succinylcholine and the anesthetic was maintained with continued infusion of (R) plus isoflurane in O_2 as needed. After surgical skin closure isoflurane was stopped followed 5 minutes later by the (R) infusion being stopped. Venous blood was taken for pharmacokinetic analysis at baseline, 1, 2, 4, 5, and 10 minutes after (R) infusion stopped.

Safety Assessments Etc.:

Monitoring heart rate (HR) by lead II-EKG, blood pressures (SBP/DBP) by automated device, respiratory rate (RR) by investigator (??)/capnometer, SaO_2 by pulse oximeter, and $P_{ET}CO_2$ by capnometer. Two iv access sites allowed study drug administration separate from fluids and other drugs.

Statistical Analyses:

There was no formal statistical analyses of background characteristics (gender, ASA status, age, weight, etc.) which were presented as tabular summaries. The extended Mantel-Haenszel test was used for pairwise comparisons of all dose groups against the lowest dose group (A). Placebo and temazepam premedication groups were compared, stratifying by dose group. The same statistical methodology was used in evaluating response to skin incision, time to adequate respiration within 10 minutes, and number of patients with moderate/severe muscle rigidity.

Pharmacokinetic analysis of venous blood concentration-time data used nonlinear mixed effects: modeling (nonmem version 4, level 2.0). The pharmacokinetic/pharmacodynamic final model was evaluated with proc probit to get probability listings for concentration and response and determine the EC_{50} for LOC.

Summary of Results:

- LOC is rather inconsistent (0 - 58%) at bolus doses of (R) from 2-10 mcg/kg and infusion doses from 0.05-1.0 mcg/kg/min (See Table I.)

Table 1. Principal Efficacy Results, All Patients (N=120)
Values are N# (% total)

Achievement of Loss of Consciousness (LOC)on Remifentanil Alone		
Remifentanil Dose Group	Placebo (n=62)	Temazepam ((n=58)
A	0/14	0/12
B	1/11 (9%)	4/11 (36%)
C	2/12 (17%)	6/11 (55%)
D	6/12 (50%)	6/12 (50%)
E	5/13 (38%)	7/12 (58%)

Group A 2mcg/kg bolus plus 0.05mcg/kg/min infusion
Group B 4mcg/kg bolus plus 0.1mcg/kg/min infusion
Group C 6mcg/kg bolus plus 0.25mcg/kg/min infusion
Group D 8mcg/kg bolus plus 0.5mcg/kg/min infusion
Group E 10mcg/kg bolus plus 1.0mcg/kg/min infusion

- Temazepam 20 mg increased the likelihood of LOC although this relationship plateaued at Group C (see Table 1).
- Group C doses (Bolus 6 mcg/kg and infusion 0.25 mcg/kg/min) in conjunction with propofol and 0.5 Mac isoflurane provided adequate anesthesia for intubation, skin incision, and surgery.
- Temazepam is reported to not effect the response to skin incision.
- Temazepam prolonged recovery at least as measured by time to adequate (??) respiration.
- Six serious adverse events were reported (see Table 2).

Conclusions:

- The contribution of (R) to the anesthetic state as measured by LOC is quite inconsistent. Although addition of temazepam (20 mg) increased the likelihood of LOC, it never occurred in more that about 50% of patients studied. None of this is surprising given the inability of (R) to act as a complete anesthetic. All patients required propofol and isoflurane to maintain the anesthetic state.
- The conclusions about LOC are made even more difficult since the study really does not clearly define the end point of LOC.
- During the 5-minute period after the bolus and starting infusion of (R) what happened to the patient's respiratory function as measured by $P_{ET}CO_2$ and SaO_2 etc. and what form of artificial ventilation was used if any?

Table 2. Serious Adverse Events, All Patients (N=120)

Patient Number	Sex	Age	Treatment	Event
	M	59	Temazepam + B	Hyperkalemia (Unrelated to remifentanil)
	M	58	Placebo +A	Nineteen hours post-operatively the patient experienced a wound dehiscence which prolonged his hospitalization. The wound was resutured and the condition was resolved six hours later. (U)
	M	24	Placebo +E	During laryngoscopy, eight minutes after infusion of remifentanil was started, the patient developed severe bradycardia considered to be life threatening. He was treated with atropine and laryngoscopy was stopped. Infusion of study drug was continued. His heart rate improved immediately and the bradycardia was reported to be resolved within one minute. (POS)
	F	45	Placebo +A	During surgery, the patient incurred a massive blood loss from the pelvic veins due to a surgical accident. She was given a rapid transfusion of blood, platelets, clotting factors and albumin and the study drug was discontinued. The event was considered life-threatening but the patient made a good recovery. (U)
	F	44	Temazepam +D	Three minutes after intubation, the patient became hypotensive (systolic blood pressure = 40mmHg) and tachycardic with accompanying erythema, vasodilation and generalized urticaria. An anaphylactoid reaction was diagnosed and she was treated with ephedrine, hydrocortisone, IV colloids and chlorphenuramine and her blood pressure recovered. The infusion of remifentanil was continued throughout, but discontinued 20 minutes later when the blood pressure had dropped to 64/49mmHg. The patient experienced transient post-operative periorbital edema for approximately 30 minutes, but she was asymptomatic one hour after anesthesia ended. The anaphylactoid reaction was confirmed to be due to sensitization to succinylcholine. (UL)
	M	22	Placebo +D	During surgery, the patient experienced bradycardia considered to be a non-serious, but drug related event. Post-surgery, nausea and shivering were noted as non-serious events with the latter considered to possibly drug related. Twenty hours after surgery, the patient developed post-operative pyrexia which prolonged his hospital stay. His condition resolved 32 hours later without drug treatment. (U)

U = Unrelated, UL = Unlikely to be repeated, POS = Possibly related to remifentanil

Study # 203 Remifentanil v Alfentanil for Anesthesia Induction

Background

Remifentanil is a potent opioid analgesic of the phenyl-piperidine class which is rapidly metabolized by blood and tissue nonspecific esterases so that drug clearance is rapid with little or no drug accumulation. Onset of action and steady-state concentrations are rapidly achieved. It is reported to have a very short duration of action and is not cumulative over a wide range of infusion doses and times.

Clinical Study

Investigators:

Patient Eligibility: 88 Male/Female ASA I and II, elective surgery patients, aged 18-65 years, recruited for an increasing dose double-blind study comparing Alfentanil (A) with Remifentanil (R).

Study Objectives:

- Compare Remifentanil (R) and Alfentanil (A) as to their contributions to the induction of anesthesia.
- Establish a D-R curve (??) for both (A) and (R)
- Adverse events which are those "symptoms...judged by the investigator to be worse than routine for the type of surgery and anesthesia".

Study Design:

Unpremedicated patients received either (R) (9 doses, 2-20 mcg/kg) or (A) (7 doses, 40-200 mcg/kg) along with oxygen and d-tubocurarine (dose??). Loss of consciousness (LOC) was the endpoint and if not achieved within 30 seconds, thiopental was given until LOC. Definition of the LOC endpoint was lack of response to 3 consecutive verbal commands. A further test in those subjects with LOC after study drug alone was insertion of a nasopharyngeal airway. After completion of the drug infusion subjects were intubated after succinylcholine. N_2O/O_2 and isoflurane were used for maintenance of anesthesia.

Efficacy Assessment:

As expected, the range of drug dose of both (R) and (A) was large [9-22 mcg/kg for (R) and 122-434 mcg/kg for (A)] when this study attempted to define an ED_{50} LOC. Attempts to find an age-related effect (decreased drug dose with increasing age) were not successful.

Safety Assessments:

- Evaluations of pre-treatment (Patient eligibility) and post-treatment histories, physical examinations and laboratory values.
- Continuous monitoring of EKG (Lead II), heart rate, arterial pressure via arterial line which was also used for sampling to measure plasma drug levels.
- Adverse experience reporting.

Statistical Analyses:

Data from both centers were pooled and evaluated using 2-sided p-values summary statistics analyzed with SAS version 6.07 procedures. The ED_{50} for LOC was evaluated by logistic regression. Pharmacokinetics of study drugs was with non-linear mixed effects modeling. Logistic regression analysis was also used to define any relationship between peak concentration and LOC.

Summary of Results:

- The dose-response (D-R) (endpoint-LOC) data demonstrate that (R) is about 15 times more potent than (A) even though the D-R curves for both drugs "demonstrate considerable patient variability when given as a sole induction agent".
- The dose of thiopental decreased as the dose of either (A) or (R) increased when LOC was used as the response endpoint. This relationship failed for a least 2 (R) groups and was attributed to "patient variability".
- A 3-compartment model and 1st order algorithm were used for analysis of both (A) and (R). Supposedly (R) kinetics were unaffected by thiopental.
- Adverse effects with both drugs at any dose included:

	(R)	(A)
muscle rigidity	83%	73%
nausea	63%	71%
vomiting	28%	29%
bradycardia	4%	0%
hypotension	17%	12%

CONCLUSIONS:

- Remifen[illegible]lied in 46 patients produced an uneven dose-response when LOC wa[illegible] pharmacodynamic endpoint. This can be interpreted as good evidence [illegible] cannot reliably produce loss of consciousness and certainly is not anesthetic in and of itself and thus cannot be labeled as a sole induction agent.

- Muscle rigidity was a rather constant finding at all dose levels of (R) with tendency to greater severity as the dose was increased. The anesthesia protocol mentions the use of d-tubocurarine (d-tc) but no dose is given. It is probable that the (d-tc) had little impact on opioid- induced muscle rigidity.

- Nausea (63% of patients) and vomiting (28% of patients) were frequent concomitants of this drug's administrat on.

- This drug is labeled as a selective μ agonist. What evidence supports this conclusion?

Study 205 P (Open) Effects of a benzodiazepine premedication on the dose-response of remifentanil (R) during anesthesia: induction, maintenance, and recovery.

Background

Remifentanil is a potent opioid analgesic of the phenyl-piperidine class which is rapidly metabolized by blood and tissue nonspecific esterases so that drug clearance is rapid with little or no drug accumulation. Onset of action and steady-static concentrations are rapidly achieved. It is reported to have a very short duration of action and is not cumulative over a wide range of infusion doses and times.

Clinical Study

Investigator:

Eligibility: 35 ASA I or II patients, aged 18-65 years, 23 male, 12 female

Study Objectives:

- To determine initial bolus size and infusion rate of (R) that would produce loss of consciousness (LOC) as determined by lack of response to verbal command, and lack of response to intubation and incision.
- NOTE: This was a pilot study to get satisfactory bolus and infusion doses that would allow an assessment of the effects of temazepam pre-medication on induction, maintenance, and recovery from an anesthetic regimen using (R), isoflurane (see review of Study 205 [DB]).

Study Design:

Six center, open-label, dose-finding study of (R) in 35 unpremedicated patients undergoing elective in-patient surgery. All received an iv bolus (B) of (R) over 1 minute and a continuous infusion (I) after which patients were evaluated for 5 minutes to assess LOC. The first 5 patients (Group C-Table 2) received a (B) of (R) of 2 mcg/kg and an (I) of 0.2 mcg/kg/min. Since this did not produce LOC in any patient, propofol (P) 2 mg/kg was added and given over 1 minute. The remaining 30 patients received (R) in a (B) of 2-10 mcg/kg plus (R) at an (I) rate of 0.05-1 mcg/kg/min. This group was then given (P) 1 mg/kg followed by 10 mg/kg every 10 seconds until LOC. In all 35 patients tracheal intubation was facilitated with succinylcholine and maintenance was with isoflurane in O2/air (??) at 1 MAC in Group C and at 0.5 MAC in Groups A, B, and D.

Table 2. Remifentanil Treatment Groups

Group A	2mcg/kg bolus plus 0.05mcg/kg/min infusion
Group B	2mcg/kg bolus plus 0.1mcg/kg/min infusion
Group C	2mcg/kg bolus plus 0.2mcg/kg/min infusion
Group D	10mcg/kg bolus plus 1mcg/kg/min infusion

Efficacy Assessment:

LOC was presumably defined as lack of response to verbal command but no patients in Groups A, B, and C achieved LOC however measured. *In only 50% of those in Group D (highest dose of (R) was it seen.* Propofol was needed for induction with isoflurane in O_2/air (??) plus continued (R) for maintenance. Succinyicholine was used to facilitate tracheal intubation. Patients in Group C were maintained at MAC isoflurane which was lowered to 0.5 MAC in Groups A, B, and D.

Safety Assessments:

- Blood pressure (non-invasive, automated), heart rate (lead II ECG), pulse oximeter, respiratory rate, SaO_2 (pulse oximeter), PCO_{2ET} by capnometer. These vital signs were monitored for some (??) period prior to induction and intubation and up to 2 minutes post-incision.

- Adverse experiences reported included muscle rigidity, frequency of nausea and vomiting, recall of operative events, postoperative pain, and a number of relatively infrequent events.

- No mention of screen and post-treatment of physical examinations and clinical laboratory values could be found in the 205 P Report dated 10/9/95.

Statistical Analyses:

"No formal statistical analyses were performed" (Page 5 of Report), followed by the statement "summary statistic computation and statistical analysis were undertaken using SAS Version 6.08". (??)

Summary of Results:

- In these 35 patients only 5 patients manifested LOC and this was at the highest (R) dose , Group D - Table 2.

- Not surprisingly, the incidence of muscle rigidity was dose related occurring in 80% of patients infused with 1.0 mcg/kg/min (highest dose) in this small patient population.

Conclusions:

- This dose selection study demonstrated a very inconsistent LOC with all doses studies. Even at the highest dose (10 mcg/kg bolus + 1 mcg/kg/min infusion) only 5 of 10 patients demonstrated LOC. It is not explained why the investigators selected a consistent bolus dose (2 mcg/kg) followed by incrementally increasing infusion of (R) and then included a study group receiving a bolus of (R) (10 mcg/kg) and an infusion (1 mcg/kg) both 5 times larger. What consideration was given to dose-response kinetics and dynamics with regard to the selected doses?

- All 35 patients received varying amounts of propofol to achieve LOC providing ample evidence that (R) is not in and of itself an anesthetic.

- The definition of LOC is never clearly stated.

- Were patients given isoflurane in O_2 or air?

- The protocol doesn't clearly identify the isoflurane concentrations. 1.0 MAC is identified for Group C, 0.5 MAC for Groups A, B, and D; but then isoflurane concentrations were used "according to patient requirement". Obviously depending on administered isoflurane concentrations and patient variability the need for (R) may vary!

Study # 204 Dose finding and comparative trial of remifentanil v alfentanil for anesthesia maintenance

Background

Remifentanil is a potent opioid analgesic of the phenyl-piperidine class which is rapidly metabolized by blood and tissue nonspecific esterases so that drug clearance is rapid with little or no drug accumulation. Onset of action and steady-state concentrations are rapidly achieved. It is reported to have a very short duration of action and is not cumulative over a wide range of infusion doses and times.

Clinical Study

Investigators:

Patient Eligibility:

Total of 118 patients (ASA I and II) age 18-64 scheduled for inpatient surgery
57 patients enrolled in the pilot phase which was open-label and dose finding
61 patients in a double-blind, randomized phase.

Study Objectives:

- To develop dose-response (D-R) and plasma concentration-response curves for remifentanil (R) at time of intubation, incision, and skin closure.
- To determine a comparative (one dose alfentanil) safety profile for (R).

Study Design:

Pilot phase was conducted by both investigators (#'s 3409 and 4677) and included 57 patients (??). Induction of all patients, who were unpremedicated, was with propofol 2 mg/kg with vecuronium (0.07-0.08 mg/kg) to facilitate tracheal intubation. The pilot phase was open label at the following bolus doses (administered just after intubation over 1 minute) and infusion rates plus 66% nitrous oxide in oxygen.

Study Medication	Initial Bolus (mcg/kg)	Infusion Rate (mcg/kg/min)
remifentanil	1	Low (0.04)
remifentanil	1	Medium (0.1)
remifentanil	1	High(0.4)
alfentanil	40	0.75

Light anesthesia was treated with (R) 0.5 mcg/kg bolus or (A) 20 mcg/kg bolus plus a 50% increase in the infusion rate. Continued light anesthesia after 2 opioid infusion rate increases was treated with propofol or isoflurane (how they decided which drug or if they could use both is not clear). The double blind portion of the study included the same doses of (R) and (A) listed above and the same anesthetic regimen.

Efficacy Assessment:

Responses to various stimuli (intubation, skin incision, skin closure, and during surgery) manifested by >15% increase in systolic blood pressure, >20% increase in heart rate, somatic or autonomic responses (lacrimation, flushing, tearing).

Safety Assessments:

- Direct arterial measurement of blood pressure.
- Arterial sampling for blood concentrations of study drug.
- Continuous ECG Lead II.
- Evaluation of screen and post-treatment clinical laboratory values, physical examinations, ECG assessments.
- Adverse experience reporting.

Statistical Analyses:

Log regression analysis was used to determine ED_{30}, ED_{50}, ED_{80}, and their respective 95% confidence intervals for intubation and skin incision for (R). Two-sided P-values were used for all statistics. Pharmacokinetic analysis of concentration-time data was with a least squares regression analysis program (penonlin vo4.2) EC_{50} for both (R) and (A) used PC SAS/PROC LOGISTIC/v.6.08.

Summary of Results:

- Most of the results were generated by investigator #4677 who participated in both pilot and double-blind phases although where the exact data originated for various parts of #204 is hard to determine. See following Tables 1, 2, and 3. Where N for skin incision/intubation is 88, 61 for skin incision and 118 for all adverse events.

Table 1. EC_{50} for Skin Incision/Intubation, Pilot and Double-Blind Phase, Investigator 4677

Values are estimate, (95% confidence interval)

PD Parameters	Pilot and Double Blind Phase, Investigator 4677 only	
	Remifentanil	Alfentanil
	N=67	N=21
EC_{50}, Intubation (ng/mL)	2.04 (1.03, 5.34)	110.96 (no estimate)
EC_{50}, Skin Incision (ng/mL)	1.50 (0.41, 2.75)	86.71 (no estimate)

Table 2. Response to Skin Incision Estimated ED_{50}/ED_{80}, Double blind Phase, N = 61

	ED_{50} (mcg/kg/min)	ED_{80} (mcg/kg/min)
Response to Skin Incision	0.11	0.47

Table 3. Adverse Events, All Patients, N = 118
Values are N (%)

	Remifentanil			Alfentanil
	Low	Medium	High	
N	36	28	32	22
Any Adverse Event	32 (89%)	23 (82%)	32 (100%)	20 (91%)
Nausea	23 (64%)	17 (61%)	25 (78%)	15 (68%)
Vomiting	15 (42%)	10 (36%)	16 (50%)	10 (45%)
Hypotension	3 (8%)	4 (14%)	4 (13%)	0
Bradycardia	0	4 (14%)	2 (6%)	0

Low = 0.0125, 0.025, 0.04, and 0.05 mcg/kg/min
Medium = 0.1 and 0.3 mcg/kg/min
High = 0.4, 0.6, and 1.0 mcg/kg/min
Alfentanil = 0.5, 0.75, 1.0 mcg/kg/min

- No muscle rigidity was seen which is quite understandable since no opioid was administered until patients had received an induction dose of propofol plus the neuromuscular blocking drug vecuronium (0.07–0.08 mg/kg).

- A number of pharmacokinetic parameters were determined for both (R) and (A). See Table 15, Page 12, Protocol #204. Note the population sizes vary considerably. Pharmacodynamic estimates of probability of no response to intubation and skin incision were prepared for data (89 patients) from Investigator #4677.

- Two (R) patients experienced intermittent bradycardia and hypotension and one (A) patient had prolonged nausea.

CONCLUSIONS:

- The ED_{50}'s for (R) (Investigator #4677) reported for intubation and skin incision must be considered as relative values since propofol, vecuronium, and nitrous oxide were part of the anesthetic management. How did the investigators know that vecuronium effects were terminated?

- Not surprisingly, the lower the dose of (R) (both bolus and infusion) the greater need for the "rescue": anesthetics propofol and/or isoflurane.

- No significant changes in screen and post-treatment clinical laboratory and physical examination are reported.

- Adverse events usual with opioids are reported at rates that are dose related. Particularly noteworthy is the high incidence of nausea (average 68%) and vomiting (average 36%) at all 3 doses.

General Anesthesia for Outpatients

FDA Consultant Review

NDA #:	**20-630**
Name:	**Remifentanil for injection**
Sponsor:	**Glaxo-Wellcome**
Reviewer:	**Matthew B. Weinger, M.D.**
Review Date:	**November-January, 1995/96**
Study #:	**212, 225 (P25), 228 (2028), 229 (2029), 303 (3003), 308 (3008)**

USA308: Remifentanil vs. Alfentanil with Propofol in Laproscopic Surgery

Experimental Design This was a multicenter, randomized, double-blind study designed to compare the intraoperative stability and recovery profile of remifentanil versus alfentanil when combined with propofol for total intravenous anesthesia for outpatient laproscopic surgery. A total of 222 healthy women (and one man), aged 18-51 years, were enrolled in the study and 200 were randomized to receive either remifentanil (n=157) or alfentanil (n=66). Following midazolam (1 mg) premedication and pre-oxygenation, patients were induced with propofol (2 mg/kg followed by a 150 µg/kg/min infusion). A bolus followed by a continuous infusion of study drug was then administered (see **Table 1**). Endotracheal intubation was facilitated with the use of vecuronium. Five minutes after laproscopic trocar insertion, the study drug infusion rate was reduced (see **Table 1**) as was the propofol infusion (to 75 µg/kg/min).

Signs of light anesthesia were treated with boluses or increases in the opiate infusion rate. If two successive opiate drug titrations were unsuccessful to treat an event then rescue propofol was administered. Propofol was also admiminstered if the maximum allowable opiate infusion rate was reached (remifentanil 1 µg/kg/min or alfentanil 4 µg/kg/min). Hypotension (SBP<80 for _1 min) was initially treated with a reduction in the opiate infusion. Bradycardia (HR<40 for _1 min) was initially treated with glycopyrrolate and then, if unsuccessful, by a reduction in the opiate infusion.

Ten minutes prior to the end of surgery, a new study drug syringe was substituted. This allowed, in a blinded manner, for the alfentanil infusion to be discontinued at this time while the remifentanil was continued until the completion of surgery. Propofol was discontinued a median of 4 minutes prior to the end of surgery and the neuromuscular blockade was pharmacologically antagonized. Times to response to verbal command, extubation, return of respiratory function and discharge were recorded. Trieger Dot and Digit Symbol Substitution tests were used to assess quality of recovery.

Table 1

Group	Bolus dose (μg/kg)	Initial Infusion Rate (μg/kg/min)	Infusion Rate 5 min Post-trocar Insertion	Mean Final Infusion Rate (μg/kg/min)
Remifentanil	1	0.5	0.25	0.26 ± 0.07
Alfentanil	20	0.5	1	1.2 ± 0.45
Potency Ratio	20	4	4	4.6

Major Results. The time to adequate respiration upon completion of surgery was not different between the two groups (median of 3 min) The recovery profile of the two groups was not appreciably different showing similar times to initiation of spontaneous ventilation, extubation, and qualification for PACU discharge The incidence of significant perioperative hypotension (11%) and bradycardia (7%) were similar Overall, 54% of the patients experienced postoperative nausea, 30% had vomiting, and 27% required postoperative ondansetron therapy (no differences between groups) The remifentanil patients appeared more awake than the alfentanil patients at 60 and 90 min post-anesthesia although the differences observed were not large

Efficacy and Safety. Almost three times as many patients in the alfentanil group (32%) responded to initial surgical stimuli compared with those in the remifentanil group (11%, P<0 001) Only two remifentanil patients (and none in the alfentanil group) had opiate-induced muscle rigidity Intraoperative awareness occurred in two cases (one in each group), in both, there was a malfunction of the propofol infusion pump Blood pressure was significantly lower in the remifentanil group throughout much of the anesthetic Heart rate was significantly lower in the remifentanil patients from the time of intubation until trocar insertion Thereafter, there were no statistically significant differences in heart rate between the two groups 18% of the patients in the alfentanil group required small propofol rescue during the maintenance phase of the case compared with only 9% of remifentanil patients More than twice as many of the patients in the remifentanil group (76%) required postoperative analgesic therapy with parenteral opiates (fentanyl) when compared with those in the alfentanil group (35%) Thirteen percent of the remifentanil patients but none of the alfentanil patients exhibited post-operative shivering

Analysis. As in Study 303, it appears that a more potent dose of remifentanil than alfentanil was administered during the anesthetic This is demonstrated by the fact that the remifentanil patients had lower blood pressure and heart rate values and required fewer supplemental propofol doses to treat light anesthesia However, the differences in perioperative responses between the two drug groups were less than in Study 303 probably because a proportionally higher alfentanil infusion rate was used (1 μg/kg/min instead of 0 5 μg/kg/min, a ratio of 4 instead of 2 based on a remifentanil infusion rate of

0.25 μg/kg/min) On the other hand, as a consequence of the higher alfentanil infusion rates, a comparable percentage of patients in the two groups responded to skin closure (despite the alfentanil being stopped 10 minutes before the end of surgery) or experienced significant hypotensive or bradycardic adverse events.

Because propofol rather than isoflurane (Study 303) was employed as the sedative-hypnotic in this study, postanesthetic recovery times were overall much faster than in Study 303. Since the remifentanil and alfentanil doses in this study were more similar (i.e., equipotent) than in Study 303, one might have expected the patients receiving remifentanil, the shorter acting opiate, to exhibit faster recoveries. In fact, with the exception of some minor differences favoring remifentanil in sedation and psychomotor scores at 60-90 min postanesthesia, the recovery profiles of the two drugs were quite similar. However, these results must be interpreted with consideration of the fact that, in contrast to Study 303, alfentanil was terminated 10 minutes prior to surgery while the remifentanil was continued until surgical completion.

On the other hand, the more rapid elimination of remifentanil's opiate effects was reflected in the higher incidence of postoperative shivering and the earlier (and greater) requirement for parenteral postoperative analgesia observed in the remifentanil patients.

Although the overall incidence of postoperative nausea/emesis was similar in the two groups, the remifentanil patients tended to experience these symptoms earlier during the postoperative period than did the alfentanil patients. In addition, the greater use of parenteral opiate analgesics in the PACU in the remifentanil group may have actually increased the incidence of postoperative nausea/vomiting in the remifentanil patients.

One of the dangers of the opiate-propofol-relaxant total intravenous anesthetic technique employed in this study is the risk of intraoperative awareness if insufficient propofol is administered. This occurred in two cases in which the propofol infusion pump malfunctioned.

Conclusions. Overall, this study demonstrates that total intravenous anesthesia employing propofol in combination with either remifentanil or alfentanil for laproscopic outpatient surgery is an effective technique with similar hemodynamic and recovery profiles. Remifentanil may more effectively block the hemodynamic responses to surgery without having to pay the price of a delayed emergence, respiratory depression, or residual psychomotor impairment. The more rapid dissolution of remifentanil's opiate effects in the early postoperative period will more frequently necessitate additional opiate therapy for the management of shivering and for postsurgical pain

USA303: Remifentanil vs. Alfentanil with Isoflurane in Outpatient Surgery

Experimental Design This was a multicenter, randomized, double-blind study designed to compare the recovery profile, efficacy, and safety of remifentanil versus alfentanil when combined with isoflurane 0.8% in air/oxygen during brief outpatient surgery A total of 201 patients (equal gender distribution), aged 18-65 years, healthy primarily caucasian patients were enrolled in the study and randomized to receive either remifentanil (n=102) or alfentanil (n=99) Glycopyrrolate (0.1-0.2 mg) preceded pre-oxygenation. Study drug was started as an initial bolus and a simultaneous continuous infusion (see **Table 1** below) Propofol was then administered in 10 mg increments every 10 seconds until LOC occurred. Isoflurane was started at 2% and vecuronium was administered to facilitate intubation. Following intubation, the isoflurane concentration was reduced and maintained at 0.8% end-tidal. Signs of light anesthesia (SBP/HR increases, somatic or autonomic signs) were treated with bolus doses (remifentanil 1 mcg/kg or alfentanil 5 mcg/kg) and doubling of the study drug infusion rate A NSAID suppository was used for post-operative pain control. Both the isoflurane and the opioid infusion were discontinued at the completion of surgery. Times to response to verbal command, extubation, return of respiratory function and discharge were recorded Trieger Dot and Digit Symbol Substitution tests were used to assess quality of recovery

Table 1

Group	Bolus dose (μg/kg)	Initial Infusion Rate (μg/kg/min)	Mean Infusion Rate (μg/kg/min)
Remifentanil	1	0.25	0.252 ± 0.024
Alfentanil	25	0.5	0.559 ± 0.206
Potency Ratio	25	2	2.22

Major Results. The median time for recovery of response to verbal command was 9 versus 7 minutes, for the remifentanil and alfentanil groups, respectively (p=0.06). The median time for resumption of spontaneous respiration was 8 versus 5 minutes (p<0.05), and for attainment of adequate spontaneous respiration it was 9 versus 6 minutes, respectively, all favoring alfentanil (p<0.05) In contrast, psychometric and psychomotor function at 30 minutes postoperatively seemed to be slightly better in the remifentanil group

Efficacy and Safety. Significantly more alfentanil patients experienced one or more responses to surgical stimulation (66% vs 53%, p<0.02) On the other hand, there was a greater incidence of perioperative hypotension and of postoperative shivering in the remifentanil group The incidence of perioperative bradycardia (<10%) and of post-operative nausea/emesis (~20%) was similar between the two study groups

Analysis. Several findings suggest that the opiate drug doses chosen for comparison in this study were not equipotent, the remifentanil dose was more potent than the alfentanil dose against which it was compared The remifentanil patients tended to have lower blood pressure values throughout the case In fact, there was a significantly higher incidence of hypotension in the remifentanil patients (15% vs 2%, respectively, p=0 001) Four patients in the remifentanil group but none in the alfentanil group required ephedrine treatment for hypotension during the maintenance phase In addition, almost twice as many remifentanil patients exhibited one or more instances of "excessive anesthesia" Consistent with these results, significantly more alfentanil patients required one or more unscheduled opiate bolus doses or infusion rate increases (57% vs 41%, respectively, p=0 03) for inadequate anesthesia Finally, at the end of the case, twice as many patients responded to skin closure in the alfentanil group (22 vs 11%, p<0 05)

These findings have important implications for the interpretation of the recovery data If, indeed, more remifentanil was administered intraoperatively, this would tend to bias the recovery phase in favor of alfentanil This might explain the failure of this study to demonstrate a faster recovery from remifentanil anesthesia despite its more rapid elimination when compared with alfentanil

However, several other methodological factors should also be mentioned First, the isoflurane was continued in both groups until the end of surgery To the extent that recovery was influenced by the rate of elimination of isoflurane, this could have blurred any differences between the two study drug groups In addition, increased ventilatory depression caused by a more potent dose of remifentanil at the end of the procedure could have limited isoflurane elimination in this group

Finally, it is important to note that both alfentanil and remifentanil were discontinued at the conclusion of the surgery However, in standard use, alfentanil infusions would typically be terminated at least several minutes prior to the completion of surgery

The lower incidence of bradycardia observed in this study compared with previous, Phase II studies, reflects the pre-induction administration of glycopyrrolate and, probably, the known effect of isoflurane on heart rate in young healthy patients The higher incidence of postoperative shivering observed in the remifentanil patients probably reflects a more rapid elimination of this opiate compared with alfentanil in the immediate postoperative period

Conclusions. Overall, this study demonstrates that anesthetics employing remifentanil and alfentanil, when administered as an infusion in combination with isoflurane in air/oxygen for brief outpatient anesthetics, exhibit similar recovery profiles The design of the present study, however, may have biased the results to understate the speed of recovery from remifentanil-based anesthesia
Remifentanil may be associated with a greater incidence of hypotension, however, this must be substantiated by a study in which the two opiates are administered in an equipotent dose

USA212: Remifentanil vs. Alfentanil in Outpatient Nitrous-Narcotic Anesthesia

Experimental Design. This was a randomized single-blind study comparing remifentanil with alfentanil as an infusion in 105 young ASA 1 or 2 female patients undergoing laproscopic bilateral tubal ligation procedures as outpatients. Patients received either remifentanil (1 µg/kg bolus followed by 0.1 or 0.4 µg/kg/min infusion) or alfentanil (20 µg/kg bolus followed by 1 µg/kg/min infusion). Propofol was given in 40 mg increments until loss of consciousness. Mivacurium was given for intubation. Anesthesia was maintained with opiate infusion plus 66% N_2O in oxygen. Signs of light anesthesia were treated with remifentanil 0.5 µg/kg bolus and/or 0.05 µg/kg/min infusion increase or alfentanil 10 µg/kg bolus and/or 0.5 µg/kg/min infusion increase. Hypotension or bradycardia were initially treated by reduction of the opiate infusion rate. Alfentanil was decreased to 0.5 µg/kg/min at the commencement of the sterilization and discontinued at the end of the procedure. Remifentanil and nitrous oxide were terminated at the end of procedure.

Group	Bolus dose (µg/kg)	Initial Infusion Rate (µg/kg/min)	Ending Infusion Rate (*median* µg/kg/min)
Remifentanil 0.1	1	0.1	0.15
Remifentanil 0.4	1	0.4	0.4
Alfentanil	20	1	0.5
Potency Ratio	20	2.5-10	1.25-3.33

Major Results. Overall, throughout the case, the patients in the Remi 0.4 group had lower blood pressure values, had fewer hemodynamic, autonomic, or somatic responses to noxious anesthetic (i.e., laryngoscopy and intubation) or surgical stimuli, and required fewer supplemental bolus doses of opiate or of "rescue" doses of propofol. On the other hand, 26% of the patients in the Remi 0.4 group required at least one reduction in infusion rate during the case (predominantly due to heart rates less than 45 beats/min) compared with only 3% in either of the other two groups. Recovery from anesthesia was rapid in all three treatment groups and occurred at comparable rates. Post-operative side-effects were also similar among the treatment groups. The Remi 0.1 group had earlier and greater post-operative analgesic requirements. There was a high incidence of post-operative nausea and vomiting in all three groups.

Efficacy and Safety. A 0.1 µg/kg/min infusion of remifentanil appeared to have similar efficacy to a 0.5 µg/kg/min infusion of alfentanil in this patient population undergoing this surgical procedure. Remifentanil 0.4 µg/kg/min was more effective at blocking response to noxious stimuli without adversely affecting recovery time. However, the higher remifentanil dose was associated with more bradycardia and hypotension. Remifentanil otherwise demonstrated a similar side-effect profile to that of other potent mu agonists.

Analysis. A number of methodological issues must be considered in the interpretation of the results of this study. This was a single-blind study so that the investigators apparently knew which study drug (and dose) was being administered (although the post-operative evaluation was

performed by a blinded investigator). Thus, despite the use of pre-defined intraoperative management criteria, the possibility of the introduction of investigator bias can not be excluded.

There were a number of protocol violations including one patient with a history of chronic benzodiazepine use who received three 10 mg doses of prazepam on the evening before and morning of surgery. Two patients in the Remi 0.4 group inadvertently received only 50% of the correct concentration of remifentanil in their infusions. All three of these subjects' data were included in all of the analyses.

The variable use of propofol between groups complicates the interpretation of the effects of the opiates on the response to surgical stimuli. Propofol rescue doses were administered by the investigators prematurely (i.e., before two rate increases of study drug as stipulated by the protocol) between the time of skin incision and 1 minute after trocar insertion in 7 patients (20%) in the Remi 0.1 group and 9 patients (26%) in the Alfentanil group.

It is troubling that the final infusion rates in the two remifentanil groups did not converge toward each other to a greater extent. One would have expected that the higher incidence of patient responses in the Remi 0.1 group and the higher incidence of bradycardia/hypotension in the Remi 0.4 group would, over the course of the anesthetic, cause the care providers to titrate the remifentanil dose to an intermediate level. In contrast, more than three-quarters of the subjects' final infusion rates in both groups were within 0.05 µg/kg/min of their starting rates. This discrepancy may have been due to short-comings in the experimental protocol (e.g., restrictions in the titratibility of the opiate infusions), propofol "rescue", significant patient variability in response to remifentanil, and/or other, unknown factors.

Alfentanil was discontinued at the time of sterilization while the remifentanil was discontinued (along with the nitrous oxide) at the conclusion of the surgery (median difference 3 minutes). This difference in timing may have been responsible for the higher incidence of response to skin closure in the Alfentanil group and may have masked a relatively more rapid awakening in the remifentanil groups.

Additionally, the failure to attain similar intraoperative response and hemodynamic profiles among the three groups makes comparison of the respective recovery characteristics of the three treatment groups problematic.

Conclusions. In this study of anesthesia for laproscopy, remifentanil 0.4 µg/kg/min effectively blunted the hemodynamic response to surgery, although this infusion rate also produced bradycardia and hypotension. In contrast, an infusion of Remi 0.1 µg/kg/min frequently required supplementation yet was associated with less cardiovascular depression. These results suggest that a remifentanil infusion rate between 1 and 4 mcg/kg/min, in combination with 66% nitrous oxide may be optimal for maintenance of anesthesia in young women undergoing laproscopic outpatient procedures. Overall, the recovery profile of remifentanil is at least comparable to alfentanil when administered in the manner described.

USA225: Spontaneous Ventilation using Remifentanil with Isoflurane/Nitrous Oxide

Experimental Design This was a single center open-label dose-escalation study of healthy primarily male patients undergoing outpatient surgery (median duration 41 min). The initial protocol stipulated the use of 1% end-tidal isoflurane in nitrous oxide with remifentanil infusion rates doubling at fixed intervals until respiratory depression occurred. However, after studying three patients, this protocol proved untenable due to profound respiratory depression and an amended protocol was substituted. Patients were induced with incremental doses of propofol until loss of consciousness occurred and then a laryngeal mask airway was inserted. 1% end-tidal isoflurane in 66% nitrous oxide was maintained until skin incision and then the end-tidal isoflurane was reduced to maintain a concentration of 0.5% (±10%) with the patient breathing spontaneously. A remifentanil infusion was started at 0.05 µg/kg/min and was then titrated upward in 0.05 µg/kg/min increments every 5 minutes. Respiratory depression, the primary "efficacy" endpoint was defined as a respiratory rate of _8 for _1 minute. However, if the end-tidal CO_2 was >55 torr then manual ventilation was instituted.

Major Results. The calculated mean infusion rate at which respiratory depression occurred was 0.125 µg/kg/min with a statistically estimated ED_{50} of 0.087 µg/kg/min. However, review of **Figure 1** suggests an somewhat higher ED_{50} value between 0.10 and 0.15 µg/kg/min. All of the patients experienced appreciable bradypnea by the time the remifentanil infusion rate was increased to between 0.15 and 0.2 µg/kg/min. Following this dose-titration analysis, the majority of the patients (58%) were able to be maintained with adequate spontaneous ventilation with remifentanil infusion rates of between 0.025 to 0.050 µg/kg/min. The hemodynamic and respiratory profile of patients maintained on remifentanil with spontaneous ventilation at 15 min post-incision is shown in **Table 1**. Twelve of the 14 patients required manual (assisted) ventilation at least once during the procedure (57% due to apnea, 29% due to SpO_2<90%, and 14% due to $P_{ET}CO_2$>60 torr)

Table 1. Vital Signs Profile of 12 Spontaneously Ventilating Patients Receiving Remifentanil in Combination with 0.5% Isoflurane and 66% N_2O.

Variable	Value (mean±SD)
Systolic Blood Pressure	113 ± 11 torr
Diastolic Blood Pressure	61 ± 11 torr
Heart Rate	67 ± 14.7 beats/min
Respiratory Rate	8 ± 3.6 breaths/min
S_pO_2	95 ± 2.6 %
End-tidal CO_2	53 ± 6.2 torr
Mean remifentanil rate	?? µg/kg/min

Efficacy and Safety. Despite the use of an amended protocol, the study was terminated early (14 out of a planned 20 subjects) because the investigator felt that the protocol was not optimal for predicting the remifentanil infusion rate associated with respiratory depression. Furthermore, the investigator felt that this combination of anesthetic agents may have caused an undesirable incidence of significant cardiovascular depression (5 of 14 patients) during maintenance anesthesia.

The most common adverse events were bradycardia (35%), shivering (19%), hypotension (18%), and nausea (18%). Four patients required atropine therapy for bradycardia. None of the patients developed muscle rigidity or had recall of any events during anesthesia or the surgical procedure.

One patient experienced a serious adverse event due to an inadvertent overdose of remifentanil (approximately 0.25 ml) which was the consequence of flushing an occluded intravenous cannula. This patient received an accidental bolus dose of approximately 23 µg (0.35 µg/kg). The resultant bradycardia, progressing to third degree heart block, with associated modest hypotension (SBP 90 torr) required treatment with atropine (0.6 mg twice) in addition to termination of the remifentanil infusion.

Analysis. The experimental design of this study limits the usefulness of the data. Several confounding factors can be identified: 1) The remifentanil infusion was started after skin incision without a loading bolus dose so that at 5 minutes after starting the infusion, at the time of the first titration increment, steady state plasma levels may not have been achieved, 2) The titration steps were too rapid for an accurate correlation of infusion dose and thus, plasma concentration to observed effects on respiratory rate; 3) The dose-response curve was based on cumulative dosing at too frequent intervals and too small of dose increments, 4) Respiratory rate alone was used as an indicator of ventilatory depression, and 5) The hemodynamic and respiratory data presented are based only on patients not yet meeting the primary efficacy criteria. Thus, the resultant calculated values for remifentanil ED_{50} to produce respiratory depression are of dubious validity.

Conclusions. Despite the limitations of this study, it does provide some general information about the impact of the addition of low doses of remifentanil by infusion to an existing isoflurane/nitrous oxide anesthetic. It is apparent that under these circumstances remifentanil infusion rates as low as 0.05 µg/kg/min can produce significant respiratory depression and well as bradycardia and hypotension. In addition, the incident in which a relatively small volume (~0.25 ml) of remifentanil was accidentally administered while attempted to clear an occluded intravenous catheter suggests that serious complications might be prevented in the future if remifentanil was provided in a less concentrated solution.

USA228: Remifentanil with Isoflurane for Spontaneous Ventilation Anesthesia

Experimental Design. This was a two center, open label, randomized, parallel group dose-ranging study of remifentanil in 63 healthy (94% ASA I), Caucasian (84%), patients scheduled for outpatient surgery. The purpose of this study was to assess the incidence of respiratory depression, hemodynamic stability, time to recovery and anesthetic dose requirements when remifentanil was added to an isoflurane/oxygen/air anesthetic in patients breathing spontaneously via a laryngeal mask airway. Patients were all pretreated with glycopyrrolate (generally 0.2 mg) and a 5 ml/kg intravenous fluid bolus. Patients were then randomized to receive one of four remifentanil dose regimens consisting of a Bolus (B: µg/kg) followed by a continuous infusion (I: µg/kg/min): 1) 0.125 B + 0.025 I; 2) 0.25 B + 0.05 I; 3) 0.375 B + 0.075 I; or 4) 0.5 B + 0.1. Three minutes later, patients received propofol 10 mg every 10 seconds until loss of consciousness and a laryngeal mask airway was then inserted. Isoflurane (~1% end-tidal) in oxygen-enriched air was then added for the maintenance of anesthesia. After skin incision, the remifentanil infusion was titrated downwards in pre-defined steps whenever respiratory depression (defined as a respiratory rate less than 8 breaths/min for _1minute and/or $P_{ET}CO_2$ >55 mmHg) occurred. Inadequate anesthesia was treated with increases in the isoflurane concentration and/or boluses of propofol.

Major Results. The data from the two study sites could not be combined for statistical analysis because of marked differences between sites in the results obtained. For example, there was a much higher incidence of respiratory depression between the time of loss of consciousness and skin incision in the two lowest remifentanil infusion dose groups (0.025 and 0.05 µg/kg/min) at one study site compared with the other. In addition, there appeared to be appreciable variability in some of the results across treatment group such that dose-dependent remifentanil effects were difficult to discern. For example, the dose of remifentanil upon anesthetic induction did not affect the dose of propofol required for LOC.

Nevertheless, there was a higher incidence of somatic responses to surgical stimulation at the lower remifentanil doses, 31% of the patients in the remi 0.025 group moved in response to skin incision whereas only one patient moved in either of the two highest dose groups. Perioperatively, hypertension (SBP>15 torr above preoperative baseline for _1 minute) was more likely in the two low dose groups (28%) compared with the two high dose groups (10%). On the other hand, patients in the two higher dose groups were much more likely to require reductions in the remifentanil infusion rate due to respiratory depression (see **Table 1** below).

By the end of the procedure, the majority of patients (_73%) had adequate spontaneous ventilation at a mean remifentanil infusion rate of between 0.025 and 0.05 µg/kg/min (with a mean end-tidal isoflurane concentration of approximately 1%). The mean remifentanil infusion rate in the three highest dose groups were, by this time, very similar.

Efficacy and Safety. Even at the lowest remifentanil dose studied, 62.5% of the patients manifested respiratory depression during the interval between induction of anesthesia and skin incision Respiratory depression was, in fact, a common occurrence throughout the anesthetic period. In addition, the ventilation of 8 patients (13%) was still depressed at the end of surgery despite all but one being at a remifentanil infusion rate of only 0.025 µg/kg/min.

Muscle rigidity occurred in 6 patients (10%) and neither the incidence nor severity appeared to be dose-related (although the one episode of severe rigidity did occur in the highest dose group) Hypotension, defined as a SBP_80 for _1 min, occurred in 11% of patients (across all dose groups) during remifentanil administration. Bradycardia (HR<40 for _1 min) was uncommon (5%) although heart rate values less than 50 were not unusual Across all treatment groups, only 5% of patients experienced postoperative nausea or emesis

Analysis. The inability to discern a dose-effect relationship between remifentanil treatment and the incidence of respiratory depression could have been due to by several confounding factors. The study design allowed appreciable investigator discretion over isoflurane and propofol dosing and these appeared to vary both between study sites and, in the case of propofol, across treatment groups. A distinction of any direct effects of remifentanil on respiratory depression may have been most clearly observed after skin incision However, at this time, the remifentanil infusion was titrated downwards by protocol if respiratory depression persisted, thus obviating any potential assessment of dose-effect relationships

In contrast to previous studies, the incidence of bradycardia and hypotension were quite low This was probably due to the combination of fluid loading and anticholinergic pretreatment as well as the use of isoflurane and/or propofol (rather than remifentanil) to treat light anesthesia In contrast to other outpatient remifentanil studies, the very low incidence of postoperative nausea and emesis was notable and may be due to a number of factors including the predominantly male subject population, absence of nitrous oxide or muscle relaxants (or reversal), use of propofol, etc

Conclusions. Remifentanil in combination with isoflurane in oxygen-enriched air can be used successfully for spontaneous ventilation anesthesia Overall, a starting dose of less than 0.05 mcg/kg/min may be expected to be associated with a lower incidence of respiratory depression compared with higher doses although appreciable patient variation may be expected However, even remifentanil infusion rates as low as 0.025 µg/kg/min may cause significant respiratory depression when combined with 1% end-tidal isoflurane in air/oxygen in healthy patients under LMA anesthesia

Table 1.

Event	Remifentanil Infusion Rate (mcg/kg/min)		
	0.025 (N=16)	**0.05 (N=16)**	**0.075 and 0.10 (N=31)**
Respiratory depression at the time of skin incision	5/14 (36%)	9 (56%)	29 (94%)
Gross movement response to skin incision	5 (31%)	2 (13%)	1 (3%)
Number (%) of patients requiring at least one decrease in the remifentanil infusion rate (due to respiratory depression)	0	6 (38%)	28 (90%)
Number (%) of patients requiring increase in isoflurane	7 (44%)	5 (31%)	6 (19%)
Mean remifentanil infusion rate at end of surgery Mean ± SD (Range)	0.025±0.000 (0.025-0.025)	0.041±0.012 (0.025-0.050)	0.042± ??? (0.024-0.098)

USA229: Remifentanil with Propofol for Spontaneous Ventilation Anesthesia

Experimental Design This was a two center, open label, randomized, parallel group dose-ranging study of remifentanil in 64 healthy (84% ASA I), Caucasian (100%), patients scheduled for outpatient surgery. The purpose of this study was to assess the incidence of respiratory depression, hemodynamic stability, time to recovery and anesthetic dose requirements when remifentanil was added to a propofol infusion in patients breathing oxygen/air spontaneously via a laryngeal mask airway. The protocol was quite similar to that of OUTPATIENT STUDY #3 (USA228) except that propofol was employed instead of isoflurane. Patients were all pretreated with a 5 ml/kg intravenous fluid bolus and were then randomized to receive one of four remifentanil dose regimens consisting of a Bolus (B: µg/kg) followed by a continuous infusion (I: µg/kg/min): 1) 0.125 B + 0.025 I; 2) 0.25 B + 0.05 I; 3) 0.375 B + 0.075 I; or 4) 0.5 B + 0.1. Three minutes later, patients received propofol at a rate of 50 mg/min until loss of consciousness and a laryngeal mask airway was then inserted. A propofol infusion was begun at a rate of 100 µg/kg/min. The remifentanil infusion was maintained at a constant rate until skin incision and thereafter could only be titrated downwards in pre-defined steps in response to respiratory depression (defined as a respiratory rate less than 8 breaths/min for _1 minute and/or $P_{ET}CO_2$ >55 mmHg) occurred. Inadequate anesthesia was treated with boluses of propofol and adjustments in the propofol infusion rate.

Major Results. The data from the two study sites could not be combined for statistical analysis because of marked differences between sites in the results obtained. For example, there was a much higher incidence of respiratory depression between the time of loss of consciousness and skin incision in the two lowest remifentanil infusion dose groups (0.025 and 0.05 µg/kg/min) at one study site compared with the other (Note that two different institutions were involved in this study than in USA 228). In addition, there appeared to be appreciable variability in some of the results across treatment group such that dose-dependent remifentanil effects were more difficult to discern. For example, the dose of remifentanil upon anesthetic induction did not affect the dose of propofol required for LOC.

Nevertheless, there was a higher incidence of somatic responses to surgical stimulation at the lower remifentanil doses, 88% of the patients in the remi 0.025 group moved in response to skin incision whereas only 33% moved in the three higher dose groups combined. Perioperatively, less total propofol was required during the maintenance phase in the Remi 0.075 and 0.10 µg/kg/min dose groups although the incidence of propofol rescue was not appreciably different between groups. Across all treatment groups, intraoperative hypertensive episodes occurred in 28% of patients.

By the end of the procedure, the majority of patients (_76%) had adequate spontaneous ventilation at a mean remifentanil infusion rate of between 0.026 and 0.053 µg/kg/min. The remifentanil infusion rate in the three highest dose groups were, by this time, very similar. Concurrently, the final propofol infusion rate ranged from 116 µg/kg/min in the Remi 0.10 µg/kg/min group to 140 µg/kg/min in the Remi 0.025 µg/kg/min group.

Efficacy and Safety. At the lowest remifentanil dose studied, 44% of the patients manifested respiratory depression during the interval between induction of anesthesia and skin incision. Respiratory depression was, in fact, a common occurrence throughout the anesthetic period ranging in incidence from 56% in the lowest dose group to 100% in the highest dose group. In addition, the ventilation of 8 patients (13%) was still depressed at the end of surgery despite all of them receiving a remifentanil infusion rate of _ 0.05 µg/kg/min at this time. This post-operative respiratory depression persisted for 6-13 minutes in the four patients who were in the two highest Remi dose groups.

Muscle rigidity occurred in 4 patients (6%) and in two of these was of sufficient severity to necessitate cessation of the remifentanil infusion. In contrast to earlier studies, hypotension, bradycardia, and postoperative nausea or emesis were rare.

Analysis. To failure to discern appreciable dose-dependent effects on respiration between the different remifentanil infusion treatment groups could have been due to a number of factors. The study design allowed appreciable investigator discretion over propofol dosing and propofol use appeared to vary between the two study sites. Individual respiratory responses to lower remifentanil doses appeared to be quite variable. A distinction of any direct effects of remifentanil on respiratory depression may have been most clearly observed after LMA insertion and skin incision. However, at this time, the remifentanil infusion was titrated downwards by protocol if respiratory depression persisted, thus obviating any potential assessment of dose-effect relationships.

The time to skin incision was not fixed in the protocol, therefore, surgical stimuli were variable in both time and intensity between cases. Due to the relatively small number of subjects in each group at the two sites, this may have contributed to the variability of response between the treatment groups. Also, it was not possible to accurately predict whether the prescribed maintenance propofol infusion had attained steady state plasma levels at the time of skin incision thus complicating assessment of the primary endpoint.

Conclusions. Remifentanil in combination with propofol in oxygen-enriched air ("total intravenous anesthesia") can be used successfully for spontaneous ventilation anesthesia in routine outpatient surgery. Overall, a starting dose of less than 0.05 mcg/kg/min may be expected to be associated with a lower incidence of respiratory depression compared with higher doses although appreciable patient variability of response may be expected. However, even these low remifentanil infusion rates may cause significant respiratory depression when combined with relatively modest doses of propofol (100-140 µg/kg/min) in air/oxygen in healthy patients under LMA anesthesia. At higher doses, respiratory depression is common and muscle rigidity can occur unexpectedly during the maintenance phase of the anesthetic despite a constant rate remifentanil infusion.

Clin. Pharm/
Bio

Clinical Pharmacology/Biopharmaceutics Review

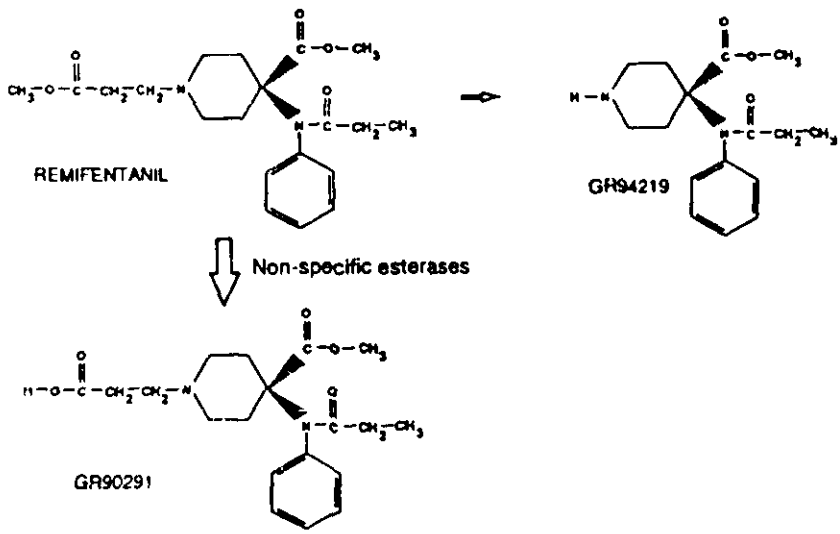
Remifentanil (GI87084B)
NDA 20-630
Ultiva® 1, 2, and 5mg/vial
Reviewer: E. D. Bashaw, Pharm.D.

Glaxo-Wellcome, Inc.
Research Triangle, NC
Submission Date:
Sept. 15, 1995

Review of an NDA

I. Background

Remifentanil is a high-potency, short acting, synthetic opioid that was developed for use as an analgesic/anesthetic agent. It is structurally related to fentanyl and the other phenyl-N-piperidines such as sufentanil and alfentanil. Remifentanil was deliberately developed by then Glaxo Resarch Inc. as a short acting agent. This was accomplished by developing a piperidine analog with a methyl ester component that is readily metabolized by non-specific esterases present in the blood. The resulting carboxcyclic acid metabolite (GR90291) has only 1/4600th of the mu opioid receptor affinity of the parent (see Fig. 1, below). The benefits of such a design is that it's metabolism would be, theoretically, unchanged in the face of either renal or hepatic failure and would be clinically stable across a range of target populations. The resulting compound, remifentanil, is very potent (20-30x that of alfentanil after bolus doses) and combined with its rapid metabolism (plasma half-life of 10 minutes) makes it very flexible for use in the surgical setting as titration of the infusion rate causes almost immediate feedback to the anesthetist.



II. Recommendation

In this NDA the sponsor has submitted the results of 20 in vivo pharmacokinetic and pharmacodynamic studies. Remifentanil has been studied in both males and females, children, the elderly and obese subjects. It has been studied after single and repeat bolus dose administration and under continuous infusion settings of up to 4 hours duration. The interaction of disease state

with remifentanil has been determined in renal failure, hepatic failure, and in patients undergoing coronary artery bypass graft (CABG) surgery. Drug-drug interaction studies have been performed to examine the dynamic effect of remifentanil on isoflurane, nitrous oxide, and temazepam. In addition to these studies, in response to concerns voiced by the reviewing pharmacologist, the applicant also conducted an in vivo bioequivalency trial comparing remifentanil produced via two different routes of synthesis. From a biopharmaceutic perspective the NDA is approvable, provided final language for the label that is mutually acceptable can be worked out. The US would be the first approval gained for remifentanil.

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Appendix I-Study Summary Sheets

Pivotal Trials

III. Application Overview

The pharmacokinetic portion of this NDA (section 6) consists of 51 volumes of data (volumes 1.53-1.104) This represents a total of 20 in vivo pharmacokinetic trials with remifentanil. Because of the mass of data this represents the sponsor provided an electronic copy of the data on a laptop computer for this reviewer's use. At the end of the review this laptop will be cleaned of residual files by the FDA's Information Systems Division prior to returning to the company. Electronic copies of the submitted dataset on 3.5 inch diskettes have been submitted by the sponsor in volume 1.54 of the NDA.

Of the total number of studies submitted 9 were considered by this reviewer to be pivotal and 7 were considered to be supportive. The remaining 4 studies are not included in this review as they were primarily pilot trials that were replaced by other trials with a larger number of subjects (such as USA-101) . For these reasons they were not considered to be relevant for approval and were not included in the final review of the product.

A. Analytical

During the development of remifentanil, samples of plasma, whole blood and urine were analyzed for remifentanil, GR90291, and in comparative studies for alfentanil. These assays were split between a number of analytical laboratories according to the following:

Name	Site	Code
Glaxo Inc. Research Institue	Research Triangle	GIRI

For each of the studies performed by the sponsor a detailed analytical report was submited and cross-indexed with the NDA in volumes 2.80-2.82. Attached in Appendix I and II are the study summary sheets for each of the trials reviewed in this NDA. On each of the individual study sheets the analytical laboratory is identified by the code name above. In general the methods used were based on high resolution GC/MS/SIM using different methods of extraction of target compounds. During the development of remifentanil there were two outstanding analytical problems that had to be dealt with.

The first of these is that given that the metabolism of remifentanil is mediated by non-specific esterases there will be continued metabolism of the drug in the sample tube unless the blood sample is immediately treated to stop this process. Any delay in the processing of plasma samples by the collecting phlebotomist/nurse/physician would result in abnormally low or non-existant plasma levels in the patients. Normally blood samples are collected and placed on ice prior to separation of the cellular and plasma components of the blood. In vitro studies showed that while icing of the whole blood samples would diminish the rate of metabolism, it would not stop it. Eventually it was decided to stabilize the blood samples upon collection by the addition of either citric acid or acetonitrile to the sample. In order to ensure some degree of standardization across all of the clinical study sites, the applicant developed a training video and held classes at each study site to ensure that the importance of this sample handling procedure was understood and followed

The second analytical problem with remifentanil developed during extraction of plasma samples for analysis. Two methods of extraction were used, either liquid-liquid extraction (LLE) or solid phase extaction (SPE). During the analysis of the samples from the pediatric study (USA-219) the analytical laboratory (Triangle) encountered a problem in that the current LLE technique was not, in their opinion, cleaning up the samples enough and they were losing efficiency in the column separation. The analytical laboratory investigated a number of alternative methods and eventually put into use a SPE method that used hot methanol as a medium. Unfortunately, as remifentanil is metabolized by the breakage of an ester linkage, the conditions used in this SPE were such that the carboxcyclic metabolite (GR90291) was converted back to parent drug in situ. When the data for the first eight pediatric subjects were analyzed using this new method the resulting plasma levels were 2x those expected and showed a half-life approaching 1 hour. The firm immediately notified the FDA in a telecon on March 25, 1994 and all protocols were put on hold until a reason could be found to explain this deviation. On April 4, 1994 another telecon was held between the FDA and Glaxo where Glaxo explained that they had found this unauthorized modification to the method. It was decided then that as the observed clinical response had not changed in these subjects, that the first 8 subjects in study USA-219 would be replaced and that corrective measures in the monitoring of the analytical program would be put in place. [*Details of these discussions and the reports to the FDA are contained in the file for IND a review by this reviewer stamp dated May 23, 1994, and faxes from the sponsor dated 3/23/94, and 3/24/94.*]

Subsequent to this the SPE extraction method was adopted by the applicant as an improvement to the LLE method with the modification of using isopropanol instead of methanol in the process. This modification was developed by GIRI in response to the original concerns of the contract labs.

All in all, while a number of analytical sites were used and considering the labile nature of the compound in question the applicant has, for the most part, presented both a detailed analytical submission and provided adequate oversight of their contractors. When lapses in oversight have taken place, the applicant has taken immediate remedial action and has kept this reviewer fully informed of their actions. Attached in Appendix I and II at the bottom of the study summary sheets are summary details of the analytical results from each study. This information includes the name of the analytical site, the method and species monitored, the assay sensitivity, accuracy, and the associated range of detection. The analytical documentation submited in this NDA is acceptable.

B. Formulation

Throughout the development of this product the applicant has used two different formulations of remifentanil. The initial drug product used for early clinical studies was comprised of 1mg of remifentanil per vial and contained 15mg of Glycine USP and 60mg of Mannitol USP as excipients in a 2ml vial. Even though the product is liquid filled and subsequently freeze dried, this formulation was found to be heat labile and required refrigeration to maintain a useable shelf life. This formulation was replaced with the to-be-marketed formulation containing either 1, 2, or 5mg of remifentanil, 15mg of Glycine USP, dilute HCl NF to adjust pH to 3 and water for injection q.s.. This product is also freeze dried and is stable at room temperature for 24 months.

More problematic than the formulation for this sponsor has been the synthesis of this product. Remifentanil is currently produced using The original systhesis route used a and had a correspondingly lower yield and was harder on the environment in terms of residual waste. During the review of pre-clinical animal work Dr. Harry Geyer (FDA) detected a difference in the number of cranial hemorrhages in beagle dogs given remifentanil from synthesis .) From a chemical standpoint there was no difference in the chemical purity of the resulting remifentanil, although there was a suggestion that the ratio of the precursors/degradents present in the two formulations was altered. In an effort to address this issue the sponsor agreed to do a biopharmaceutic trial in beagle dogs and a protocol was submitted and approved. At the request of both the sponsor and the reviewing medical officer and pharmacologist, this reviewer was asked to review the results of this beagle dog study as a neutral party. In my review of the data [*IND* . *review stamp date 8/8/94*] I concluded that there was no significant pharmacokinetic difference between the two routes of synthesis based on pharmacokinetics. Reproduced below is the summary data table from that review:

Summary Results from Beagle Dog Study
Mean (%C.V.)

	Remifentanil		GI90291 Metabolite	
	AUC (hr*ng/ml)	Cmax (ng/ml)	AUC (hr*ng/ml)	Cmax (ng/ml)
Route 1	12 (28)	180 (38)	76.3 (20)	56.4 (17)
Route 2	11.6 (28)	166 (31)	69.8 (12)	50.5 (9)
90% C.I.*	83-112%	77-117%	84-102%	84-97%

*90% C.I.-Log transformed 90% Confidence Interval Acceptance Interval = 80-125%

Even though this reviewer considered the difference in Cmax for the new route trivial, given the setting of the model and the severe nature of the observed side effect (cerebral hemorrhages), it was decided by the then reviewing medical officer and the pharmacologist that the sponsor should be required to do an in vivo equivalency trial in humans. This trial was subsequently done by the sponsor and is in this NDA as study USA-106.

From a pharmacokinetic/biopharmaceutic standpoint there are no outstanding formulation issues for this product.

IV. Summary of Bio/PK Characteristics

The main body of this review presents an overview of the information contained in the pharmacokinetic portion of this NDA in a summary form. More detailed information on the individual studies is contained in Appendix I in the form of individual study summaries. These summaries were primarily written by the sponsor with input from both this reviewer and the reviewing Medical Officer, Dr. Barbara Palmisano. Strictly speaking adherence to the standard ADME format was not possible for this review as, being an intravenously administered drug, absorption issues are moot. As for the description of the general pharmacokinetics of remifentanil (i.e. distribution and elimination), this is best done by examining the results of in vivo dose proportionality trials that were done as part of the dose ranging work up on remifentanil.

A. Distribution (USA-202)

This study was the second bolus dose study to be done in man. The first study USA-101 was not included in this review as of the 7 dosage levels used only 1 (the 2mcg/kg dose level) gave reproducible data results, albeit in a small number of subjects. With the information learned from the previous study a new dose proportionality study was initiated using higher bolus doses of remifentanil. Starting from where the last study left off, doses of 2, 5, 15, and 30mcg/kg were administered as bolus infusions over 1 minute. In addition to using higher doses, a larger number of subjects was also included in the study design. Full study design details and study demographics are attached in Appendix I as pages 2-14.

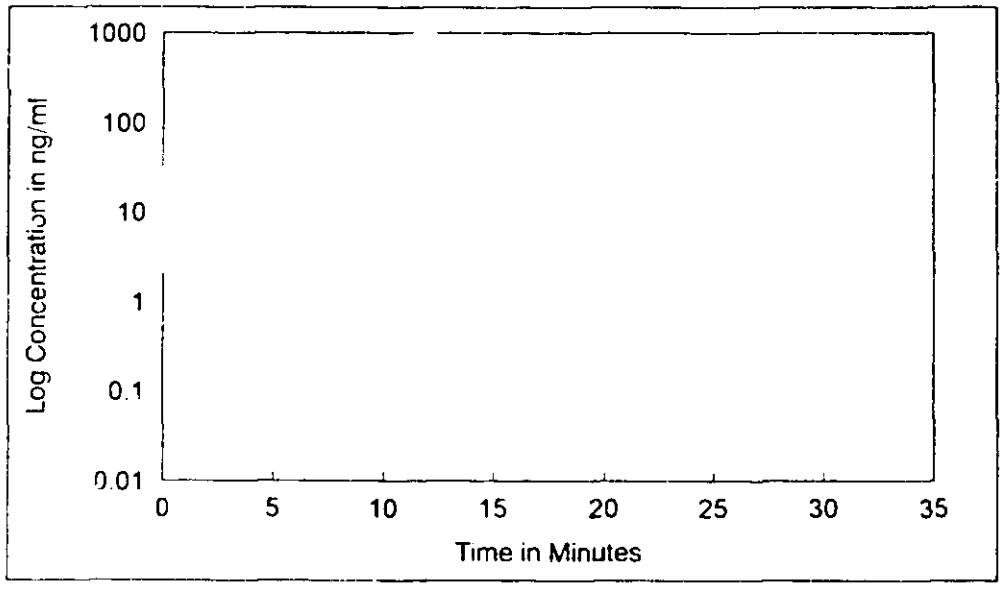
A total of 25 subjects were enrolled in the trial and 24 were considered evaluable for pharmacokinetic analysis. One subject was removed from the pharmacokinetic dataset when it was found out that the syringe pump that was used to administer the drug to all subjects had failed during his dosing period, such that less than the projected dose was administered. He was replaced. The collected plasma samples were analyzed for remifentanil and its primary

metabolite and the resulting dataset was analyzed using both compartmental and non-compartmental methods. Reproduced below is a graphical representation of the data from the 2 and 30mcg/kg dose group and a summary data table from the resulting compartmental analysis of the data:

Compartmental Analysis USA-202

Dose	AUC (ng*min/ml)	λ1t1/2 (min)	λ2t1/2 (min)	λ3t1/2 (min)	Vdss (ml/kg)	Cl (ml/min/kg)
2mcg/kg	38.9 (36.6)				303.2 (53.5)	59.5 (47.4)
5mcg/kg	87.6 (41.1)				336.3 (52.1)	63.9 (32.1)
15mcg/kg	270 (30)				368.2 (21.3)	61 (34.5)
30mcg/kg	512.7 (34)				497.7 (53.4)	64 (29.1)

USA-202, 2mcg/kg and 30mcg/kg Data



The results from this study indicate that the pharmacokinetics of remifentanil are dose independent over the range of doses tested with both AUC and Cmax for remifentanil and GR90291 increasing in proportion to the dose administered. Compartmental analysis of the data indicates, especially for the higher doses, that remifentanil follows a three compartment model with two distributional phases of 0.5min. and 2.4min. respectively. The terminal elimination phase ranged from minutes (which is similar to the rate of remifentanil degradation in human plasma, see Pharmacologists review). This rapid elimination of remifentanil from the plasma translates into a clearance of approximately ~65ml/min/kg. This greatly exceeds the usual reference standard for liver blood flow of 20ml/min/kg, validating the existence of extra-hepatic metabolic processes. While this study did not measure the pharmacodynamic response of the subjects (the dose were given 10min. after intubation) it does point to a potential problem with this drug. With a plasma half-life as short as it is, it appears that continuous infusion of remifentanil at a controlled rate will be the preferred way to administer the drug. With the short half life of remifentanil it means that when the infusion is terminated at the end of surgery,

secondary narcotics/analgesics must already be "on board" as the effect of remifentanil will be very, very, short lived and the patients might have an abrupt onset of severe pain and anxiety.

Dose Proportionality (4-hour Infusion) (USA-102)

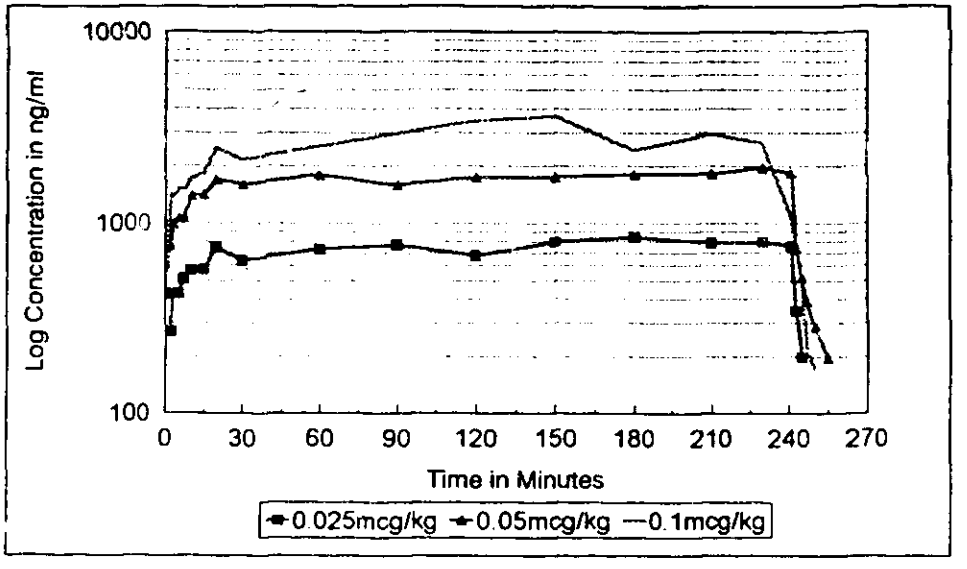
Following the preliminary determination of the pharmacokinetics of remifentanil following a single bolus dose, the applicant decided to investigate the use of remifentanil following continuous infusion. Unfortunately the applicant decided to make this study a combined pk/pd/clinical study. As such beyond studying the pharmacokinetics of remifentanil, the study also included various treatment factors and analysis designed to test the effect of remifentanil on minute volume, PaO2, PaCO2, pain stimulus, and potency vs. alfentanil. While some of these objectives can easily be combined in a trial, other elements cannot and as such the trial suffered proportioniate to the baggage it was forced to carry.

The study was originally designed to study the pharmacokinetics of remifentanil following a 4 hour continuous infusion of either 0.025, 0.05, 0.075, 0.1, or 0.2mcg/kg/min versus alfentanil at 0.5 and 1.0mcg/kg/min. After discussions with the reviewing medical officer this reviewer will defer to their interpretation of the pharmacodynamic data as it relates to PaCO2, PaO2, and minute volume. As for analysis of the pain and potency issues, this study is inappropriately designed for such comparisons (i.e. the doses used were not sufficient to attenuate the full pain response). Reproduced below is a summary data table from this study and a graphical representation of the data from the 0.025, 0.05 and 0.1mcg/kg/min dose levels.

	Compartmental Analysis			Non-Compartmental Analysis			
	Vc (ml/kg)	Cl (ml/min/kg)	ke	Vss (ml/kg)	Cl (ml/min/kg)	K	T1/2 (min)
0.025mcg/kg/min	227 (49)	34.4 (21.9)	0.178 (46.8)	442 (41)	33.8 (23.2)	0.231 (77.7)	
0.05mcg/kg/min	153 (25)	29.6 (22.3)	0.195 (5.9)	308 (97)	36.4 (21)	0.135 (31)	
0.1mcg/kg/min	208	40.4	0.19	516	38.7	0.19	

As noted earlier, the applicant attempted to do too much in this one trial to provide good data for analysis. The 0.075, 0.1 and 0.2mcg/kg/min treatment legs were confounded by changes in the infusion rate for those subjects. The infusion rates were altered to maintain the subjects in a conscious state for questioning regarding their pain perception. In using this approach to measure pharmcodynamic response, the data for the higher level doses was essentially lost as the infusion rate had to continually be adjusted downward in these treatment groups to maintain a semi-conscious state. The mean data presented below represents stable data from those subjects in the protocol who did not recieve infusion rate changes.

USA-102 Mean Data



While this study, like the previous study has limitations, if one limits it to the demonstration of dose proportionality, then one can make some conclusions from the data. Clearly remifentanil demonstrates rough dose proportionality across the doses used. In addition there does not seem to be any alteration in the terminal elimination rate following an infusion. This is both a consequence of the rapid clearance by non-hepatic mechanisms but also a fact of its relatively small volume of distribution. In contrast, propofol (another injectable anesthetic agent) shows a marked prolongation in recovery after infusion due to the return of drug from deep compartments into the plasma compartment.

In attempting to demonstrate dose proportionality the applicant has reported out the results of three in vivo pharmacokinetic trials (USA-101, 102, and 202). Of these USA-101 was unevaluable due to the lack of detectable plasma concentrations in the majority of the subjects, while in study 202 the number of infusion changes made to incorporate pharmacodynamic testing tended to invalidate the study's use for dose proportionality. What has been shown is that following bolus dose administration, remifentanil demonstrates a triexponential elimination profile with a terminal rate of approximately 10 minutes. The applicant has shown that following single bolus doses of from 2mcg/kg to 30mcg/kg the pharmacokinetics of remifentanil are dose proportional. Following intravenous infusion the pharmacokinetics of remifentanil also appear to be dose proportional, but the need of the applicant to add extraneous measures into their trial handicapped it in this area.

B Metabolism

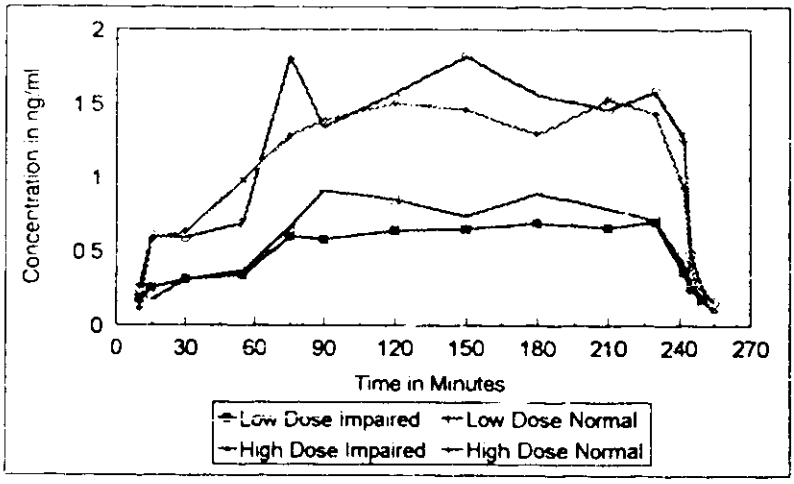
The original design objective for remifentanil was to develop a potent opioid analog that had a short duration of action. This was accomplished by designing remifentanil with an ester linkage that was easily broken by the effect of non-specific plasma esterases. Fig. 1., on page one of this review presents the metabolic pathway of remifentanil in man. The primary route, via the non-specific esterases, forms the resulting carboxcyclic acid metabolite (GR90291) and a desalkyl metabolite (GR94219). Of these two metabolites only GR90291 appears in the plasma to an appreciable extent. Neither of the two metabolites show significant opiate activity (GR90291 is estim have 1/4600th of the binding affinity of remifentanil to the opiate receptor).

According to the reviewing pharmacologist the affinity of GR94219 for the opiate receptor is insignificant. The results from the previous in vivo pharmacokinetic studies with remifentanil suggested that non-hepatic mechanisms of metabolism were involved with the de-activation of remifentanil. Demonstration of this was via the calculation of remifentanil clearances in excess of hepatic blood flow. In order to assess the role, if any, of the liver in remifentanil metabolism, the applicant undertook two studies designed to look at the influence of hepatic insufficiency/transplant on the pharmacokinetics of remifentanil: USA-211 and USA-224. As USA-224 was done in a smaller number of subjects than USA-211, the primary discussion of hepatic insufficiency will revolve around USA-211.

1. Hepatic Insufficiency (USA-211)

As alluded to above, one of the theoretical design benefits of remifentanil is it's lack of reliance upon hepatic metabolism for the termination of clinical effect. In this study USA-211, 10 healthy and 10 subjects with hepatic insufficiency were enrolled in the trial and randomized to either of two treatments such that each treatment arm consisted of five and five. As in the renal insufficiency study, the subjects were randomized to either a low dose group which received remifentanil as a 0.0125mcg/kg/min infusion for one hour followed by 0.025mcg/kg/min for three hours or as a high dose group who received 0.025mcg/kg/min for one hour followed by 0.05mcg/kg/min for three hours. Both plasma and urine were monitored throughout the study for both remifentanil and GR90291 and any other trace metabolites (primarily GR94219). Reproduced below are both graphical and tabular representations of the data from this trial.

USA-211 Remifentanil Mean Data



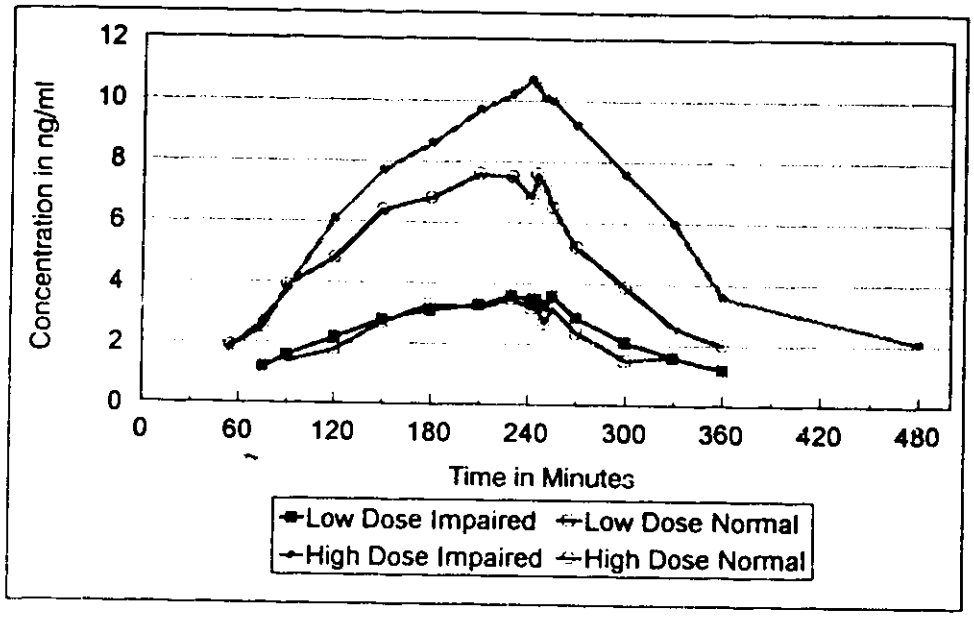
USA-211 Remifentanil Mean Data (+/-S.D.)

	Hepatic Impaired		Healthy	
Parameter	Low Dose*	High Dose*	Low Dose*	High Dose*
Cl (ml/min/kg)	39.4 (5)	34.5 (9.6)	32.1 (7.2)	33.1 (3.6)
Vd (ml/kg)	270 (68)	290 (114)	229 (115)	206 (21)
T1/2 (min)	4.7 (0.88)	5.8 (1.65)	4.8 (1.6)	4.3 (0.16)

*N=5

This data clearly shows that, as predicted, the pharmcokinetics of remifentanil are unaffected by hepatic insufficiency, with both volume and clearance being unaffected. A similar pattern was also seen for the primary metabolite GR90291.

USA-211 GR90291 Mean Data



USA-211 GR90291 Mean Data (+/-S.D.)

	Hepatic Impaired		Healthy	
Parameter	Low Dose*	High Dose*	Low Dose*	High Dose*
AUCinf(ng*min/ml)	820 (170)	1408 (592)	792 (216)	1008 (258)
Cmax(ng/ml)	3.7 (0.56)	5.4 (1.8)	4 (0.85)	3.4 (1.23)
T1/2 (min)	71.3 (9.2)	121.3 (39.5)	72.8 (25.8)	120.1 (57)

*N=5

As noted above for the parent, it appears that hepatic insufficiency has no impact on the disposition of GR90291. As for GR94219, another theoretical metabolite of remifentanil, it was detected only intermittantly during the study and never at levels exceeding the minimum quantifiable level.

2. Anhepatic (USA-224)

While the previous study dealt with the impact of hepatic impairment on the pharmacokinetics of remifentanil, it did not include a true anhepatic phase (i.e., total absence of liver function). In order to look at this issue six subjects undergoing liver transplantation received a 1 minute infusion of remifentanil (10mcg/kg/min) during both the dissection phase and during the anhepatic (prior to transplantation) phase. The results of this trial are summarized in the table below:

USA-224 Remifentanil Mean Data (+/-S.D.)

	Cl (ml/min/kg)	Vss (ml/kg)	T1/2b (min)
Dissection Phase	79.5 (29.3)	748 (440)	10.5 (4.1)
Anhepatic Phase	39.6 (17.4)	410 (173)	10 (1.5)

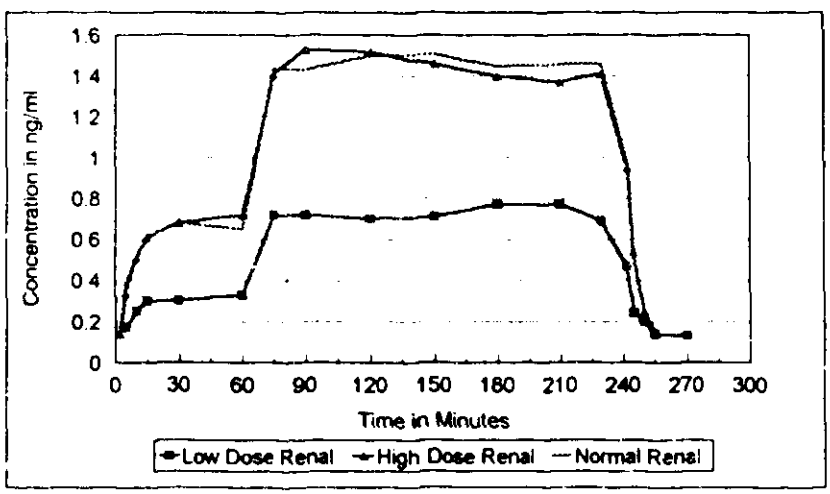
The data from the dissection phase is quite striking in that the clearance is almost twice what has been seen in other trials. This high clearance value is most likely due to the large fluid losses encountered with the removal of the liver and the subsequent dilutional effect by the addition of intravenous fluids. The data from the anhepatic phase, prior to transplantation, is more in line with what has been seen in other studies and strongly suggests that the liver plays no or if any only a minor role in the metabolism of remifentanil and that the proposed mechanism of plasma esterases is the primary route of metabolism.

C. Elimination-Renal Insufficiency (USA-210)

Theoretically, the impact of renal insufficiency on the pharmacokinetics of remifentanil should be minimal to non-existant. However, the principal metabolite (GR90291) is predominately eliminated by the kidneys and thus should display altered pharmacokinetics. A total of 15 subjects with renal impairment (ClCr ~9ml/min/1.73m2) were enrolled in the study. Of these 14 were receiving hemodialysis. An additional eight subjects with normal renal function (ClCr ~88ml/min/1.73m2) were enrolled in this trial as a control group.

Upon enrollment into the trial the renally impaired subjects were randomized into two groups (high and low dose). Subjects randomized to the low dose group received remifentanil as a 0.0125mcg/kg/min infusion for one hour followed by 0.025mcg/kg/min for three hours. The subjects randomized to the high dose group (and all of the healthy subjects) received 0.025mcg/kg/min for one hour followed by 0.05mcg/kg/min for three hours. Both plasma and urine were monitored throughout the study for both remifentanil and GR90291 and any other trace metabolites. Reproduced below are both graphical and tabular representations of the data from this trial.

USA-210, Median Data-Remifentanil

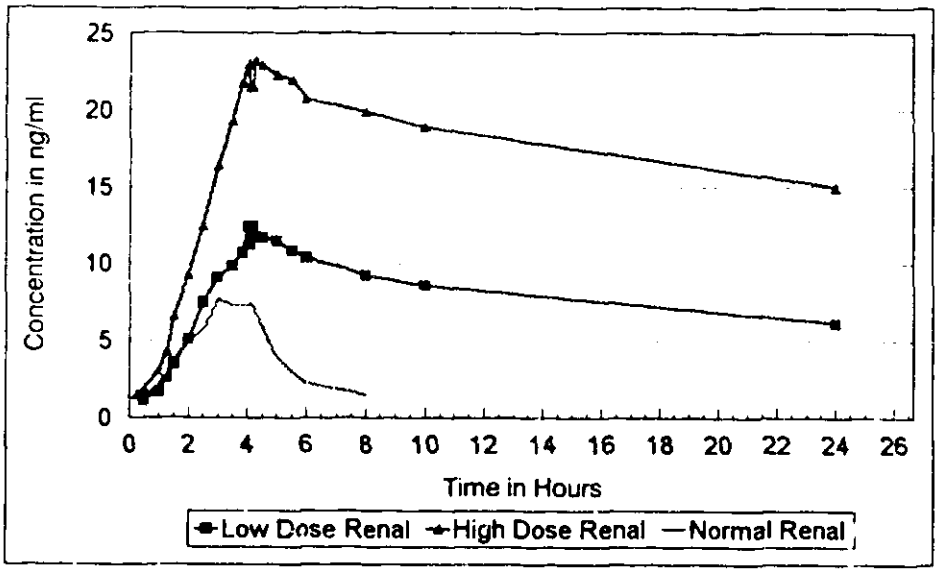


USA-210, Remifentanil Mean (%CV)

Parameter	Low Dose Renal N=6	High Dose Renal N=9	Normal Renal N=8
Cl (ml/min/kg)	36.7 (34)	34.6 (48)	34 (44)
Vd (ml/kg)	298 (37)	230 (11)	197 (26)
K10 (min-1)	0.135 (38)	0.157 (20)	0.178 (24)
T1/2 (min)	6.3 (62)	4.5 (15)	4.1 (19)

For remifentanil, it can be shown that while there are minor differences between the impaired and normal renal function subjects, these differences are by in large small and related to the small number of subjects present in this trial and the associated large variances seen in the data. What is interesting to note is the stability of the Cl estimate in the face of marked change in renal function. The stability of the is parameter is further indcation of the lack of effect of renal function on the elimination of remifentanil. In regards to the metabolite, GR90291, the situation is quite a bit different.

USA-210, Median Data-GR90291



USA-210, GR90291 Mean(%CV)

Parameter	Low Dose Renal N=6	High Dose Renal N=9	Normal Renal N=8
AUCinf (ng*min/ml)	24790 (51)	35149 (39)	993.5 (26)
AUClast (ng*min/ml)	10502 (29)	11784 (27)	872 (29)
Cmax (ng/ml)	15.2 (36)	12.7 (22)	4.2 (15)
T1/2 (hrs)	22.8 (39)	34.6 (38)	1.49 (19)

The results for GR90291 are what one would expect for a drug or metabolite that is renally cleared. The marked prolongation of half-life has resulted in a many fold increase in both Cmax and AUC. This excess accumulation of GR90291 is also in evidence by the ratio of AUC's between itself and remifentanil. Using the data for normal volunteers the ratio for GR90291 to remifentanil is approximately 6.3:1, for high dose renal impairment the ratio increases to 241.9:1. This clearly indicates the total dependence of GR90291 upon renal clearance.

As for the usefulness of dialysis in removing GR90291, the 14 subjects in the trial undergoing dialysis were given a second dose of remifentanil and samples on both sides of the system were analyzed for GR90291. It was determined that GR90291 had an A/V ratio of 1 and that dialysis could remove between 25 and 35% of the total amount during a standard dialysis treatment.

The objective of this study was to demonstrate the effect of renal insufficiency upon the pharmacokinetics of remifentanil. While statistically significant differences were detected between the renally impaired subjects and matched controls, the overall small number of subjects, the associated variance in the parameters, and the small absolute magnitude of the observed differences suggest that the pharmacokinetics of remifentanil are essentially unchanged in the face of renal insufficiency. The pharmacokinetics of the primary metabolite GR90291 are markedly changed and it accumulates dramatically. As GR90291 has only 1/4600th the potency of remifentanil it would not be expected to pose a therapeutic risk under normal conditions and durations

D Special Populations

As part of this NDA the sponsor looked at the pharmacokinetics in a number of special populations including gender, the elderly, pediatrics, and the obese. As the primary objective of these trials was to detect deviations between these subsets and the healthy male volunteer, these studies will be ranked as pivotal as they expanded the knowledge base of the use of remifentanil in the clinical setting

1 Gender (USA-104)

As part of their work-up for this NDA the applicant undertook an analysis of the effect of gender on the pharmacokinetics and pharmacodynamics of remifentanil during a 20 minute infusion. Unlike most gender studies done in support of an NDA this study was designed not as a head to head equivalency demonstration, but as a pk/pd comparison employing spectral edge analysis of the EEG. That portion of this study will be reviewed separately under the pharmacodynamics subsection of this review.

The gender portion of study USA-104 consisted of two phases:

Phase I	10 male subjects receiving 1-8mcg/kg/min of remifentanil
Phase III	10 females receiving 3mcg/kg/min remifentanil

The pharmacokinetic results from this trial are reproduced below:

USA-104 Remifentanil Pharmacokinetics by Gender Mean Data +/- S.D.

	Cl (ml/min/kg)	Vc (ml/kg)	Vss (ml/kg)
Phase I-Males	37+/-5	98+/-19	349+/-85
Phase III-Females	48+/-8	103+/-31	380+/-243

These results clearly suggest that there are no significant differences between the pharmaccokinetics of remifentanil in men and women on a weight normalized basis (i.e., by kilogram). If weight is not considered, then both the estimates for volume and clearance would demonstrate some correlation with gender. In general, given the mechanism of action and the metabolic route for deactivation, the lack of a gender effect is not unexpected.

2. Elderly (USA-216)

This study was an ambitious pk/pd study in middle aged (40-65years old) and elderly (>65 years old) subjects, both male and female. This study uses as a pd measurement the spectral edge technique to compare the opioid effect on the brain across study groups. A summary discussion of this technique is presented in the pharmacodynamics subsection of this review.

This study enrolled a total of 50 subjects (29 males and 21 females). The subjects were stratified for age and gender and received an infusion of remifentanil at 3mcg/kg/min for up to 20 minutes. The duration of the infusion varied up to 20 minutes or until maximal slowing of the EEG occurred or if the mean arterial pressure decreassed 30% from baseline. Because of these criteria a graphical presentation of the mean data would be misleading as the data represented by each timepoint could be composed of both pre-and post-infusion data. Attached in Appendix I are the so called "spaghetti" plots plotting all of the data from each group on a cumulative graphs.

As for the tabular results from this study, they are summarized below:

USA-216 Remifentanil Mean Data +/- S.D.

Subject Group	Cl (ml/min/kg)	Vc (ml/kg)	Vss (ml/kg)	EC50 (ng/ml)	$T_{1/2}$keo (min)
MA Male (n=11)	32+/-7	81+/-36	206+/-73	12+/-4	1.8+/-0.9
MA Female (n=6)	33+/-5	52+/-27	187+/-33	16+/-8	1.6+/-0.7
Eld Male (n=7)	31+/-4	74+/-26	196+/-42	8+/-3	2.8+/-1.5
Eld Female (n=11)	30+/-6	53+/-13	160+/-34	9+/-5	1.9+/-0.7

Analysis of the pharmacokinetic data generated by this trial reveals only a modest change in the Vc for elderly males versus the middle aged men. This finding is of little significance, however, the results from this study were combined with the results from USA-104 (a pk/pd study in young volunteers) and age related changes were identified. A combined regression analysis was done on the data and a significant inverse relationship was found between subject age and Cl, Vc, Vss, and EC50 and keo. Graphical representations of these relationships are reproduced as part of the summary study report in Appendix I. In an effort to explore the observed differences the applicant used the data from the combined regression model to develop the following table of parameter values relative to a 30yr old subject.

USA-216 Remifentanil Combined Regression
Predicted Mean Value (% variation from 30yr old)

Parameter	30yr old	50yr old	75yr old
Cl (ml/min/kg)	39	35 (10%)	29 (26%)
Vss (ml/kg)	312	245 (21%)	162 (48%)
Vc (ml/kg)	96	80 (17%)	59 (39%)
Ec50 (ng/ml)	17.3	13.5 (22%)	8.7 (50%)
keo (min^{-1})	1	0.71 (29%)	0.29 (71%)

The data from this analysis strongly suggests that there is an age related reduction in clearance, volume, EC50, and keo. Based on this analysis doses in the elderly should be reduced by 50% in subjects over 65 years of age and the infusion rate should be titrated closely to the observed need of the patient in question.

3. Pediatrics (USA-219P)

As part of their work-up of this agent the applicant undertook a pharmacokinetic study of pediatric subjects from 2 to 12yrs old. This study was the study that was alluded to in the analytical validation section as the one that had the unauthorized change in the analysis technique. The data from all of the affected children was discarded. A total of 23 pediatric subjects were enrolled in this trial, 13 in the 2-6 yr old range and 10 in the 7-12 yr. old group. After removal of the affected subjects the numbers of subjects in each group was reduced to 6 and 7, respectively. Each subject received a single 1 minute infusion of remifentanil at a rate of 5mcg/kg/min. Arterial blood samples were taken and analyzed for both parent and metabolite for up to 4 hours following the infusion. The mean results from this trial are presented below:

USA-216P Remifentanil Mean Data +/- S.D.

Parameter	2-6yrs old (n=6)	7-12yrs old (n=7)
AUCinf (ng*min/ml)	114.5+/-63.5	154.7+/-56.13
Cmax (ng/ml)	35.8+/-9.5	47.2+/-16
Vss (ml/kg)	572.9+/-1000	420+/-446.3
Cl (ml/min/kg)	51.4+/-17.5	35.6+/-11.8

Although the data from this trial seems a bit extreme compared to some of the data seen in this NDA, once allowances are made for dose and body weight most of these apparent differences drop out. Unfortunately the relatively small number of subjects per treatment group made statistical comparisons across the groups meaningless with the observed variance present. In addition the study was unable to address whether or not there is a dynamic difference between adults and pediatric patients. Upon some reflection such a difference most likely does not exist. With the $T_{1/2}$Keo value in adults hovering between 1-2 minutes, it can be readily demonstrated that arterial concentrations rapidly come into equilabration with the effect compartment. The theoretical concern with children is that, due to an incompletely formed blood brain barrier, that

such a transferrence rate would be markedly faster. Given the very high rate of equilibration found with adults (~1.4min.), it is unlikely that children would have a markedly increased value for equilibration. However, the small number of subjects in each treatment group is grounds for some concern.

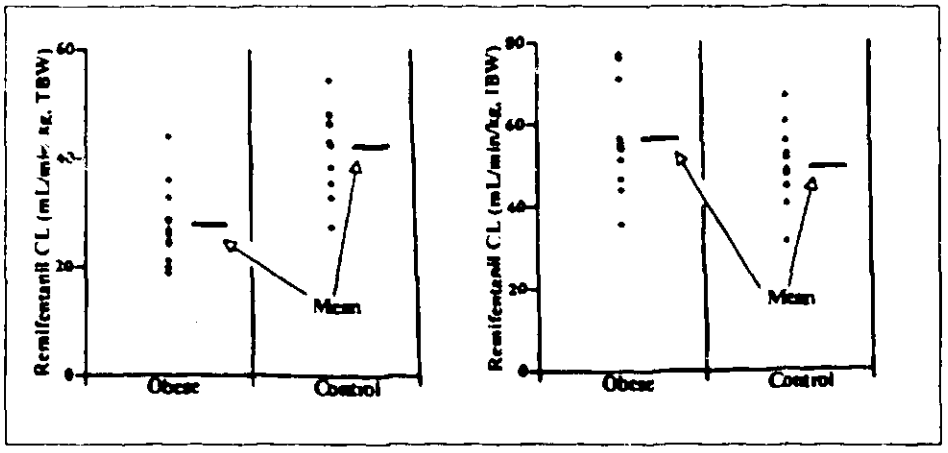
4. Obesity (USA-227)

One of the common problems with anesthetic medications is the problem of the obese patient and whether or not total body weight (TBW) or ideal body weight (IBW) should be used. In this study 12 obese subjects (>80% above IBW) were given a single dose of remifentanil at either 10 or 7.5mcg/kg/min over 1 min. An additional 12 healthy normal matched controls were included in this trial for comparison. Reproduced below is a summary data table of the mean pharmacokinetic parameters for volume and clearance:

USA-227 Remifentanil Mean Data +/- S.D.

	Obese Subjects		Control Subjects	
	TBW	IBW	TBW	IBW
V1(ml/kg)	68.2+/-29.6	136.6+/-52.9	101.9+/-34.4	119.9+/-45.5
Vss (ml/kg)	146.2+/-54.5	294.3+/-99.2	217.4+/-65.9	257.2+/-92.7
Cl (ml/min/kg)	27.7+/-7.2	56.4+/-12.7	42.4+/-7.5	49.4+/-9.2

One thing that clearly comes across from this data set is the significant and large differences seen between the TBW corrected parameters between the two groups. The obese patients have lower parameter values when corrected for TBW. However, obese patients demonstrated the same absolute (TBW-uncorrected) pharmacokinetic parameter values (CL, V1, and Vss) as their matched controls despite almost two fold weight difference. When corrected for IBW, the pharmacokinetic parameters for the two groups were again similar. These findings indicate that the pharmacokinetic parameters of remifentanil are better correlated with IBW than TBW. See figure below



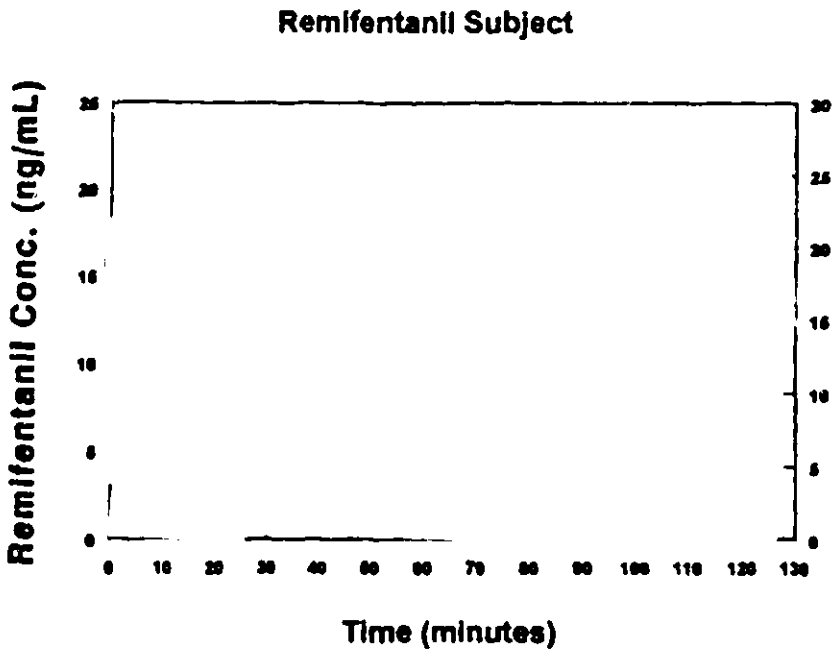
E. Pharmacodynamics

1. EEG Spectral Analysis Study in Volunteers (USA-104)

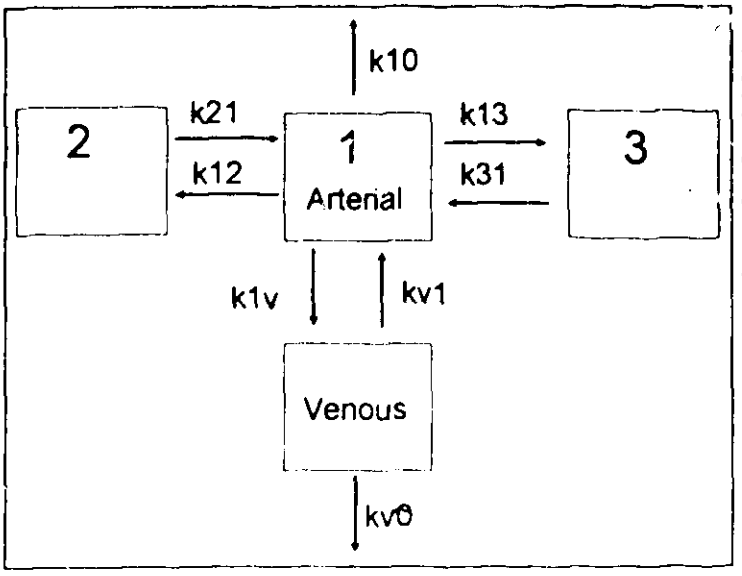
Spectral edge analysis is based upon the finding that the depressant effects of opioids upon the central nervous system can be quantified by use of the EEG. By initiating continuous monitoring 15 minutes before opioid administration a baseline EEG waveform can be determined. The complex EEG waveform is subjected to fourier transformation and converted to a univariate parameter, spectral edge (the frequency below which 95% of the total power in each epoch was found) A pharmacokinetic/pharmacodynamic model can then be used to describe the temporal relationship between changes in opioid concentration and changes in spectral edge.

The study itself was a three part trial with a dose ranging part, a comparison of remifentanil to alfentanil, and finally a comparison of the pk/pd parameters of remifentanl between males and females (this part of the trial has already been analyzed as the Special Populations-Gender section previously in this review).

As noted above part I was an open label study in 10 healthy male subjects. Remifentanil was infused at rates of 1, 1.5, 2, 4, and 8mcg/kg/min for 20 minutes. Remifentanil produced classic mu opioid effects on the EEG. As concentrations increased the EEG changed from a high frequency low amplitude wave form to a low frequency high amplitude wave from (delta wave). A representative time course of the observed remifentanil arterial blood concentrations and opioid effect on the EEG(spectral edge) for subject 001 are depicted in the following figure.



Pharmacokinetic Model



A standard three compartment pharmacokinetic model was developed for remifentanil that allowed for drug elimination to occur from both the arterial and venous sides of the model. For those subjects for whom only a two compartment model was needed, the model was collapsed to the simplier situation by zeroing out the k13 and k31 constants.

This pharmacokinetic model developed during phase I was used to provide parameter estimates of the pk parameters from all three phases of the trial. Phase II was a pk/pd comparative study between remifentanil and alfentanil in healthy male subjects. Phase III was a pk/pd study of remifentanil in women. It was the data from phases I and III of this study that was used to demonstrate the lack of a gender effect with remifentanil.

Pharmacodynamic Model

The pharmacodynamic model used to describe the EEG opioid effect as it relates to opioid concentration was an inhibitory Emax model (Hill equation)

$$E(t) = E_0 - \frac{Emax + Ce(t)\gamma}{IC_{50}\,\gamma + Ce(t)\gamma}$$

Where

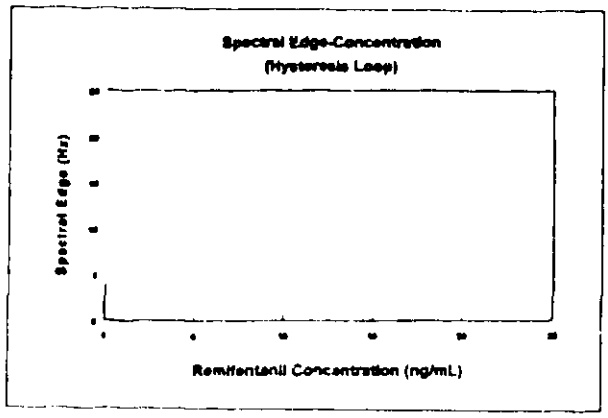
$E(t)$	=	Spectral Edge at time t (Hz)
E_0	=	Baseline Spectral Edge
Emax	=	Maximal Effect
$Ce(t)$	=	Theoretical concentration at the effect site
IC_{50}	=	Concentration required to produce half of the maximal effect
γ	=	Sigmoidicity Factor

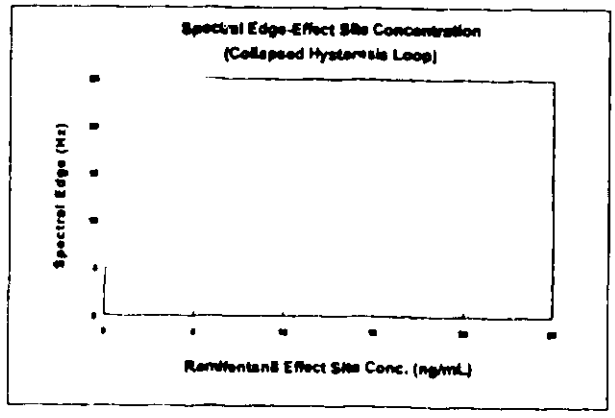
The lag time between changes in effect (i.e., Spectral Edge) and changes in opioid arterial concentration was incorporated into the model as a first order process linking effect site opioid

concentrations to arterial blood concentrations. This parameter (keo) and the pharmacodynamic parameters (E_0, Emax, IC_{50}, and γ) were estimated using non-linear regression (PC-Nonlin v4.0). The pharmacokinetic parameters used were constrained to the values obtained in the pharmacokinetic fit.

The net result of this modeling of the pk and pd data was to collapse the relationship between observed concentration and effect. Using the data from subject again the net result of this analysis is demonstrated by the following figures:

Subject Pharmacodynamic Analysis





Using these techniques the following pharmacodynamic results were obtained for all three phases of study USA-104:

USA-104 Remifentanil PD Mean Data +/- S.D.

Phase	IC_{50} (ng/ml)	$T_{1/2}$keo (min)	γ
I-Males	16+/-16	1.4+/-1.2	3.0+/-2.4
II-Remifentanil	20+/-5	0.8+/-0.5	4.8+/-2.3
II-Alfentanil	348+/-151	0.9+/-0.9	6.8+/-4.7
III-Females	15+/-5	1.2+/-1.0	2.8+/-1.6

The net result of this analysis is to demonstrate that relative to a commonly used anesthetic agent, remifentanil is 17x as potent of a suppressor of brain wave activity as alfentanil is. With a temporal delay in changes in drug effect relative to changes in opioid concentration ($T_{1/2}$keo) was 1.4 minutes for remifentanil indicating that blood concentrations equilibrate rapidly with the site of drug effect, i.e., the brain. The data also demonstrates that there is not a pharmacodynamic difference between males and females.

An issue that is brought up in the analysis of this data by the applicant's consultant is the concept of a context sensitive half-time (the time required for effect site concentrations to decline to some percent of baseline). They have done simulations using supra-maximal doses of remifentanil and time required for the effect site concentration to decline by 75%, a decline sufficient to result in recovery (see figures above). Based on their analysis it appears that within

10 minutes after discontinuation of an infusion of remifentanil, the effect site concentrations would have dropped out of the therapeutic range. This points to the two-edged nature of a drug with rapid metabolism. When remifentanil is used as a surgical adjunct, alternative opiates must be readily at hand and should be given before infusions of remifentanil are terminated. Otherwise the subjects will recover rapidly and feel the full burden of surgical trauma. Unlike most opiates where there is an upside toxicity issue, there is less of one with remifentanil as an accidental overdose in surgery will resolve by itself in ~10minutes. The dynamic issue of recovery is a real issue and one that will require adequate labeling to interpret.

2. Drug Interactions

The drug interaction studies that were included in this NDA are not of the normal type of drug interaction studies normally seen in an NDA. They were primarily concerned not with pharmacokinetic interaction, but pharmacodynamic interaction. For the majority of these trials minimal pharmacokinetic information was collected and then only on the remifentanil moiety. This lack of analysis of both target species does not allow us to rule out the possibility that the changes seen are not due to changes in the disposition of the co-administered agent.

As for the pharmacodynamic endpoints measured they were primarily clinical ones corresponding to either resistance to intubation or response to skin incision. As such these measures are subject to interpretation, technique, and other factors. They do not provide the fine resolution of methods such as spectral edge mapping for opioid effects. The measures used do lend themselves to the detection of gross differences in pharmacologic response and it is for this reason these studies are included in this NDA as supportive studies only.

a. Nitrous Oxide (USA-204)

In this study a total of 118 subjects (79 male, 39 females) received 1-40mcg/kg of remifentanil as a bolus dose followed by a continuous infusion of remifentanil in the presence of nitrous oxide. Nitrous oxide is a widely used anesthetic gas that is relatively non-toxic and has a low potency. Although it can be used as a single anesthetic agent under certain conditions, it is most widely used in mixtures of it with other halogenated anesthetic agents or opiates. This study was conducted at two centers in general surgical subjects who were to receive 66% nitrous oxide/34% oxygen by facial mask for anesthesia. Normally, this amount of nitrous oxide is insufficient to produce usable anesthesia on its own (in this study a single 2 mg/kg bolus dose of propofol was used to assure loss of consciousness). By adding remifentanil to the mixture at different rates and assessing the plasma level of remifentanil following a clinical event; at intubation, incision, every 30minutes post-incision, skin closure, spontaneous respiration, etc., a dynamic picture of the effect of differing rates of remifentanil infusion can be determined. From this it was determined that the co-administration of remifentanil with nitrous oxide does not cause a significant change in plasma levels. The calculated plasma clearance for remifentanil in this study was approximately 40-33ml/min/kg which agrees favorable with the results obtained with other trials in man. No clear pharmacokinetic difference was discernable from the data. This is most likely due to the uncontrolled nature of the study design and it's sparse sampling data which resulted in relatively high estimates of variability (%C.V.) ranging from % for the calculated pharmacokinetic parameter estimates. Even with this variability the mean data obtained does correlate with the results obtained in previous studies.

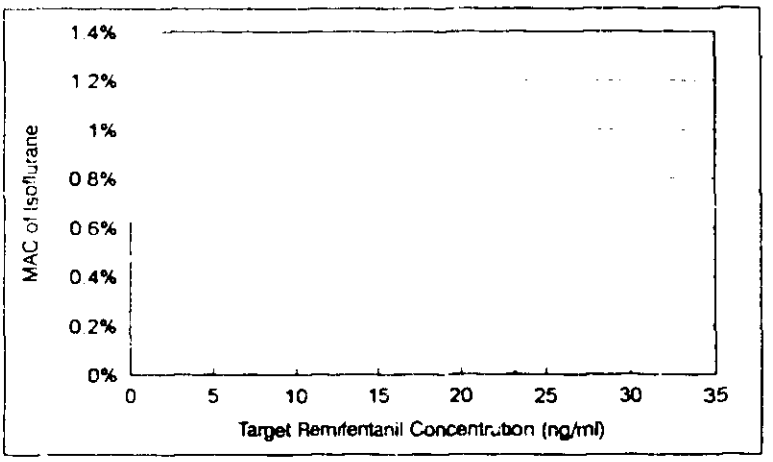
b. Isoflurane (USA-220)

Isoflurane is a widely used halogenated anesthetic gas. It is very potent, is poorly metabolized and is generally considered a safe anesthetic gas relative to agents like halothane. In this study the effect of remifentanil on the MAC (minimum alveolar concentration) was studied. MAC itself is a commonly used measure of relative potency between anesthetic agents. It correlates with the amount of an inhaled anesthetic agent required to reduce by 50% a response to surgical activity, most usually skin incision. In this study 220 male and female subjects received sufficient isoflurane/oxygen to induce a loss of conciousness.

Once this was achieved, a continuous infusion of remifentanil was started using various infusion rates designed to produce steady-state levels ranging from ng/ml. This was done by using a computer assisted infusion pump and an algorithim based upon body weight (i.e., volume) to produce the desired levels. Plasma levels of remifentanil were monitored at 5min after stable levels of isoflurane were reached, at skin incision, and 2 minutes following skin incision.

Skin incisions were made of standardized length and depth and the patients response to the incison was noted. If there was no response at a particular isoflurane/remifentanil concentration, the inhaled concentration of isoflurane was lowered in the next patient and the skin incision in that patient was monitored for response. Although a crude measure, this up-down method of assessing MAC is standard in anesthesia (it is called the up-down method as between subjects the inspired concentration can either go up or down). The results of this trial are summarized graphically below.

USA-220 MAC Reduction



From this study it appears clear that increasing the target concentration of remifentanil over 10mcg/ml is not associated with as steep a reduction in MAC as that which was fully acheived with lower doses. According to the sponsor, the mechanism of this interaction appears to be synergism at the level of the central nervous system. This conclusion is based on the stability of the end tidal concentrations of isoflurane and the stability of remifentanil concentrations (as measured by observed plasma concentration and back calculated clearance estimates) While agreeing in general with this conclusion, the paucity of plasma concentrations with which the necessary clearances were calculated by running the infusion model "backward" is somewhat disconcerting-although in theory it is acceptable.

c. Temazepam (USA-205)

Commonly benzodiazepines are used to calm a patient prior to being brought down to surgery. In addition, intra-operative use of injectable benzodiazepines can also be used as part of the anesthetic management of a patient using agents such as midazolam. In this study the interaction between temazepam (Restoril®) and remifentanil was investigated using a fixed 20mg dose of temazepam (a maximal dose) and one of five different infusion rates in a parallel study of 120 patients.

The subjects in this study were generally healthy subjects undergoing elective surgery. Each subject received their dose of temazepam approximately one hour prior to surgery. During surgery venous blood samples were obtained at baseline, induction, intubation, incision, termination of infusion, and a 1, 2, 4, 6, and 10 min. post-termination of infusion. Although the plasma level time curve was not especially well documented, the results presented in this study report does not indicate any pharmacokinetic interaction (as measured by changes in clearance) with the co-administration of a representative benzodiazepine. Temazepam did potentiate the effects of remifentanil with regards to loss of consciousness but not to skin incision. The lack of an anti-noiciecptive response is characteristic of benzodiazepines. While plasma levels of temazepam were not determined, given that the metabolic pathway of remifentanil does not involve cytochrome P-450, it is most likely that synergy at a conciousness receptor site is responsible for the potentiation of remifentanil for loss of conciousness.

d. Propofol (USA-226)

Propofol is an intravenous anesthetic agent that is administered via the I.V. route as an emulsion. It is used both as an induction agent and as a primary anesthetic agent with or without other anesthetics. In this study 55 subjects undergoing elective orthopedic arthroscopic surgery were randomized into three treatment groups based on target steady-state propofol concentrations. Following a bolus dose of 2mg/kg of propofol (sufficient to provide anesthetic induction) each subject was started on a computer assisted infusion of propofol. Once the target steady-state concentrations were reached, various infusion rates of remifentanil were administered to each subject. Once sufficient time to achieve steady-state had elapsed the subjects response to both intubation and skin incision was monitored using the previously mentioned up-down method to assess anesthetic potency. From this analysis it was determined that that there was a synergism between propofol and remifentanil, similar to that seen with isoflurane. For the three measures of surgical stress used: intubation skin incision, and intraoperative stress, the relationship between these measures and the plasma concentrations of propofol and remifentanil required were reduced. As the clearance of remifentanil was unchanged, the mechanism proposed by the sponsor is one of synergism

e. Thiopental (USA-203)

Thiopental is a rapid onset barbituate that is used to induce anesthesia. It is commonly given with a skeletal muscle relaxant to facilitate tracheal intubation prior to administering a general anesthetic agent. This study was an assessment of the comparative potency of remifentanil vs. alfentanil in the induction setting. A total of nine different dose groups of remifentanil (ranging from mcg/kg) were compared to seven different dose groups of alfentanil (ranging from mcg/kg). For each dose group the study drug was

administered as a 2min. infusion. If there was no loss of consciousness within 30sec. of drug administration 2mg/kg/min of thiopental was administered until loss of conciousness.

By using the large number of dosage levels the applicant was able to determine with a high degree of precision both the ED50 and EC50 values for both remifentanil and alfentanil for induction (i.e. loss of consciousness). The values determined are reproduced below:

Mean Values (range)

	ED50 (ug/kg)	EC50 (ng/ml)
Remifentanil	12 (9-22)	54 (35-118)
Alfentanil	169 (122-434)	1012 (712-9149)
Potency:R to A	14	18.7

These values compare very favorably to those determined in USA-104 using spectral edge analysis which predicted that remifentanil was 17 times as potent as alfentanil. This high degree of correlation suggests that either estimate is an acceptable one and that the true potency probably is near the average of the two or approximately 15.5x. While relative potency ratios are useful for calculating doses and for making general comparisons across drugs they do not tell the whole story. One could argue that a better measure of relative potency would include the variable of duration of effect. Clearly the data here suggests that remifentanil is 15x as potent in **onset,** but due to its short half-life a single bolus dose of remifentanil is not going to have the same duration of action as a bolus dose of alfentanil. Potency, potency ratios, and the general concepts are a slippery slope and should be viewed with extreme caution when used in advertising as it is not the whole story. One could theorize that a new parameter that incorporates an AUC approach, that is comparative AUC above the EC50 level would provide a better basis of comparison, between the drugs being tested. Until such a metric is developed the advertising of potency will need to be balanced with statements regarding either context sensitive half-time or some other measure of duration of action.

F Surgical Settings

Remifentanil is being developed as a general surgical adjunctive agent with the same range of indications as sufentanil, fentanyl, and alfentanil. One particular area of interest in the use of narcotic assisted anesthesia is in cardiac surgery. This presents a unique problem for remifentanil in that as its mechanism of elimination in biochemical in nature, i.e. interaction with plasma esterases, the degrqdation reaction, like all biochemical reactions, is subject to outside influences such as pH and temperature. While pH is never much of a concern, due to the physiologic mechanisms that keep blood pH within relatively tight limits, temperature is a concern in that during cardiac surgery the blood is cooled to decrease the metabolic requirement of the heart tissue. This cooling of the blood will, therefore, cause a decrease rate of drug metabolism causing accumulation of remifentanil in excess of what would be predicted using a standard model incorporating a standard clearance. In order to assess this issue the applicant undertook two studies to address this issue under clinical conditions (USA-207 and USA-221P). Of these two studies USA-221P was a pilot study in a small number of subjects with limited plasma sampling. As the data from USA-207 was more complete and was from a larger pool of subjects, USA-221P was not included in this review.

1 CABG (USA-207)

This was a study in 16 subjects undergoing coronary artery bypass grafting (i.e. CABG). During the surgical procedure each subject received a 1 minute infusion of remifentanil prior to the beginning of bypass, during bypass, and during the re-warming phase. Originally the study was designed to incorporate 4 different dosage levels: 2, 5, 10 and 20mcg /kg. The study was stopped following completion of the 5mcg/kg dosage level due to episodes of hypotension exceeding the pre-determined safety limit (30% below baseline) for dose escalation.

During each phase of the study (pre-bypass, bypass, and re-warming) arterial levels were collected for both remifentanil and the primary metabolite GR90291 for up to 40minutes post dosing. The results of this trial for remifentanil are reproduced below:

USA-207 Mean Data (+/-S.D.)

	Pre-Bypass	Bypass	Warming
Cl (ml/min/kg)	31.48 (13.4)	25.17 (9.1)	34.8 (17)
Vss (ml/kg)	176.6 (96)	328.8 (443)	246 (224.6)
$\lambda z T_{1/2}$ (min)	6.4 (1.76)	11.9 (7.5)	7.23 (2.4)

The data from this trial suggests that the cooling effect of coronary bypass caused a 20% decrease in plasma clearance that resulted in a doubling of both volume and terminal elimination rate. This increase in volume is most likely due to the deeper compartmentalization taking place due to the longer plasma half-life. In comparison GR90291 showed little if any change in its pharmacokinetics. This would be expected as it is eliminated in the urine by glomerular filtration. Cooling should have minimal effect upon such a system. The data for GR90291 is somewhat nosier than that of the parent as, due to its longer plasma half-life of 2 hours, both the bypass and warming phase showed residual metabolite from the previous doses. With remifentanil, as the half-life is so short, over a 40 minute interval plasma levels are basically undetectable. With GI90291 the appearance of seemingly significant increases in plasma levels over the first observation interval is due to the lack of time to eliminate the previous dose causing accumulation of the metabolite in the later observation intervals.

All in all this study has shown that the metabolism of remifentanil is sensitive to temperature and under the conditions associated with CABG surgery clearance is reduced approximately 20%. This reduction was associated with increases in the plasma concentration of remifentanil and an apparent dose related increase in hypotension. The link between hypotension and remifentanil is being reviewed by the reviewing medical officer. In light of this information it would seem prudent to indicate in the label that while subjects are on cardiac bypass the infusion rate of remifentanil should be reduced 20-30% to avoid or minimize the potential for dose related hypotension.

G Bioequivalency (USA-106)

As noted in the formulation section of this NDA there was some concern regarding the equivalency of remifentanil from the two different routes of synthesis. This issue was brought to a head by the reviewing pharmacologist after reviewing the results of a beagle dog study in which the rate of microhemmorhages in the brain was felt to be higher with the route 2 product. In an

attempt to demonstrate the equivalence of the two formulations the sponsor agreed to do a bioequivalency trial in 26 healthy adult subjects using sub-anesthetic doses of remifentanil. A dose of 0.2mcg/kg/min was administered to the subjects as a 10min infusion on two separate occasions with a 2-14 day washout period in between. Not suprisingly the sponsor was able to demonstrate bioequivalency between the two formulations for both AUC and Cmax.

USA-106 Mean Data

	Remifentanil	
	AUC (min*ng/ml)	Cmax (ng/ml)
Route 1	55.6	5.14
Route 2	50.9	4.72
90% C.I.*	88-95	86-98

*90% C.I.-Log transformed 90% Confidence Interval Acceptance Interval = 80-125%

While this study was primarily a bioequivalence determination, it also yielded relatively stable estimates of Cl, Vdss and half-life that were unaffected by surgical procedure or disease state. These values, from both treatments agree favorably with those from USA-102, 104, 210 and 211.

USA-106 Mean Data (+\-S.D.)

	Remifentanil		
	Cl (ml/min/kg)	Vss (ml/kg)	$\lambda z T_{1/2}$ (min)
Route 1	36.4 (6)	345 (45)	6.6
Route 2	40 (6)	392 (93)	6.8

The only conclusion that can be drawn from this study is that it appears that the two formulations are pharmacokinetically bioequivalent. Whether or not route 2 material contains a trace precursor or some entity that causes microhemmorhages is beyond the scope of the study. In the absence of an altered clinical response it appears that the issue with the microhemmorhages in the dogs is more related to the lack of ventilation rather than differences in the two formulations.

V Conclusions

Based upon this reviewers analysis of the information contained in the pharmacokinetic section of the NDA the following conclusions can be drawn:

1. The pharmacokinetics of remifentanil after IV administration are best described by a three compartment model.
2. Estimates of the plasma half-life of remifentanil range from minutes
3. Remifentanil is metabolized by non-specific plasma esterases in the plasma, it is not metabolized by the liver to any appreciable extent.

4. The primary metabolite of remifentanil, the carboxcyclic acid, has (according to the reviewing pharmacologist) approximately 1/4600th of the potency of the parent compound.
5. The pharmacokinetics of remifentanil are unchanged in the presence of renal impairment. The elimination kinetics of the primary metabolite are changed, however, based on the data presented in this NDA using infusions of up to 4 hours duration, the accumulation of metabolite was not associated with any pharmacologic activity or toxicity. The metabolite can be removed via hemodialysis.
6. The pharmacokinetics of remifentanil are dose independent for both volume and clearance.
7. From a pharmacodynamic standpoint, using Spectral Edge, remifentanil is 17x as potent as alfentanil and has a blood-brain equilibration half-time of approximately 90s.
8. In elderly patients (over 65 years of age) there appears to be a greater sensitivity to the effects of remifentanil as determined by EC50, such that starting doses of remifentanil should be halved and subsequent doses should be titrated to individual response.
9. In a small study, pediatric patients appeared to have similar pharmacokinetic profiles as compared to adults from other trials. Pharmacodynamics have not been done in the pediatric population.
10. In obese patients (>80% above IBW) remifentanil can be used without dosage modification, however, the pharmacokinetic parameters did correlate better with dosing based on ideal body weight.
11. Nitrous oxide did not interact with remifentanil.
12. Both propofol and isoflurane are potentiated by remifentanil.
13. Temazepam did not affect the pharmacokinetics of remifentanil, however, it did speed up the rate of loss of conciousness.
14. Remifentanil is synergistic with thiopental in causing loss of conciousness as part of induction.
15. The effect of the cooling of the blood during cardiac bypass caused a 20% decrease in plasma clearance. Once the blood was re-warmed, clearance returned to pre-bypass levels.
16. The route of synthesis has no impact on the pharmacokinetics of remifentanil.

VI. Comments

1. Due to the analytical difficulties encountered with USA-216P (pediatrics), more than 1/2 of the total number of subjects were unevaluable. While the remaining subjects did not demonstrate markedly different pharmacokinetics from adults, the sponsor should commit to replication of USA-216P with the full complement of subjects prior to approval of a limited pediatric indication. Such a study should also incorporate dynamic comparisons of the effect of remifentanil in pediatrics along with standard pharmacokinetics.
2. Throughout this NDA the applicant has made repeated comparisons between itself and alfentanil and their relative potencies. While it is indeed true that remifentanil is 17x as potent as alfentanil, according to spectral edge analysis, this arguement does not take into consideration the longer duration of action of alfentanil. Remifentanil may be more potent on a mg to mg level but this is not the only issue

relating to the ease of use of a product. When potency claims are being used by the sponsor they should be required to put potency into perspective regarding the comparative half-lives of the agents.

E. Dennis Bashaw 4/9/96

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Secondary Review, John Hunt, Dep. Dir. (DPE-II) 5/2/96

CC: NDA 20-630 (ORIG),
HFD-550/DIV File
HFD-550/CSO/ Morgan
HFD-870 (Clarence Bott, Drug, Chron Files)
HFD-880(Fleischer)
HFD-870 (Hunt)
HFD-860 (Malinowski)
HFD-550(Bashaw)
HFD-344(Viswanathan)
HFD-205

Appendix I-Study Summary Sheets

Pivotal Trials

Supportive Trials

USA-202 (UCP/92/029)
Pharmacokinetic Study Summary

NDA # 20-630 Submission Date: 9/15/95 Volume 71-73

Investigator:
Site:

Single Dose: X . Multiple Dose:_____.
Subjects: Normal:____. Patients: X . Young: X. Elderly:____.
Hepatic:____. Renal: ___.
Cross-Over:____. Parallel: X. N= 25 M= 14 F= 9

Subject Type: Patients scheduled for elective inpatient surgery

Category	Remifentanil Dosage Group			
	2 µg/kg N = 7	5 µg/kg N = 6	15 µg/kg N = 6	30 µg/kg N = 6
Gender - male/female	3(43%)/4(57%)	3(50%)/3(50%)	3(50%)/3(50%)	3(50%)/3(50%)
Age - years	43 ± 6 (34-49)	38 ± 9 (22-48)	32 ± 11 (18-40)	46 ± 11 (32-60)
Weight - kg	79 ± 20 (55-109)	79 ± 16 (58-99)	77 ± 9 (64-93)	80 ± 19 (50-107)

Treatment Summary:
Remifentanil, 1-minute infusion, Lot # CS-USA10001 and CS-USA10007
Doses 2.0, 5.0, 15, and 30µg/kg

Sample Strategy:

Blood Samples: Arterial samples were collected prior to dosing (≤30min), at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 15, 20, 25, 30, 40, 60, 90, 120, 180, 240, and 360min after the infusion and 1440min post infusion.

Histamine: Blood samples were collected predose, 1, 3, and 5 minutes post-infusion.

Assay Method:
Remifentanil GC-High Resolution Mass Spectrometry-Selected Ion Monitoring
GR90291 Gas chromatography with tandem mass spectrometry (GC/MS/MS)

Sample	Sensitivity	Site	%CV (QC Conc)	QC Range
Remifentanil	0.1 ng/mL	Triangle	3.0% (20ng/ml) - 11.5% (0.2ng/ml)	0.2-20ng/ml
GR90291	1ng/mL	Phoenix	6.5% (75ng/ml) - 13.2% (1.5ng/ml)	1.5-75ng/ml

Labeling Claims From Study: The clearance and volume of distribution of remifentanil are independent of dose. The pharmacokinetics of the principle metabolite of remifentanil (GR90291) are independent of remifentannil dose. Histamine concentrations were not altered by the administration of remifentanil.

Study 202 - Remifentanil Pharmacokinetics in Inpatient Surgical Patients

Conclusions: The pharmacokinetics of remifentanil (R) were independent of dose over the dose range studied (2-30mcg/kg). The mean clearance for R ranged from 59.5-64.0mL/min/kg and mean volume of distribution ranged from 303-498 mL/kg. No differences between dose groups were observed in the pharmacokinetics of GR90291, the primary metabolite of R. Mean dose-normalized AUC_{∞} for GR90291 ranged from 380-457ng/mL and mean dose-normalized C_{max} ranged from 2.77-3.02ng/mL. Systolic and diastolic blood pressure and heart rate showed a decrease during and immediately following the R infusion, although this effect did not appear to be dose-related except in the case of SBP. R infusion did not result in an increase in blood histamine concentrations.

Investigators:

Purpose: 1) to evaluate the pharmacokinetics of bolus intravenous doses of R in ASA I-III patients; 2) to evaluate the hemodynamic response to intravenous administration of R; 3) to evaluate the potential for histamine release following R administration

Study Design: Single-center, open-label, parallel study in four groups of patients undergoing elective surgery. Patients received a single intravenous infusion of 2, 5, 15 or 30mcg/kg R over one-minute at approximately 10 minutes post-intubation.

Demographics: 25 patients, aged 18-60 years, male and female, ASA status I-III.

Anesthesia Protocol: *Premedication:* Diazepam (2.5-10mg p.o.) administered 60-90 minutes prior to surgery, or midazolam (0.5-3mg IV) administered prior to induction, as necessary. *Induction:* Etomidate (0.1-0.5mg/kg) and oxygen. Vecuronium (0.1mg/kg) was administered intravenously to facilitate intubation. Following intubation, glycopyrrolate (up to 0.5mg) was administered intravenously followed by R. *Maintenance:* 66% nitrous oxide in oxygen with supplementation using isoflurane as needed.

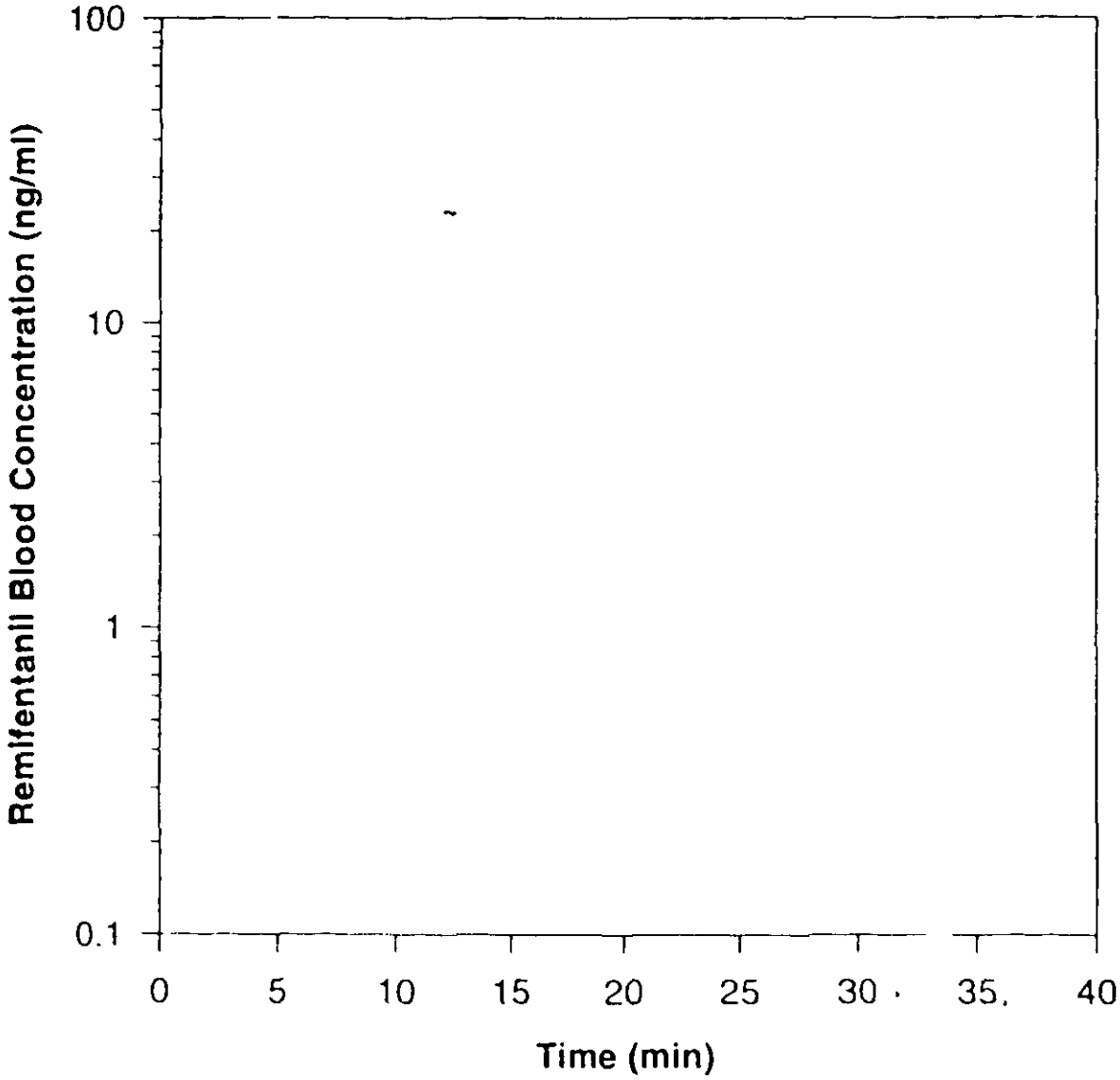
Results: **Table of Principle PK and Safety Results, All Subjects (N=25)**
Values are N (% Total) or Mean ± SD

	R Dose Groups			
	2 µg/kg	5 µg/kg	15 µg/kg	30 µg/kg
Pharmacokinetics	N = 6	N = 6	N = 6	N = 6
R CL (mL/min/kg)	59.5 ± 28.2	63.9 ± 20.5	70.0 ± 21.0	64.0 ± 18.6
R Vd_{ss} (mL/kg)	303 ± 162	336 ± 175	368 ± 79	498 ± 266
GR90291 AUC_{∞} (ng•min/mL)[1]	452 ± 64	323 ± 53	348 ± 34	380 ± 111
GR90291 C_{max} (ng/mL)[1]	3.02 ± 0.54	2.67 ± 0.61	2.76 ± 0.48	2.77 ± 0.61
Safety	N = 7	N = 6	N = 6	N = 6
Any adverse event	4 (57%)	6 (100%)	6 (100%)	5 (83%)
Systolic blood pressure (mmHg)[2]	-21.9 (9.9)	-31.7 (5.4)	-40.2 (5.8)	-37.7 (8.4)
Blood Histamine Concs (nmol/L)[3]	0.30 (0.27)	0.41 (0.23)	-0.19 (0.44)	-0.30 (0.09)

[1] Values for 5, 15 and 30 µg/kg R dose groups are normalized to a 2 µg/kg dose.
[2] Maximum decrease within 10 minutes of dosing, expressed as change from baseline
[3] Mean change from predose

The adverse event incidence was similar in the four groups.

Remifentanil Blood Concentration-Time Profiles Following 2.0~~mg/kg~~ mcg/kg



GI87084 COMPARTMENTAL PHARMACOKINETIC PARAMETERS

DOSE = 2.0 mcg/kg

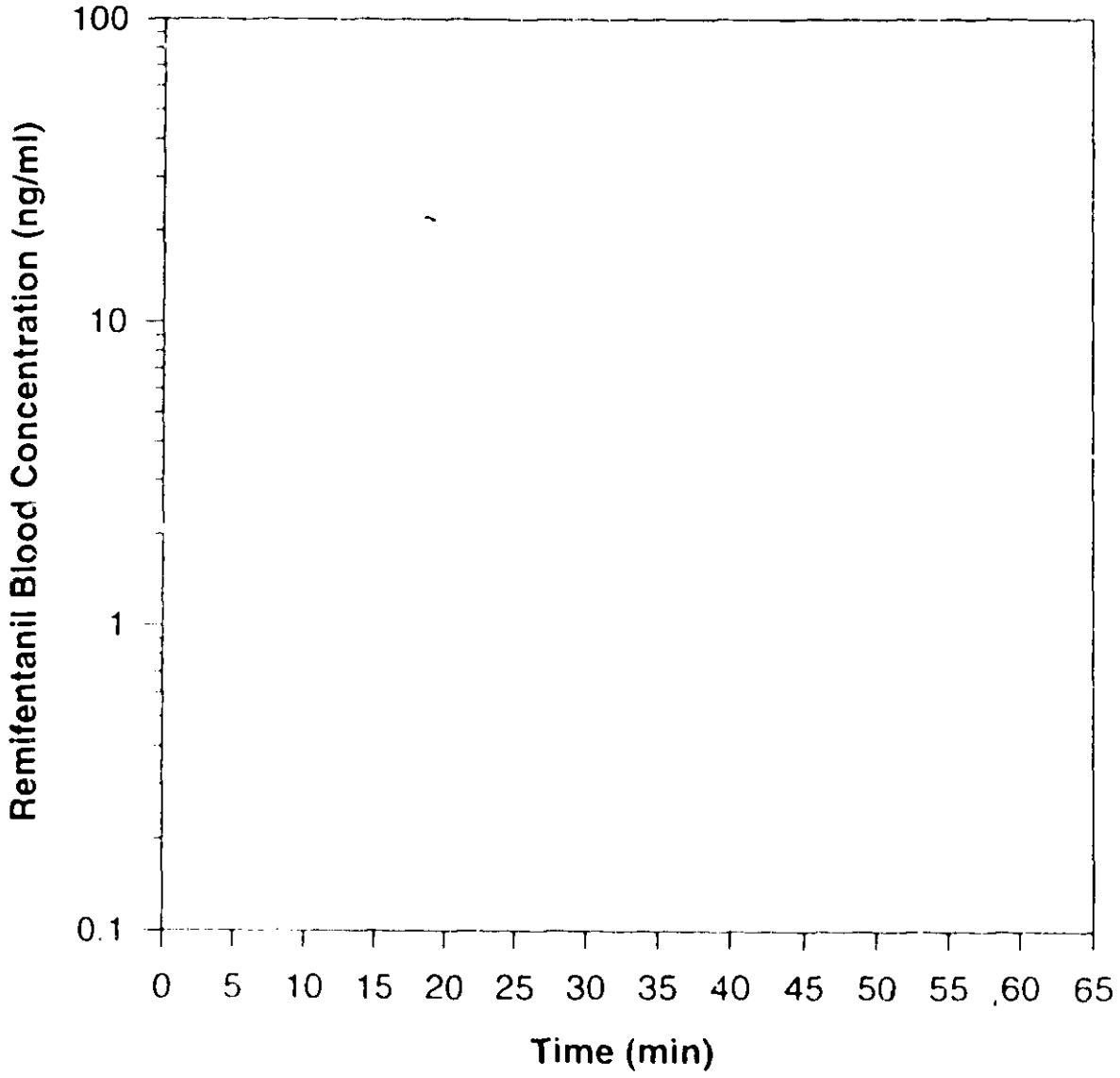
SUBJECT	AUC (ng*min/mL)	λ_1 t1/2 (min)	λ_2 t1/2 (min)	λ_3 t1/2 (min)	Vdss (mL/kg)	Vdss (L)	CL (mL/min/kg)	CL (L/hr)
	43.97							
	52.54							
	27.59							
	18.07							
	54.29							
	37.19							
Arithmetic Mean	38.94	0.47	2.10	9.64	303.02	22.62	59.48	262.20
SD	14.24	0.09	0.49	4.32	162.04	9.04	28.19	71.78
%CV	36.56	19.09	23.39	44.79	53.47	39.98	47.39	27.38
Geometric Mean	36.41	0.46	2.05	8.93	268.98	20.72	54.88	253.60
Median	40.58	0.49	2.02	8.27	268.46	23.03	49.52	269.09
Range								
Low	18.07	0.36	1.63	5.80	141.74	8.50	36.84	162.93
High	54.29	0.57	2.72	16.97	564.89	32.45	110.44	364.45
Harmonic Mean		0.45	2.01	8.34				
Jackknife SD		0.09	0.45	3.12				

GI87084 NONCOMPARTMENTAL PHARMACOKINETIC PARAMETERS

DOSE = 2.0 mcg/kg

SUBJECT	AUC (ng*min/mL)	AUCinf (ng*min/mL)	AUMCinf (ng*min²/mL)	MRT (min)	Vdss (mL/kg)	Vdss (L)	CL (mL/min/kg)	CL (L/hr)
Arithmetic Mean		34.59		6.37	535.29	37.40	72.73	314.33
SD		14.07		2.39	558.58	28.86	48.35	131.95
%CV		40.69		37.48	104.35	77	66.48	41.98
Geometric Mean		31.44		5.98	380.20	29.28	63.56	293.72
Median		35.55		5.95	368.67	29.15	56.40	293.43
Range								
Low		11.87		3.23	146.09	8.77	37.88	162.90
High		52.81		9.76	1643.92	90.42	168.49	556.01

Remifentanil Blood Concentration-Time Profiles Following 5.0~~mg/kg~~ mcg/kg



GI87084 COMPARTMENTAL PHARMACOKINETIC PARAMETERS

DOSE = 5.0 mcg/kg

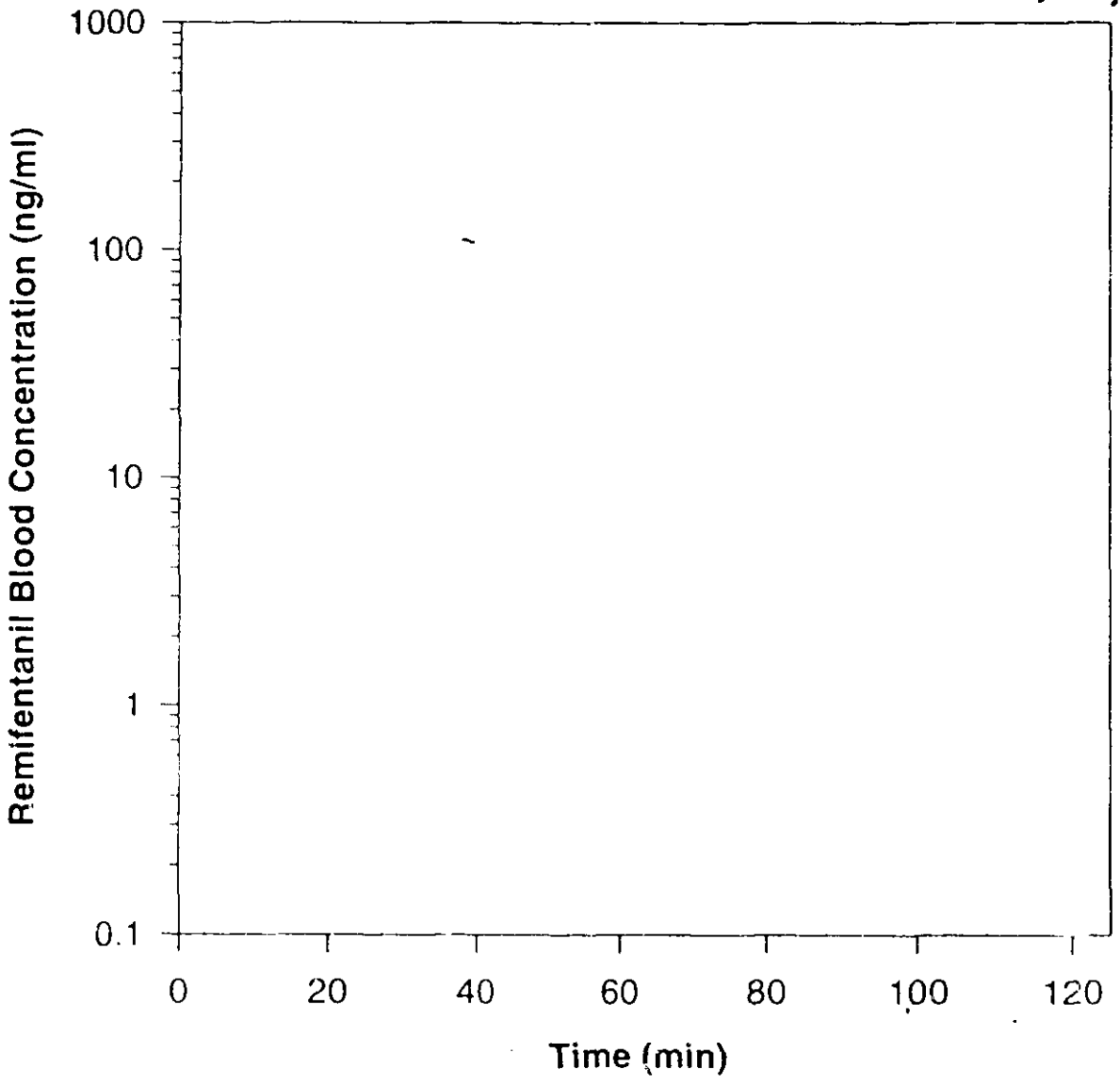
SUBJECT	AUC (ng*min/mL)	$\lambda_1 t_{1/2}$ (min)	$\lambda_2 t_{1/2}$ (min)	$\lambda_z t_{1/2}$ (min)	Vdss (mL/kg)	Vdss (L)	CL (mL/min/kg)	CL (L/hr)
	151.48				93.98	9.30	33.01	196.07
	66.12				296.81	17.21	75.62	263.17
	76.21				308.56	18.95	65.61	241.71
	56.89				610.34	51.27	87.89	442.99
	108.30				446.26	40.57	46.17	251.79
	66.71				262.02	21.43	74.96	367.89
Arithmetic Mean	87.62	0.53	2.48	10.88	336.33	26.46	63.88	293.94
SD	36.00	0.15	0.56	6.37	175.36	15.97	20.53	92.43
%CV	41.09	27.26	22.73	58.52	52.14	60.38	32.14	31.44
Geometric Mean	82.43	0.52	2.43	9.63	291.56	22.66	60.66	282.82
Median	71.46	0.56	2.54	9.74	302.68	20.19	70.28	257.48
Range								
Low	56.89	0.33	1.88	5.60	93.98	9.30	33.01	196.07
High	151.48	0.68	2.96	22.79	10.34	51.27	87.89	442.99
Harmonic Mean		0.50	2.38	8.69				
Jackknife SD		0.16	0.57	4.03				

GI87084 NONCOMPARTMENTAL PHARMACOKINETIC PARAMETERS

DOSE = 5.0 mcg/kg

SUBJECT	AUC (ng*min/mL)	AUCinf (ng*min/mL)	AUMCinf (ng*min²/mL)	MRT (min)	Vdss (mL/kg)	Vdss (L)	CL (mL/min/kg)	CL (L/hr)
	50.71	53.54	435.19	7.63	712.47	70.53	93.39	544.75
	65.78	67.22	331.78	4.44	329.93	19.14	74.38	258.85
	51.75	52.71	442.93	7.90	749.58	46.02	94.85	349.44
	54.22	57.14	428.17	6.99	611.93	51.40	87.50	441.02
	107.34	111.61	1158.46	9.88	442.60	40.23	44.80	244.33
	65.82	67.00	310.51	4.13	308.51	25.24	74.62	366.25
Arithmetic Mean		68.20		6.83	525.84	42.09	78.26	369.11
SD		22.20		2.20	192.27	18.58	18.64	116.41
%CV		32.55		32.16	36.57	44.13	23.82	31.54
Geometric Mean		65.79		6.51	495.07	38.47	76.00	354.37
Median		62.07		7.31	527.26	43.13	81.06	357.84
Range								
Low		52.71		4.13	308.51	19.14	44.80	244.33
High		111.61		9.88	749.58	70.53	94.85	554.75

Remifentanil Blood Concentration-Time Profiles Following 15.0~~mg/kg~~ mg/kg



GI87084 COMPARTMENTAL PHARMACOKINETIC PARAMETERS

DOSE = 15.0 mcg/kg

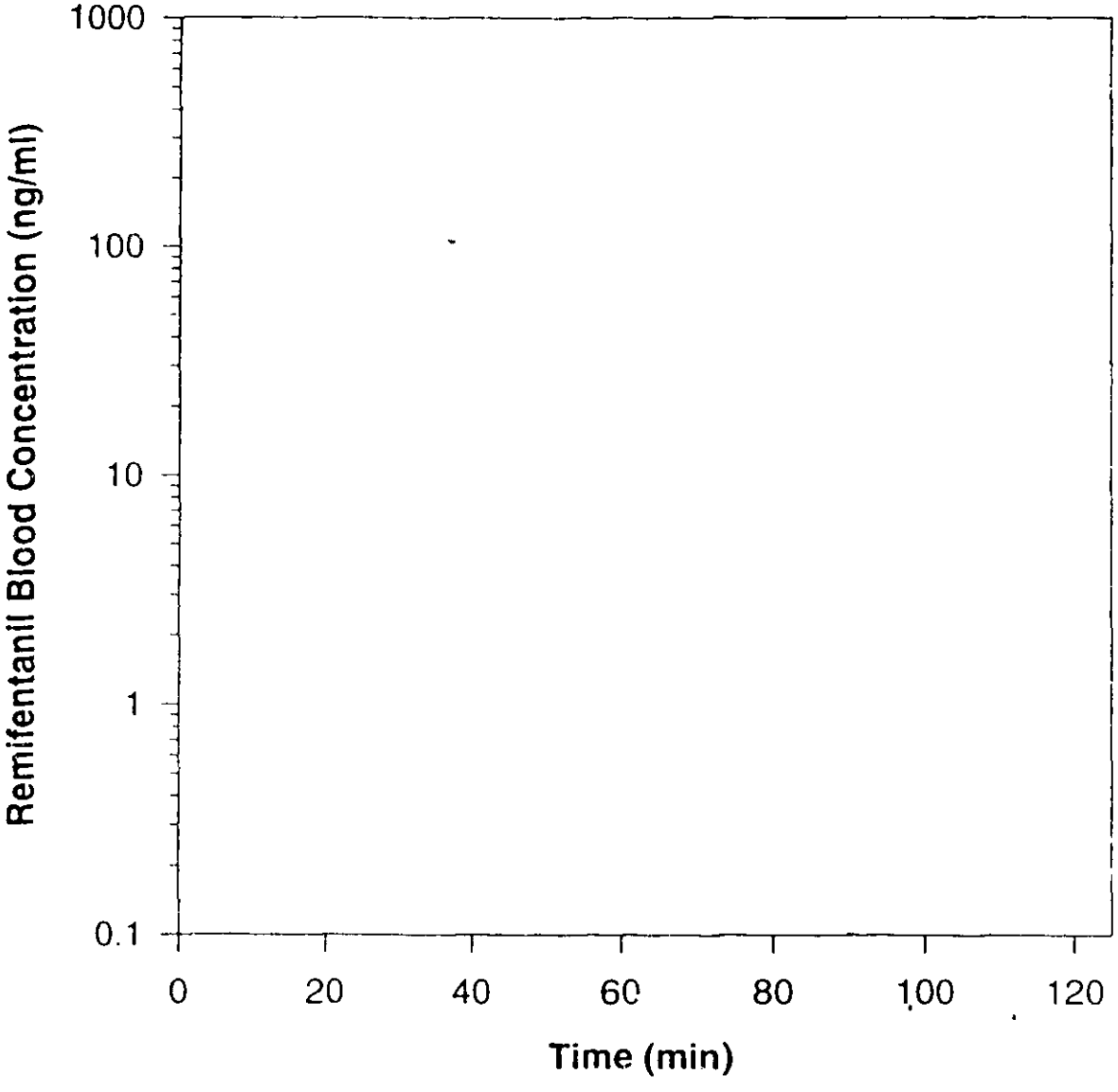
SUBJECT	AUC (ng*min/mL)	$\lambda_1 t_{1/2}$ (min)	$\lambda_2 t_{1/2}$ (min)	$\lambda_3 t_{1/2}$ (min)	Vdss (mL/kg)	Vdss (L)	CL (mL/min/kg)	CL (L/hr)
	276.27							
	193.35							
	358.49							
	161.00							
	347.58							
	283.01							
Arithmetic Mean	269.95	0.56	3.24	18.40	368.21	27.98	60.99	279.36
SD	79.77	0.14	0.82	8.72	78.53	5.30	21.03	97.53
%CV	29.55	25.51	25.29	47.40	21.33	18.95	34.48	34.91
Geometric Mean	259.20	0.54	3.16	16.90	361.55	27.55	58.25	266.38
Median	279.64	0.56	3.16	16.09	360.78	28.75	54.18	247.37
Range								
Low	161.00	0.37	2.28	10.27	284.44	21.33	41.84	188.29
High	358.49	0.79	4.48	33.70	497.02	34.57	95.03	432.91
Harmonic Mean		0.53	3.08	15.67				
Jackknife SD		0.14	0.78	6.31				

GI87084 NONCOMPARTMENTAL PHARMACOKINETIC PARAMETERS

DOSE = 15.0 mcg/kg

SUBJECT	AUC (ng*min/mL)	AUCinf (ng*min/mL)	AUMCinf (ng*min²/mL)	MRT (min)	Vdss (mL/kg)	Vdss (L)	CL (mL/min/kg)	CL (L/hr)
Arithmetic Mean	230.54			8.12	568.84	43.37	71.13	325.60
SD	79.76			2.97	259.38	19.55	20.07	93.01
%CV	34.60			36.65	45.60	45.08	28.21	28.56
Geometric Mean	220.71			7.71	527.37	40.19	68.41	312.84
Median	193.96			7.51	472.29	36.52	77.34	354.36
Range								
Low	162.28			5.34	349.48	26.21	40.36	184.75
High	371.68			13.25	1027.72	77.08	94.28	430.37

Remifentanil Blood Concentration-Time Profiles Following 30.0~~mg/kg~~ mcg/kg



GI87084 COMPARTMENTAL
PHARMACOKINETIC PARAMETERS

DOSE = 30.0 mcg/kg

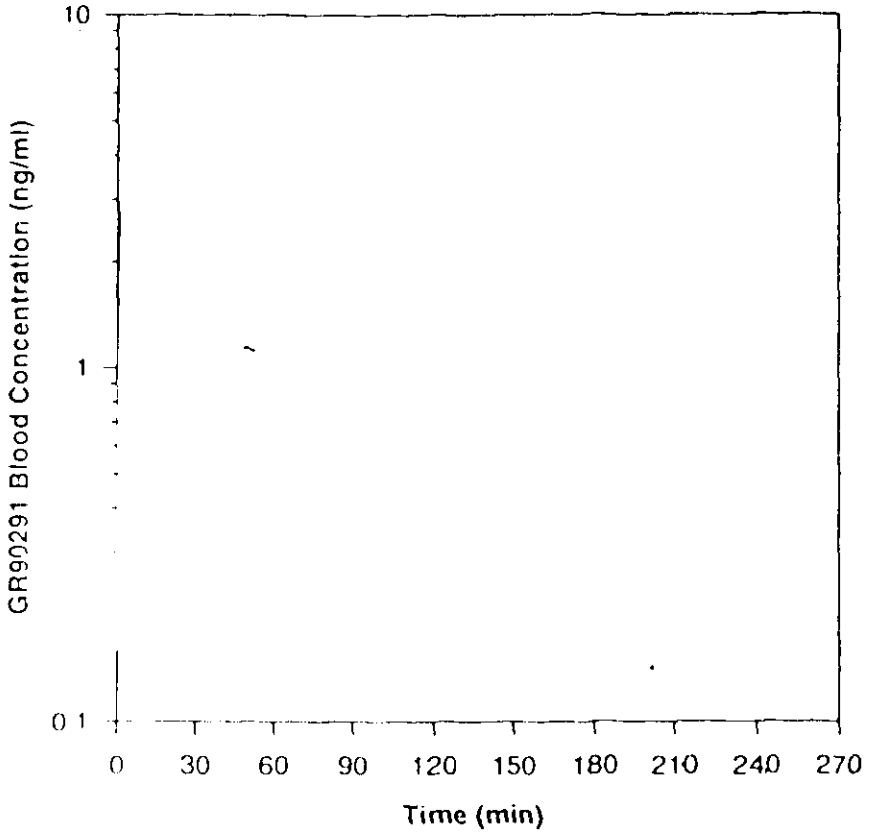
SUBJECT	AUC (ng*min/mL)	$\lambda_1 t_{1/2}$ (min)	$\lambda_2 t_{1/2}$ (min)	$\lambda_3 t_{1/2}$ (min)	Vdss (mL/kg)	Vdss (L)	CL (mL/min/kg)	CL (L/hr)
Arithmetic Mean	512.69	0.64	4.12	32.22	497.72	39.75	64.04	296.82
SD	171.91	0.33	1.25	25.90	265.59	23.66	18.64	75.20
%CV	33.53	51.30	30.34	80.38	53.36	59.52	29.10	25.34
Geometric Mean	491.02	0.58	3.92	25.09	445.21	34.79	61.57	288.72
Median	462.80	0.50	4.32	19.31	448.40	26.75	66.02	310.65
Range								
Low	346.23	0.39	2.02	10.75	240.10	20.84	37.57	195.67
High	803.82	1.24	5.46	75.11	961.26	75.94	87.22	413.44
Harmonic Mean		0.54	3.69	20.47				
Jackknife SD		0.20	1.80	13.03				

GI87084 NONCOMPARTMENTAL
PHARMACOKINETIC PARAMETERS

DOSE = 30.0 mcg/kg

SUBJECT	AUC (ng*min/mL)	AUCInf (ng*min/mL)	AUMCInf (ng*min²/mL)	MRT (min)	Vdss (mL/kg)	Vdss (L)	CL (mL/min/kg)	CL (L/hr)
Arithmetic Mean		541.82		7.68	479.31	38.33	60.51	280.97
SD		174.94		3.45	303.27	26.14	18.12	75.40
%CV		32.29		44.94	63.27	68.19	29.94	26.84
Geometric Mean		519.70		7.06	410.96	32.12	58.17	272.79
Median		522.24		6.61	412.76	25.70	58.32	277.30
Range								
Low		354.97		4.07	228.02	16.87	36.19	188.48
High		334.49		11.96	1017.89	80.43	85.08	403.27

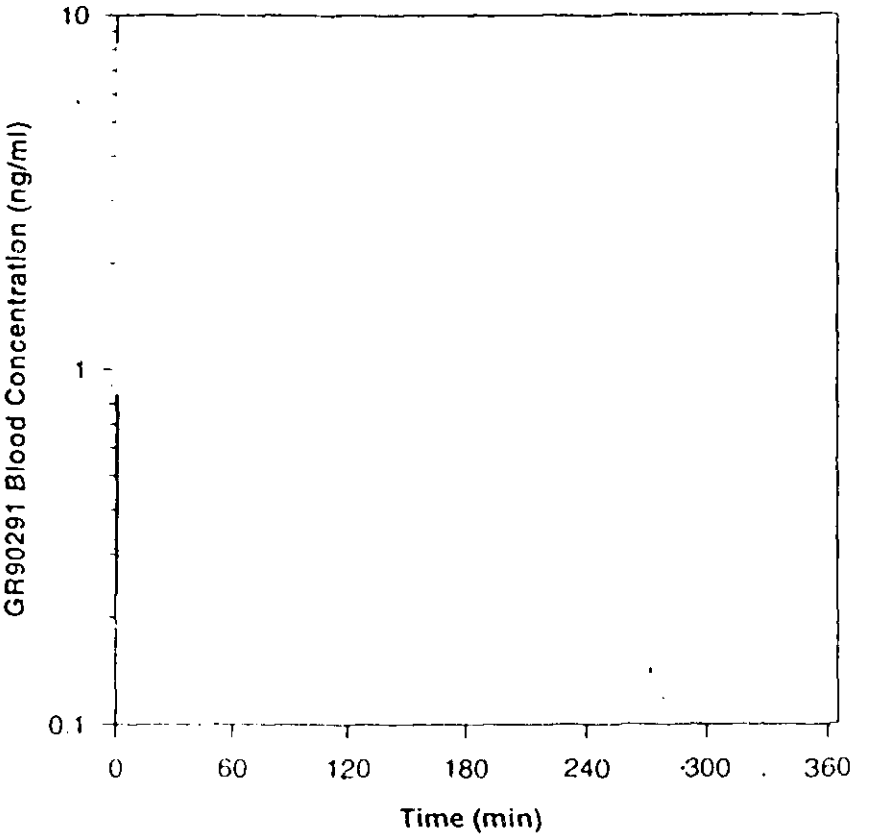
GR90291 Blood Concentration-Time Profiles Following 2.0~~mg/kg~~ mcg/kg



DOSE = 2.0 mcg/kg

SUBJECT	Tmax (min)	Cmax (ng/mL)	AUCinf (ng*min/mL)	Half-life (min)	AUC Ratio
MEAN	34	3.02	456.6	137.4	15.96
SD	16	0.54	64.1	55.9	8.97

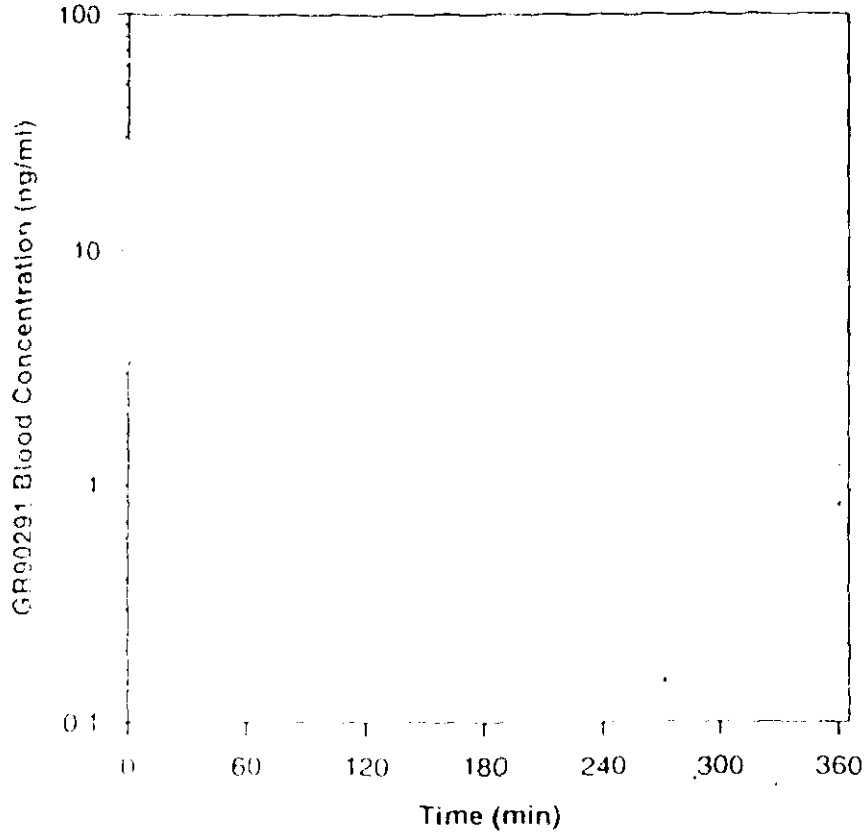
GR90291 Blood Concentration-Time Profiles Following 5.0~~mg/kg~~ mcg/kg



DOSE = 5.0 mcg/kg

SUBJECT	Tmax (min)	Cmax (ng/mL)	AUCinf (ng*min/mL)	Half-life (min)	AUC Ratio
MEAN	26	6.68	807.1	128.0	12.35
SD	6	1.52	131.3	34.0	2.51

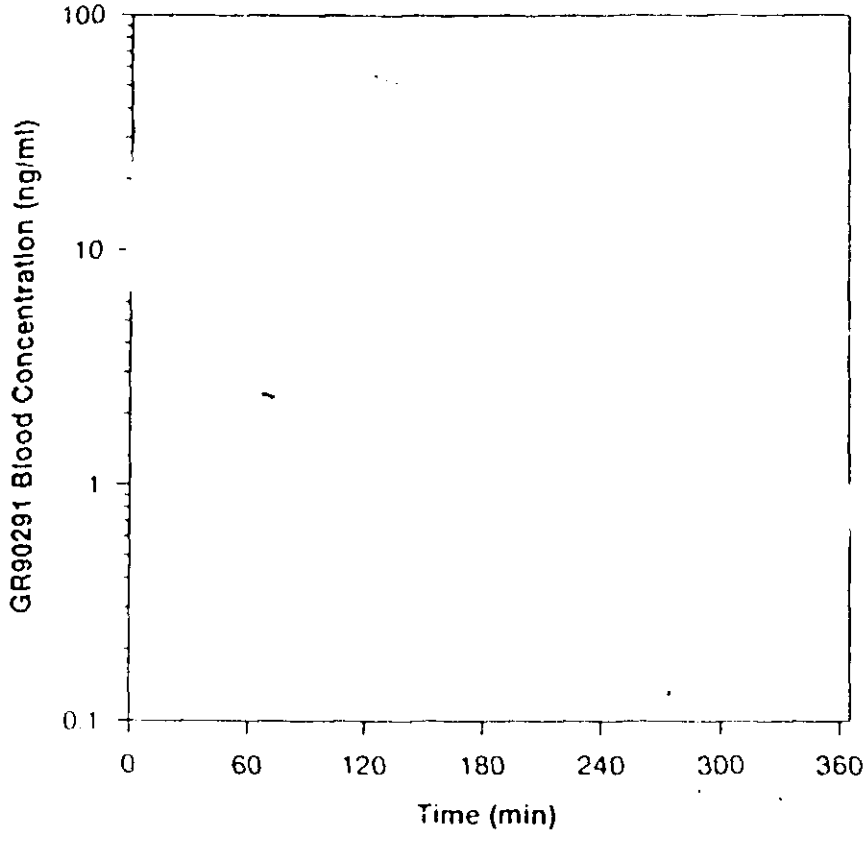
GR90291 Blood Concentration-Time Profiles Following 15.0mg/kg



DOSE = 15 mcg/kg

SUBJECT	Tmax (min)	Cmax (ng/mL)	AUCinf (ng*min/mL)	Half-life (min)	AUC Ratio
MEAN	29	20.7	2609.2	88.1	12.13
SD	7	3.6	258.4	10.1	3.04

GR90291 Blood Concentration-Time Profiles Following 30.0mg/kg mg/kg



DOSE = 30 mcg/kg

SUBJECT	Tmax (min)	Cmax (ng/mL)	AUC (ng*min/mL)	Half-life (min)	AUC Ratio
MEAN	31	41.5	5698.8	99.2	11.36
SD	10	9.1	1663.8	27.7	5.03

Study USA-102 (UCP/91/012)
Pharmacokinetic Summary

NDA # 20-630 Submission Date: 9/15/95 Volume 57-60

STUDY TYPE: Single escalating 4-hour infusion, Safety and PK/PD

Investigator:
Site

Single Dose: XXX Multiple Dose: ____

Subjects:
Normal: XXX Patients ____ Young: ____ Elderly: ____
Impaired Hepatic: ____ Renal ____

Cross-Over: ____ Parallel: XXX N= 33 M= 33 F= 0

Subject Type: Healthy Male Volunteers

	Remifentanil (µg/kg/min)						Alfentanil (µg/kg/min)	
	Placebo	0.025	0.05	0.075	0.1	0.2	0.5	1.0
N	6	3	6	3	3	3	6	3
Gender male/female	6/0	3/0	6/0	3/0	3/0	3/0	6/0	3/0
Age (years)	23.0 ± 2.8 (20-65)	25.7 ± 5.0 (21-31)	22.7 ± 4.4 (19-31)	20.3 ± 0.6 (20-21)	22.0 ± 1.0 (21-23)	25.3 ± 4.2 (22-30)	24.7 ± 1.8 (22-26)	29.3 ± 4.2 (26-34)
Weight (kg)	83.8 ± 9.7 (75.5-100.5)	90.4 ± 3.3 (86.6-93.0)	77.6 ± 11.8 (64.0-97.0)	72.4 ± 8.7 (64.0-81.3)	82.4 ± 17.0 (72.0-102.0)	86.6 ± 13.1 (74.0-100.2)	72.5 ± 5.5 (65.4-78.8)	76.8 ± 0 (76.8-76.8)

Treatment Summary

Treatment
Placebo
Remifentanil, Zero Order IV Infusion, Infused for 4-hours, 0.025, 0.05, 0.075, 0.1, 0.2 µg/kg/min.
Alfentanil, Zero Order IV Infusion, Infused for 4-hours. 0.5, 1.0 µg/kg/min.

Remifentanil Lot # CS-USA-10001

Sample Strategy

Arterial Blood Samples: Prior to dosing, at 1, 2, 3, 5, 7, 10, 15, 20, 30, 60, 90, 120, 150, 180, 210, and 230 minutes after the start of the infusion and 1, 3, 5, 7, 10, 15, 20, 30, 60, 90 minutes, and 2, 3, 4, 5, and 6 hours after the infusion was stopped. If the infusion rate was decreased additional samples were collected immediately before and 1, 3, 5, and 20 minutes after the infusion rate change

Assay Method
Remifentanil (blood): GC-High Resolution MS-Selected Ion Monitoring
GR90291 (blood): GC with Mass Selective Detection (GC-MSD)
Alfentanil (blood): GC-High Resolution MS-Selected Ion Monitoring

Sample	Sensitivity	%CV (QC Conc)	QC Range
Remifentanil Blood	0.1 ng/mL	4.6% (4ng/ml) -17.3% (0.20ng/ml)	0.2-20ng/ml
GR90291 Blood	1ng/mL	9.8% (15ng/ml) - 16.9% (4.0ng/ml)	4.0-150ng/ml
Alfentanil	1ng/mL	2.7% (200ng/ml) - 13.3% (3.0ng/ml)	3.0-90ng/ml

Labeling Claims From Study: Remifentanil is rapidly eliminated after continuous intrvenous infusions with a half life of minutes. The pharmacokinetics of remifentanil are linear over the range of mcg/kg/min for hours

Study 102 - Four-Hour Continuous Infusion Study in Volunteers

Conclusions: Remifentanil (0.025-0.2mcg/kg/min) exhibited a more rapid clearance (37.8±8.9mL/min/kg) and similar volume of distribution (Vc 195±57) compared to alfentanil clearance 7.23±2.57mL/min/kg and Vc 168±47 at doses of 0.5-1mcg/kg/min. The pharmacokinetics of remifentanil were independent of dose over the range of mcg/kg/min. CO_2-stimulated minute ventilation (MV, measure of respiratory drive) showed a dose-related decrease during administration of both drugs but returned to baseline within 15 min of termination of infusion for remifentanil and 75-90 min for alfentanil. Remifentanil was 40 times more potent than alfentanil for reduction in MV based on blood concentrations, and 7 times more potent than alfentanil based on infusion rate. Based on blood concentrations, remifentanil was 37 times more potent than alfentanil for hypercarbic response (change in arterial carbon dioxide tension). Based on infusion rate, potency ratios (remifentanil:alfentanil) for peak hypercarbic and hypoxic response (change in arterial carbon dioxide tension) were 5.55 and 6.26, respectively. Analgesic response (pain tolerance at the tibia and sternum) were difficult to estimate because of the low doses employed. However, remifentanil was shown to be more potent than alfentanil in this regard. No significant changes were observed in mean systolic and diastolic blood pressure and heart rate.

Investigators:

Purpose: 1) to evaluate the safety and tolerability (including analgesic, respiratory and hemodynamic responses) of 4 hour continuous intravenous infusion of remifentanil; 2) to evaluate the pharmacokinetics of remifentanil.

Study Design: Double-blind, placebo-controlled, parallel, ascending dose study in five groups of healthy, young, male subjects at remifentanil doses of 0.025, 0.05, 0.075, 0.1 or 0.2mcg/kg/min (maximum tolerated dose). Maximum tolerated dose was defined as the dose at which ≥50% of subjects had to be verbally prompted to breathe to maintain the peripheral oxyhemoglobin saturation above 85%. Each group had three remifentanil and one placebo subject, except for the 0.5mcg/kg/min group which had six remifentanil and two placebo subjects. Six 0.5mcg/kg/min and three 1mcg/kg/min alfentanil subjects (active controls) added as an open-label extension.

Demographics: 33 healthy male subjects (18 subjects on remifentanil, nine subjects on alfentanil and six subjects on placebo), ages 19-34 years.

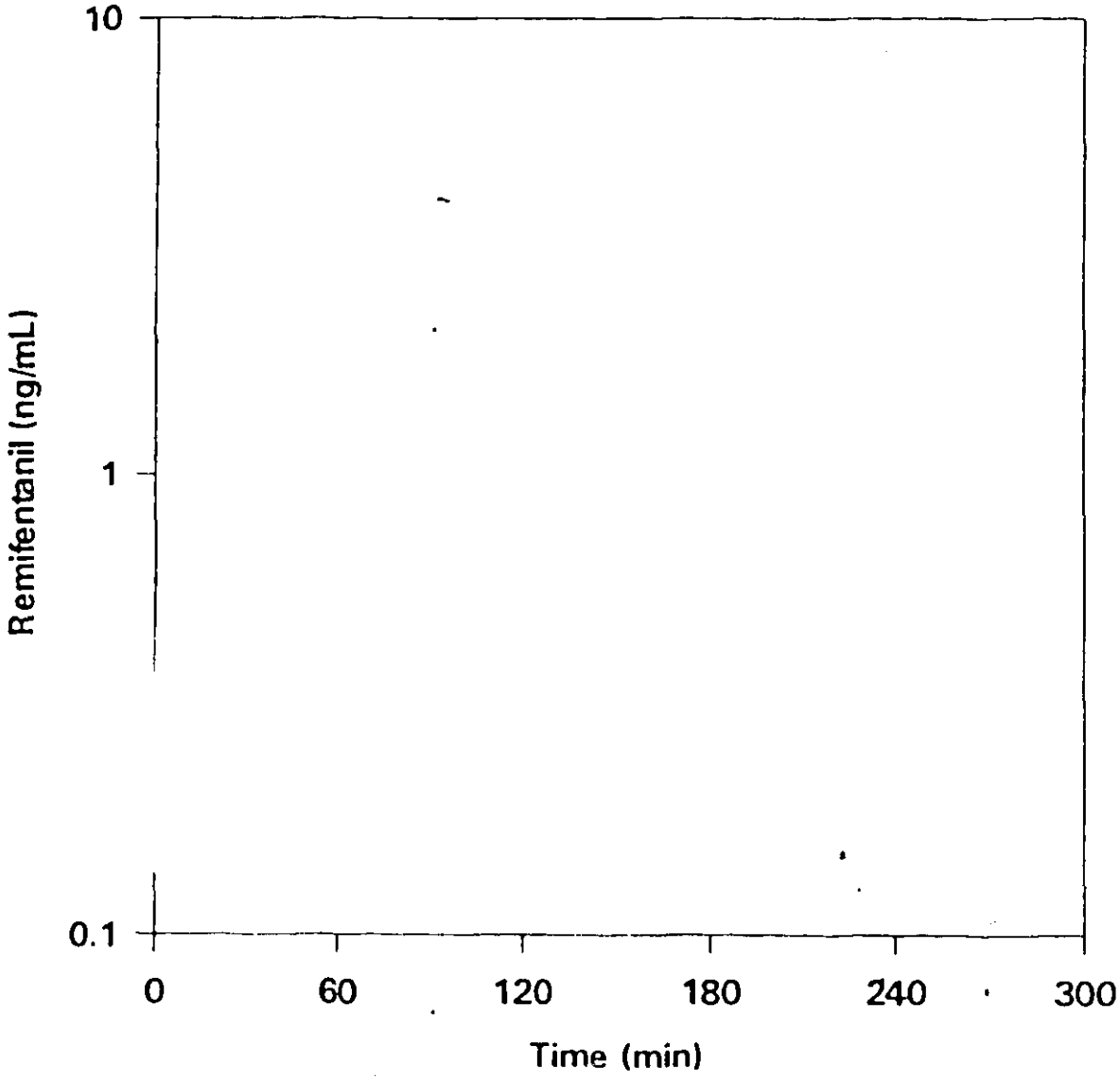
Anesthesia Protocol: Remifentanil, alfentanil or placebo was administered to conscious subjects as a constant-rate intravenous infusion over four hours.

Results: Table of Principle PK, PD and Safety Results

	Remifentanil	Alfentanil	Placebo
Pharmacokinetics[1] Mean±SD	N = 13	N = 9	-
CL (mL/min/kg)	37.8 ± 8.9	7.23 ± 2.37	-
VDc (ml/kg)[1]	195 ± 57	168 ± 47	-
λ_z $t_{1/2}$ (min)	3.62 ± 0.94	63.0 ± 16.4	-
Pharmacodynamics[1] Mean±SD	n = 13	n = 9	-
EC_{50} MV (ng/mL)	1.53 ± 1.47	63.4 ± 37.4	-
Safety, N (%)	N = 18	N = 9	N = 6
Any adverse event	18 (100%)	9 (100%)	5 (83%)

[1] Data are summarized across doses.

USA-102
Dose =0.025μg/kg/min



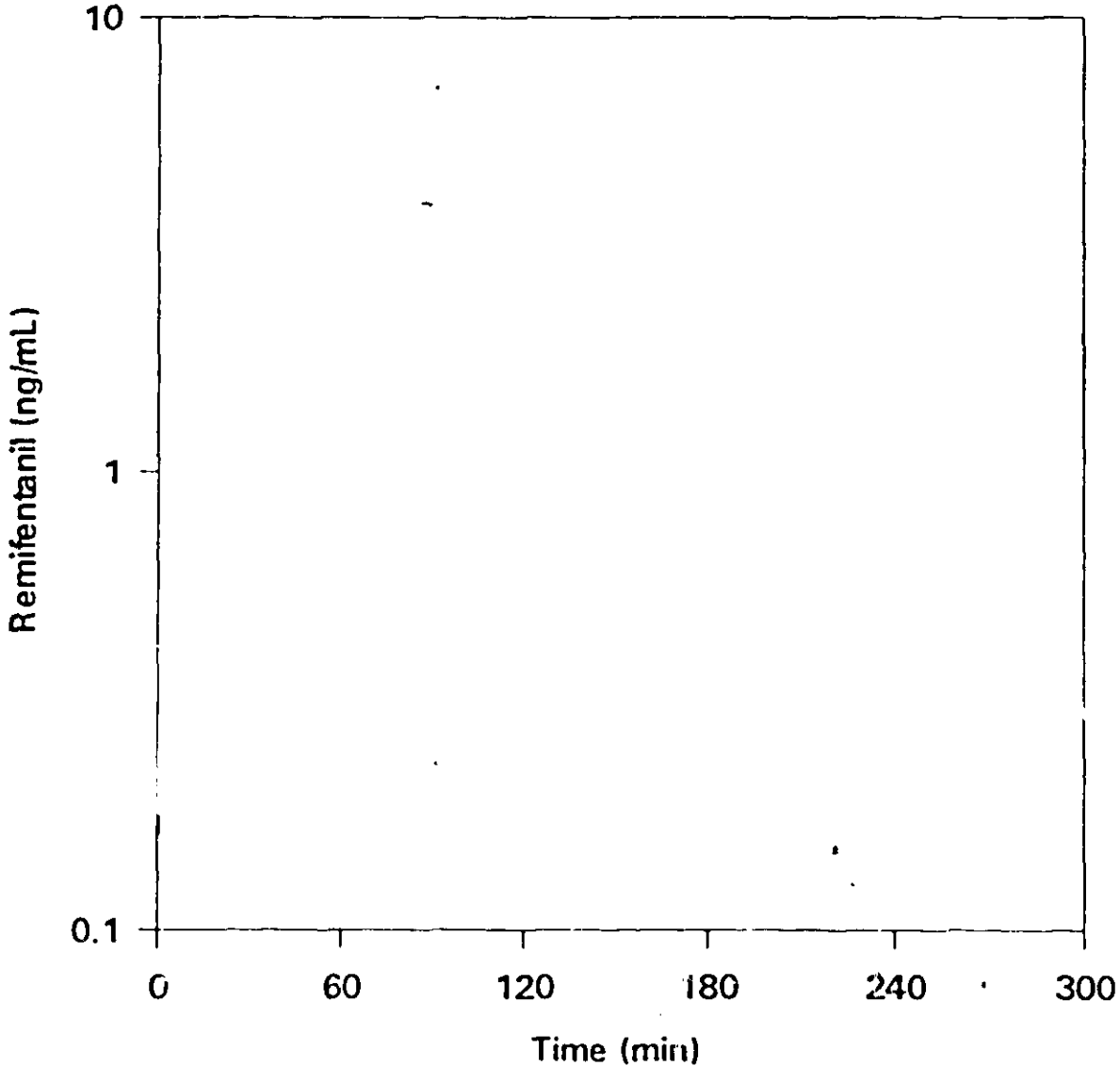
DOSE=0.025

SUBJECT	VOLUMEc (mL/kg)	Clearance (mL/min/kg)	AUC Model (ng*min/mL)	K elimination (min-1)	Elimination HL (min)
MEAN	227	34.41	180	0.1781	**3.9
SD	111	7.53	38	0.0834	2.2
CV	49	21.88	21	46.8119	56

DOSE (mcg/kg/min)=0.025

SUBJECT	AUC to last (ng*min/mL)	AUC to infinity (ng*min/mL)	AUC/AUCINF	TERMINAL K (min-1)	TERMINAL HL (min)	AUMC to infinity (ng*min*min/mL)	Mean Residence Time (min)	VOLUMEss (mL/kg)	Clearance (mL/min/kg)
MEAN	182	184	99.0	.2312	3.00	24331	14.1	442	33.77
SD	37	39	1.2	.1796	2.07	4816	1.4	180	7.83
CV	21	21	1.2	77.70	69.2	20	9.7	41	23.18

USA-102
Dose =0.05μg/kg/min



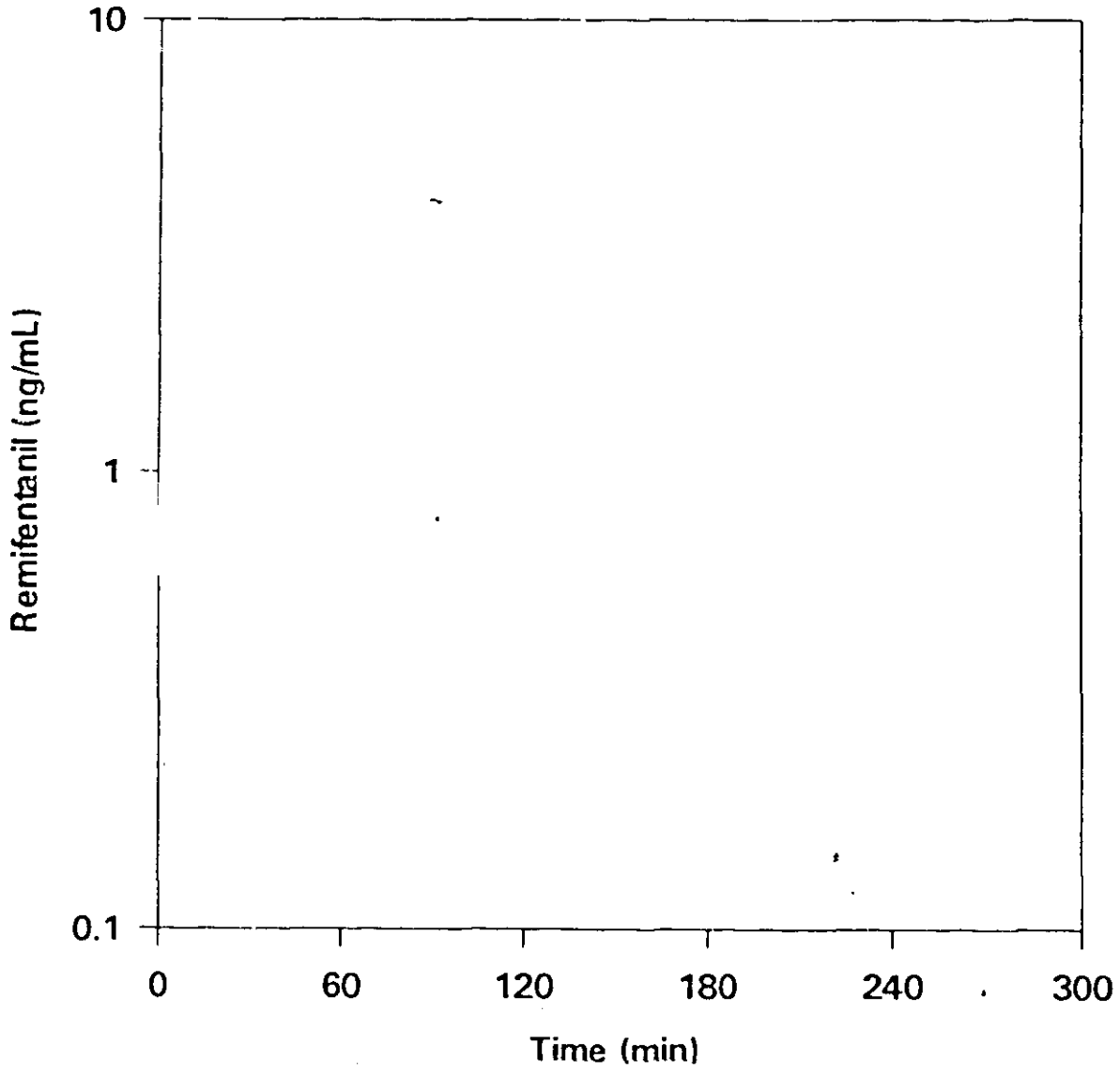
DOSE=0.05

SUBJECT	VOLUMEc (mL/kg)	Clearance (mL/min/kg)	AUC Model (ng*min/mL)	K elimination (min-1)	Elimination HL (min)
MEAN	153	29.63	417	0.1950	**3.6
SD	39	6.59	82	0.0115	0.7
CV	25	22.26	20	5.9213	6.0

DOSE (mcg/kg/min)=0.05

SUBJECT	AUC to last (ng*min/mL)	AUC to infinity (ng*min/mL)	AUC/AUCINF	TERMINAL K (min-1)	TERMINAL HL (min)	AUMC to infinity (ng*min*min/mL)	Mean Residence Time (min)	VOLUMEss (mL/kg)	Clearance (mL/min/kg)
MEAN	419	420	99.7	.1348	**5.14	54010	9.8	308	29.33
SD	79	79	0.1	.0418	1.71	7478	7.5	299	6.16
CV	19	19	0.1	31.00	33.2	14	76.6	97	21.00

USA-102
Dose =0.075μg/kg/min



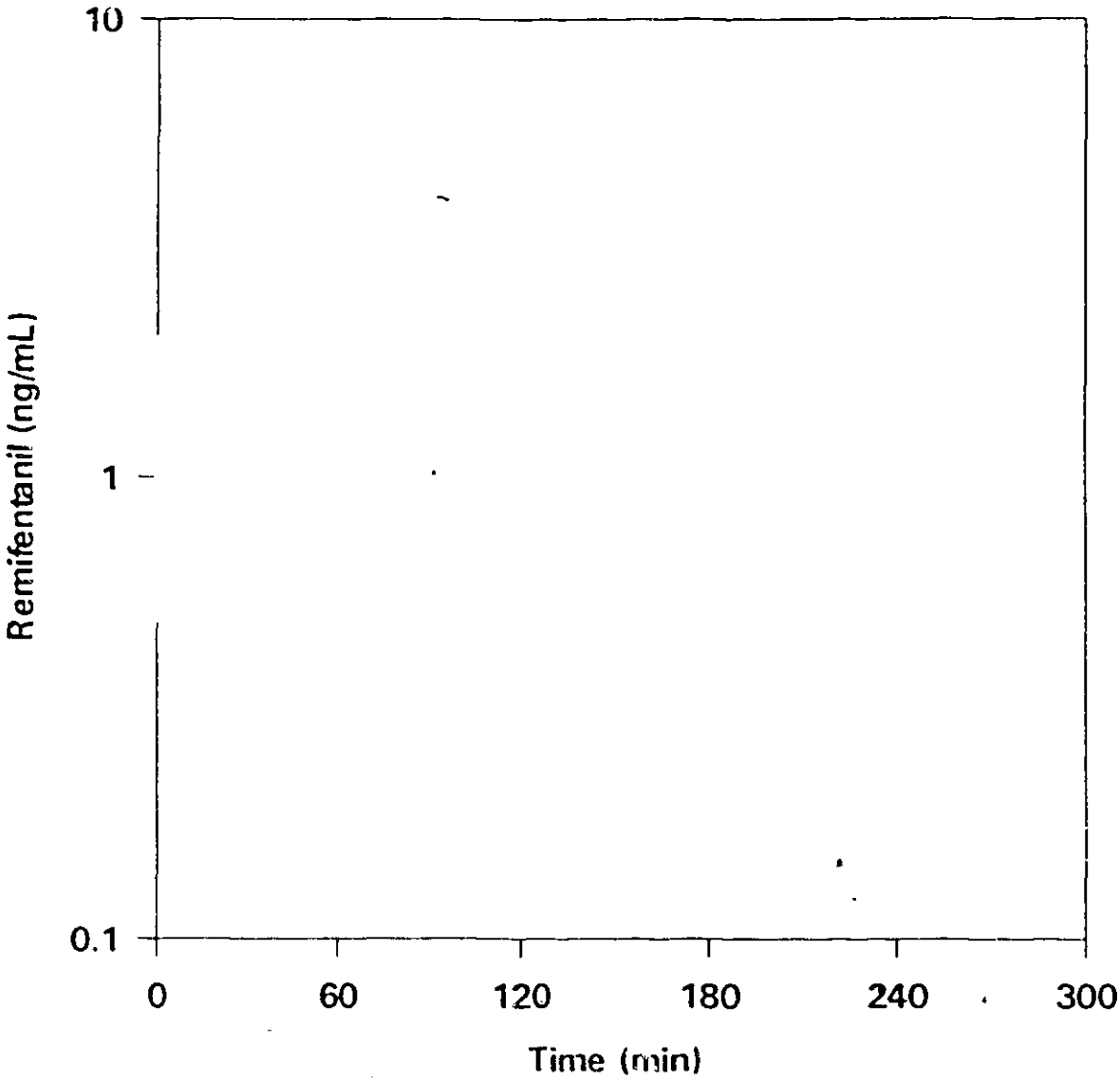
DOSE=0.075

SUBJECT	VOLUMEc (mL/kg)	Clearance (mL/min/kg)	AUC Model (ng*min/mL)	K elimination (min-1)	Elimination HL (min)
MEAN	181	38.87	470	0.2164	**3.2
SD	12	5.76	66	0.0392	0.6
CV	7	14.82	14	18.0958	18

DOSE (mcg/kg/min)=0.075

SUBJECT	AUC to last (ng*min/mL)	AUC to infinity (ng*min/mL)	AUC/AUCINF	TERMINAL K (min-1)	TERMINAL HL (min)	AUMC to infinity (ng*min*min/mL)	Mean Residence Time (min)	VOLUMEss (mL/kg)	Clearance (mL/min/kg)
MEAN	482	483	99.7	.1476	**4.70	62522	9.*	363	37.99
SD	80	80	0.0	.0441	1.46	10098	0.6	87	6.61
CV	17	17	0.0	29.87	31.1	16	6.0	24	17.39

USA-102
Dose =0.1μg/kg/min



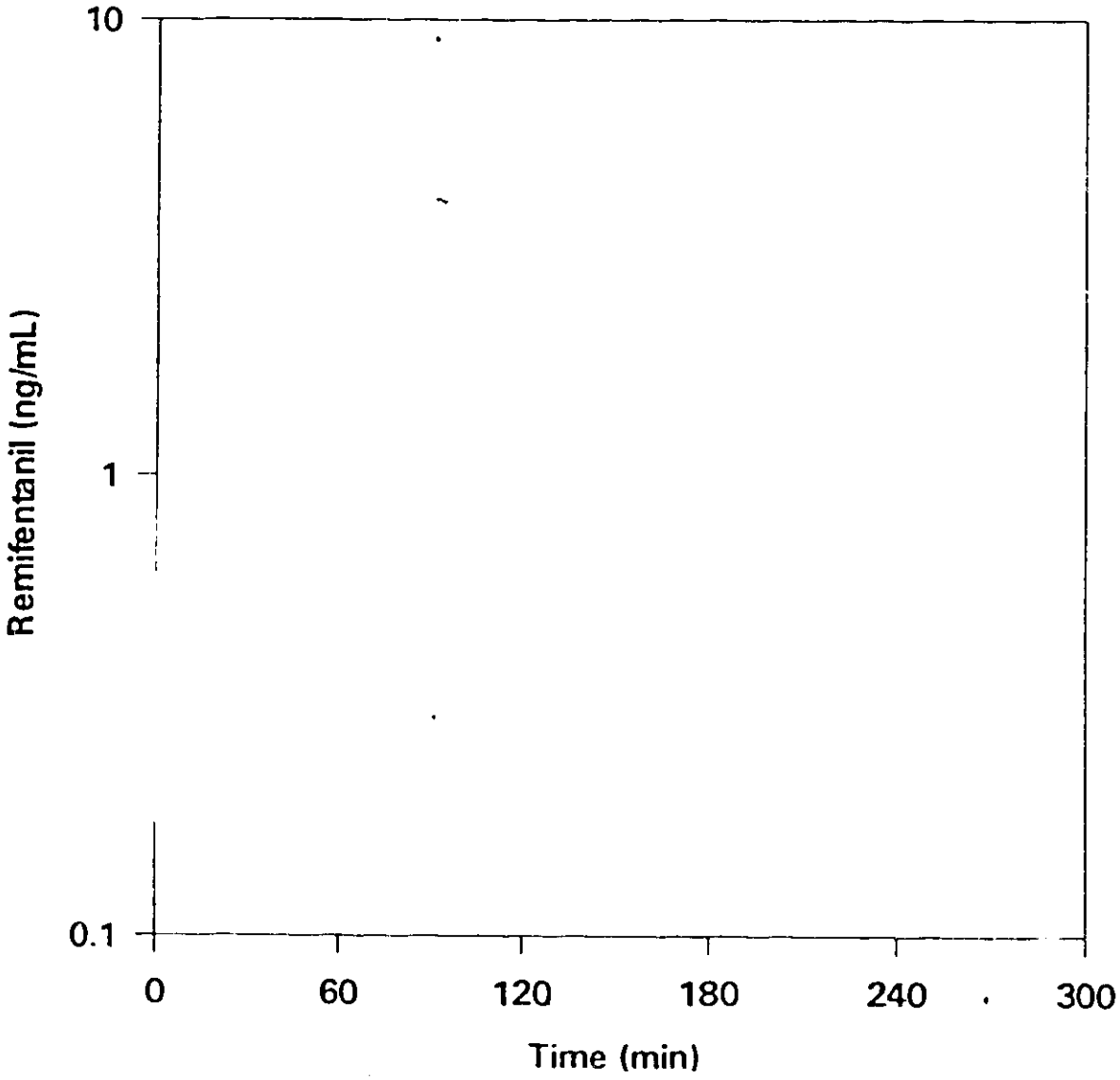
DOSE=0.1

SUBJECT	VOLUMEc (mL/kg)	Clearance (mL/min/kg)	AUC Model (mg*min/mL)	K elimination (min-1)	Elimination HL (min)

DOSE (mcg/kg/min)=0.1

SUBJECT	AUC to last (ng*min/mL)	AUC to infinity (ng*min/mL)	AUC/AUCINF	TERMINAL K (min-1)	TERMINAL HL (min)	AUMC to infinity (ng*min*min/mL)	Mean Residence Time (min)	VOLUMEss (mL/kg)	Clearance (mL/min/kg)
	620	621	99.9				13.6	516	38.65

USA-102
Dose =0.2μg/kg/min



DOSE=0.2

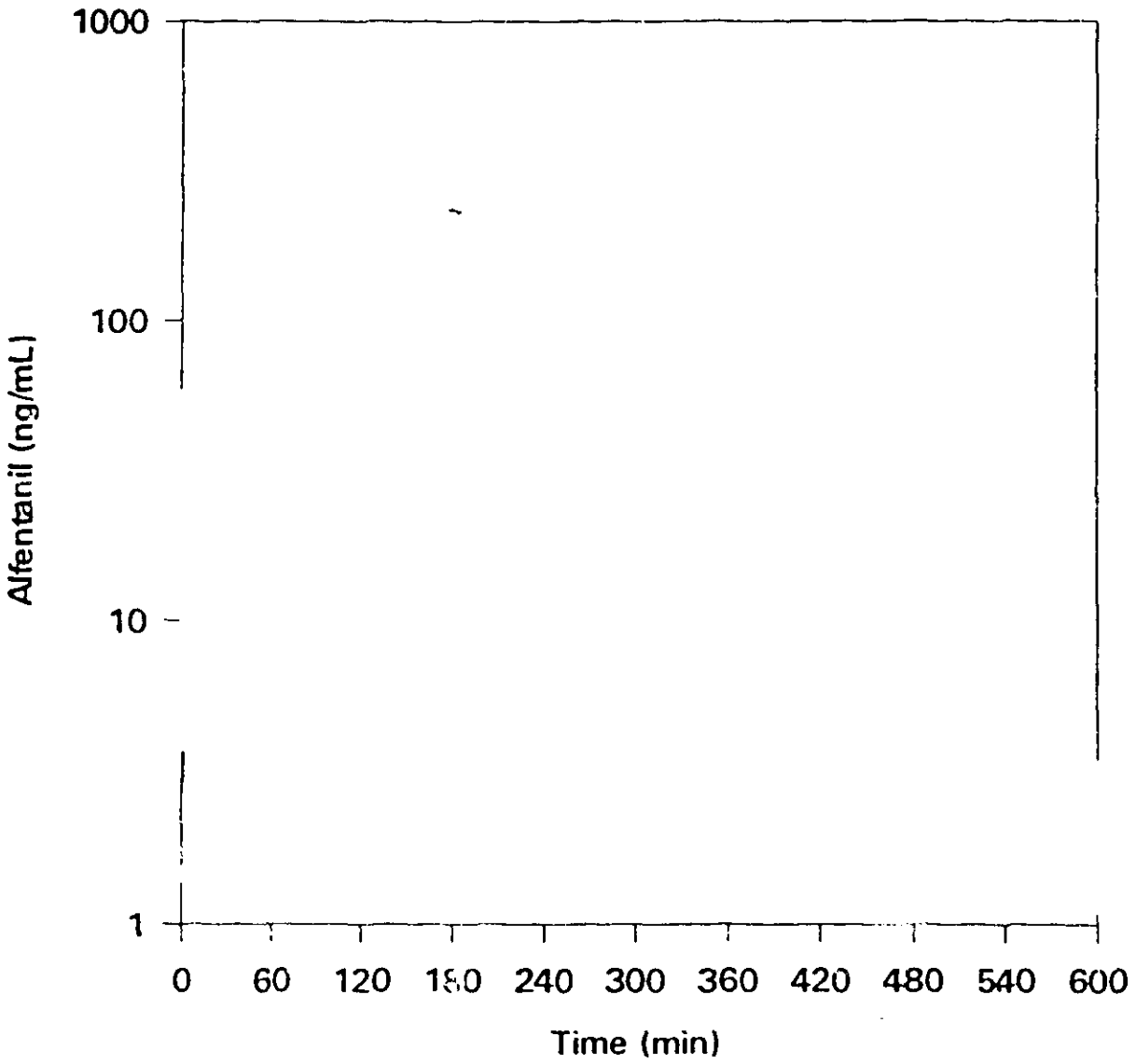
SUBJECT	VOLUMEc (mL/kg)	Clearance (mL/min/kg)	AUC Model (mg*min/mL)	K elimination (min-1)	Elimination HL (min)
MEAN	216	47.54	NA	0.2246	**3.1
SD	21	9.05	NA	0.0663	1.0
CV	10	19.04	NA	29.5026	32.6

DOSE (mcg/kg/min)=0.2

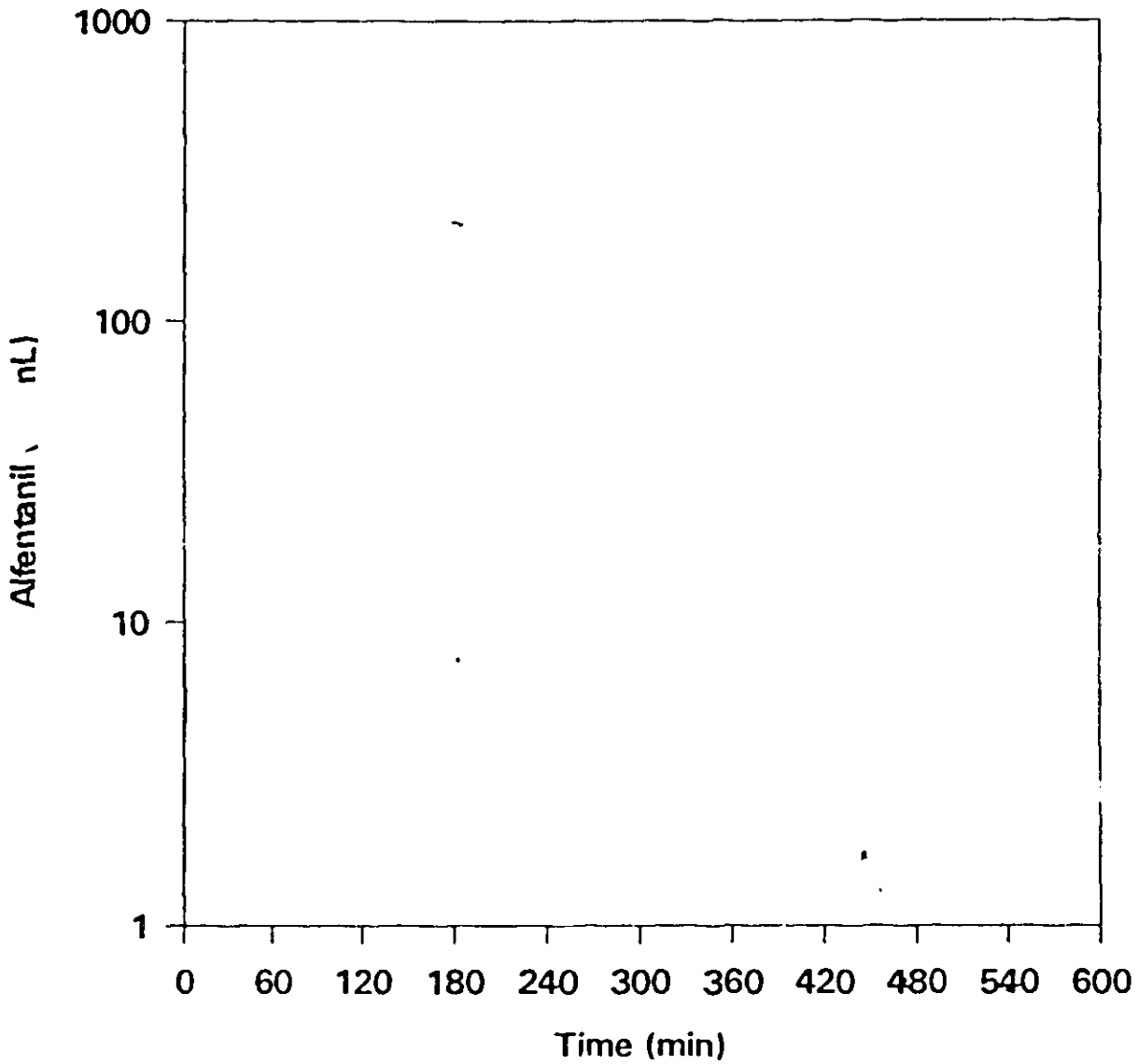
SUBJECT	AUC to last (mg*min/mL)	AUC to infinity (mg*min/mL)	AUC/AUCINF	TERMINAL K (min-1)	TERMINAL HL (min)	AUMC to infinity (mg*min*min/mL)	Mean Residence Time (min)	VOLUMEss (mL/kg)	Clearance (mL/min/kg)
							-	-	40.45
							-	-	39.42
							-	-	58.24
MEAN	NA	NA	NA	.1275	**5.44	NA	-	-	46.20
SD	NA	NA	NA	.0499	2.01	NA	-	-	10.43
CV	NA	NA	NA	39.13	37.1	NA	-	-	39.13

NA=NOT APPLICABLE
* SUBJECT HAD INFUSION RATE CHANGE
** HARMONIC MEAN, JACKKNIFE DEVIATION

USA-102
Dose =Alfentanil 0.5μg/kg/min



USA-102
Dose =Alfentanil 1.0μg/kg/min



USA-211 (UCP/95/010)
Pharmacokinetic Study Summary

NDA # 20-630 Submission Date: 9/15/95 Volume: 82-87

Investigator:
Site:

Single Dose: X . Multiple Dose: ____.
Subjects: Normal: X. Patients: ___. Young: X. Elderly: ___.
Hepatic: X. Renal: ___.
Cross-Over: ___. Parallel: X. N= 20 M= 16 F= 4

Subject Type: Hepatic Impairment and Healthy Volunteers
Hepatic function was assessed at screening using serum albumin, prothrombin time, and liver biopsy.

Category	Hepatic Impairment		Healthy	
	Low Dose (N = 5)	High Dose (N = 5)	Low Dose (N = 5)	High Dose (N = 5)
Gender - male/female	4 /1	4 / 1	4 / 1	4 /1
Age - years	43 ± 7 (37-55)	49 ± 8 (40-60)	38 ± 6 (31-47)	51 ± 10 (42-65)
Weight - kg	81 ± 21 (60-114)	82 ± 15 (64-102)	82 ± 15 (66-107)	82 ±15 (71-105)

Treatment Summary
Remifentanil, Zero Order IV Infusion
Low Dose Rate 0.0125µg/kg/min x 1 hour followed by 0.025µg/kg/min x 3 hours
High Dose Rate 0.025µg/kg/min x 1 hour followed by 0.05µg/kg/min x 3 hours
Lot # CS-USA1008

Sample Strategy:
Blood Samples: Arterial samples were collected prior to dosing (≤30min), at 2, 5, 10, 15, 30, 55, 75, 90, 120, 150, 180, 210, and 230min during the infusion, and at 2, 5, 10, 15, 30, 60, 90, 120, 240, and 360min post infusion. A venous sample was collected at 120, 240, 360, and 1440min post infusion.
Urine: A urine sample was collected prior to dosing, then pooled over the intervals 0-6, 6-10, and 10-24 hours.
Minute Ventilation: Measured at baseline, and at 15, 55, 75, 120, 180, and 230min during the infusion, and at 15, 30, and 60min after the end of the infusion.

Assay Method:
Remifentanil (blood/urine): GC-High Resolution Mass Spectrometry-Selected Ion Monitoring
GR90291 (blood): Gas chromatography with mass selective detection (GC-MSD)
GR90291 (urine): High performance liquid chromatography with UV detection (HPLC-UV)
GR94219 (urine) GC-High Resolution Mass Spectrometry-Selected Ion Monitoring

Sample	Sensitivity	Site	%CV (QC Conc)	QC Range
Remifentanil Blood	0.1 ng/mL	Triangle	4.0% (5ng/ml) -10.7% (0.25ng/ml)	0.25-80ng/ml
Remifentanil Urine	0.5ng/mL	Phoenix	2.9% (250ng/ml) -5.3% (450ng/ml)	1.5-450ng/ml
GR90291 Blood	1ng/mL	Phoenix	4.0% (80ng/ml) - 12.1% (4.0ng/ml)	4.0-180ng/ml
GR90291 Urine/dialysate	0.1mcg/mL	Phoenix	2.3% (40mcg/ml) - 11.5% (0.3mcg/ml)	0.3-40mcg/ml
GR94219 Urine	0.5ng/mL	Oneida	2.7% (40ng/ml) - 5.3% (1.5ng/ml)	1.5-80ng/ml

Labeling Claims From Study: The pharmacokinetics of remifentanil and GR90291 are not altered in subjects with hepatic impairment. The healthy subjects receiving the high dose infusion of remifentanil had a higher EC_{50} for minute ventilation compared to the hepatic impairment subjects. The clinical significance of this finding is unclear.

Study 211 - Remifentanil PK/PD Study in Hepatic Impairment

Conclusions: The pharmacokinetics of remifentanil at low and high infusion dose regimens were not altered in conscious volunteers with severe hepatic impairment (CL of 39.4 and 34.5mL/min/kg, respectively) compared to healthy subjects (CL of 32.1 and 33.1mL/min/kg, respectively). In addition, no differences in the pharmacokinetics of GR90291, the primary metabolite of remifentanil, were observed between hepatic impairment and healthy subjects. The EC_{50} values for response to hypercarbic challenge (measurement of minute ventilation (MV) as an assessment of sensitivity to the respiratory effects of remifentanil) were not significantly different between hepatic impairment and healthy subjects at low doses (1.99 vs 2.73ng/mL, respectively) but showed an apparent difference at high doses (1.51 vs 5.65ng/mL) due to unexpectedly high EC_{50} values in the high dose healthy subjects.

Investigator:

Purpose: 1) to evaluate the effect of hepatic function on the elimination of remifentanil and its metabolites, GR90291 and GR94219; 2) to evaluate the effects of hepatic impairment on the pharmacodynamics (respiratory drive, psychomotor tests, and visual analogue scales) of remifentanil.

Study Design: Single-center, balanced, open-label, parallel study in hepatic impairment versus matched healthy subjects at two infusion regimens (low dose and high dose) of remifentanil.

Demographics: 20 subjects (10 hepatic impairment subjects, 10 healthy subjects), aged 31-65 years, male and female. Hepatic impairment classification was determined using medical history, serum albumin, prothrombin time, and liver biopsy. Hepatic impairment and healthy subjects in each dose group were matched for age, weight and gender.

Anesthesia Protocol: *Premedication:* N/A. *Induction/Maintenance:* N/A. *Other:* Ten subjects (five hepatic impairment and five healthy subjects) received a 1-hour infusion of 0.0125mcg/kg/min remifentanil followed by a 3-hour infusion of 0.025mcg/kg/min remifentanil (Low dose regimen). Ten subjects (five hepatic impairment and five healthy subjects) received a 1-hour infusion of 0.025µg/kg/min remifentanil followed by a 3-hour infusion of 0.05mcg/kg/min remifentanil (High dose regimen).

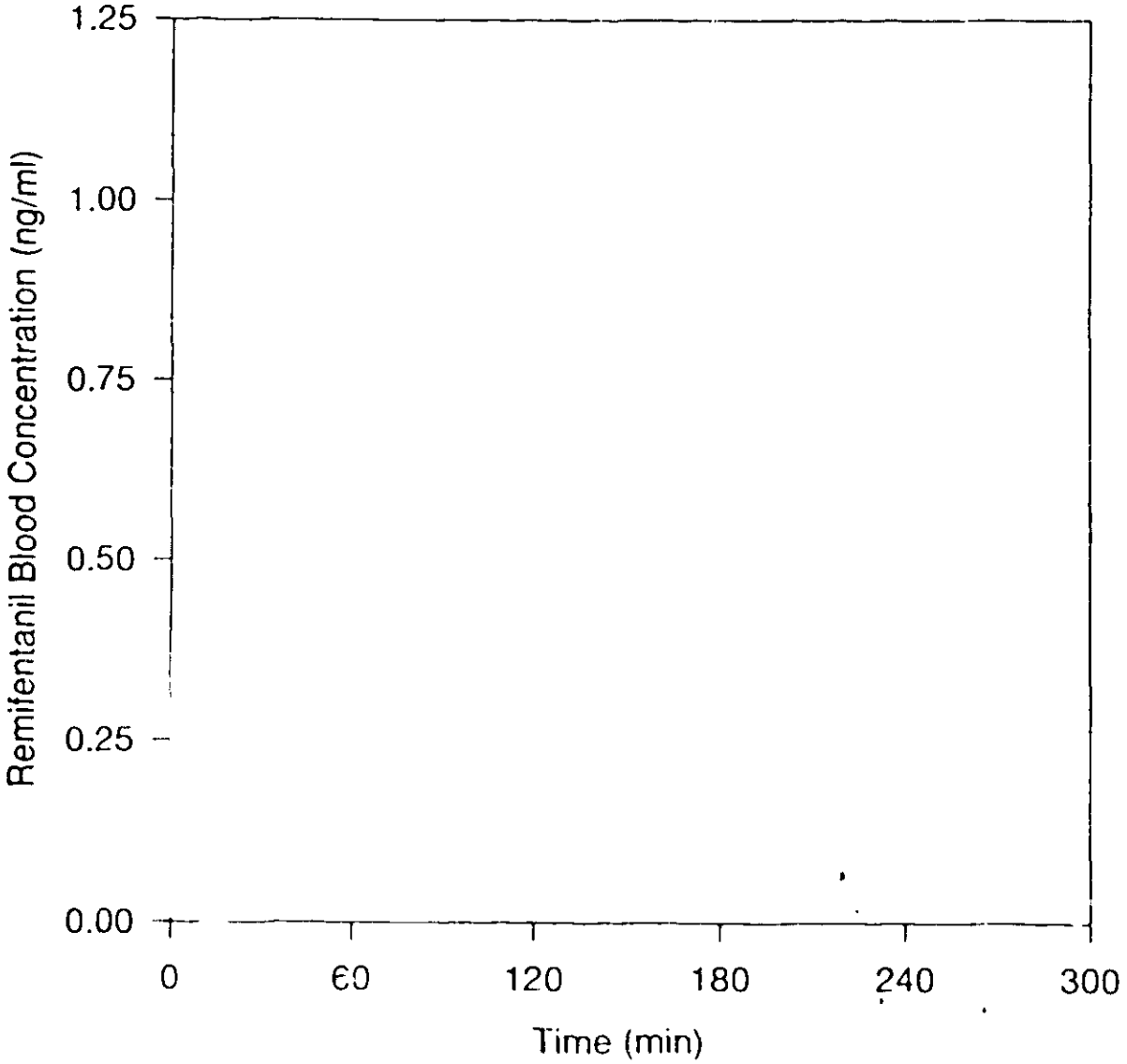
Results: **Table of Principle PK, PD and Safety Results, All Subjects (N = 20)**

Values are N (% Total) or Mean ± SD

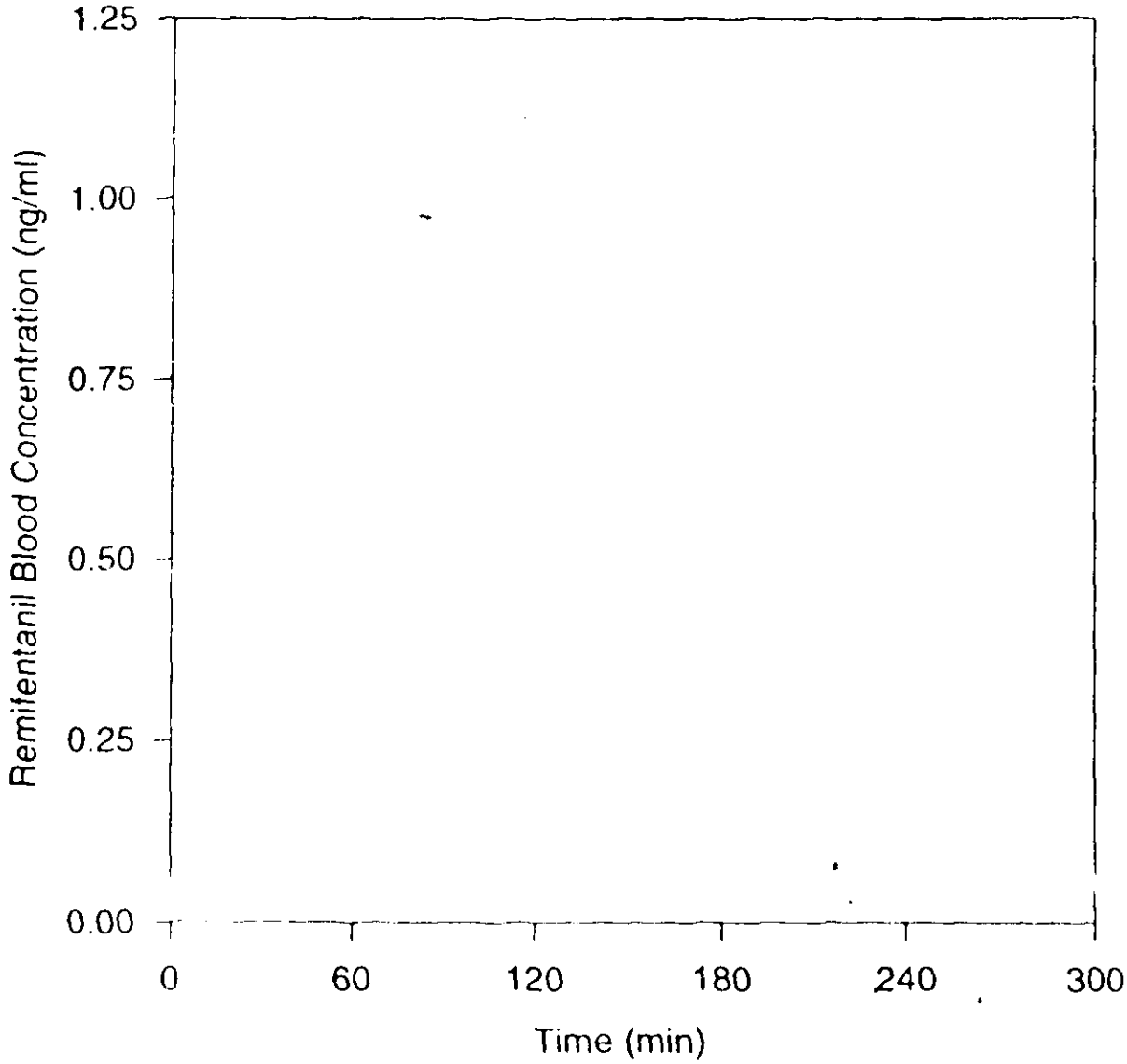
	Hepatic Impairment		Healthy	
	Low Dose	High Dose	Low Dose	High Dose
Pharmacokinetics	N = 5	N = 5	N = 5	N = 5
Remifentanil CL (mL/min/kg)	39.4 ± 5.0	34.5 ± 9.6	32.1 ± 7.2	33.1 ± 3.6
Remifentanil Vd (mL/kg)	270 ± 68	290 ± 114	229 ± 115	[illegible]6 ± 21
Remifentanil $t_{1/2}$ (min)	4.74 ± 0.88	5.84 ± 1.65	4.83 ± 1.62	4.31 ± 0.16
GR90291 AUC_{∞} (ng•min/mL)[1]	820 ± 170	1408 ± 592	792 ± 216	1008 ± 258
GR90291 C_{max} (ng/mL)[1]	3.70 ± 0.56	5.39 ± 1.78	3.96 ± 0.85	3.38 ± 1.23
GR90291 $t_{1/2}$ (min)	71.3 ± 9.2	121.3 ± 39.5	72.8 ± 25.8	120.1 ± 57.1
Pharmacodynamics	N = 5	N = 5	N = 5	N = 5
Remifentanil EC_{50} MV (ng/mL)	1.99 ± 0.95	1.51 ± 0.46	2.73 ± 0.91	5.65 ± 5.34
Safety	N = 5	N = 5	N = 5	N = 5
Any to adverse event	5 (100%)	4 (80%)	5 (100%)	5 (100%)

[1] Values for high dose groups are normalized to low dose

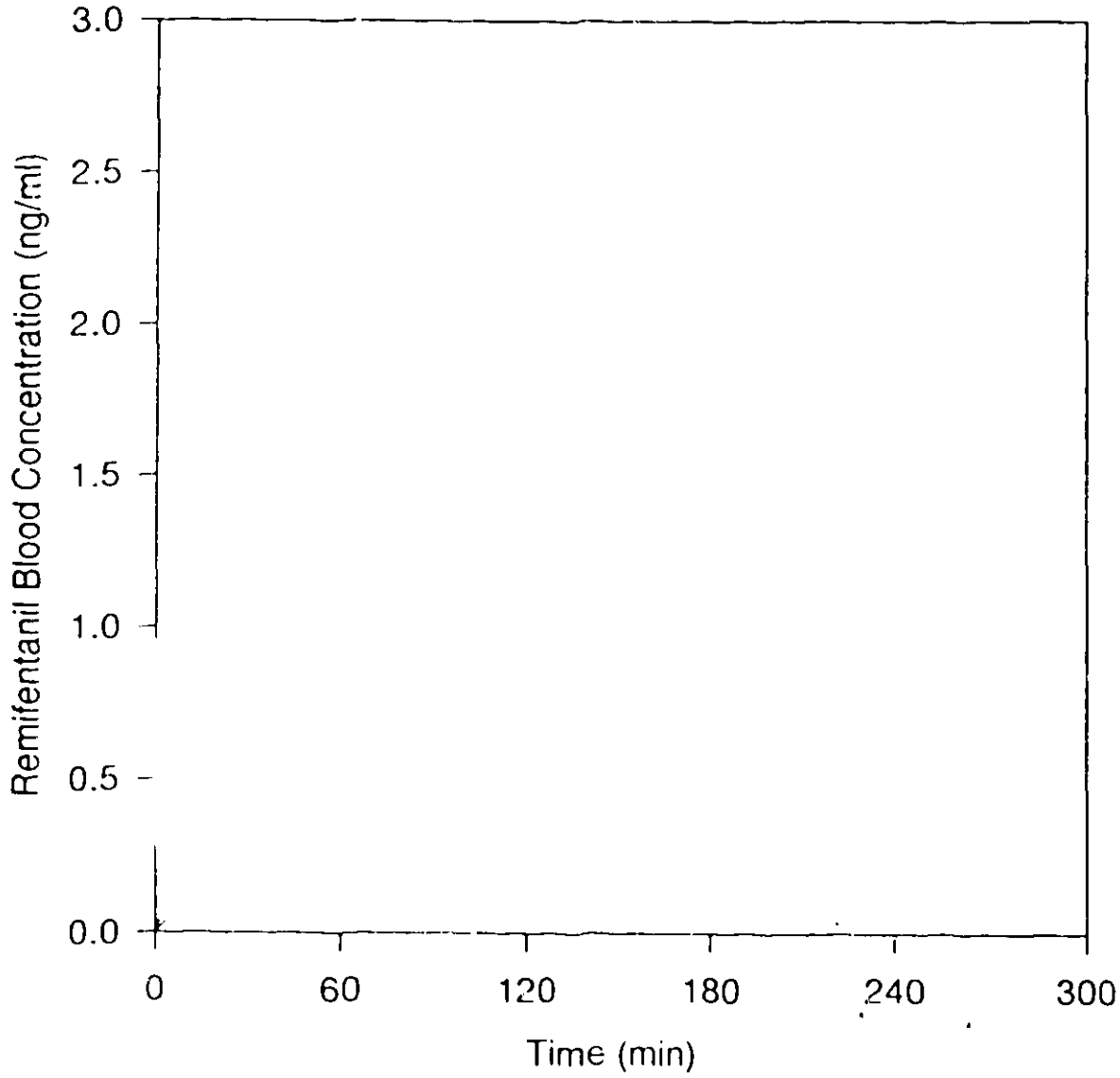
Remifentanil Concentration-Time Profile in Low Dose Healthy Subjects



Remifentanil Concentration-Time Profile in Low Dose Hepatic Impairment Subjects



Remifentanil Concentration-Time Profile in High Dose Hepatic Impairment Subjects



Remifentanil Concentration-Time Profile in Low Dose Hepatic Impairment Subjects

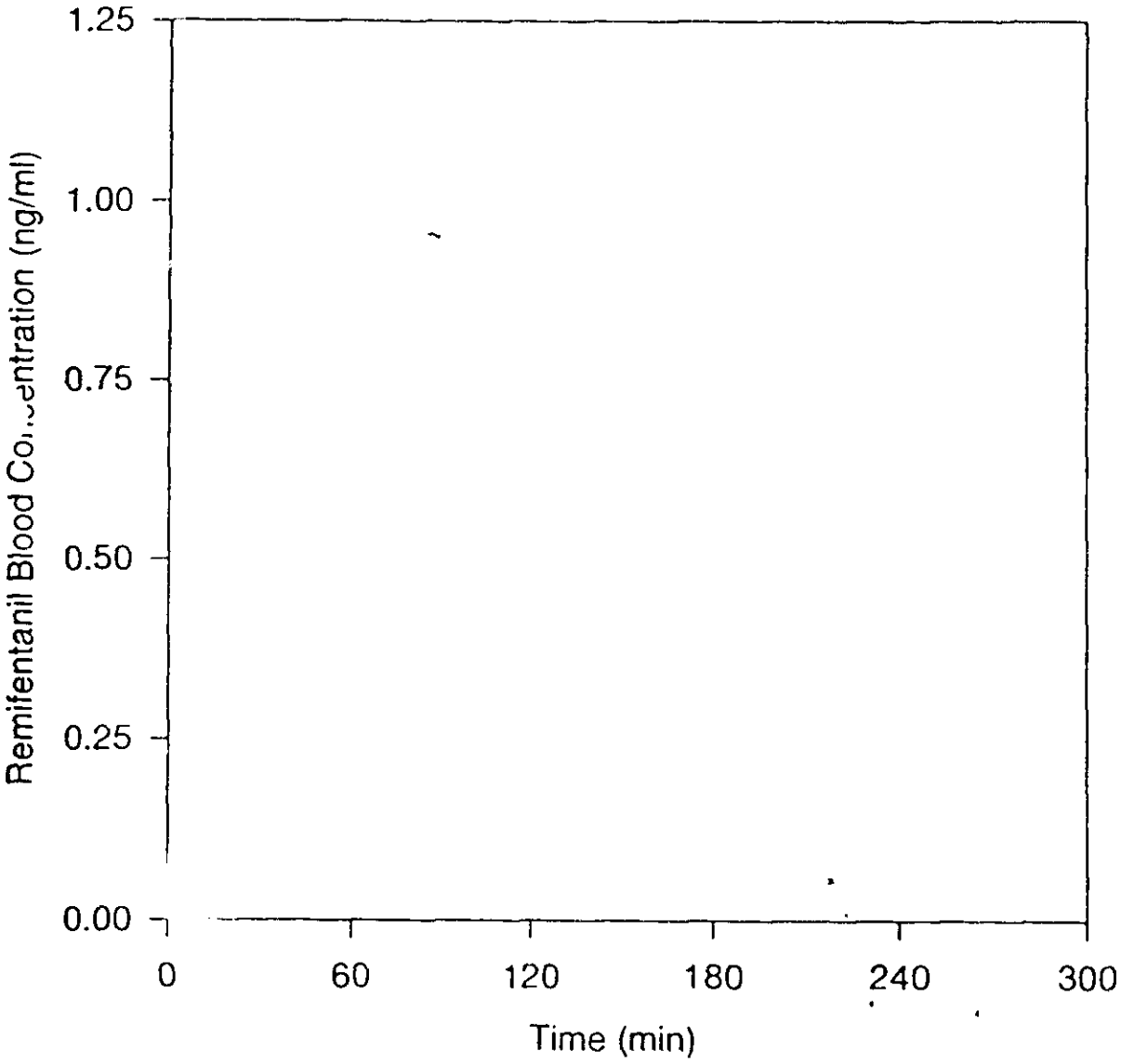
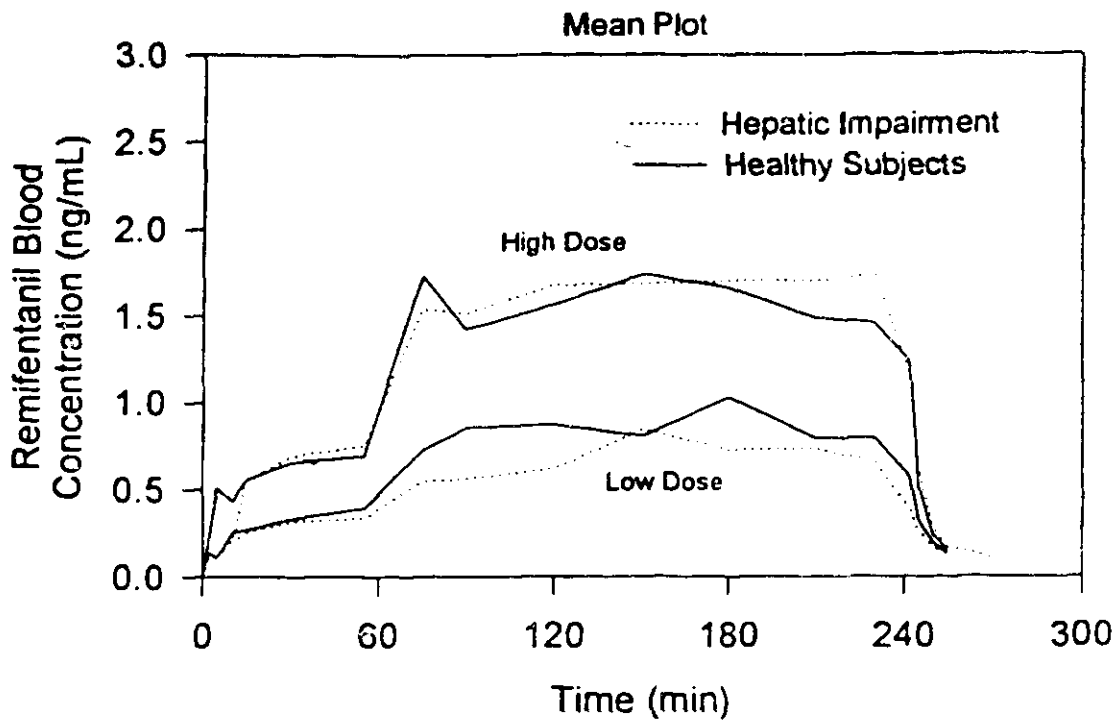


Figure 10

Mean and Median Remifentanil Blood Concentrations



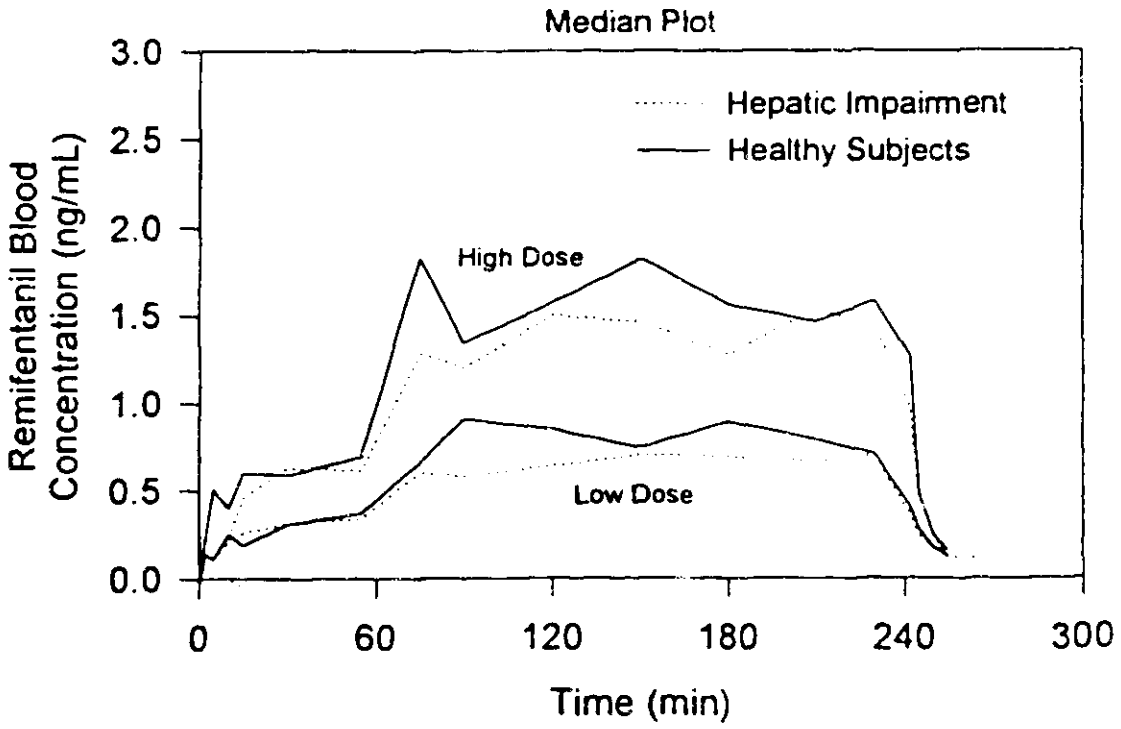


Table 41

Individual Remifentanil Volume of Distribution (ml/kg) Values with Summary Statistics

	Hepatic				Healthy			
	Subj.	low dose	Subj.	high dose	Subj.	low dose	Subj.	high dose
Geometric LSMean	263.787		271.614		207.601		204.644	
Arithmetic LSMean	270.172		290.297		228.886		205.600	
Median	242.033		259.903		190.957		210.227	
Minimum	208.645		147.899		106.408		166.961	
Maximum	372.743		449.785		410.080		221.801	
Arithmetic Mean	270.172		290.297		228.886		205.600	
95% CI (lower)	185.631		148.619		86.759		179.219	
95% CI (upper)	354.713		431.975		371.013		231.980	
SD	68.087		114.103		114.465		21.246	
CV	25.201		39.306		50.010		10.334	
Geometric Mean	263.787		271.614		207.601		204.644	
95% CI (lower)	185.692		161.653		112.210		178.454	
95% CI (upper)	355.604		456.376		384.085		234.677	
Mean of logs	5.575		5.604		5.336		5.321	
SD of logs	0.241		0.418		0.495		0.110	

LSmean = Lease Square Mean, adjust for design imbalance if present
CI = confidence interval for LS mean
SD = Standard deviation
%CV = percent coefficient of variation

Individual Remifentanil Cl (ml/min/kg) Values with Summary Statistics

	Hepatic				Healthy			
	Subj.	low dose	Subj.	high dose	Subj.	low dose	Subj.	high dose
Geometric LSMean	39.1058		33.3252		31.4607		32.9478	
Arithmetic LSMean	39.3653		34.4874		32.1028		33.1198	
Median	40.4522		39.4515		29.7942		34.2199	
Minimum	31.9270		23.8886		23.0853		27.0692	
Maximum	45.7374		43.2039		42.0209		36.0844	
Arithmetic Mean	39.3693		34.4874		32.1028		33.1198	
95% CI (lower)	33.1661		22.5495		23.1859		28.6125	
95% CI (upper)	45.5725		46.4252		41.0096		37.6270	
SD	4.9959		9.6144		7.1733		3.6300	
CV	12.6898		27.8780		22.3448		10.9602	
Geometric Mean	39.1058		33.3252		31.4607		32.9478	
95% CI (lower)	33.2350		22.9822		23.7702		28.5150	
95% CI (upper)	46.0137		48.3229		41.6393		38.0697	
Mean of logs	3.666		3.506		3.449		3.495	
SD of logs	0.131		0.299		0.226		0.116	

LSmean = Lease Square Mean, adjust for design imbalance if present
CI = confidence interval for LS mean
SD = Standard deviation
%CV = percent coefficient of variation

Table 42

Individual Remifentanil K_{el} (min^{-1}) Values with Summary Statistics

	Hepatic				Healthy			
	Subj.	low dose	Subj.	high dose	Subj.	low dose	Subj.	high dose
Geometric LSMean	0.14824		0.12269		0.15154		0.16100	
Arithmetic LSMean	0.15047		0.12675		0.16159		0.16109	
Median	0.13301		0.11949		0.14006		0.16021	
Minimum	0.12271		0.08771		0.10247		0.15428	
Maximum	0.18308		0.16623		0.28000		0.16904	
Arithmetic Mean	0.15047		0.12675		0.16159		0.16108	
95% CI (lower)	0.11398		0.08230		0.07457		0.15365	
95% CI (upper)	0.18695		0.17120		0.24860		0.16853	
SD	0.02939		0.03580		0.07008		0.00599	
CV	19.5297		28.2413		43.3690		3.71867	
Geometric Mean	0.14824		0.12269		0.15154		0.16100	
95% CI (lower)	0.11685		0.08598		0.09391		0.15376	
95% CI (upper)	0.18807		0.17509		0.24454		0.16859	
Mean of logs	-1.91		-2.10		-1.89		-1.83	
SD of logs	0.192		0.286		0.385		0.037	

LSMean = Lease Square Mean, adjust for design imbalance if present
CI = confidence interval for LS mean
SD = Standard deviation
%CV = percent coefficient of variation

Individual Remifentanil Half-Life (min) Values with Summary Statistics

	Hepatic				Healthy			
	Subj.	low dose	Subj.	high dose	Subj.	low dose	Subj.	high dose
Geometric LSMean	4.67578		5.64945		4.57391		4.30524	
Arithmetic LSMean	4.74341		5.83602		4.82712		4.30760	
Median	5.21112		5.80069		4.94907		4.32649	
Minimum	3.78610		4.16978		2.47553		4.10044	
Maximum	5.64889		7.90254		6.76439		4.49273	
Aritmetic Mean	4.74341		5.83602		4.82712		4.30760	
95% CI (lower)	3.65456		3.78336		2.81572		4.11000	
95% CI (upper)	5.83225		7.87868		6.83851		4.50520	
SD	0.87692		1.64510		1.61992		0.15914	
CV	18.4872		28.1887		33.5588		3.69446	
Geometric Mean	4.67578		5.64945		4.57391		4.30524	
95% CI (lower)	3.68559		3.95887		2.83451		4.11156	
95% CI (upper)	5.93200		8.06195		7.38070		4.50804	
Mean of logs	1.542		1.732		1.520		1.460	
SD of logs	0.192		0.286		0.385		0.037	

LSMean = Lease Square Mean, adjust for design imbalance if present
CI = confidence interval for LS mean
SD = Standard deviation
%CV = percent coefficient of variation

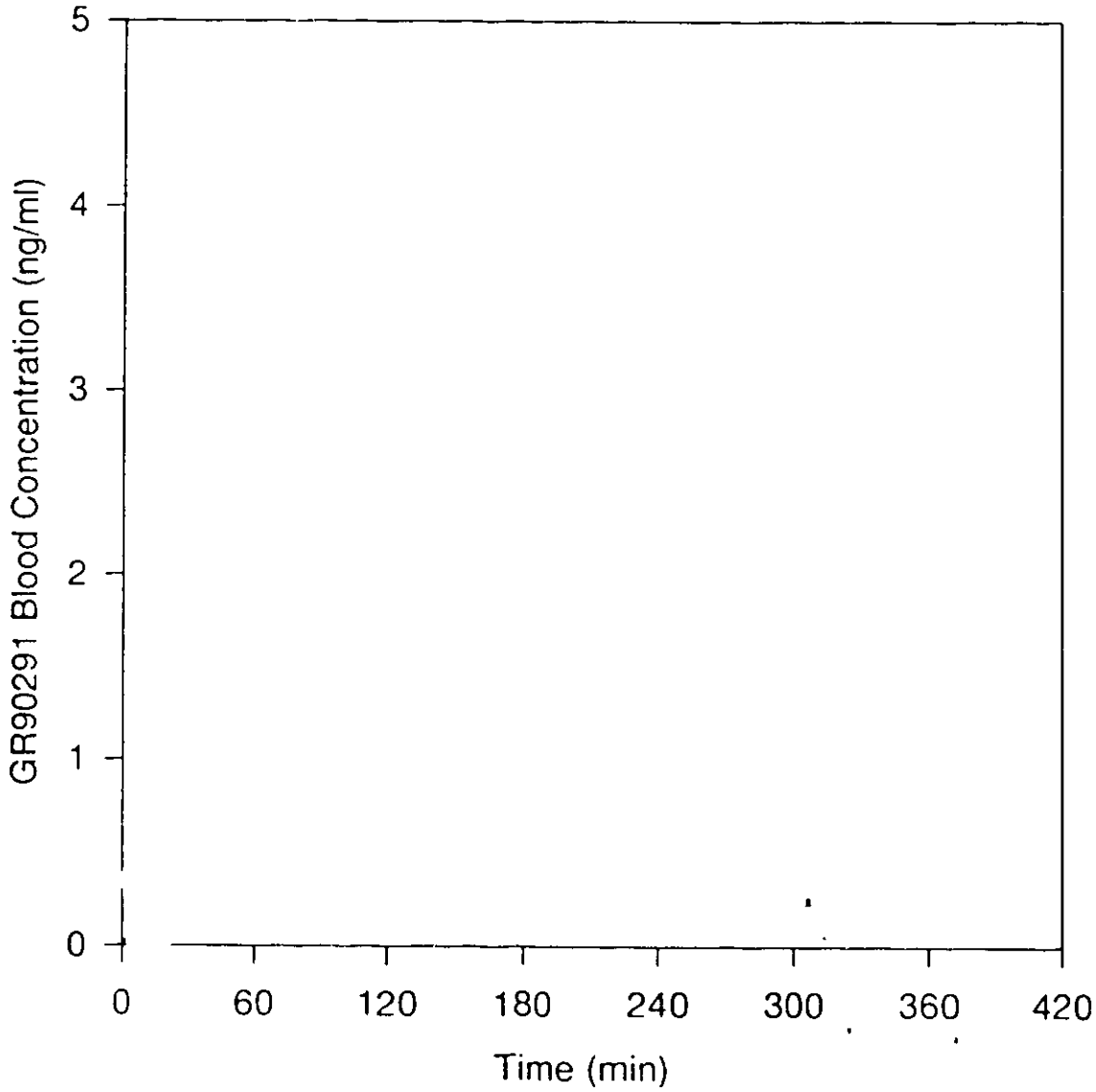
Table 44

Statistical Analysis of Log-Transformed Remifentanil Pharmacokinetic Parameters

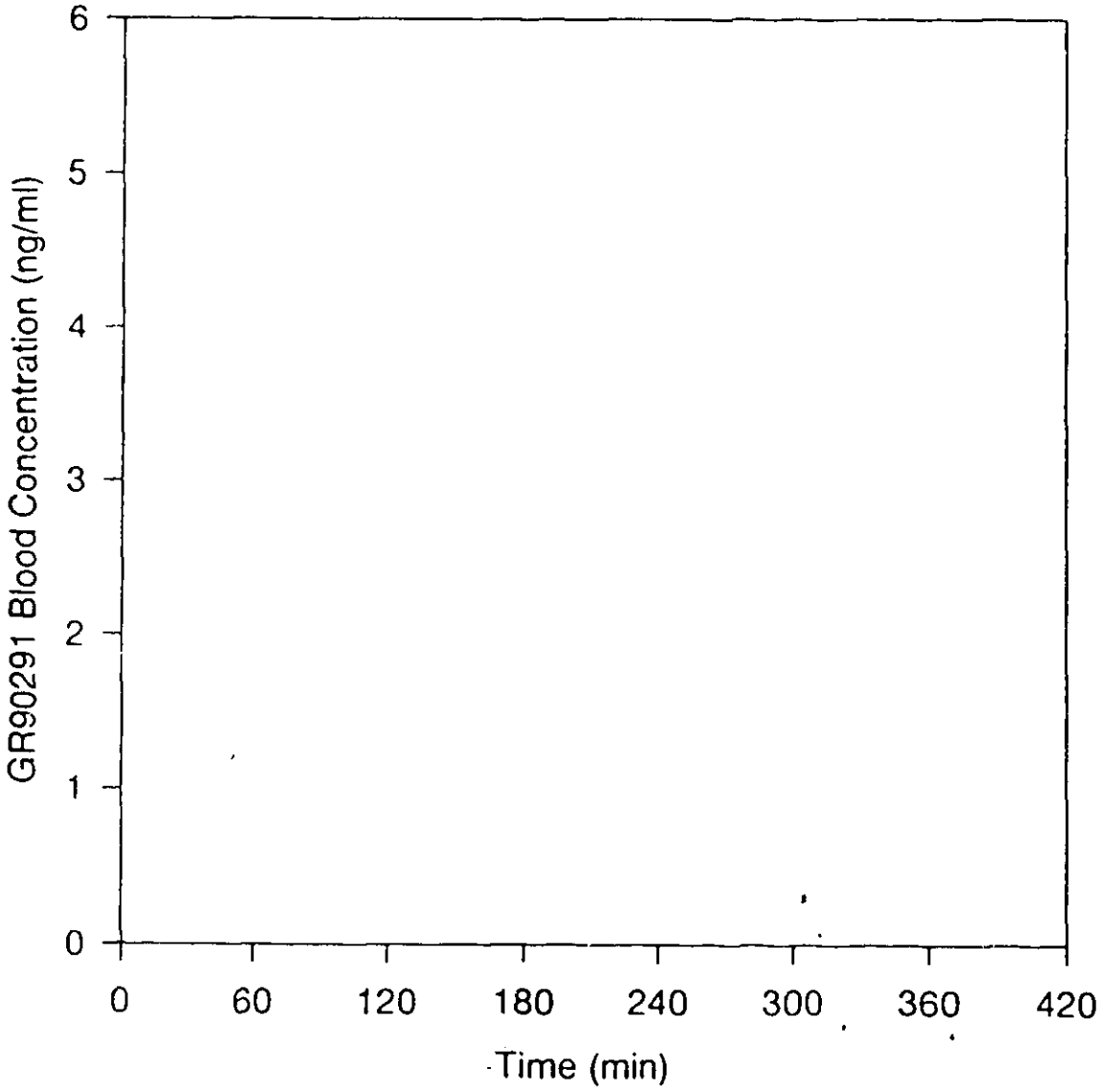
Parameter	Subject Group	Ratio	90% CI	p-value
Cl (ml/min/kg)	Low Dose Hepatic/Low Dose Healthy	1.24	(0.989, 1.56)	0.116
	High Dose Hepatic/High Dose Healthy	1.01	(0.805, 1.27)	0.932
	Low Dose Hepatic/High Dose Hepatic	1.17	(0.934, 1.47)	0.388
	Low Dose Healthy/High Dose Healthy	0.955	(0.760, 1.20)	0.729
Vd (ml/kg)	Low Dose Hepatic/Low Dose Healthy	1.27	(0.863, 1.87)	0.295
	High Dose Hepatic/High Dose Healthy	1.33	(0.902, 1.95)	0.219
	Low Dose Hepatic/High Dose Hepatic	0.971	(0.660, 1.43)	0.897
	Low Dose Healthy/High Dose Healthy	1.01	(0.689, 1.49)	0.949
K10 (min^{-1})	Low Dose Hepatic/Low Dose Healthy	0.978	(0.735, 1.30)	0.895
	High Dose Hepatic/High Dose Healthy	0.762	(0.572, 1.01)	0.117
	Low Dose Hepatic/High Dose Hepatic	1.21	(0.908, 1.61)	0.265
	Low Dose Healthy/High Dose Healthy	0.941	(0.707, 1.25)	0.717
$t_{1/2}$ (min)	Low Dose Hepatic/Low Dose Healthy	1.02	(0.768, 1.36)	0.895
	High Dose Hepatic/High Dose Healthy	1.31	(0.986, 1.75)	0.117
	Low Dose Hepatic/High Dose Hepatic	0.828	(0.622, 1.10)	0.265
	Low Dose Healthy/High Dose Healthy	1.06	(0.798, 1.41)	0.717
EC_{50}* (ng/ml)	Low Dose Hepatic/Low Dose Healthy	0.730	(-.386, 1.85)	0.678
	High Dose Hepatic/High Dose Healthy	0.268	(-0.272, 0.807)	0.031
	Low Dose Hepatic/High Dose Hepatic	1.32	(-0.697, 3.33)	0.786
	Low Dose Healthy/High Dose Healthy	0.483	(-0.056, 1.02)	0.114

* Untransformed analysis

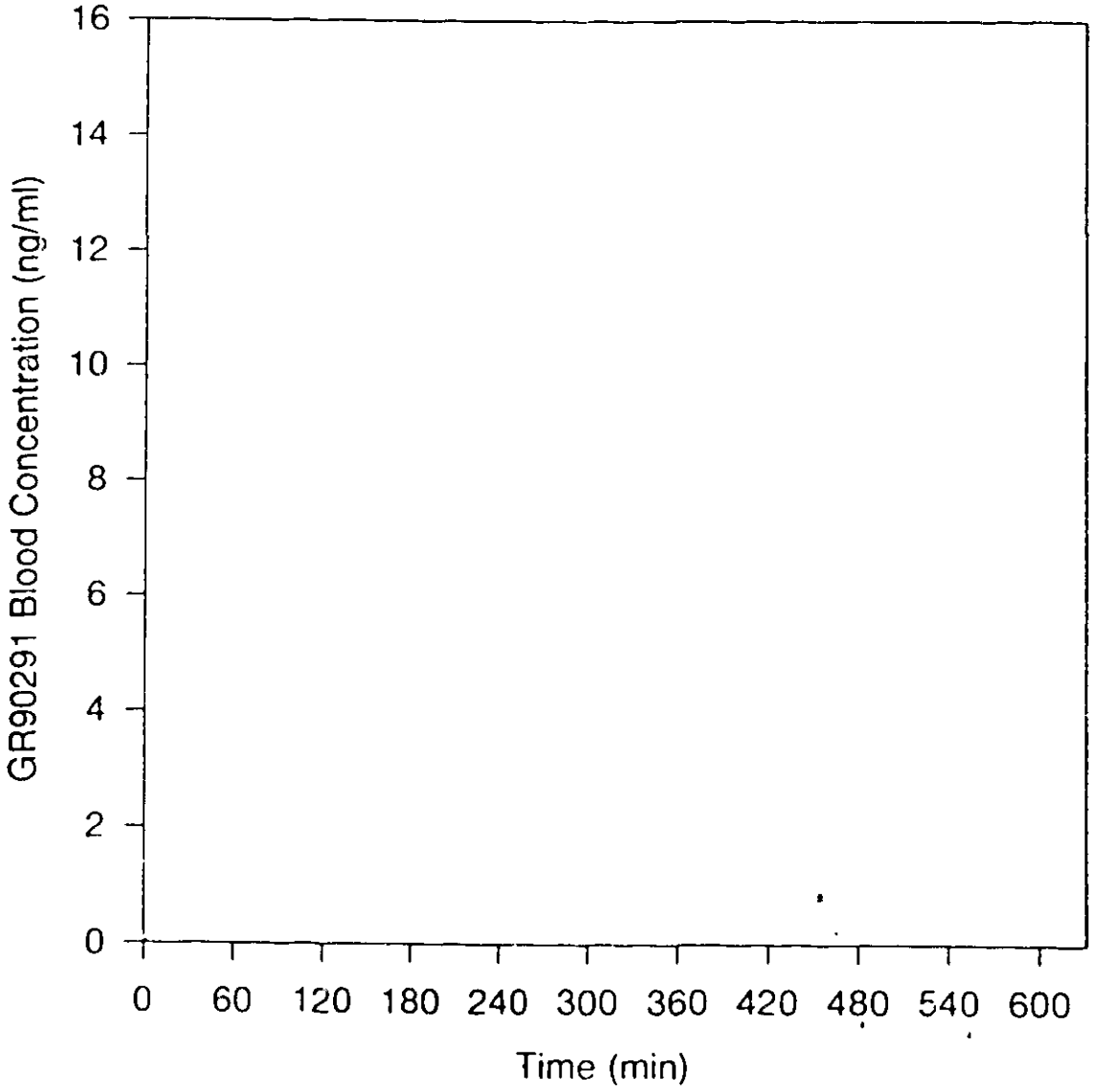
GR90291 Concentration-Time Profile in Low Dose Hepatic Impairment Subjects



GR90291 Concentration-Time Profile in Low Dose Healthy Subjects



GR90291 Concentration-Time Profile in High Dose Hepatic Impairment Subjects



GR90291 Concentration-Time Profile in Low Dose Hepatic Impairment Subjects

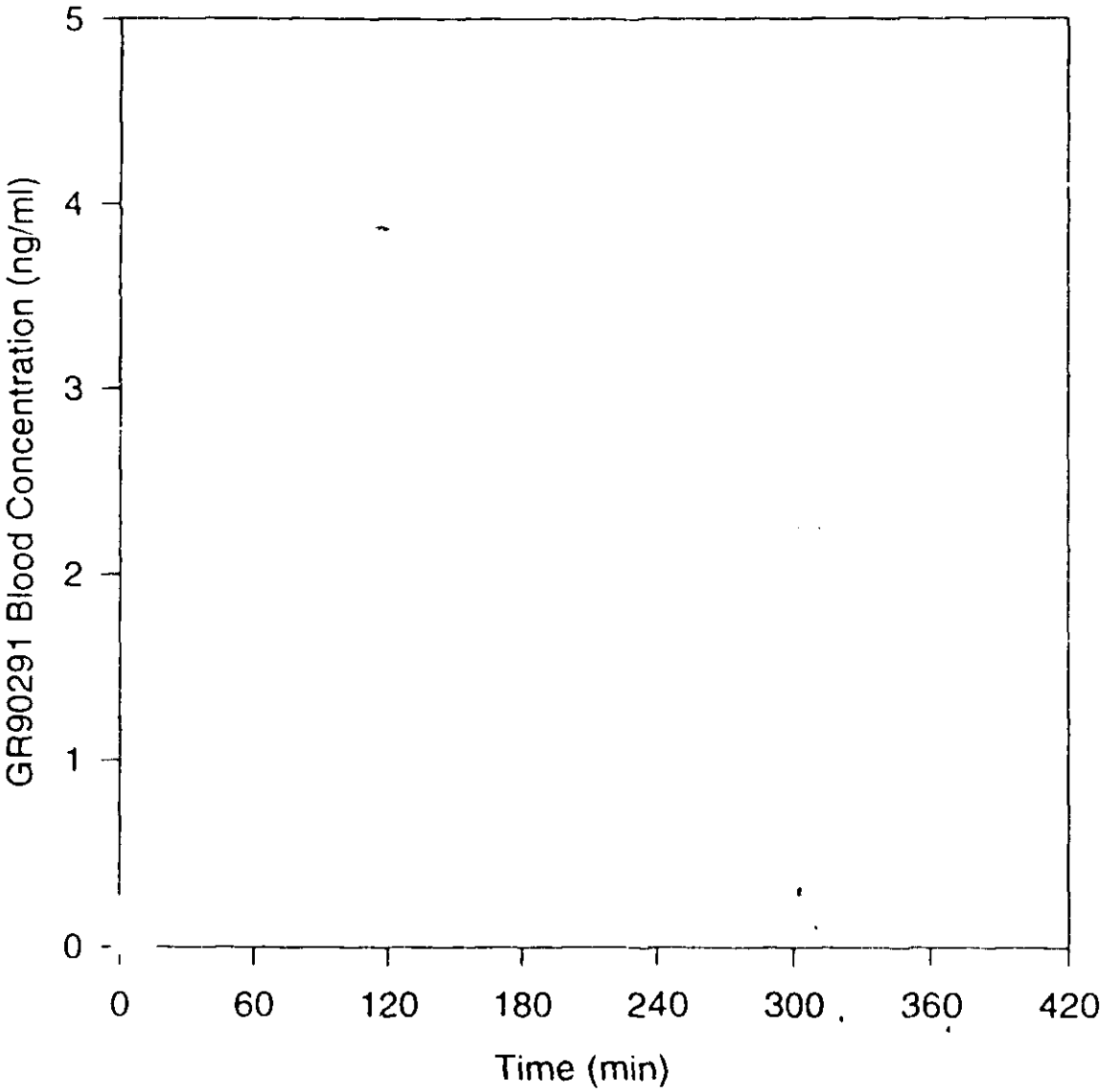
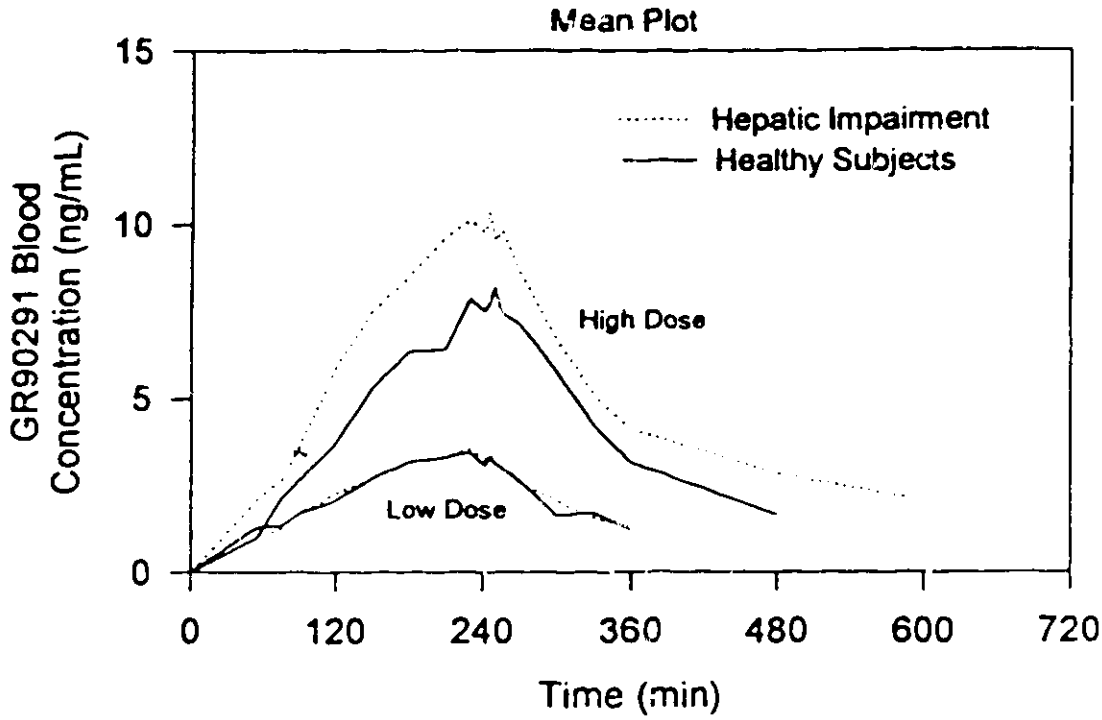


Figure 11

Mean and Median GR90291 Blood Concentrations



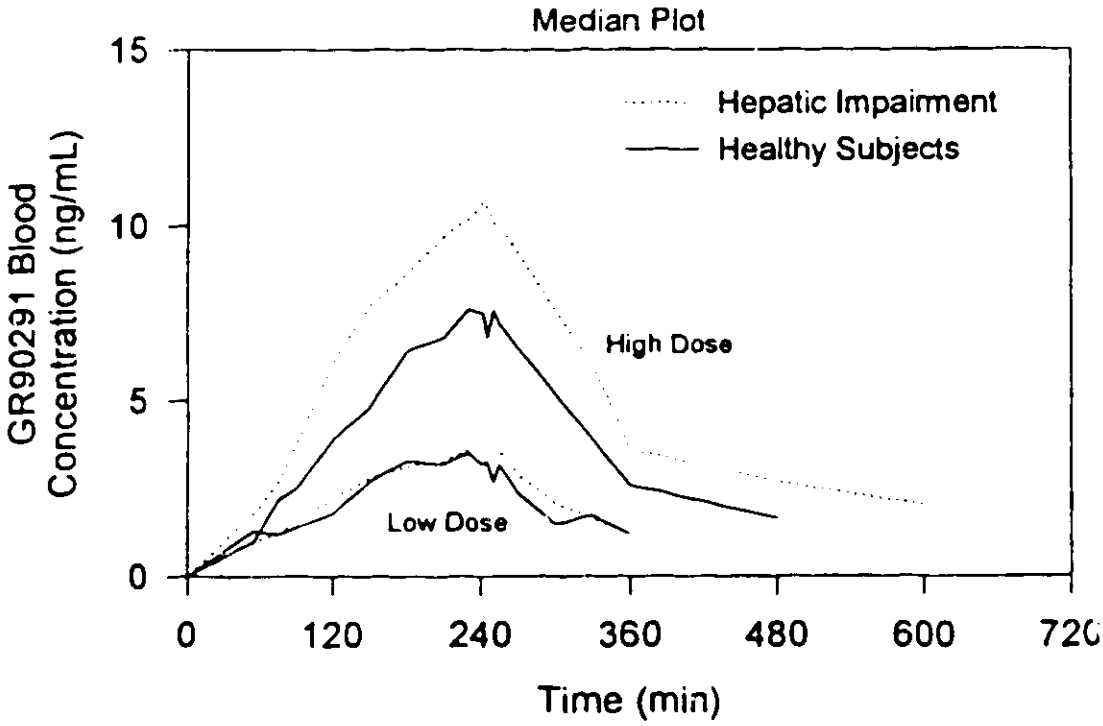


Table 45

Individual GR90291 AUClast (ng·min/ml) Values with Summary Statistics

	Hepatic				Healthy			
	Subj.	low dose	Subj.	high dose	Subj.	low dose	Subj	high dose
Geometric LSMean	667.80		1121.96		632.74		818.00	
Arithmetic LSMean	684.86		1225.67		651.00		850.80	
Median	733.60		1444.93		684.40		791.55	
Minimum	499.60		615.85		456.45		579.65	
Maximum	874.55		1878.50		897.65		1314.78	
Arithmetic Mean	684.86		1225.67		651.00		850.80	
95% CI (lower)	477.06		560.06		435.87		501.60	
95% CI (upper)	892.66		1891.28		866.13		1200.00	
SD	167.35		536.06		173.26		281.23	
CV	24.44		43.74		26.61		33.06	
Geometric Mean	667.80		1121.96		632.74		818.00	
95% CI (lower)	486.99		613.29		454.60		559.44	
95% CI (upper)	915.76		2052.53		881.83		1196.05	
Mean of logs	6.504		7.023		6.450		6.707	
SD of logs	0.254		0.486		0.267		0.306	

LSmean = Lease Square Mean, adjust for design imbalance if present
CI = confidence interval for LS mean
SD = Standard deviation
%CV = percent coefficient of variation

Individual GR90291 AUCo (ng·min/ml) Values with Summary Statistics

	Hepatic				Healthy			
	Subj.	low dose	Subj.	high dose	Subj	low dose	Subj	high dose
Geometric LSMean	805.44		1300.96		747.17		985.74	
Arithmetic LSMean	819.75		1407.48		792.27		1008.08	
Median	862.60		1589.12		844.16		925.99	
Minimum	644.98		788.15		534.79		811.34	
Maximum	1034.92		2141.35		1013.38		1458.49	
Arithmetic Mean	819.75		1407.48		792.27		1008.08	
95% CI (lower)	608.64		671.99		523.68		688.17	
95% CI (upper)	1030.86		2142.97		1060.86		1327.98	
SD	170.02		592.34		216.31		257.64	
CV	20.74		42.09		27.30		25.54	
Geometric Mean	805.44		1300.96		747.17		985.74	
95% CI (lower)	618.86		739.77		535.98		743.04	
95% CI (upper)	1046.59		2287.07		1098.10		1307.71	
Mean of logs	6.691		7.171		6.643		6.893	
SD of logs	0.211		0.455		0.289		0.228	

LSmean = Lease Square Mean, adjust for design imbalance if present
CI = confidence interval for LS mean
SD = Standard deviation
%CV = percent coefficient of variation

Table 47

Individual GR90291 Cmax (ng/ml) Values with Summary Statistics

	Hepatic				Healthy			
	Subj.	low dose	Subj.	high dose	Subj.	low dose	Subj.	high dose
Geometric LSMean		3.66		5.14		3.89		4.24
Arithmetic LSMean		3.70		5.39		3.96		4.38
Median		3.80		5.35		3.60		4.20
Minimum		2.90		3.25		3.00		3.20
Maximum		4.20		7.40		5.00		5.65
Arithmetic Mean		3.70		5.39		3.96		4.38
95% CI (lower)		3.01		3.18		2.80		2.85
95% CI (upper)		4.39		7.60		5.02		5.91
SD		0.56		1.78		0.85		1.23
CV		15.0		33.1		21.5		28.1
Geometric Mean		3.66		5.14		3.89		4.24
95% CI (lower)		3.01		3.33		2.98		2.96
95% CI (upper)		4.45		7.93		5.07		6.04
Mean of logs		1.299		1.637		1.358		1.445
SD of logs		0.157		0.349		0.214		0.284

LSMean = Lease Square Mean, adjust for design imbalance if present
CI = confidence interval for LS mean
SD = Standard deviation
%CV = percent coefficient of variation

Individual GR90291 Half-Life (min) Values with Summary Statistics

	Hepatic				Healthy			
	Subj	low dose	Subj.	high dose	Subj	low dose	Subj	high dose
Geometric LSMean		70.839		115.033		69.255		111.903
Arithmetic LSMean		71.324		121.285		72.798		120.131
Median		74.317		126.645		63.925		102.665
Minimum		59.670		61.463		45.251		79.258
Maximum		81.415		157.594		107.926		220.683
Arithmetic Mean		71.324		121.285		72.798		120.131
95% CI (lower)		59.927		72.248		40.812		49.221
95% CI (upper)		82.722		170.321		104.784		191.040
SD		9.179		39.492		25.760		57.108
CV		12.869		32.562		35.384		47.539
Geometric Mean		70.839		115.033		69.255		111.903
95% CI (lower)		60.161		71.299		44.682		68.491
95% CI (upper)		83.412		185.581		107.340		182.829
Mean of logs		4.260		4.745		4.238		4.718
SD of logs		0.132		0.385		0.353		0.395

LSMean = Lease Square Mean, adjust for design imbalance if present
CI = confidence interval for LS mean
SD = Standard deviation
%CV = percent coefficient of variation

Table 49

Statistical Analysis of Log-Transformed GR90291 Pharmacokinetic Parameters

Parameter	Subject Group	Ratio	90% CI	p-value
AUClast (ng·min/ml)	Low Dose Hepatic/Low Dose Healthy	1.06	(0.724, 1.54)	0.806
	High Dose Hepatic/High Dose Healthy	1.37	(0.941, 2.00)	0.163
	Low Dose Hepatic/High Dose Hepatic	0.595	(0.408, 0.868)	0.029
	Low Dose Healthy/High Dose Healthy	0.774	(0.531, 1.13)	0.252
AUC∞ (ml/kg)	Low Dose Hepatic/Low Dose Healthy	1.05	(0.745, 1.48)	0.808
	High Dose Hepatic/High Dose Healthy	1.32	(0.936, 1.86)	0.177
	Low Dose Hepatic/High Dose Hepatic	0.619	(0.439, 0.873)	0.027
	Low Dose Healthy/High Dose Healthy	0.778	(0.552, 1.10)	0.220
Cmax (ng/ml)	Low Dose Hepatic/Low Dose Healthy	0.943	(0.706, 1.26)	0.725
	High Dose Hepatic/High Dose Healthy	1.21	(0.908, 1.62)	0.261
	Low Dose Hepatic/High Dose Hepatic	0.713	(0.534, 0.951)	0.057
	Low Dose Healthy/High Dose Healthy	0.917	(0.687, 1.22)	0.606
$t_{1/2}$ (min)	Low Dose Hepatic/Low Dose Healthy	1.02	(0.707, 1.48)	0.916
	High Dose Hepatic/High Dose Healthy	1.03	(0.711, 1.49)	0.898
	Low Dose Hepatic/High Dose Hepatic	0.616	(0.426, 0.891)	0.036
	Low Dose Healthy/High Dose Healthy	0.619	(0.428, 0.895)	0.037

Table 50

AUC Ratio for GR90291 and Remifentanil in Hepatic Impairment and Healthy Subjects

Low Dose Hepatic Impairment				Low Dose Healthy Subjects			
Subject	Remifentanil AUC	GR90291 AUC	Ratio (GR/Remi)	Subject	Remifentanil AUC	GR90291 AUC	Ratio (GR/Remi)
Mean			6.15				4.75
SD			1.42				1.39

High Dose Hepatic Impairment				High Dose Healthy Subjects			
Subject	Remifentanil AUC	GR90291 AUC	Ratio (GR/Remi)	Subject	Remifentanil AUC	GR90291 AUC	Ratio (GR/Remi)
Mean			4.53				3.11
SD			1.94				0.41

Study USA-224 (GGN/95/09)
Pharmacokinetic Summary

NDA # 20 | Submission Date: 9/15/95 | Volume 99-101

Investigator:
Site:

Single Dose: XXX . Multiple Dose: ____.

Subjects:
Normal: ___. Patients: XXX Young: ___. Elderly: ___.
Impaired Hepatic: XXX. Renal: ___.

Cross-Over: ___. Parallel: ___. N= 6 M= 3 F= 3

Subject Type: Male and Female Patients Scheduled for Elective Hepatic Transplant Surgery

N	6
Gender: male/female	3/3
Age (yrs)	45 ± 9.0 (31-52)
Weight (kg)	67 ± 118.2 (43.8-88.2)

Treatment Summary

Treatment
Remifentanil, Zero Order IV Infusion, Infused for 1 minute.
Rate: First dose, 10 µg/kg/min, was administered during dissection (hepatic) phase and the second dose, 10 µg/kg/min, was administered five minutes after removal of the liver (anhepatic phase).

Lot # CS-USA10008

Sample Strategy:

Arterial Blood Samples for Both Phases: Prior tc dosing, at the end of infusion (1min), and at 3, 5, 7, 10, 15, 20, 25, 30, 40, 50 and 60 minutes after the start of the infusion.

Mixed Venous Blood Samples for Both Phases: Prior to dosing, at the end of infusion (1min), and at 3, 5, 10, 20 and 30 minutes after the start of the infusion.

Assay Method
Remifentanil (blood/urine): GC-High Resolution Mass Spectrometry-Selected Ion Monitoring
GR90291 (blood): GC with mass selective detection (GC-MSD)

Sample	Sensitivity	Site	%CV (QC Conc)	QC Range
Remifentanil Blood	0.1 ng/mL	Triangle	3.3% (5ng/ml) -9.3% (0.25ng/ml)	0.25-80ng/ml
GR90291 Blood	0.5ng/mL	Oneida	3.64% (75ng/ml) - 6.35% (1.5ng/ml)	1.5-75ng/ml

Labeling Claims From Study: The pharmacokinetics of remifentanil in anhepatic patients was similar to that of healthy patients.

Study P24 - Remifentanil Hepatic Transplant

Conclusions: The pharmacokinetics of remifentanil in anhepatic patients were similar to that of healthy (ASA 1) patients. The pharmacokinetics of remifentanil in the dissection phase, when extraordinary blood loss, fluid replacement and hemodilution occurs, were difficult to interpret. The apparently increased clearance and volume of distribution reflected the lower blood concentrations during this phase. The low blood concentrations were attributed to physical loss of remifentanil due to hemorrhage and to the effects of hemodilution. This explanation is supported by lower metabolite concentrations during the dissection phase, given that an increase in metabolite concentration would be expected if the metabolic clearance of remifentanil were truly greater during this phase.

Investigators:

Purpose: 1) to assess the extrahepatic metabolism of remifentanil in man by determining the pharmacokinetics of remifentanil prior to, and during, the anhepatic phase of liver transplantation, 2) to assess the involvement of the lung in the metabolism, or sequestration, of GI87084, 3)to examine *in vitro* hydrolysis of remifentanil in whole blood.

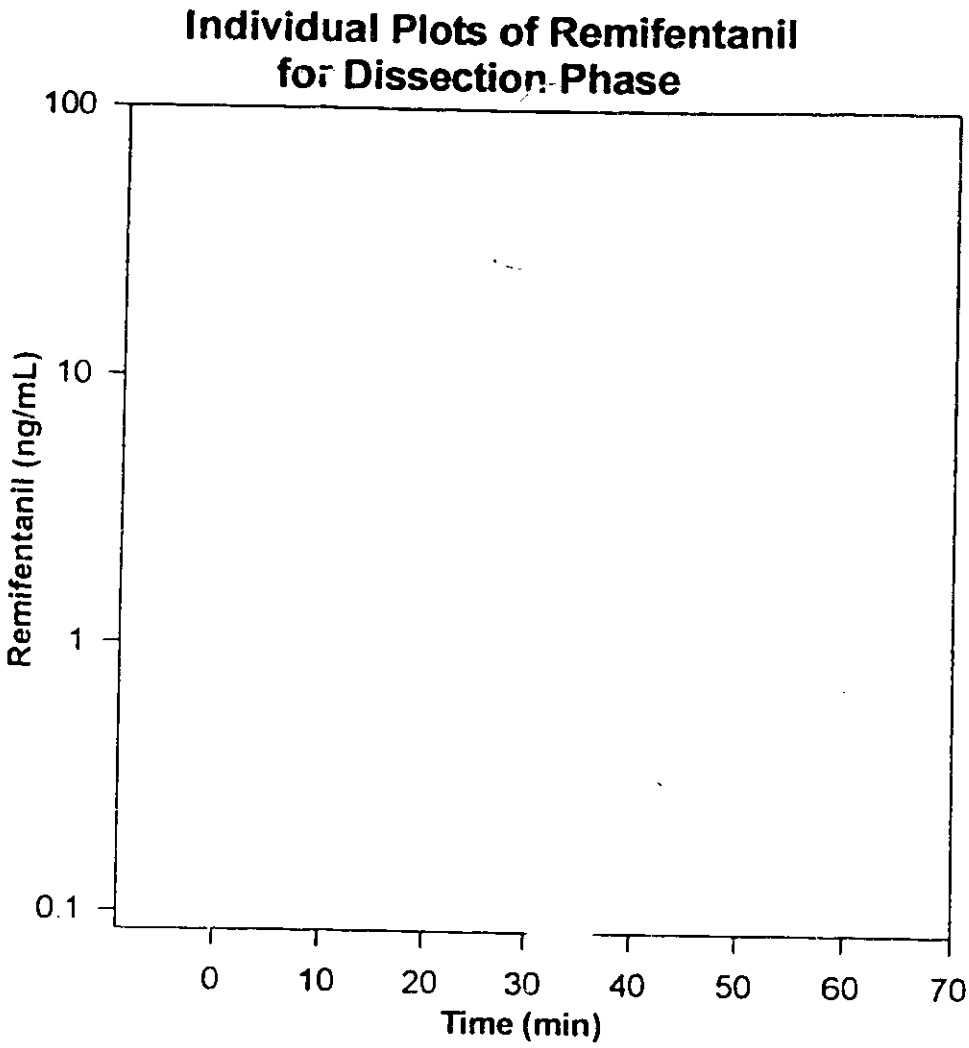
Study Design: Each subject received two intravenous bolus doses of remifentanil 10μg/kg, each given over one minute. The first bolus dose of remifentanil was administered following endotracheal intubation - as soon as the peripheral and pulmonary arterial catheter were in-situ (dissection phase).The second bolus dose of remifentanil was administered five minutes after removal of the liver (anhepatic phase)

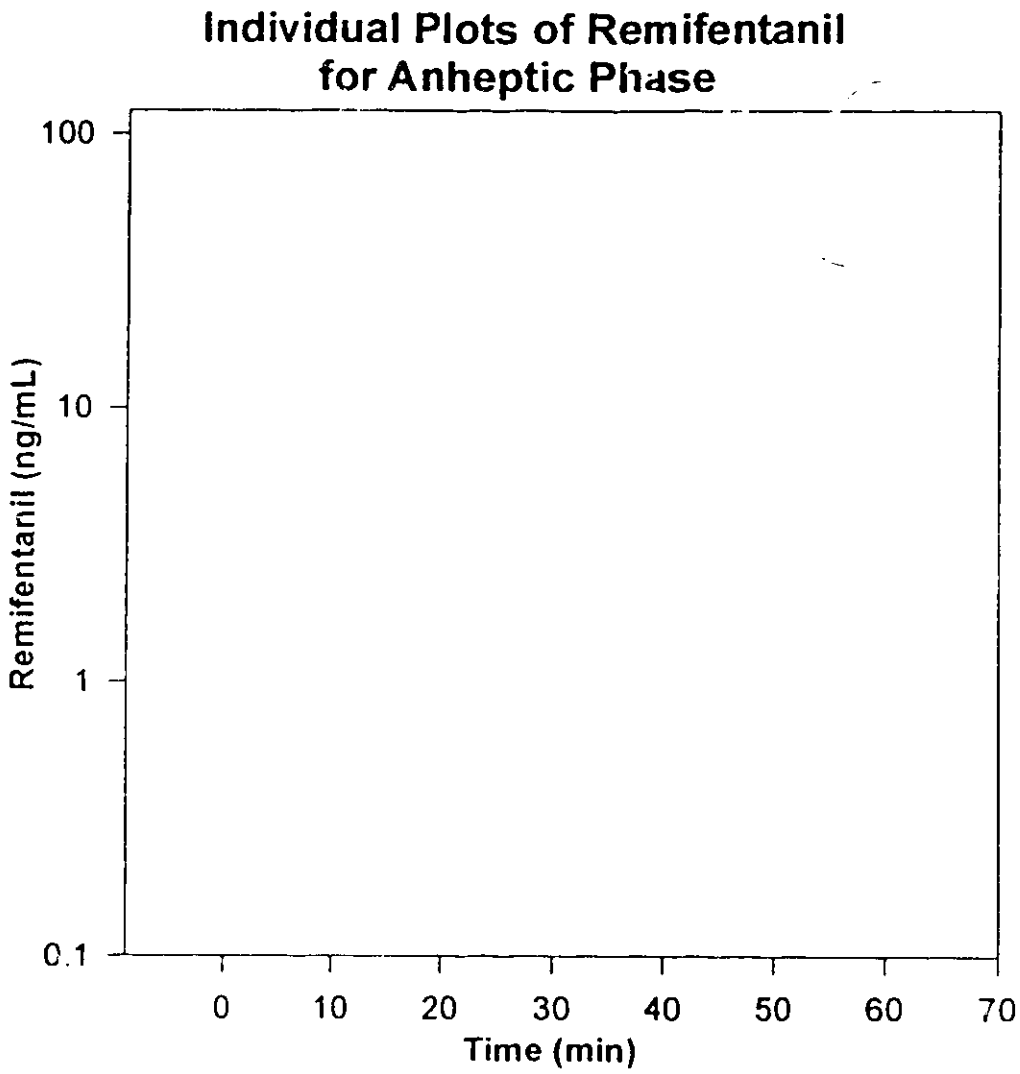
Demographics: 6 patients (3 male, 3 female) aged 31-57 years, undergoing liver transplant.

Anesthesia Protocol: *Premedication:* Oral benzodiazepine or parenteral opioid. *Induction/Maintenance:* Thiopental or etomidate, suxamethonium or atracurium to facilitate intubation. N_2O/Oxygen, isoflurane supplement and incremental fentanyl for analgesia. *Other:* Remifentanil (10mcg/kg) was administered as 1 minute infusions on two occasions, after endotracheal intubation, and after removal of the liver.

Results: **Table of Principal PK and Safety Results (N=6)**
Values are N (% Total) or Mean ± SD

	Hepatic Transplant	
	Dissection Phase	Anhepatic Phase
Pharmacokinetics	N = 6	N = 6
Remifentanil		
CL_{est} (mL/min/kg)	79.54 (29.34)	39.57 (17.39)
$V_{1,est}$ (mL/kg)	443 (265)	255 (115)
$V_{ss,est}$ (mL/kg)	748 (440)	410 (173)
$t_{1/2}$ b (min)	10.43 (4.08)	9.96 (1.51)
GR 90291		
AUC (ng.min/mL)	705 (121)	1098 (589)
Safety	N = 6	N = 6
Any adverse event	0	3 (50%)
During Treatment	0	0
After Treatment	0	3 (50%)


Individual Plots of Remifentanil
for Dissection Phase
100
10
1
0.1
Remifentanil (ng/mL)
0
10
20
30
40
50
60
70
Time (min)


Individual Plots of Remifentanil
for Anheptic Phase
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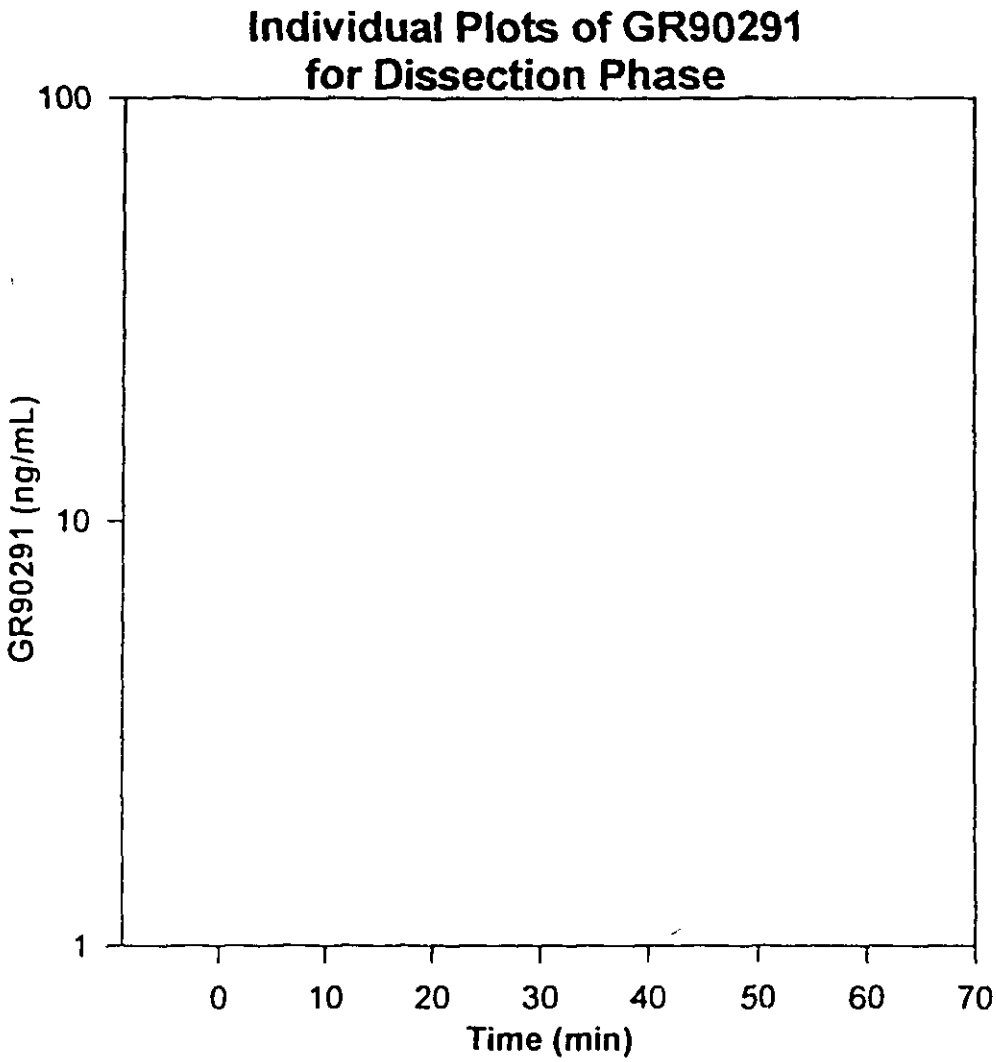
1
0.1
Remifentanil (ng/mL)
0
10
20
30
40
50
60
70
Time (min)


Individual Plots of GR90291
for Dissection Phase
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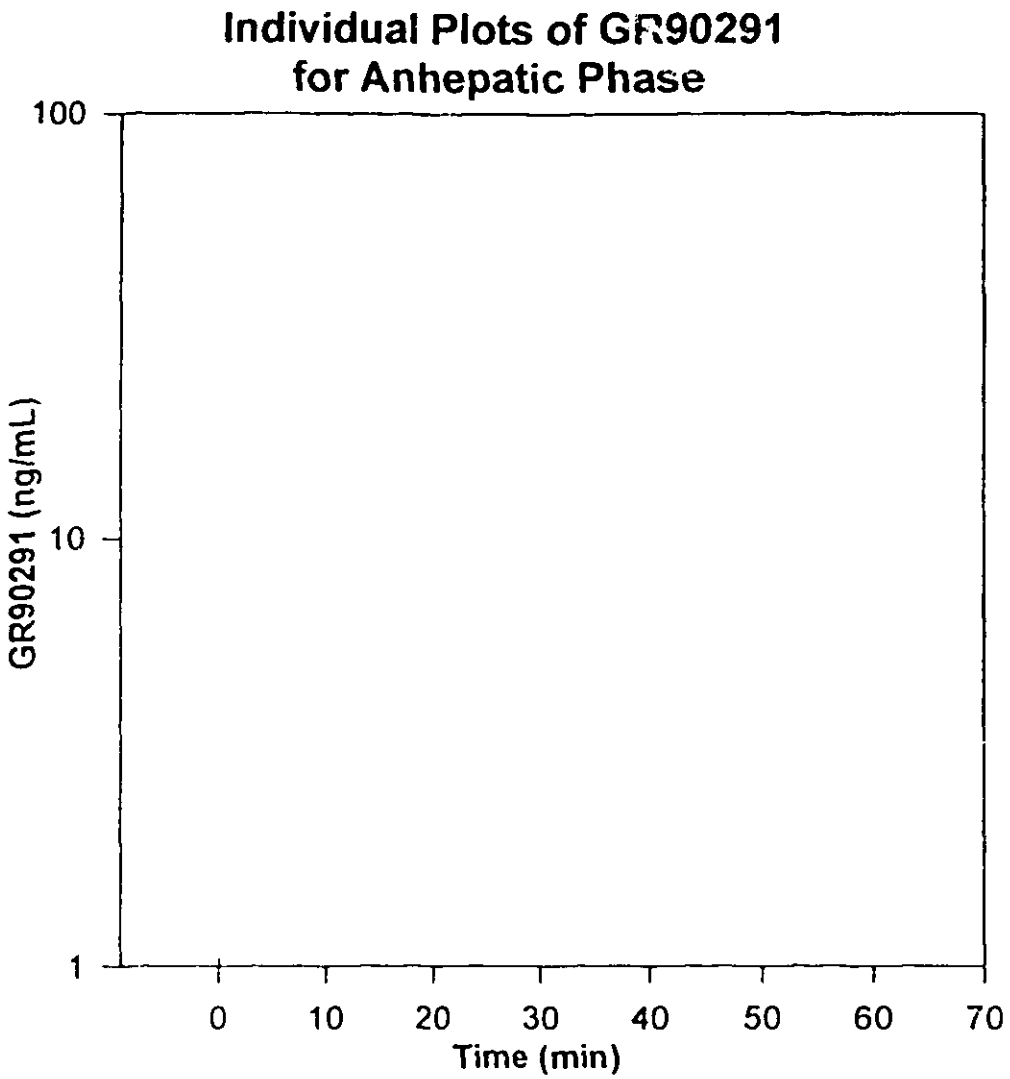
10
1
GR90291 (ng/mL)
0
10
20
30
40
50
60
70
Time (min)


Individual Plots of GR90291
for Anhepatic Phase
100
10
1
GR90291 (ng/mL)
0
10
20
30
40
50
60
70
Time (min)

USA-210 (UCP/95/009)
Pharmacokinetic Study Summary

NDA # 20-630 Submission Date: 9/15/95 Volume 76-81

Investigator:
Site:

Single Dose: X . Multiple Dose: ____.
Subjects: Normal: X. Patients: ____. Young: X. Elderly: ____.
Hepatic: ____. Renal: X.
Cross-Over: ____. Parallel: X. N= 23 M= 14 F= 9

Subject Type: Renal Impairment and Healthy Volunteers
Renal function assessed at screening using creatinine clearance (Clcr) estimated by Cockcroft-Gault method and normalized for body surface area (renal impairment CLcr<30mL/min/m^2).

Category	Renal Impairment		Healthy
	Low Dose (N = 6)	High Dose (N= 9)	High Dose (N = 8)
Gender - male/female	3 / 3	6 / 3	5 / 3
Age - years	51.2 ± 8.8 (41-62)	38.8 ± 7.6 (28-51)	39.9 ± 6.7 (31-52)
Weight - kg	69.7 ± 17.5 (48.5-93.5)	75.4 ± 21.8 (47.3-116.0)	76.3 ±21.0 (45.5 -114.0)

Treatment Summary:
Remifentanil, Zero Order IV Infusion, Lot # CS-USA1008
Low Dose Rate 0.0125µg/kg/min x 1 hour followed by 0.025µg/kg/min x 3 hours
High Dose Rate 0.025µg/kg/min x 1 hour followed by 0.05µg/kg/min x 3 hours

Sample Strategy:
Blood Samples: Arterial samples were collected prior to dosing (≤30min), at 2, 5, 10, 15, 30, 60, 75, 90, 120, 150, 180, 210, and 230min during the infusion, and at 2, 5, 10, 15, 30, 60, 90, 120, 240, and 360min post infusion. A venous sample was collected at 120, 240, 360, and 1440min post infusion.
Urine: Urine was collected prior to dosing then pooled over the intervals 0-6, 6-10, and 10-24 hours.
Dialysis: For subjects undergoing dialysis, a blood sample was collected from the venous and arterial sides of the shunt at 30min after starting dialysis, and then just prior to the end of dialysis. Dialysate samples were collected at the same time as the arterial and venous samples.
Minute Ventilation: Measurements collected at baseline, and at 15, 30, 60, 75, 90, 120, 180, and 230min during the infusion, and at 5, 15, 30, and 60min post infusion.

Assay Method:
Remifentanil (blood/urine): GC-High Resolution Mass Spectrometry-Selected Ion Monitoring
GR90291(blood): Gas chromatography with mass selective detection (GC-MSD)
GR90291(urine/dialysate): High performance liquid chromatography with UV detection (HPLC-UV)
GR94219 (urine): GC-High Resolution Mass Spectrometry-Selected Ion Monitoring

Sample	Sensitivity	Site	%CV (QC Conc)	QC Range
Remifentanil Blood	0.1 ng/mL		5.2% (5ng/ml) -10.6% (0.25ng/ml)	0.25-80ng/ml
Remifentanil Urine	0.5ng/mL		2.6% (250ng/ml) -5.50% (450ng/ml)	1.5-450ng/ml
GR90291 Blood	1ng/mL		3.9% (180ng/ml) - 11.0% (4.0ng/ml)	4.0-180ng/ml
GR90291 Urine/dialysate	0.1mcg/mL		1.0% (40mcg/ml) - 5.40% (0.3mcg/ml)	0.3-40mcg/ml
GR94219 Urine	0.5ng/mL		3.3% (40ng/ml) - 6.90% (1.5ng/ml)	1.5-80ng/ml

Labeling Claims From Study: The pharmacokinetics and pharmacodynamics of remifentanil are not altered in subjects with renal impairment. The elimination of GR90291 is markedly reduced in subjects with renal impairment. GR90291 undergoes approximately 25-35% extraction during hemodialysis.

Study 210 - Remifentanil PK/PD Study in Renal Impairment

Conclusions: The pharmacokinetics of remifentanil were not altered in conscious volunteers with severe renal impairment (CL of 36.0 mL/min/kg) compared to healthy subjects (CL of 34.2mL/min/kg). The elimination $t_{1/2}$ of GR90291, the primary metabolite of remifentanil, was increased 15-20 fold in renal impairment. GR90291 underwent 25-35% extraction during hemodialysis. The EC_{50} values for response to hypercarbic challenge (measurement of minute ventilation (MV) as an assessment of sensitivity to the respiratory effects of remifentanil) were not significantly different in renal impairment (2.3ng/mL) and healthy subjects (3.7ng/mL), respectively.

Investigators:

Purpose: 1) to evaluate the effect of renal function on the elimination of remifentanil and its metabolites, GR90291 and GR94219; 2) to evaluate the effects of remifentanil on respiratory drive in renal impairment versus healthy subjects.

Study Design: Two-center, open-label, parallel study in severe (end stage) renal impairment versus healthy subjects at two infusion regimens (low dose and high dose) of remifentanil.

Demographics: 23 subjects (15 severe renal impairment subjects with Clcr≤ 30mL/min/1.73m^2, 8 healthy subjects), ages 28-62 years, male and female. Renal impairment and healthy subjects in the high dose group were matched for age, weight, gender and race.

Anesthesia Protocol: *Premedication:* N/A. *Induction/Maintenance:* N/A. *Other:* Six subjects (renal impairment) received a 1-hour infusion of 0.0125mcg/kg/min remifentanil followed by a 3-hour infusion of 0.025mcg/kg/min remifentanil (Low dose regimen). Seventeen subjects (nine renal impairment and eight healthy subjects) received a 1-hour infusion of 0.025mcg/kg/min remifentanil followed by a 3-hour infusion of 0.05mcg/kg/min remifentanil (High dose regimen).

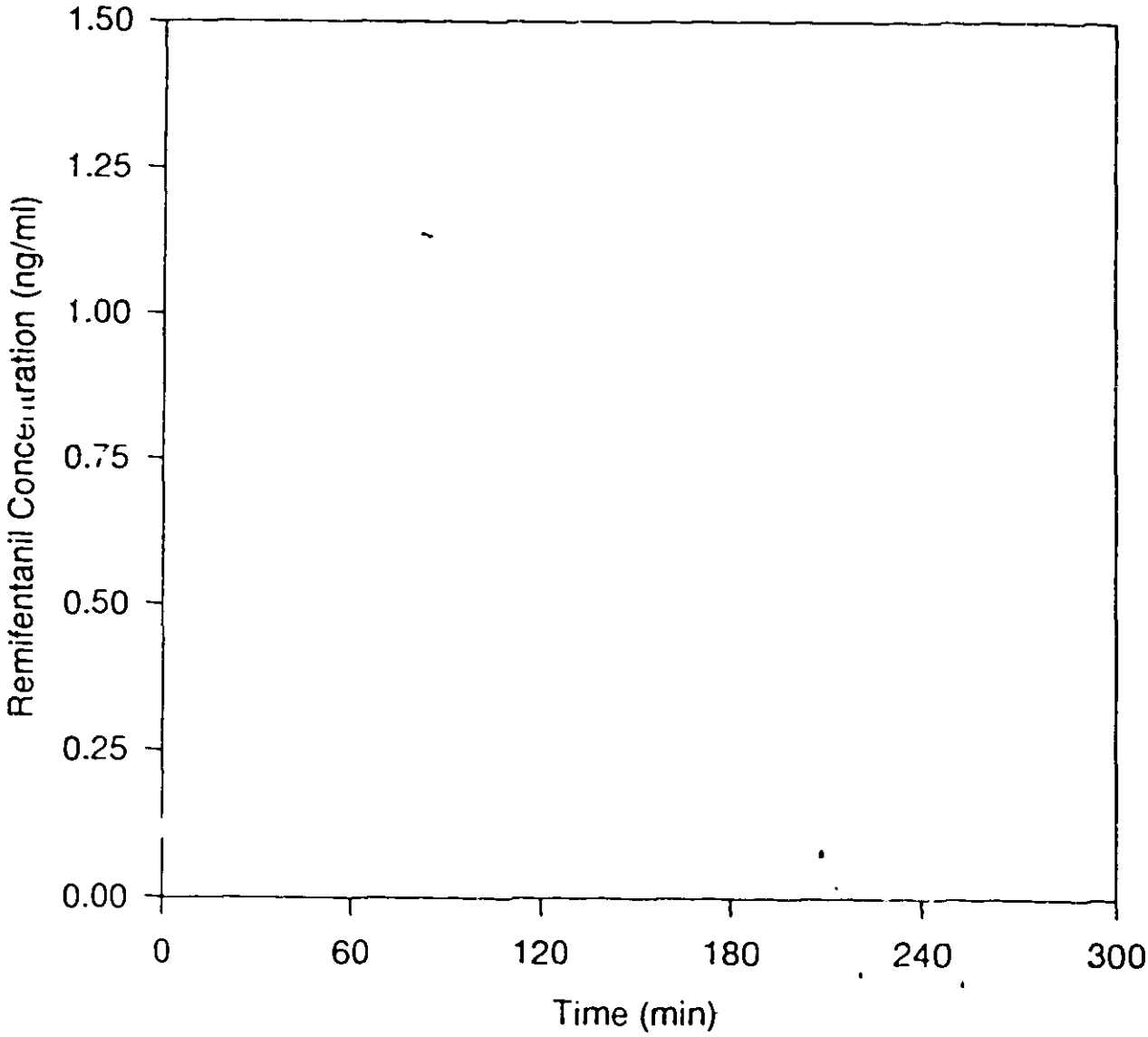
Results: Table 1. Principle PK, PD and Safety Results, All Subjects (N = 23)

	Renal Impairment		Healthy
Values are N (% Total) or Mean ± SD	Low Dose	High Dose	High Dose
Pharmacokinetics	N = 6	N = 9	N = 8
Remifentanil CL (mL/min/kg)	36.7 ± 12.6	36.0 ± 5.7	34.2 ± 8.0
Remifentanil Vd (mL/kg)	298 ± 111	230 ± 26	197 ± 52
Remifentanil $t_{1/2}$ (min)	6.27 ± 3.87	4.51 ± 0.69	4.06 ± 0.78
GR90291 AUC_∞ (ng•min/mL)[1]	24791 ± 12517	35150 ± 13800	993 ± 254
GR90291 C_{max} (ng/mL)[1]	15.2 ± 5.5	12.7 ± 2.8	4.2 ± 0.6
GR90291 $t_{1/2}$ (min)	1369 ± 533	2077 ± 783	89 ± 17
Pharmacodynamics		N = 9	N = 8
EC_{50} MV (ng/mL)	N/A	3.68 ± 2.72	2.32 ± 1.62
Safety	N = 6	N = 9	N = 8
Any adverse event	3 (50%)	9 (100%)	9 (100%)

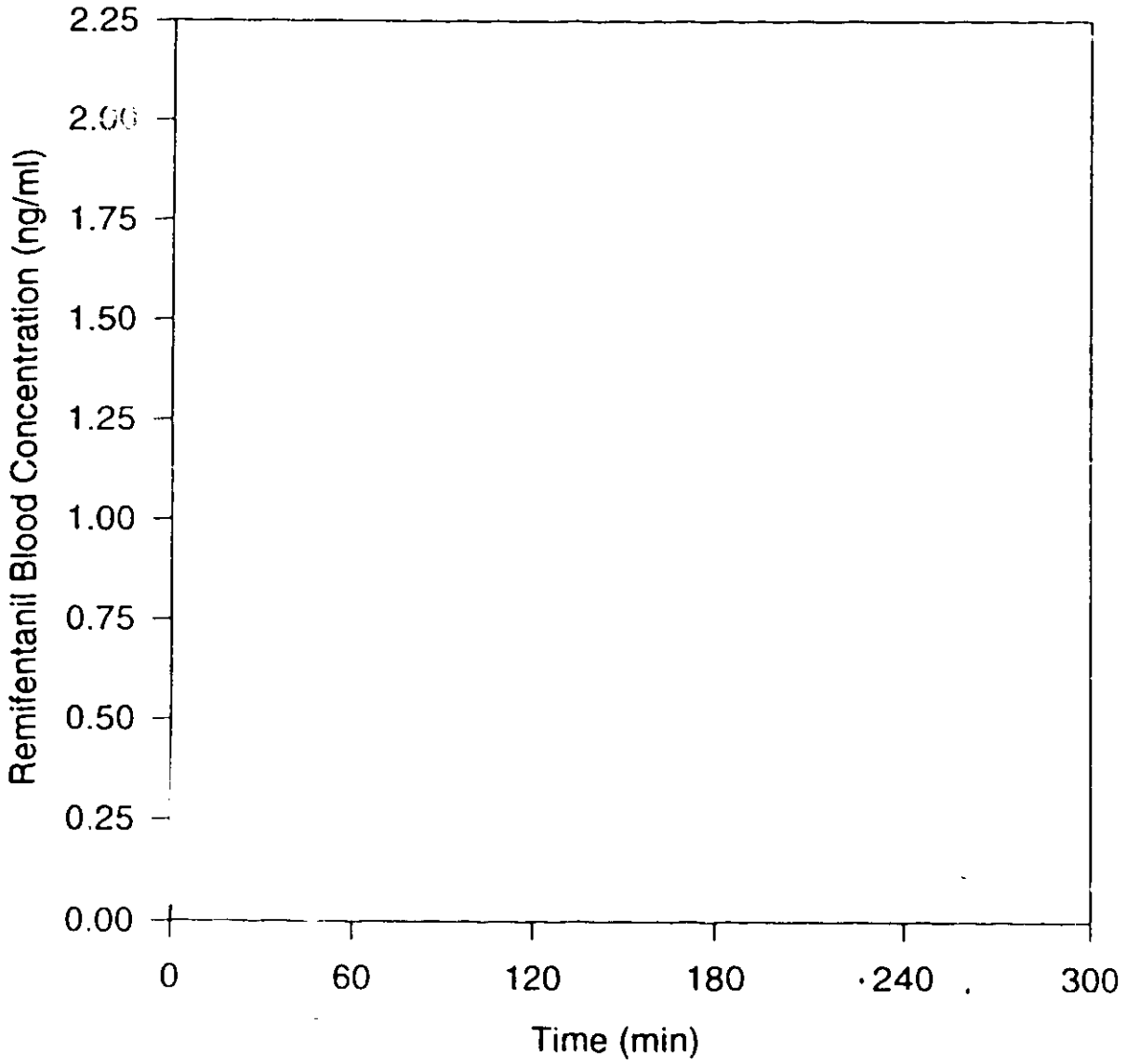
[1]AUC_∞ for high dose groups are normalized to low dose.

The adverse event incidence was similar between the two populations.

Remifentanil Concentration-Time Profiles for Low Dose Renal Impairment Subjects



Remifentanil Concentration-Time Profile in High Dose Healthy Subjects



Remifentanil Concentration-Time Profile in High Dose Renal Impairment Subjects

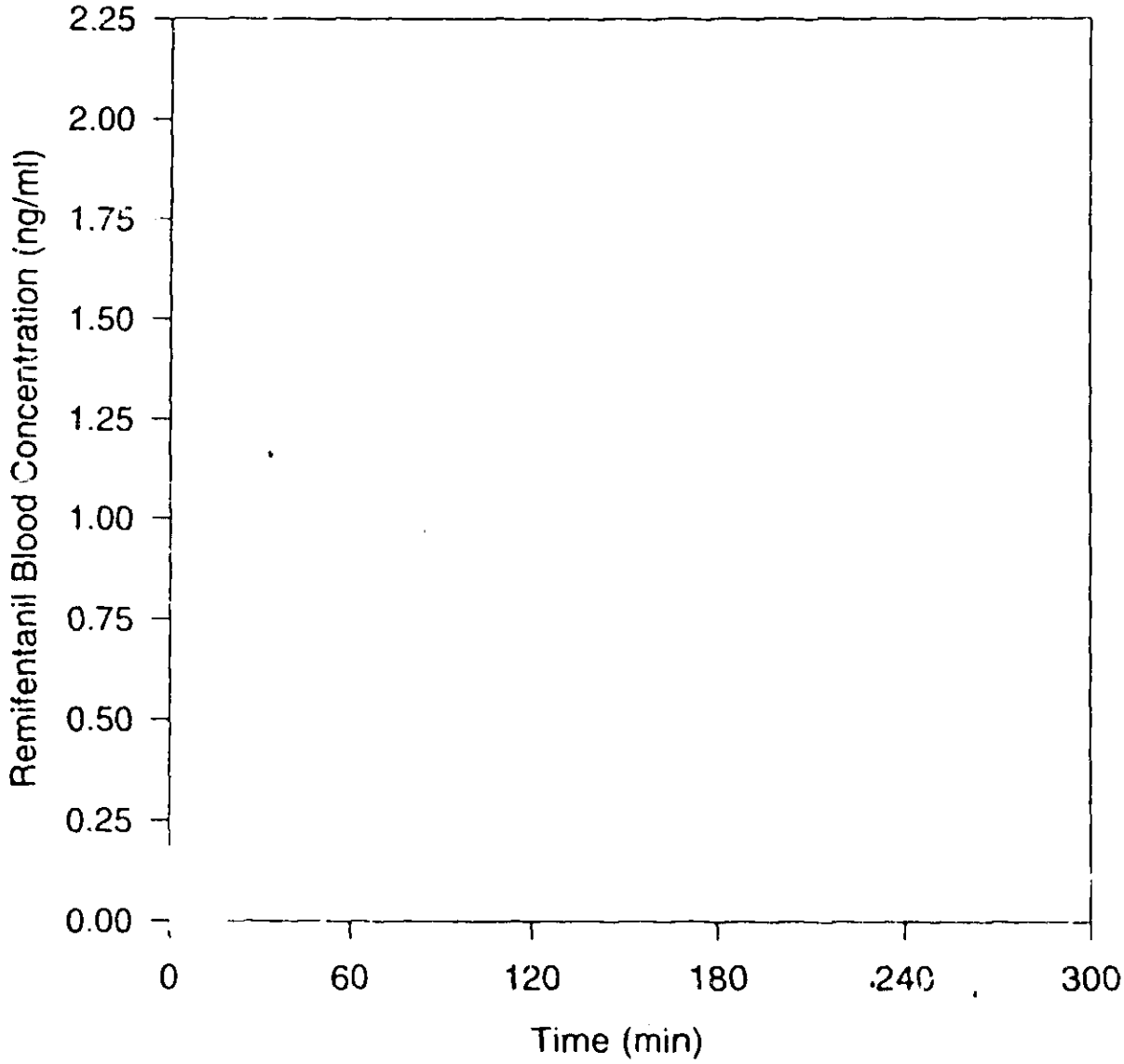
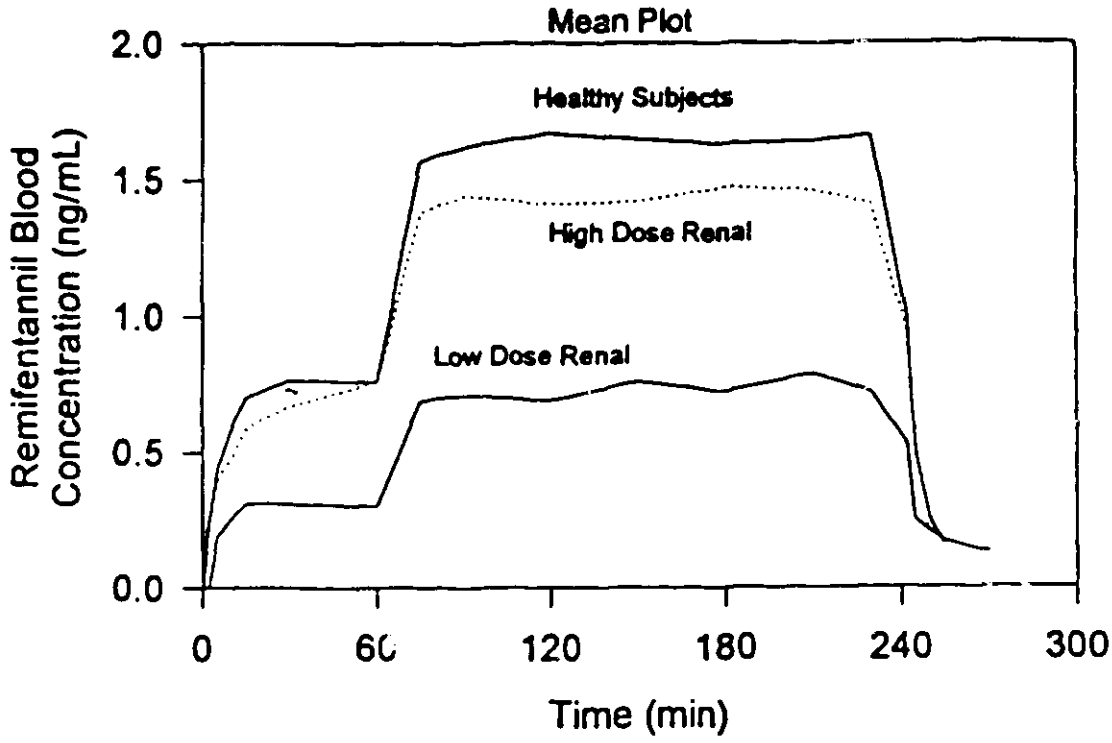
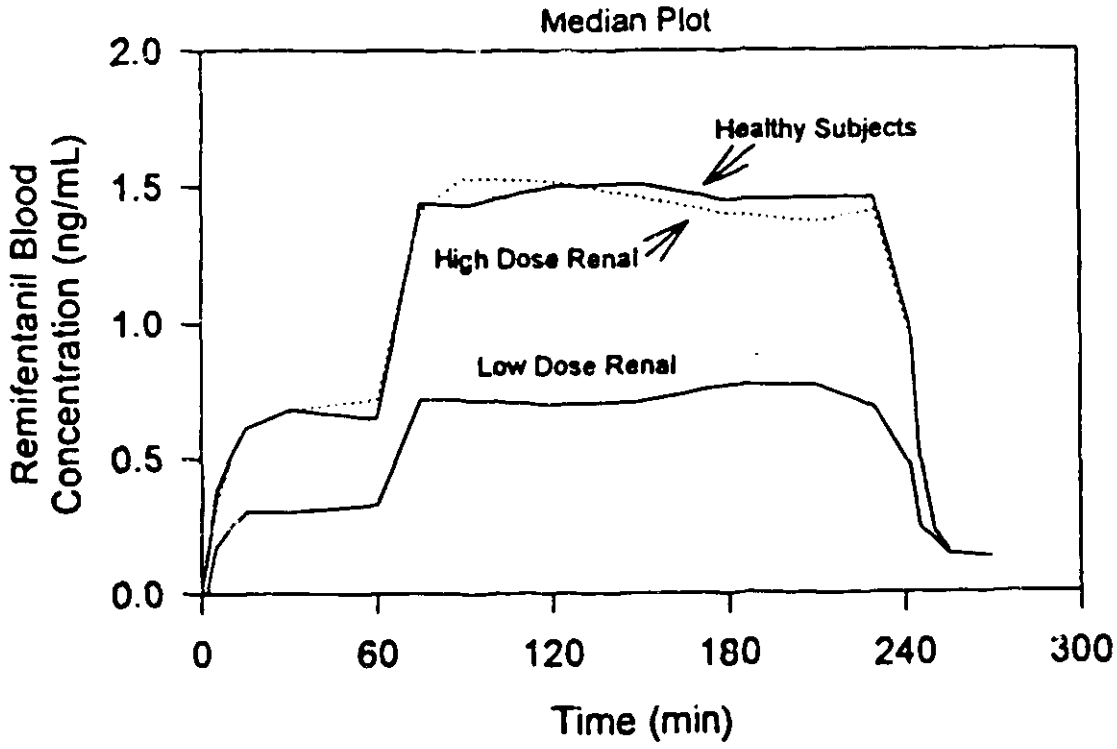


Figure 10

Mean and Median Remifentanil Blood Concentrations





Individual Clearance (ml/min/kg) Values with Summary Statistics

	Low Dose Renal Impairment	High Dose Renal Impairment	High Dose Healthy Subjects
	Subject	Subject	Subject
Geometric LSMean	35.1035	35.5990	33.2162
Arithmetic LSMean	36.6840	35.9697	34.1897
Median	35.6800	34.5707	36.8973
Minimum	24.3673	29.6833	18.8482
Maximum	59.8276	48.2266	43.9962
Arithmetic Mean	36.6840	35.9697	34.1857
95% CI (lower)	23.4391	31.5906	27.5320
95% CI (upper)	49.9288	40.3408	40.8474
SD	12.6209	5.6866	7.9636
CV	34.4045	15.8094	23.2924
Geometric Mean	35.1035	35.5990	33.2162
95% CI (lower)	25.1629	31.7163	26.4889
95% CI (upper)	48.9710	39.9571	41.6520
Mean of logs	3.558	3.572	3.503
SD of logs	0.317	0.150	0.271

LSmean = Least Square Mean, adjust for design imbalance if present
CI = Confidence interval for LS mean
SD = Standard deviation
%CV = Percent coefficient of variation

Individual Volume of Distribution (mL/kg) Values with Summary Statistics

	Low Dose Renal Impairment	High Dose Renal Impairment	High Dose Healthy Subjects
	Subject	Subject	Subject
Geometric LSMean	282.291	228.835	190.722
Arithmetic LSMean	298.113	230.052	197.037
Median	287.362	228.403	193.798
Minimum	191.741	199.360	116.782
Maximum	489.599	289.994	272.814
Arithmetic Mean	298.113	230.052	197.037
95% CI (lower)	181.192	210.028	153.602
95% CI (upper)	415.034	250.076	240.471
SD	111.413	26.050	51.954
CV	37.373	11.324	26.368
Geometric Mean	282.291	228.835	190.722
95% CI (lower)	194.098	210.697	151.115
95% CI (upper)	410.555	248.534	240.710
Mean of logs	5.643	5.433	5.251
SD of logs	0.357	0.107	0.278

LSmean = Least Square Mean, adjust for design imbalance if present
CI = Confidence interval for LS mean
SD = Standard deviation
%CV = Percent coefficient of variation

Individual K10 (min^{-1}) Values with Summary Statistics

	Low Dose Renal Impairment	High Dose Renal Impairment	High Dose Healthy Subjects
	Subject	Subject	Subject
Geometric LSMean	0.12435	0.15557	0.17416
Arithmetic LSMean	0.13522	0.15785	0.17798
Median	0.13744	0.14889	0.16507
Minimum	0.04977	0.13474	0.13383
Maximum	0.19009	0.23586	0.27259
Arithmetic Mean	0.13522	0.15785	0.17798
95% CI (lower)	0.08117	0.23377	0.14223
95% CI (upper)	0.18927	0.18193	0.21373
SD	0.05150	0.03133	0.04276
CV	38.0880	19.8470	24.0256
Geometric Mean	0.12435	0.15557	0.17416
95% CI (lower)	0.07430	0.13618	0.14554
95% CI (upper)	0.20812	0.17772	0.20841
Mean of logs	-2.08	-1.86	-1.75
SD of logs	0.491	0.173	0.215

LSmean = Least Square Mean, adjust for design imbalance if present
CI = Confidence interval for LS mean
SD = Standard deviation
%CV = Percent coefficient of variation

Individual Half-life (min) Values with Summary Statistics

	Low Dose Renal Impairment	High Dose Renal Impairment	High Dose Healthy Subjects
	Subject	Subject	Subject
Geometric LSMean	5.5741	4.4556	3.9799
Arithmetic LSMean	6.2660	4.5103	4.0552
Median	5.0441	4.6553	4.1993
Minimum	3.6464	2.9388	2.5428
Maximum	13.9270	5.1445	5.1799
Arithmetic Mean	6.2660	4.5103	4.0552
95% CI (lower)	2.2061	3.9835	3.3992
95% CI (upper)	10.3258	5.0370	4.7113
SD	3.8686	0.6853	0.7847
CV	61.7403	15.1941	19.3511
Geometric Mean	5.5741	4.4556	3.9799
95% CI (lower)	3.3305	3.9063	3.3259
95% CI (upper)	9.3290	5.0901	4.7627
Mean of logs	1.718	1.494	1.381
SD of logs	0.491	0.173	0.215

LSmean = Least Square Mean, adjust for design imbalance if present
CI = Confidence interval for LS mean
SD = Standard deviation
%CV = Percent coefficient of variation

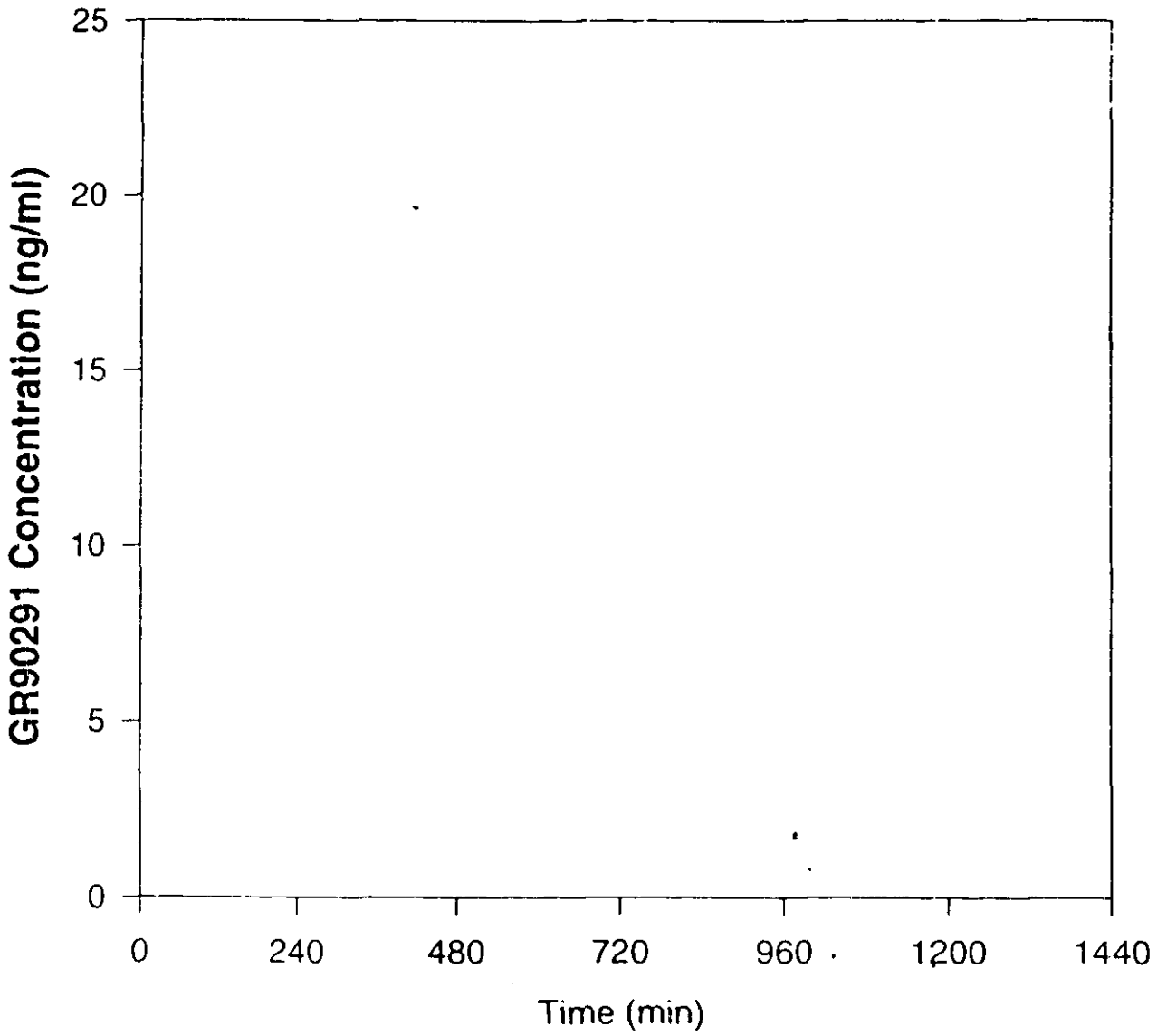
Table 41

Statistical Analysis Results of Log-Transformed Remifentanil Pharmacokinetic and Pharmacodynamic Parameters

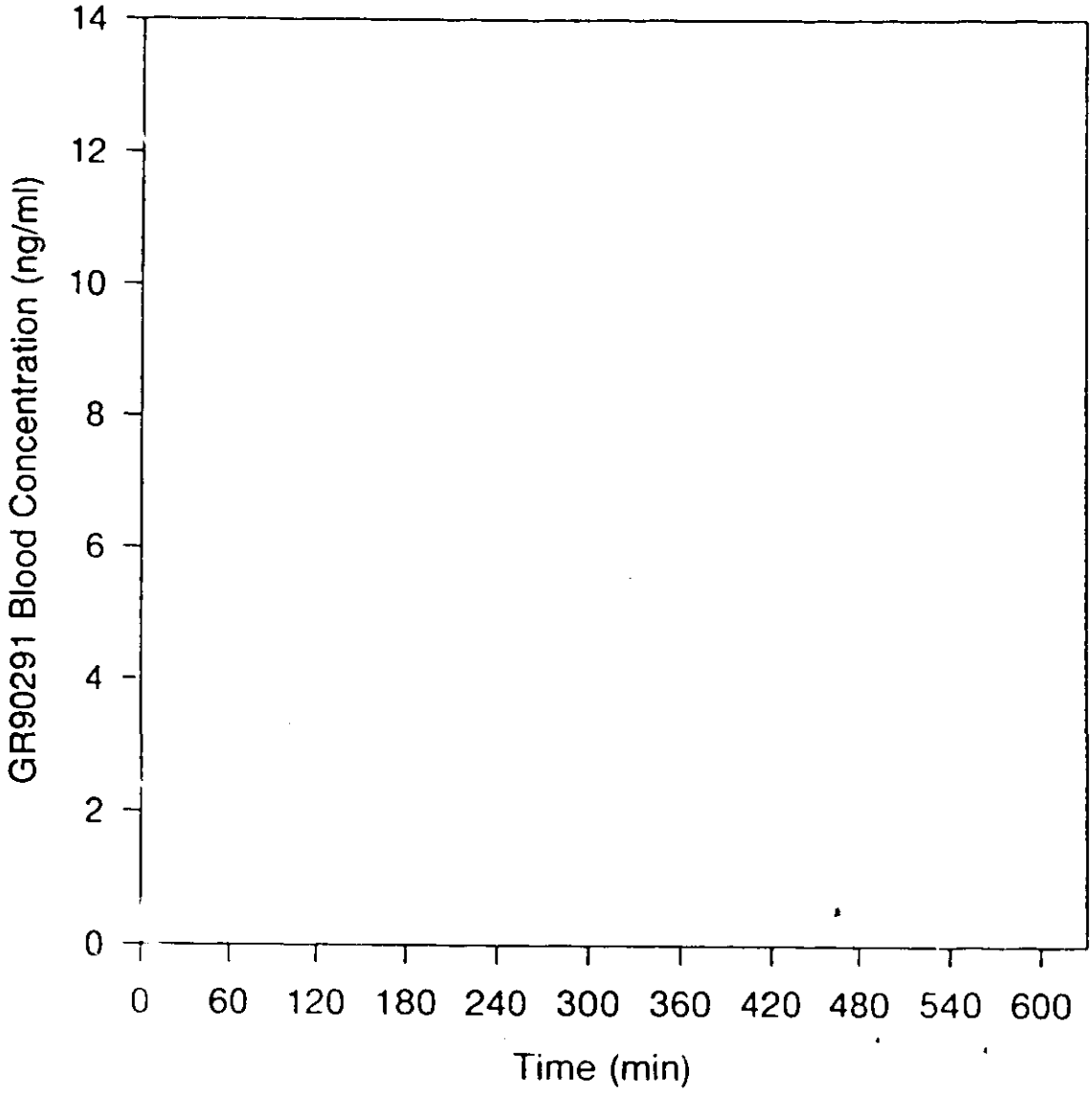
Parameter	Subject Group	Ratio	90% CI	p-value
CL (ml/min/kg)	Low Dose Renal/High Dose Renal	0.986	(79.6, 1.22)	0.909
	High Dose Renal/High Dose Healthy	1.07	(0.892, 1.29)	0.517
Vd (ml/kg)	Low Dose Renal/High Dose Renal	1.23	(0.989, 1.54)	0.116
	High Dose Renal/High Dose Healthy	1.20	(1.01, 1.43)	0.088
K10 (min^{-1})	Low Dose Renal/High Dose Renal	0.799	(0.586, 1.09)	0.225
	High Dose Renal/High Dose Healthy	0.893	(0.757, 1.05)	0.249
$t_{1/2}$ (min)	Low Dose Renal/High Dose Renal	1.25	(0.917, 1.71)	0.225
	High Dose Renal/High Dose Healthy	1.12	(0.949, 1.32)	0.249
EC_{50} (ng/ml)*	High Dose Renal/High Dose Healthy	1.58	(0.750, 2.42)	0.239

* Untransformed analysis

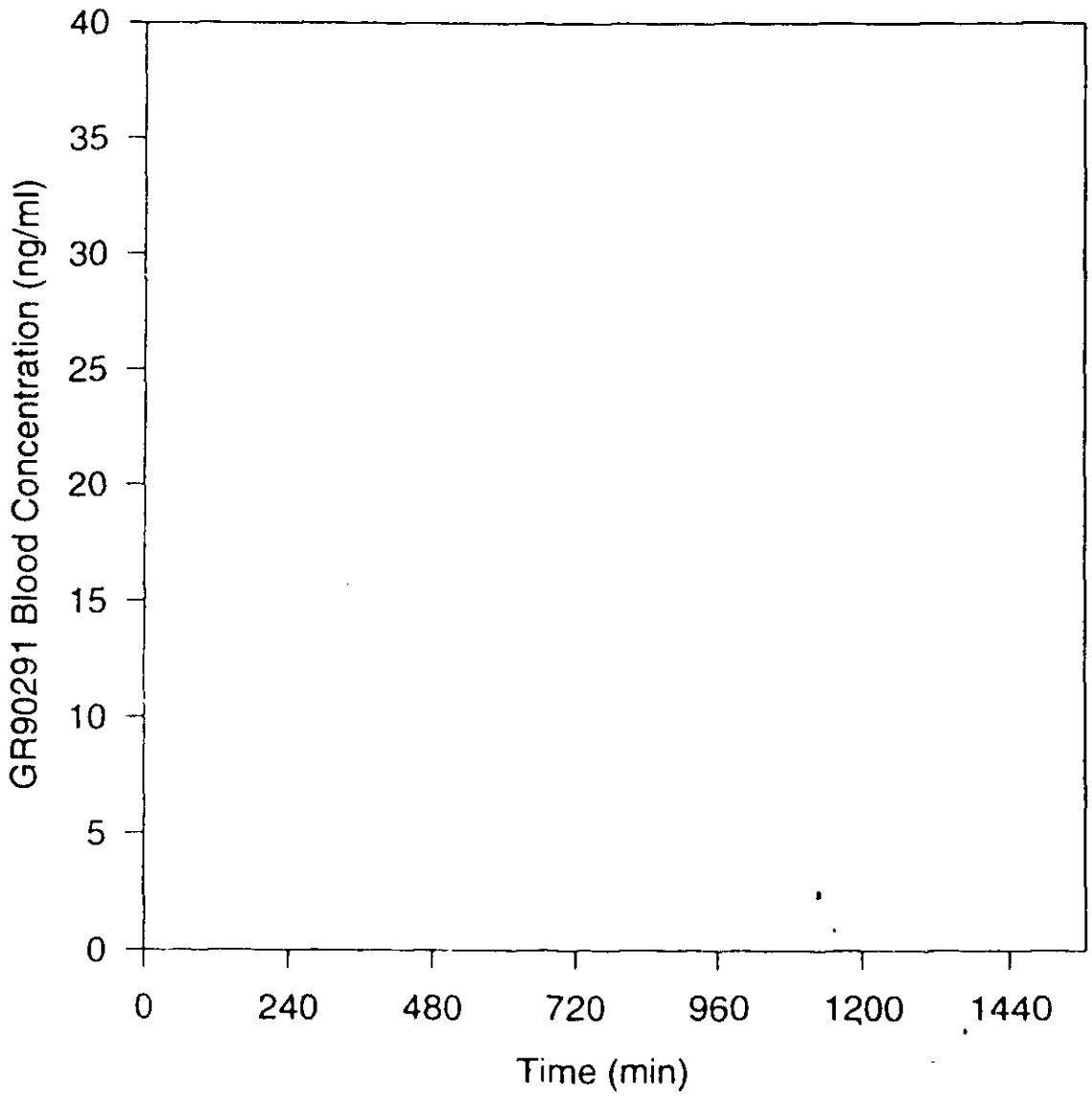
GR90291 Concentration-Time Profiles for Low Dose Renal Impairment Subjects



GR90291 Concentration-Time Profile in High Dose Healthy Subjects



GR90291 Concentration-Time Profile in High Dose Renal Impairment Subjects



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Individual AUC∞ (ng.min/ml) Values with Summary Statistics

	Low Dose Renal Impairment	High Dose Renal Impairment*	High Dose Healthy Subjects*
	Subject	Subject	Subject
			925.89
			837.20
			998.27
			1424.26
			832.00
			1312.21
			951.60
			666.13
Geometric LSMean	21541.01	32389.91	966.71
Arithmetic LSMean	24790.88	35149.98	993.45
Median	22648.20	32488.45	938.75
Minimum	6883.45	12745.97	666.13
Maximum	42567.34	54312.01	1424.26
Arithmetic Mean	24790.88	35149.98	993.45
95% CI (lower)	11655.07	24542.34	781.20
95% CI (upper)	37926.68	45757.63	1205.69
SD	12517.02	13800.03	253.87
CV	50.49	39.26	25.55
Geometric Mean	21541.01	32389.91	966.71
95% CI (lower)	11050.35	22843.21	786.06
95% CI (upper)	41990.96	45928.41	1188.87
Mean of logs	9.978	10.39	6.874
SD of logs	0.636	0.454	0.247

LSmean = Least Square Mean, adjust for design imbalance if present
CI = Confidence interval for LS mean
SD = Standard deviation
%CV = Percent coefficient of variation
* = Values are normalized to dose

Individual AUClast (ng.min/ml) Values with Summary Statistics

	Low Dose Renal Impairment	High Dose Renal Impairment*	High Dose Healthy Subjects*
	Subject	Subject	Subject
Geometric LSMean	10097.95	11443.05	841.05
Arithmetic LSMean	10502.02	11784.84	872.25
Median	10761.05	10610.90	806.45
Minimum	6011.75	8491.48	532.05
Maximum	13972.55	18525.80	1268.18
Arithmetic Mean	10502.02	11784.84	872.25
95% CI (lower)	7324.40	9313.10	659.99
95% CI (upper)	13679.64	14256.57	1084.51
SD	3027.93	3215.61	253.89
CV	28.83	27.29	29.11
Geometric Mean	10097.95	11443.05	841.05
95% CI (lower)	7238.77	9440.66	660.92
95% CI (upper)	14086.44	13870.14	1070.36
Mean of logs	9.220	9.345	6.735
SD of logs	0.317	0.250	0.288

LSmean = Least Square Mean, adjust for design imbalance if present
CI = Confidence interval for LS mean
SD = Standard deviation
%CV = Percent coefficient of variation
* = Values are normalized to dose

Individual Cmax (ng/ml) Values with Summary Statistics

	Low Dose Renal Impairment	High Dose Renal Impairment*	High Dose Healthy Subjects*
	Subject	Subject	Subject
Geometric LSMean	14.43	12.43	4.17
Arithmetic LSMean	15.22	12.71	4.21
Median	13.50	11.75	4.00
Minimum	9.60	8.75	3.55
Maximum	22.70	17.60	5.10
Arithmetic Mean	15.22	12.71	4.21
95% CI (lower)	9.45	10.53	3.69
95% CI (upper)	20.98	14.89	4.72
SD	5.49	2.83	0.61
CV	36.08	22.28	14.58
Geometric Mean	14.43	12.43	4.17
95% CI (lower)	9.96	10.48	3.70
95% CI (upper)	20.91	14.75	4.70
Mean of logs	2.670	2.520	1.428
SD of logs	0.353	0.223	0.142

LSmean = Least Square Mean, adjust for design imbalance if present
CI = Confidence interval for LS mean
SD = Standard deviation
%CV = Percent coefficient of variation
* = Values are normalized to dose

Individual Half-life (min) Values with Summary Statistics

	Low Dose Renal Impairment	High Dose Renal Impairment	High Dose Healthy Subjects
	Subject	Subject	Subject
Geometric LSMean	1240.92	1880.37	88.00
Arithmetic LSMean	1369.42	2076.88	89.37
Median	1423.52	2096.01	87.68
Minimum	429.01	510.35	67.60
Maximum	1943.18	2929.71	119.22
Arithmetic Mean	1369.42	2076.88	89.37
95% CI (lower)	810.28	1475.14	75.25
95% CI (upper)	1928.56	2678.61	103.50
SD	532.80	782.82	16.90
CV	38.91	37.69	18.90
Geometric Mean	1240.92	1880.37	88.00
95% CI (lower)	698.16	1240.61	73.16
95% CI (upper)	2205.66	2850.05	103.02
Mean of logs	7.124	7.539	4.477
SD of logs	0.548	0.541	0.189

LSmean = Least Square Mean, adjust for design imbalance if present
CI = Confidence interval for LS mean
SD = Standard deviation
%CV = Percent coefficient of variation

Table 46

Statistical Analysis Results of Log-Transformed GR90291 Pharmacokinetic Parameters

Parameter	Subject Group	Ratio	90% CI	p-value
AUClast (ng·min/ml)	Low Dose Renal/High Dose Renal	0.882	(0.681, 1.14)	0.409
	High Dose Renal/High Dose Healthy	13.6	(10.8, 17.1)	<0.001
AUC∞ (ng·min/ml)	Low Dose Renal/High Dose Renal	0.665	(0.405, 1.09)	0.169
	High Dose Renal/High Dose Healthy	33.5	(24.4, 46.0)	<0.001
Cmax (ng/ml)	Low Dose Renal/High Dose Renal	1.16	(0.894, 1.51)	0.331
	High Dose Renal/High Dose Healthy	2.98	(2.54, 3.51)	<0.001
$t_{1/2}$ (min)	Low Dose Renal/High Dose Renal	0.660	(0.397, 1.10)	0.171
	High Dose Renal/High Dose Healthy	21.4	(15.0, 30.5)	<0.001

Table 47

AUC Ratio for GR90291 and Remifentanil in Renal Impairment and Healthy Subjects

Low Dose Renal Impairment				High Dose Renal Impairment				High Dose Healthy Subjects			
Subject	Remifentanil AUC	GR90291 AUC	Ratio (GR/Remi)	Subject	Remifentanil AUC	GR90291 AUC	Ratio (GR/Remi)	Subject	Remifentanil AUC	GR90291 AUC	Ratio (GR/Remi)
Mean			175.84				241.89				6.34
SD			104.84				98.46				1.75

Pharmacokinetic Parameters for the Simultaneous Modeling of Remifentanil and GR90291 in the High Dose Renal Subjects

Subject	V (ml/kg)	Kt (min^{-1})	Ke (min^{-1})	Kmu (min^{-1})
Mean	207.7	0.1751	0.0865	0.00048
SD	24.63	0.0296	0.0092	0.00021

GR90291 Extraction During Hemodialysis

Subject	Extraction at 30min After Initiating Dialysis	Extraction Just Before the End of Dialysis
Mean	0.35	0.25
SD	0.08	0.37

USA-104
Pharmacokinetic Study Summary

NDA # 20-630 Submission Date: 9/15/95 Volume 63-68

Investigator:
Site:

Single Dose: XXX . Multiple Dose: ____

Subjects:
Normal: XXX Patients: ____ Young: XXX Elderly: ____
Impaired Hepatic: ____ Renal: ____

Cross-Over: ____ Parallel: XXX N= 30 M= 20 F= 10

Subject Type: Healthy Male and Female Volunteers

	Part I - Remifentanil	Part II - Remifentanil/Alfentanil	Part III - Remifentanil
N	10	10	10
Gender male/female	10/0	10/0	0/10
Age (years)	27.4 ± 4.6 (22-37)	28.5 ± 5.1 (23-39)	25.2 ± 4.8 (20-33)
Weight (kg)	79.0 ± 12.2 (62.7-97.7)	83.5 ± 11.8 (70.5-100)	83.5 ± 11.8 (70.5-100)

Treatment Summary:
Fasted 6 hours prior to dosing and for 0.75 hours after dosing.
Remifentanil, Zero Order IV Infusion, Infused for ≤ 20 minutes or until maximal opioid effect was observed.
Part I Rate 1-8 µg/kg/min
Part II Rate 2-3 µg/kg/min
Part III Rate 3 µg/kg/min
Lot # CS-USA-1001

Alfentanil, Zero Order IV Infusion, Infused for ≤ 20 minutes or until maximal opioid effect was observed.
Part II Rate 1500 µg/min, (Part II only)

Sample Strategy:

Arterial Blood Samples: Prior to dosing (<45min), and every 30 seconds from 0.5 to 5 minutes, every minute from 6 to 10 minutes, and every 2 minutes from 12 to 20 minutes after the start of the infusion. Samples were also collected every 30 seconds from 0.5 to 5 minutes, every minute from 6 to 10 minutes, and every 2 minutes from 12 to 20 minutes, and at 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, 100, 120, 150, 180, 210, and 240 minutes after the end of the study drug infusion. In subjects receiving alfentanil, additional samples were obtained at 360, 480, and 600 minutes following the infusion.

Venous Blood Samples (Part III Females only): Every 2 minutes during the infusion and every 2 minutes after the infusion until 10 minutes and then at 15, 20, 30, 40, 60, 90, 120, 180, and 240 minutes after the infusion

Assay Method:
Remifentanil (blood): GC-High Resolution MS-Selected Ion Monitoring
GR90291 (blood): GC with Mass Selective Detection (GC-MSD)
Alfentanil (blood) GC-High Resolution MS-Selected Ion Monitoring

Sample	Sensitivity	%CV (QC Conc)	QC Range
Remifentanil Blood	0.1 ng/mL	3.7% (80ng/ml) -14.0% (0.20ng/ml)	0.2-200ng/ml
GR90291 Blood	1ng/mL	5.8% (40ng/ml) - 6.5% (80ng/ml)	4.0-80ng/ml
Alfentanil	1ng/mL	4.4% (500ng/ml) - 9.5% (2.5ng/ml)	2.5-2500ng/ml

Labeling Claims From Study: Blood-brain equilibration half time is 1.1 min which is similar to alfentanil and more rapid than fentanyl or sufentanil. Remifentanil is approximately 17 times more potent than alfentanil (blood concentration/blood concentration)

Study 104 - EEG Spectral Analysis Study in Volunteers

Conclusions: Remifentanil infusion rates in excess of 2mcg/kg/min produced loss of conscious response to an auditory stimulus and maximal EEG slowing within 5-10 minutes of starting the infusion in healthy subjects. Doses of 1-8mcg/kg/min were infused for 20 minutes without serious adverse effect. Using the EEG as a measure of opioid effect, the temporal delay in drug effect associated with changes in arterial remifentanil concentrations was very short ($t_{½}$ k_{eo}=1.1±0.9 [mean±sd] min) and remifentanil was 17 times more potent than alfentanil (IC_{50}=20±5 and 348±151 [mean±sd] ng/mL, respectively). Young female subjects did not show a statistically significant difference in pharmacokinetic or pharmacodynamic parameters whn compared to male subjects.

Investigator:

Purpose: The study was conducted in three parts. The specific objectives of each part were as follows: **Part I,** Determine the rate of remifentanil administration to produce maximal EEG slowing within 5-10 minutes of starting the infusion. **Part II,** Compare the pharmacokinetic and pharmacodynamic parameters of remifentanil to those for alfentanil. **Part III,** Compare the pharmacokinetic and pharmacodynamic parameters determined for remifentanil in female subjects to those in male subjects.

Study Design: Part I was an unblinded single-dose, dose-ranging study conducted in 10 healthy mal subjects. Part II was a randomized, two-period, crossover comparison of remifentanil and alfentan in 10 healthy male subjects. Part III was a single-dose study of remifentanil conducted in 10 healthy female volunteers. The remifentanil infusion rate used in Part II (3mcg/kg/min) was also used in Part III.

Demographics: 30 healthy volunteers, ASA status I, male and female, aged 18-40 years

Anesthesia Protocol: Glycopyrrolate, 0.2mg (to prevent bradycardia) and pancuronium, 0.5mg (to prevent muscle rigidity) were given 1 minute before opioid administration. Succinylcholine was infused if muscle rigidity prevented adequate ventilation. Remifentanil (1-8mcg/kg/min) was infused for up to 20 minutes and alfentanil (1500mcg/min) was infused for 10-16 minutes.

Results: Table of Primary PK/PD Results, All Subjects n=30, Mean±SD

Part	n[1] PK/PD	IC_{50}[2] (ng/mL)	$t_{1/2}$ k_{eo}[3] (min)	γ[4]	Cl[5,6] (mL/min/kg)	V_c[6,8] (mL/kg)	V_{ss}[7,8] (mL/kg)
I	10/8	16±16	1.4±1.2	3.0±2.4	37±5	98±19	349±85
II-REMI	10/10	20±5	0.8±0.5	4.8±2.3	36±5	102±28	280±70
II-ALF	10/10	348±151	0.9±0.9	6.8±4.7	4.7±1	66±20	416±64
III Female	10/7	15±5[2]	1.2±1.0	2.8±1.6	48±8	103±31	380±243

[1] Evaluable subjects for PK analysis or PD analysis.
[2] Concentration required to produce half maximal EEG effect (IC_{50}) Two-sample t-test, p=0.4. Female n=7 vs Males (Part I and II) n=28
[3] Half-time for lag in EEG effect ($t_{1/2}$ K_{eo}), No difference between groups. [4] Steepness parameter (γ), No difference between groups
[5] Clearance (Cl) [6] Central Volume (V_c) [7] Steady-state Volume (V_{ss}) [8] Cl and Vc were positively correlated with total body weight, while Vss was not. None of the parameters were significantly related to gender when adjusted for differences in weight

No serious adverse events or deaths occurred during this study.

USA-104 Part I
Remifentanil 1-8μg/kg/min

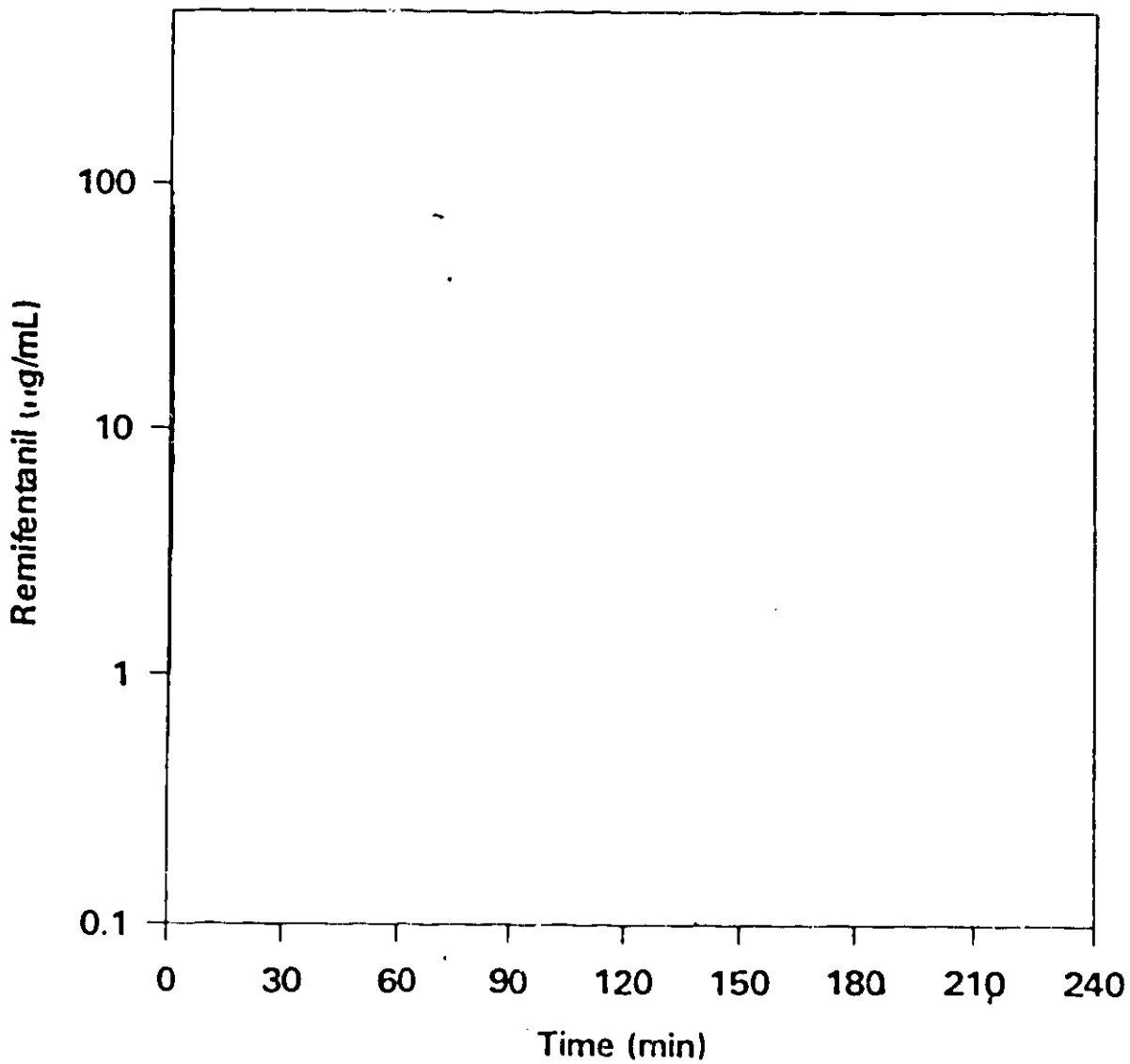

Table 87.

USA-104 (Part I)

Remifentanil
Pharmacokinetic Parameter Estimates

Subject	Hybrid Rate Constants (min-1)			Half - Lifes (min)			Coefficients (ng/mL)			Micro Rate Constants (min-1)					Volume (mL/kg)		Clearance
ID	λ1	λ2	λ3	λ1	λ2	λ3	A1	A2	A3	k10	k12	k13	k21	k31	Central	SS	(mL/min/kg)
Mean	0.8730	0.1073	0.0271	0.91	7.22	34.17	NA***	NA	NA	0.3994	0.336	0.0347	0.206	0.0310	98.4	349	37.4
SD	0.3695	0.0435	0.0158	0.34	2.15	19.63	NA	NA	NA	0.1193	0.212	0.0353	0.081	0.0206	19.3	85	6.3
CV%	42	41	58	37	30	57	NA	NA	NA	30	63	102	39	67	20	24	14
Median	0.7764	0.0859	0.0235	0.89	8.07	29.66	NA	NA	NA	0.3852	0.274	0.0152	0.182	0.0253	101.6	336	36.1
*G Mean	0.8113	0.1009	0.0234	0.85	6.87	29.58	NA	NA	NA	0.3845	0.287	0.0214	0.193	0.0258	96.4	341	37.1
**H Mean	.	.	.	0.79	6.46	25.61	NA	NA	NA	.	.	.	.	.	.	.	36.7

*G Mean = Geometric Mean

**H Mean = Harmonic Mean

***NA=Not applicable, different doses have different intercepts

P1PKTABL.XLS 2/19/95

USA-104 Part II
Remifentanil 2-3μg/kg/min

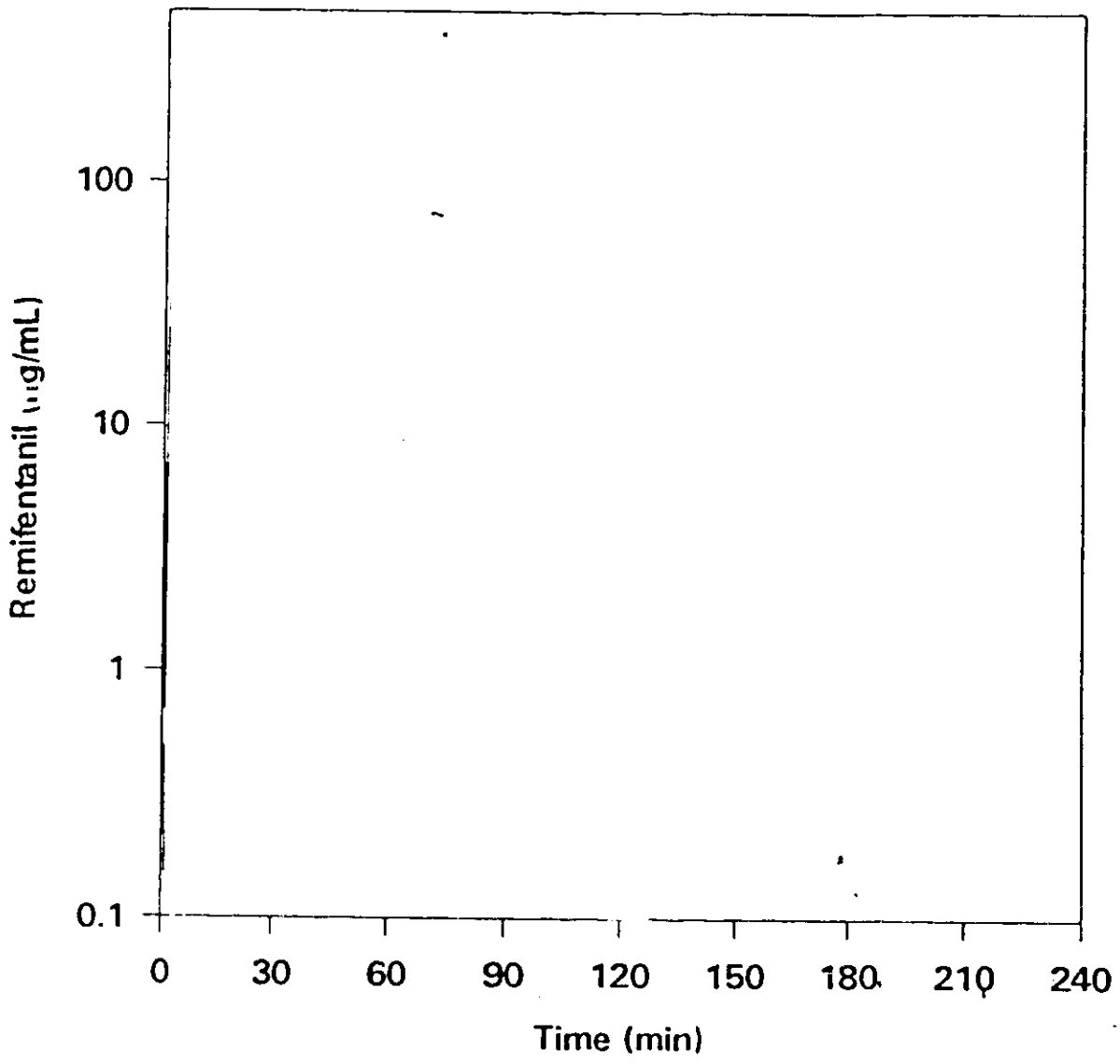

Table 88.

USA-104 (Part II)

Remifentanil
Pharmacokinetic Parameter Estimates

Subject	Hybrid Rate Constants (min-1)			Half - Lifes (min)			Coefficients (ng/mL)			Micro Rate Constants (min-1)					Volume (mL/kg)		Clearance
ID	λ1	λ2	λ3	λ1	λ2	λ3	A1	A2	A3	k10	k12	k13	k21	k31	Central	SS	(mL/min/kg)
Mean	0.7220	0.1081	0.0246	1.10	6.76	51.5	282	42.2	2.47	0.361	0.243	0.0216	0.187	0.0275	101.6	280	35.8
SD	0.3536	0.0211	0.0227	0.35	1.31	36.6	130	9.4	3.13	0.134	0.190	0.0151	0.048	0.0261	28.1	70	5.1
CV%	48.9746	19.9367	91.5487	32	19	71	46	22	127	35	78	70	26	95	28	25	14
Median	0.6620	0.1064	0.0172	1.05	6.52	40.2	235	40.2	0.96	0.346	0.207	0.0143	0.169	0.0182	109.2	274	33.8
*G Mean	0.6688	0.1042	0.0178	1.04	6.65	38.9	262	41.3	0.91	0.365	0.203	0.0170	0.182	0.0191	97.3	272	35.5
**H Mean				0.96	6.54	27.9											35.2

*G Mean = Geometric Mean

**H Mean = Harmonic Mean

P2PKTABL.XLS 2/19/95

USA-104 Part II
Alfentanil 1500μg/min

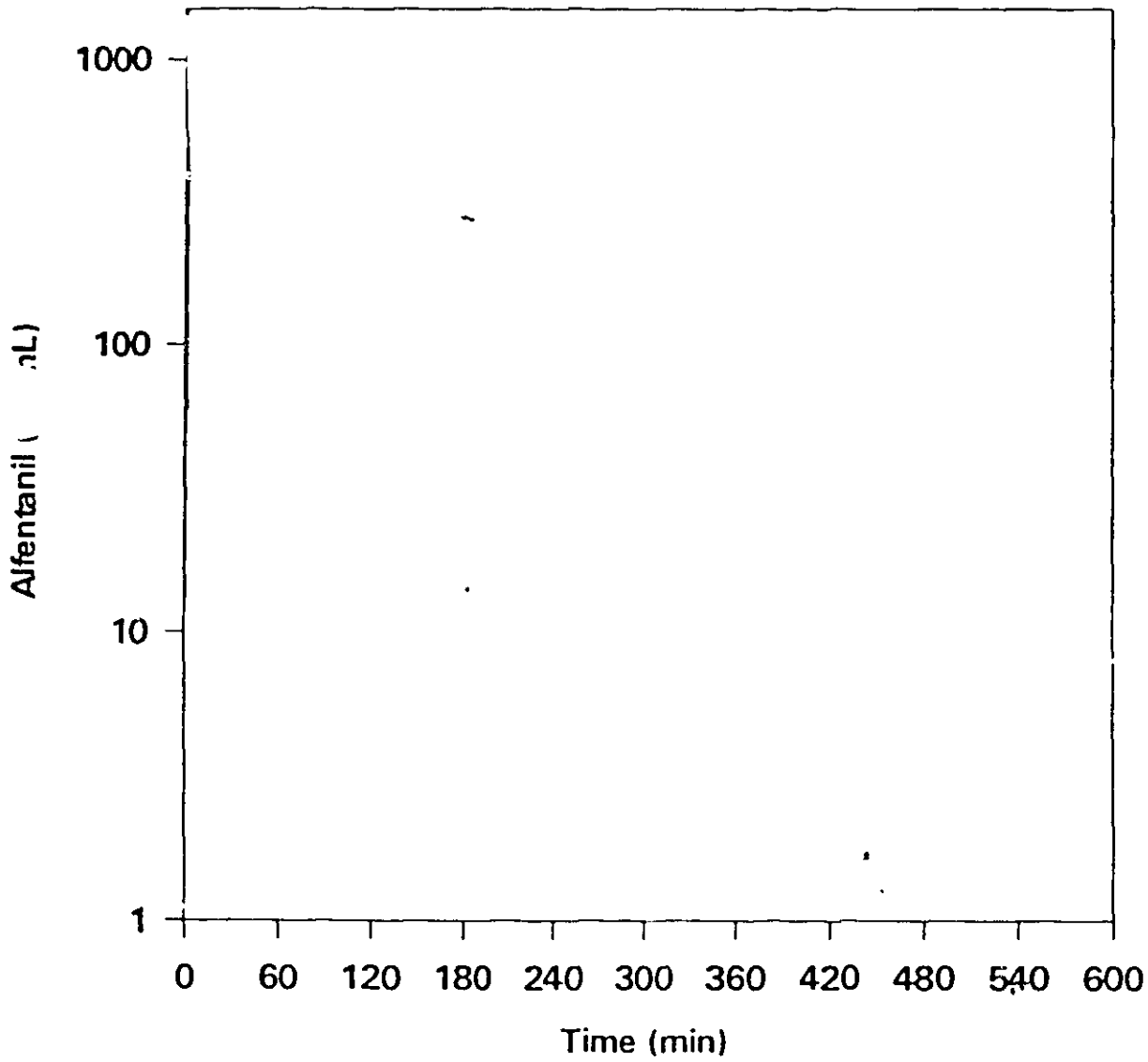

Table 91.

USA-104 (Part II)

Alfentanil
Pharmacokinetic Parameter Estimates

Subject	Hybrid Rate Constants (min-1)			Half - Lifes (min)			Coefficients (ng/mL)			Micro Rate Constants (min-1)					Volume (mL/kg)		Clearance
ID	λ1	λ2	λ3	λ1	λ2	λ3	A1	A2	A3	k10	k12	k13	k21	k31	Central	SS	(mL/min/kg)
Mean	0.792	0.0422	0.00759	1.0	18.0	92.8	2536	520	214	0.0781	0.492	0.0597	0.196	0.0164	65.9	416	4.65
SD	0.405	0.0125	0.00101	0.4	6.2	12.3	986	149	84	0.0326	0.327	0.0346	0.064	0.0036	20.2	64	1.02
CV%	51	30	13	38	35	13	39	29	39	42	66	58	33	22	31	15	22
Median	0.632	0.0423	0.00762	1.1	16.4	91.1	2318	509	204	0.0636	0.336	0.0572	0.177	0.0163	71.8	395	4.71
*G Mean	0.720	0.0404	0.00753	1.0	17.2	92.1	2379	502	200	0.0726	0.425	0.0497	0.187	0.0161	62.7	411	4.55
**H Mean				0.9	16.4	91.4											4.46

*G Mean = Geometric Mean

**H Mean = Harmonic Mean

ALFPKTBL.XLS 2/19/95

USA-104 Part III
Remifentanil 3μg/kg/min
Female Subjects

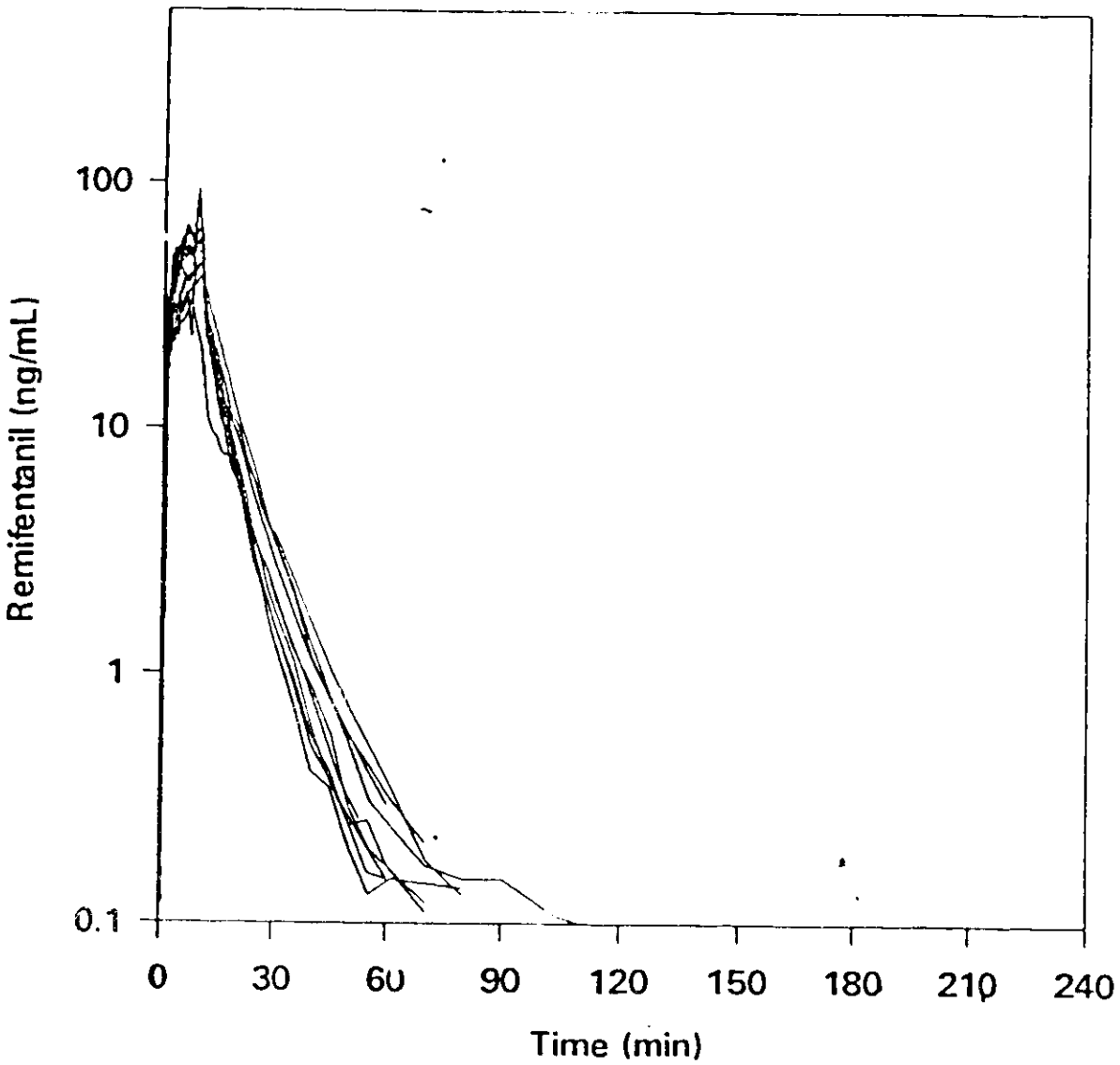

Table 89.

USA-104 (Part III)

Remifentanil
Pharmacokinetic Parameter Estimates

Subject	Hybrid Rate Constants (min-1)			Half - Lifes (min)			Coefficients (ng/mL)			Micro Rate Constants (min-1)					Volume (mL/kg)		Clearance
ID	λ1	λ2	λ3	λ1	λ2	λ3	A1	A2	A3	k10	k12	k13	k21	k31	Central	SS	(mL/min/kg)
Mean	1.12	0.222	0.0400	0.72	5.29	38.1	258	46.4	2.82	0.468	0.455	0.0254	0.287	0.0433	103.7	380	47.5
SD	0.46	0.258	0.0213	0.28	1.11	49.7	85	14.1	2.49	0.135	0.305	0.0093	0.082	0.0236	31.4	243	8.0
CV%	41	116	53	39	21	130.5	33	30	89	28	67	37	29	54	30	64	17
Median	1.03	0.142	0.0424	0.67	5.16	16.3	259	44.3	2.43	0.490	0.333	0.0261	0.273	0.0447	93.5	316	45.3
*G Mean	1.04	0.168	0.0306	0.67	5.18	22.7	246	44.3	1.64	0.470	0.379	0.0237	0.277	0.0328	99.6	336	46.9
**H Mean				0.62	5.08	17.3											46.3

*G Mean = Geometric Mean

**H Mean = Harmonic Mean

USA-216
Pharmacokinetic Study Summary

NDA # 20-630 Submission Date: 9/15/95 Volume:88-94

Investigator: Donald R. Stanski, MD.
Site: Stanford University Medical Center
Stanford, CA 94305

Single Dose: X . Multiple Dose: ____.

Subjects: Normal: X. Patients: ___ Young: ___ Elderly: X .
Hepatic: ___ Renal: ___.

Cross-Over: ___. Parallel: X . N= 50 M= 29 F= 21

Subject Type: Middle-age and elderly volunteers

Subjects aged 40-65yrs were categorized as middle-aged and subjects >65yrs were categorized as elderly

	Age Group			
	Middle aged males (N=18)	Elderly males (N=11)	Middle aged females (N=8)	Elderly females (N=13)
Age (yrs)	51.3±8.9 40-64	72.5±4.3 66-81	53.9±7.8 41-63	76.7±4.8 71-85
Weight (kg)	81.8±10.4 66-106	80.7±13.6 62-100	66.7±13.8 45-90	63.6±10.2 48-87

Treatment Summary

Remifentanil Infusion (Lot # CS-USA1008)
Infusion rate 3μg/kg/min until one or more of the following occurred:

- maximal slowing of the EEG (delta wave)
- infusion duration reached 20 minutes (60μg/kg)
- mean arterial pressure decreased >30% for >1min or heart rate decreased <50bpm for >1min

Sample Strategy:

Arterial samples were collected prior to, during, and after the infusion for analysis of remifentanil and its metabolite GR90291.

EEG (spectral edge) was used as a measure of the pharmacodynamic effects of remifentanil.

Assay Method:

GC-High Resolution Mass Spectrometry-Selected Ion Monitoring

Sample	Sensitivity	Site	%CV (QC Conc)	QC Range
Remifentanil Blood	0.1 ng/mL		4.4% (5ng/ml) -8.7% (0.25ng/ml)	0.25-80ng/ml
GR90291 Blood	1ng/mL		3.9% (180ng/ml) - 11.0% (4.0ng/ml)	4.0-180ng/ml

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Labeling Claims From Study: The initial loading/maintenance infusion doses of remifentanil should be reduced in elderly patients and then carefully titrated to the individual patient needs

Study 216 - Pharmacokinetic and Pharmacodynamic Study in Middle Age and Elderly Volunteers

Conclusions: No gender differences in remifentanil clearance, steady-state distribution volume, and half-lives were evident between middle age (40-65yrs) and elderly (>65yrs) subjects, but a moderate reduction in central compartment volume was noted in females compared to males. The AUC, Cmax, and terminal $t_{1/2}$ of the principal metabolite, GR90291, was increased in elderly subjects compared to middle-age subjects, and females had an increased AUC and Cmax and reduced terminal $t_{1/2}$ compared to males. Using EEG spectral edge, no gender differences in remifentanil's EC_{50} and ke0 were observed, but the EC_{50} and ke0 were lower in the elderly compared to the middle age subjects.

Integrated regression analysis of the data from this study and that from an identical study in young healthy subjects showed that the pharmacokinetics and pharmacodynamics of remifentanil change with age. Based on an overall assessment of the magnitude of the age-related changes, it is recommended that the initial doses of remifentanil be reduced by 50% in patients over 65 years of age and then carefully titrated to the individual patient need.

Investigators:

Purpose: 1) to characterize the pharmacokinetic and pharmacodynamic (EEG) profile of remifentanil and its primary metabolite (GR90291) in male and female subjects 40 years of age and older, and 2) to conduct an integrated analysis of the effects of gender and age on the pharmacokinetics and pharmacodynamics of remifentanil in subjects aged 20-85 yrs.

Study Design: Single-center, open-label, parallel study in middle-aged and elderly subjects

Demographics: 50 subjects - 26 middle aged (40-65yrs, 18 male/8 female) and 24 elderly (>65yrs, 11 male/13 female).

Anesthesia Protocol: *Premedication:* Glycopyrrolate, 0.2mg (for bradycardia) and pancuronium, 0.5mg (for muscle rigidity) were given 1 minute prior to opioid administration. *Induction/Maintenance:* N/A. *Other:* Succinylcholine was infused if muscle rigidity prevented adequate ventilation. Remifentanil (3mcg/kg/min) was infused for up to 15 min.

Results: Table 1. Principle PK, PD and Safety Results, (N = 35) Values are Mean ± SD

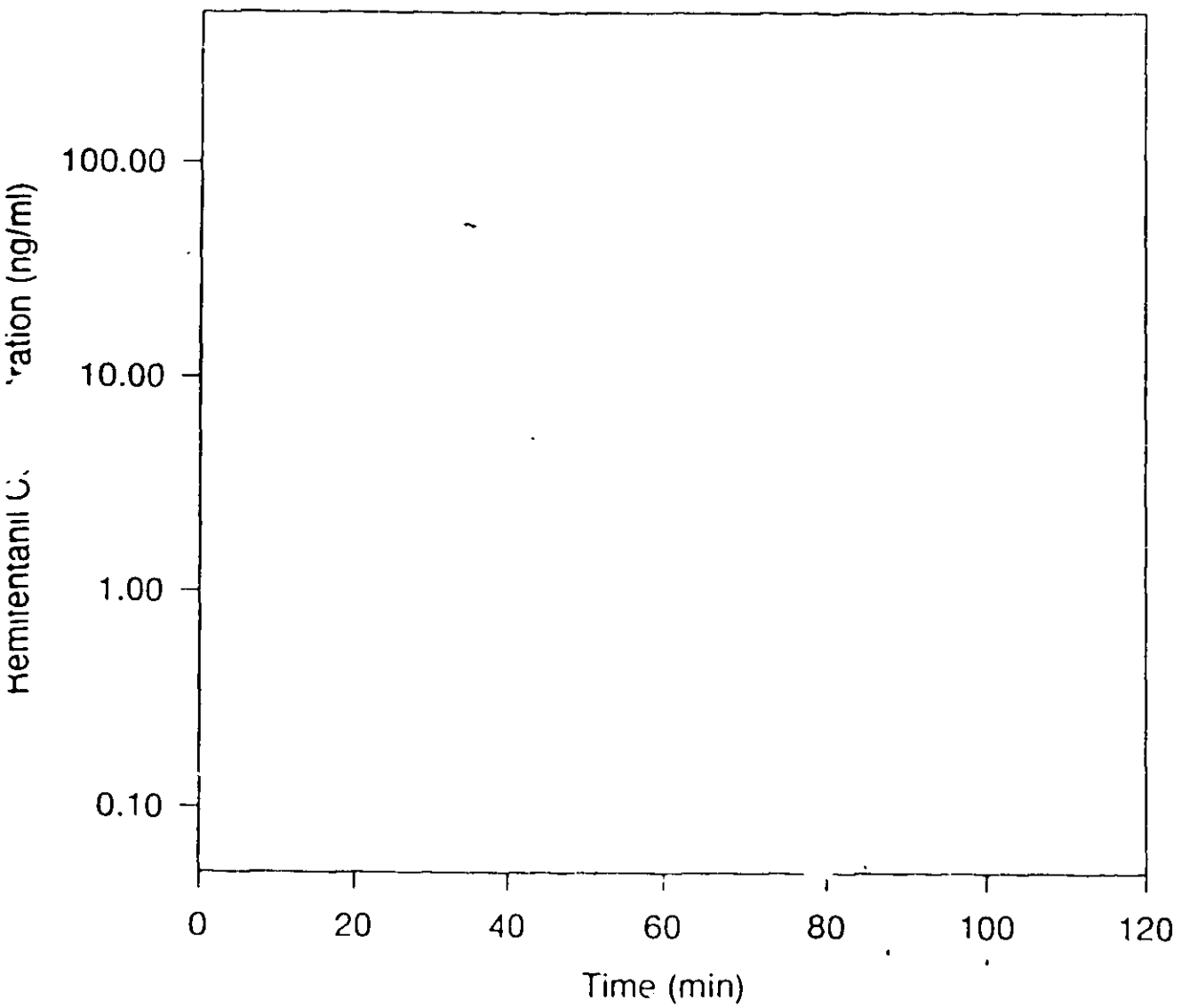
Subjects	n[1] PK/PD	EC_{50}[2,3] (ng/mL)	$t_{1/2}$ k_{eo}[2,3] (min)	γ	Cl[2,3] (mL/min/kg)	V_c[2,3] (mL/kg)	V_{ss}[2,3] (mL/kg)
MA Male	11/10	12±4	1.8±0.9	4.7±4.5	32±7	81±36	206±73
MA Fem	6/6	16±8	1.6±0.7	2.9±2.0	33±5	52±27	187±33
Eld Male	7/7	8±3	2.8±1.5	3.1±1.6	31±4	74±26	196±42
Eld Fem	11/11	9±5	1.9±0.7	4.3±4.0	30±6	54±13	160±34

Safety	Middle Age Male n=18	Middle Age Female n=8	Elderly Male n=11	Elderly Female n=13
Any Adverse Event	15 (83%)	8 (100%)	9 (82%)	13 (100%)

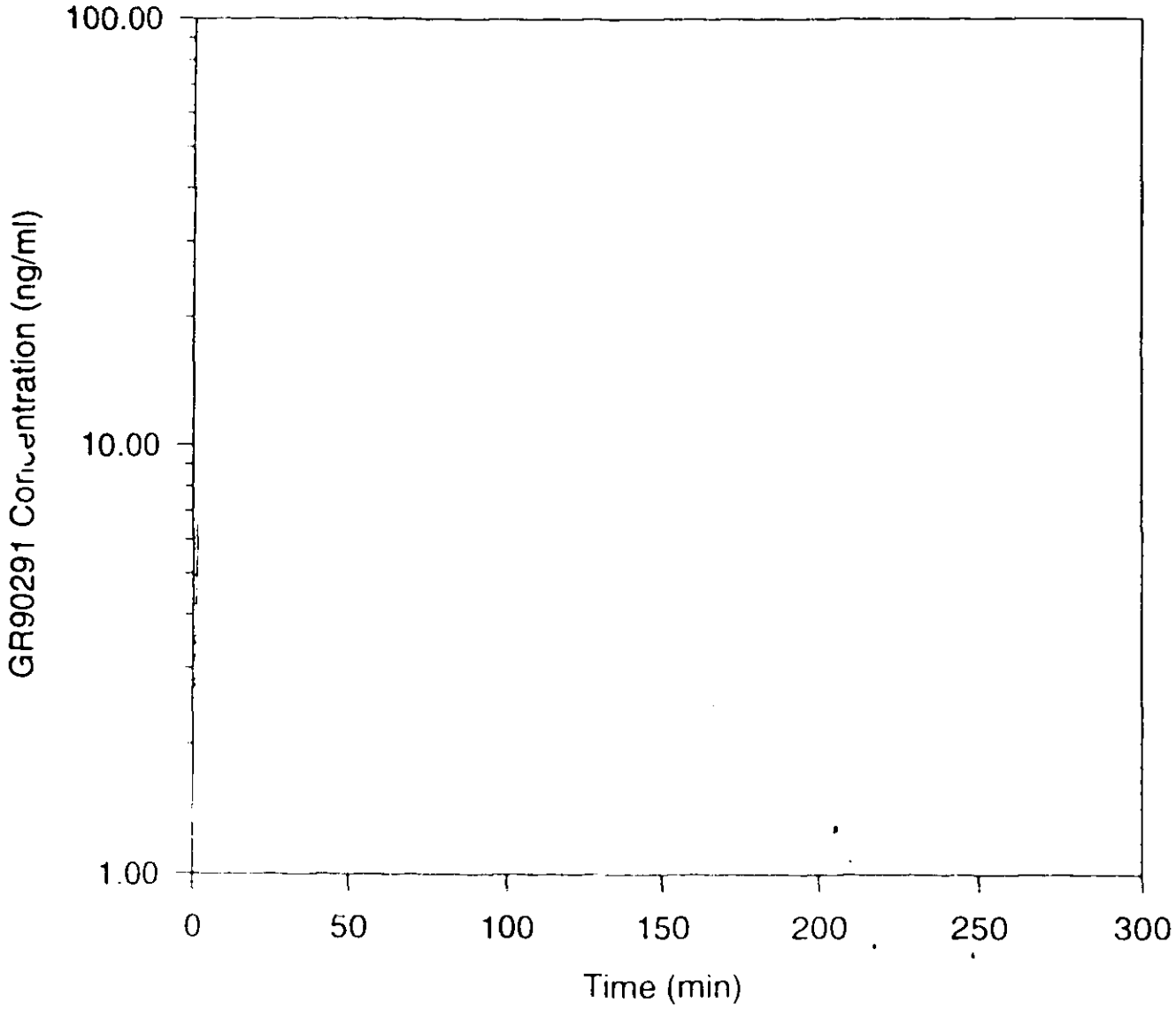
[1] Evaluable subjects for PK analysis or PD analysis.
[2] Comparison of middle age and elderly (EC_{50} p=0.01, $t_{1/2}$ ke0 p=0.02, CL p=0.40, Vc p=0.92, Vss p=0.31)
[3] Comparison of males and females (EC_{50} p=0.22, $t_{1/2}$ ke0 p=0.09, CL p=0.91, Vc p=0.01, Vss p=0.13)

No serious adverse events or deaths occurred during this study.

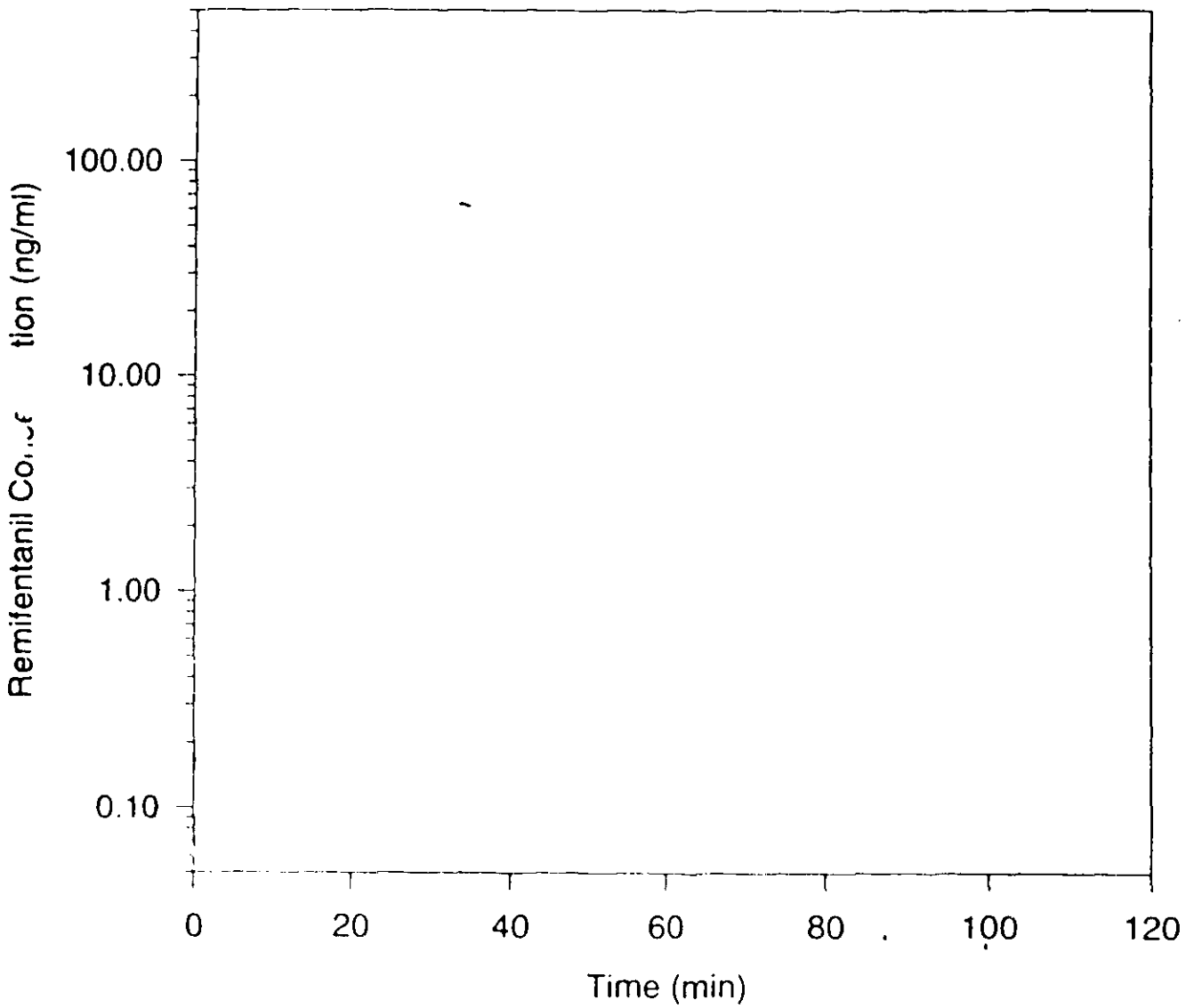
Individual Remifentanil Concentration-Time Profiles for Middle Age Subects



Individual GR90291 Concentration-Time Profiles for Middle Age Subects



Individual Remifentanil Concentration-Time Profiles for Elderly Subects



Individual GR90291 Concentration-Time Profiles for Elderly Subects

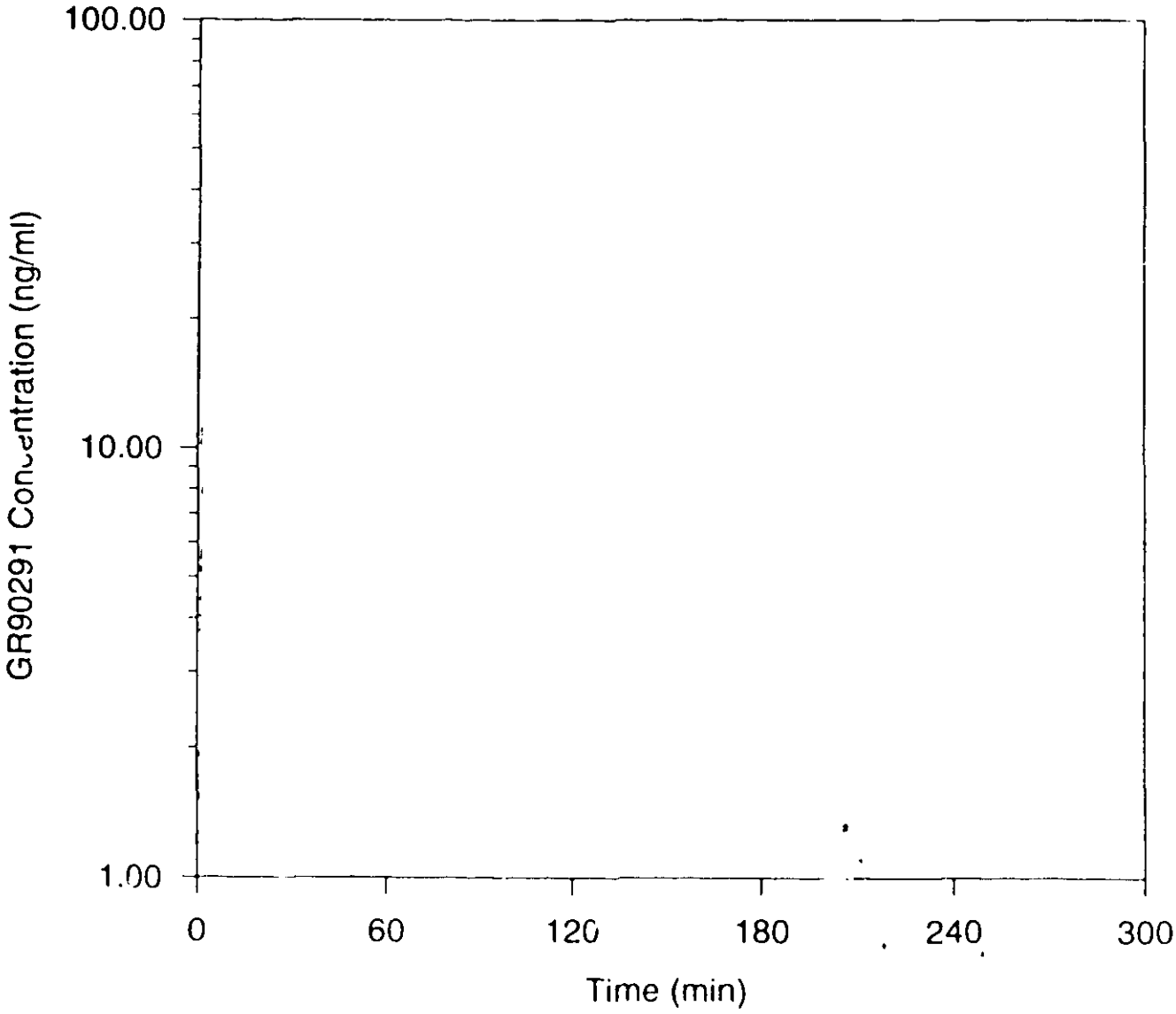


Table 55

Individual Normalized AUC∞ Values with Summary Statistics

	Middle (40-65)		Elderly (> 65)	
	Female	Male	Female	Male
	Subj. Age	Subj. Age	Subj. Age	Subj. Age
Geo. LSMean	2843.24	2331.60	3926.76	3171.20
Arith. LSMean	2873.42	2364.68	4013.23	3276.12
Median	2760.55	2379.88	3992.67	3429.05
Minimum	2450.84	1598.23	2919.56	1887.34
Maximum	3804.52	3055.08	5652.26	4703.82
Arith. Mean	2873.42	2364.68	4013.23	3276.12
95% CI (lower)	2437.35	2162.36	3443.37	2668.27
95% CI (upper)	3309.29	2567.00	4583.09	3883.98
SD	471.29	393.50	896.89	849.73
CV	16.40	16.64	22.35	25.94
Geometric Mean	2843.24	2331.60	3926.76	3171.20
95% CI (lower)	2466.58	2129.03	3423.79	2605.11
95% CI (upper)	3277.42	2553.45	4503.62	3860.32
Mean of logs	7.95	7.75	8.28	8.06
SD of logs	0.15	0.18	0.22	0.27

LSmean = Lease Square Mean, adjust for design imbalance if present
CI = confidence interval
SD = Standard deviation
%CV = percent coefficient of variation
Values normalized to a 1mcg/kg remifentanil dose

BIOSSTAT_CP 1000000 USA USA216 SUMMARY_TAB_NORMCET SAS 07/20/95

Table 56

Individual Normalized Cmax Values with Summary Statistics

	Middle (40-65)		Elderly (> 65)	
	Female	Male	Female	Male
	Subj. Age	Subj. Age	Subj. Age	Subj. Age
Geo. LSMean	25.5255	18.1096	30.6333	20.5616
Arith. LSMean	25.6883	18.3447	31.1819	20.9228
Median	25.6410	19.0413	29.1029	19.7766
Minimum	21.6801	13.7083	24.1553	15.4406
Maximum	29.9410	23.9525	45.4183	27.7487
Arith. Mean	25.6883	18.3447	31.1819	20.9228
95% CI (lower)	22.8057	16.8093	27.0151	17.9431
95% CI (upper)	28.5706	19.8802	35.3487	23.9024
SD	3.1168	2.9864	6.5581	4.1653
CV	12.1331	16.2795	21.0316	19.9080
Geometric Mean	25.5255	18.1096	30.6339	20.5616
95% CI (lower)	22.8011	16.6184	27.1437	17.8759
95% CI (upper)	28.5755	19.7347	34.5728	23.6508
Mean of logs	3.2397	2.8964	3.4221	3.0234
SD of logs	0.1220	0.1671	0.1903	0.1957

LSmean = Lease Square Mean, adjust for design imbalance if present
CI = confidence interval
SD = Standard deviation
%CV = percent coefficient of variation
Values normalized to a 1mcg/kg remifentanil dose

BIO$STAT_CP (000000 USA USA216)SUMMARY_TAB_NORMCET SAS 07/20/95

Table 53

Overall Summary of Remifentanil Pharmacokinetic Results

Subject	Rate Constants (min-1)			Half-Life (min)			Micro Rate Constants (min-1)					Volume (ml/kg)		Clearance
	λ_1	λ_2	λ_3	λ_1	λ_2	λ_3	k10	k12	k13	k21	k31	Central	SS	mL/min/kg

Table 51

Individual Remifentanil V_{ss} (mL/kg) Values with Summary Statistics

	Middle (40-65)		Elderly (> 65)	
	Female	Male	Female	Male
	Subj. Age	Subj. Age	Subj. Age	Subj. Age
Geo. LSMean	184.241	196.498	157.233	191.460
Arith. LSMean	186.863	206.093	160.419	195.500
Median	195.377	190.675	157.687	184.315
Minimum	139.550	135.555	112.102	135.147
Maximum	223.060	373.325	222.412	252.909
Arith. Mean	186.863	206.093	160.419	195.500
95% CI (lower)	151.993	157.014	137.709	156.300
95% CI (upper)	221.733	255.171	183.129	234.699
SD	33.227	73.055	33.805	42.385
CV	17.782	35.447	21.073	21.680
Geometric Mean	184.241	196.498	157.233	191.460
95% CI (lower)	151.353	159.515	136.531	155.788
95% CI (upper)	224.277	242.056	181.073	235.300
Mean of logs	5.216	5.281	5.058	5.255
SD of logs	0.187	0.310	0.210	0.223

LSmean = Least Square Mean, adjust for design imbalance if present
CI = confidence interval
SD = Standard deviation
%CV = percent coefficient of variation

BIO$STAT_CV.(000000.USA.USA216)SUMMARY_TAB_PK.SAS 04/09/95

Table 52

Individual Remifentanil CL (mL/min/kg) Values with Summary Statistics

	Middle (40-65)		Elderly (> 65)	
	Female	Male	Female	Male
	Subj. Age	Subj. Age	Subj. Age	Subj. Age
Geo. LSMean	32.2712	30 8504	29.4303	30.2482
Arith. LSMean	32.5280	31 5823	29.9085	30.4669
Median	30.4538	31 0070	28.6313	29.3381
Minimum	28.3469	22 7014	21.9581	24.1972
Maximum	38.4608	46 3441	38.0924	34.8515
Arith. Mean	32.5280	31 5823	29.9085	30.4669
95% CI (lower)	27.7294	26 5861	26.1413	26.8825
95% CI (upper)	37.3266	36 5785	33.6757	34.0513
SD	4.5725	7 4369	5.6076	3.8756
CV	14.0573	23 5477	18.7492	12.7208
Geometric Mean	32.2712	30 8504	29.4303	30.2482
95% CI (lower)	27.9621	26 5490	25.9241	26.7977
95% CI (upper)	37.2444	35 8487	33.4106	34.1429
Mean of logs	3.474	3.429	3.382	3.409
SD of logs	0.137	0.224	0.189	0.131

LSmean = Least Square Mean, adjust for design imbalance if present
CI = confidence interval
SD = Standard deviation
%CV = percent coefficient of variation

Table 68

Overall Summary of Remifentanil Individual Pharmacodynamic Parameters

Subject	EC50 (ng/mL)	Emax (Hz)	E0 (Hz)	Gamma	Ke0 (min-1)	t1/2 Ke0 (min)

Table 62

Individual Remifentanil EC_{50} (ng/mL) Values with Summary Statistics

	Middle (40-65)		Elderly (> 65)	
	Female	Male	Female	Male
	Subj. Age	Subj. Age	Subj. Age	Subj. Age
Geo. LSMean	14.1732	10.8801	8.0452	8.0668
Arith. LSMean	15.6244	11.6759	9.1012	8.4475
Median	12.3917	12.4934	7.4379	8.2211
Minimum	8.9947	5.6459	3.5027	4.8148
Maximum	26.8905	17.8646	18.1613	12.2956
Arith. Mean	15.6244	11.6759	9.1012	8.4475
95% CI (lower)	7.5231	8.5499	5.8925	5.9899
95% CI (upper)	23.7257	14.8019	12.3099	10.9052
SD	7.7196	4.3698	4.7762	2.6573
CV	49.4076	37.4257	52.4786	31.4569
Geometric Mean	14.1732	10.8801	8.0452	8.0668
95% CI (lower)	8.5938	8.1270	5.6662	5.9121
95% CI (upper)	23.3749	14.5658	11.4230	11.0067
Mean of logs	2.651	2.387	2.085	2.088
SD of logs	0.477	0.408	0.522	0.336

LSmean = Least Square Mean, adjust for design imbalance if present
CI = confidence interval
SD = Standard deviation
%CV = percent coefficient of variation

BIO$STAT_CP:[000000 USA USA216]SUMMARY_TAB_PD.SAS 04/09/95

Table 63

Individual Remifentanil E_{max} (Hz) Values with Summary Statistics

	Middle (40-65)		Elderly (> 65)	
	Female	Male	Female	Male
	Subj. Age	Subj. Age	Subj. Age	Subj. Age
Geo. LSMean	14.9157	17.2612	13.9650	14.9818
Arith. LSMean	15.3056	17.4094	14.2854	15.7085
Median	14.2429	16.5235	14.1467	14.4028
Minimum	11.8826	13.8288	9.3675	10.8308
Maximum	22.0974	21.6167	19.4550	24.9477
Arith. Mean	15.3056	17.4094	14.2854	15.7086
95% CI (lower)	11.1482	15.6818	12.1794	10.6691
95% CI (upper)	19.4631	19.1371	16.3915	20.7480
SD	3.9616	2.4151	3.1349	5.4489
CV	25.8833	13.8724	21.9446	34.6877
Geometric Mean	14.9157	17.2612	13.9650	14.9818
95% CI (lower)	11.5447	15.6441	11.9998	11.0885
95% CI (upper)	19.2712	19.0454	16.2522	20.2422
Mean of logs	2.702	2.848	2.637	2.707
SD of logs	0.244	0.138	0.226	0.325

LSmean = Least Square Mean, adjust for design imbalance if present
CI = confidence interval
SD = Standard deviation
%CV = percent coefficient of variation

BIO$STAT_CP:[000000.USA.USA216]SUMMARY_TAB_PD.SAS 04/09/95

Table 64

Individual Remifentanil F_0 (Hz) Values with Summary Statistics

	Middle (40-65)		Elderly (> 65)	
	Female	Male	Female	Male
	Subj. Age	Subj. Age	Subj. Age	Subj. Age
Geo. LSMean	20.8470	22.6819	20.8219	21.3788
Arith. LSMean	20.9497	22.8398	20.8777	21.6288
Median	21.0229	22.7596	20.7372	21.5828
Minimum	17.3780	17.4090	17.8094	16.5044
Maximum	24.0071	26.9317	23.4945	26.5068
Arith. Mean	20.9497	22.8398	20.8777	21.6288
95% CI (lower)	18.5986	20.8616	19.8112	18.3656
95% CI (upper)	23.3009	24.8179	21.9442	24.8920
SD	2.2404	2.7653	1.5875	3.5284
CV	10.6940	12.1075	7.6039	16.3132
Geometric Mean	20.8470	22.6819	20.8219	21.3788
95% CI (lower)	18.5825	20.7289	19.7705	18.3421
95% CI (upper)	23.3874	24.8189	21.9293	24.9184
Mean of logs	3.037	3.122	3.036	3.062
SD of logs	0.110	0.126	0.077	0.166

LSmean = Least Square Mean, adjust for design imbalance if present
CI = confidence interval
SD = Standard deviation
%CV = percent coefficient of variation

BIO$STAT_CP:(000000 USA USA216)SUMMARY_TAB_PD SAS 04/09/95

Table 65

Individual Remifentanil Gamma Values with Summary Statistics

	Middle (40-65)		Elderly (> 65)	
	Female	Male	Female	Male
	Subj. Age	Subj. Age	Subj. Age	Subj. Age
Geo. LSMean	2.4021	3.4351	3.1795	2.7684
Arith. LSMean	2.9094	4.7177	4.2851	3.0972
Median	1.9393	2.7202	2.2146	2.7147
Minimum	1.1258	1.1515	1.3145	1.2846
Maximum	5.8291	15.7445	13.3787	5.8968
Arith. Mean	2.9094	4.7177	4.2851	3.0972
95% CI (lower)	0.8019	1.5093	1.6045	1.6077
95% CI (upper)	5.0168	7.9261	6.9658	4.5868
SD	2.0082	4.4850	3.9902	1.6106
CV	69.0252	95.0686	93.1162	52.0019
Geometric Mean	2.4021	3.4351	3.1795	2.7684
95% CI (lower)	1.1921	1.9344	1.9186	1.7240
95% CI (upper)	4.8405	6.1000	5.2691	4.4454
Mean of logs	0.876	1.234	1.157	1.018
SD of logs	0.668	0.803	0.752	0.512

LSmean = Least Square Mean, adjust for design imbalance if present
CI = confidence interval
SD = Standard deviation
%CV = percent coefficient of variation

Table 66

Individual Remifentanil K_{e0} (min^{-1}) Values with Summary Statistics

	Middle (40-65)		Elderly (> 65)	
	Female	Male	Female	Male
	Subj. Age	Subj. Age	Subj. Age	Subj. Age
Geo. LSMean				
Arith. LSMean	0.51502	0.44694	0.39654	0.29149
Median	0.53689	0.45106	0.41096	0.28332
Minimum	0.27698	0.18446	0.22169	0.11600
Maximum	0.81359	0.59404	0.59530	0.43855
Arith. Mean	0.51502	0.44694	0.39654	0.29149
95% CI (lower)	0.30470	0.32733	0.31116	0.19833
95% CI (upper)	0.72535	0.56654	0.48191	0.38466
SD	0.20042	0.16720	0.12709	0.10074
CV	38.9137	37.4094	32.0492	34.5589
Geometric Mean				
95% CI (lower)				
95% CI (upper)				
Mean of logs				
SD of logs				

LSmean = Least Square Mean, adjust for design imbalance if present
CI = confidence interval
SD = Standard deviation
%CV = percent coefficient of variation

BIO$STAT_CP:[000000.USA.USA216]SUMMARY_TAB_PD SAS 04/09/95

Table 67

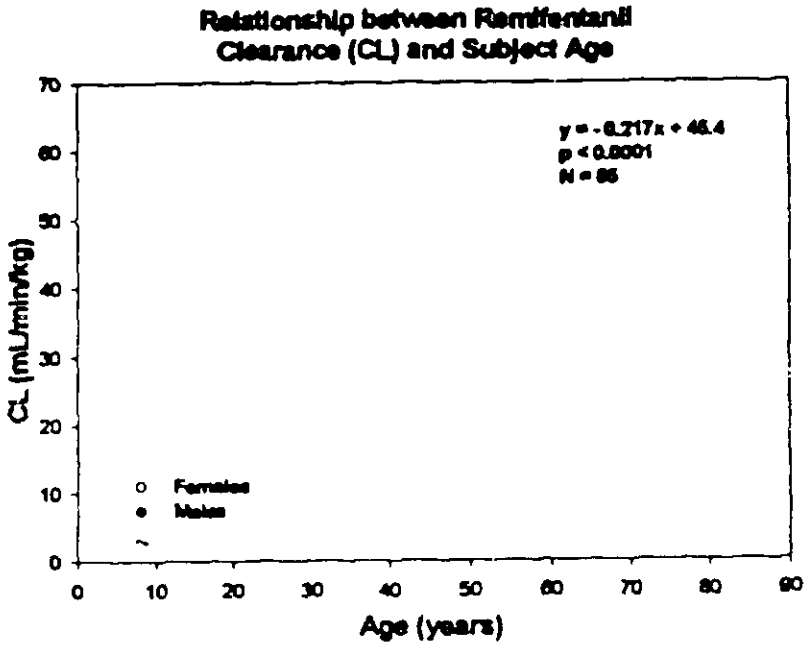
Individual Keo Half I fe Values with Summary Statistics

	Middle (40-65)		Elderly (> 65)	
	Female	Male	Female	Male
	Subj. Age	Subj. Age	Subj. Age	Subj. Age
Geo. LSMean	1.44071	1.66806	1.83933	2.54046
Arith. LSMean	1.54833	1.81500	1.94348	2.77645
Median	1.30430	1.53936	1.68665	2.44656
Minimum	0.85197	0.99872	1.16438	1.58053
Maximum	2.50250	3.75763	3.12664	5.97551
Arith. Mean	1.54833	1.81500	1.94348	2.77645
95% CI (lower)	0.86370	1.20870	1.47454	1.41658
95% CI (upper)	2.23295	2.42129	2.41242	4.13631
SD	0.65238	0.84754	0.69803	1.47037
CV	42.1343	46.6965	35.9164	52.9586
Geometric Mean	1.44071	1.66806	1.83933	2.54046
95% CI (lower)	0.93376	1.23529	1.46063	1.71651
95% CI (upper)	2.22290	2.25246	2.31621	3.75992
Mean of logs	0.36514	0.51166	0.60940	0.93235
SD of logs	0.41325	0.41987	0.34315	0.42391

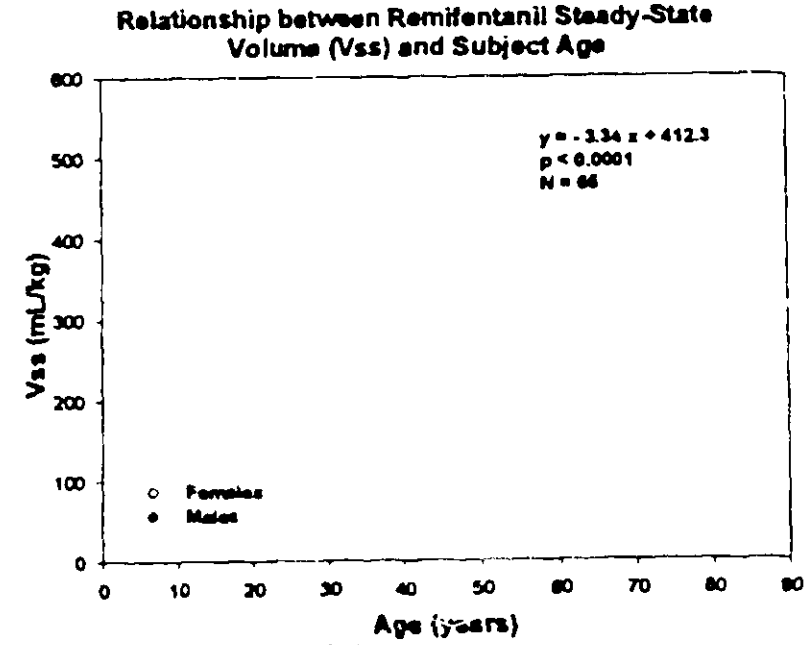
LSmean = Lease Square Mean, adjust for design imbalance if present
CI = confidence interval
SD = Standard deviation
%CV = percent coefficient of variation

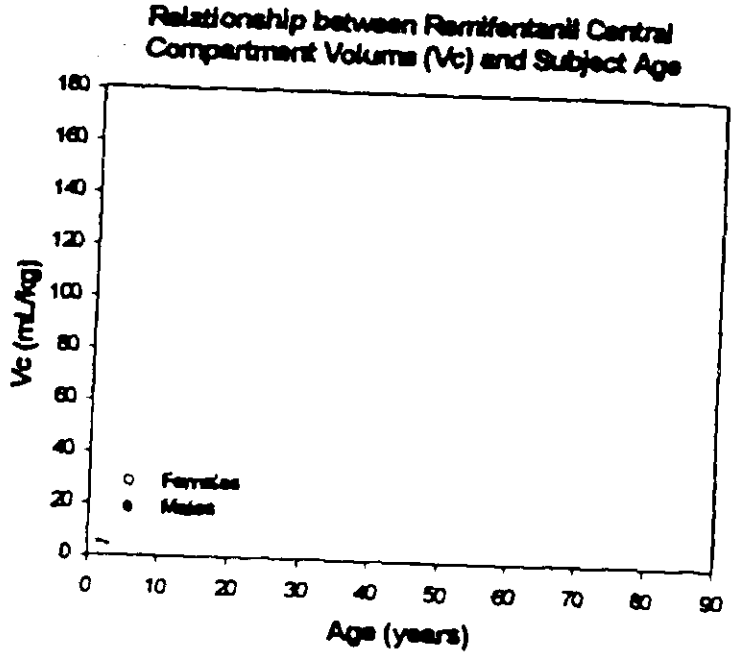
BIO$STAT_CP:[000000.USA.USA216]SUMMARY_TAB_KEOHL.SAS 07/21/95

The following plot shows that clearance decreased with increasing age of subjects ($p<0.0001$).

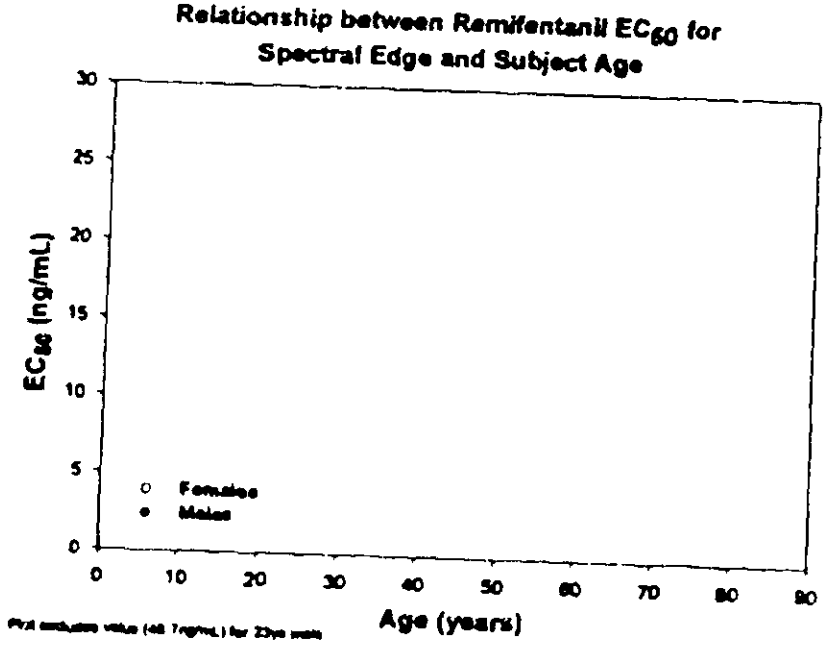


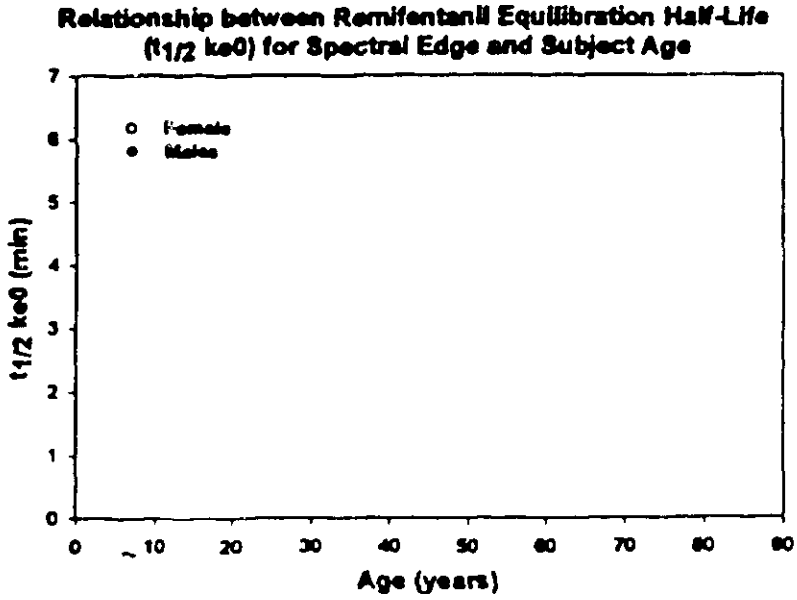
The following plots show that remifentanil steady-state volume of distribution and central compartment volume decrease with increasing subject age ($p<0.0001$).





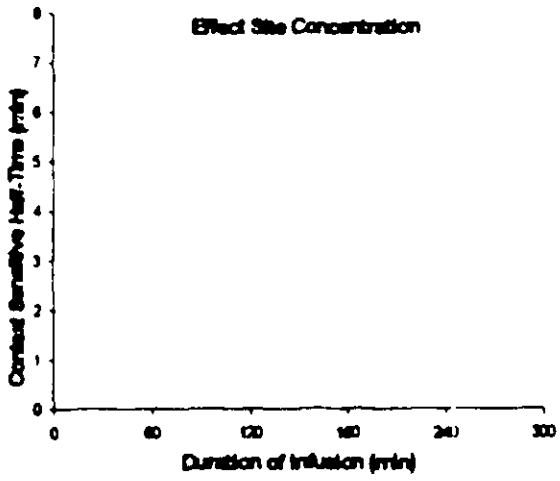
A significant relationship between remifentanil pharmacodynamics and subject age was also observed. The following plots show an age-related decrease in spectral edge EC_{50} ($p<0.0001$), equilibration rate constant ke0 ($p<0.0014$), and the equilibration half-life $1_{1/2}$ ke0 ($p<0.0001$)

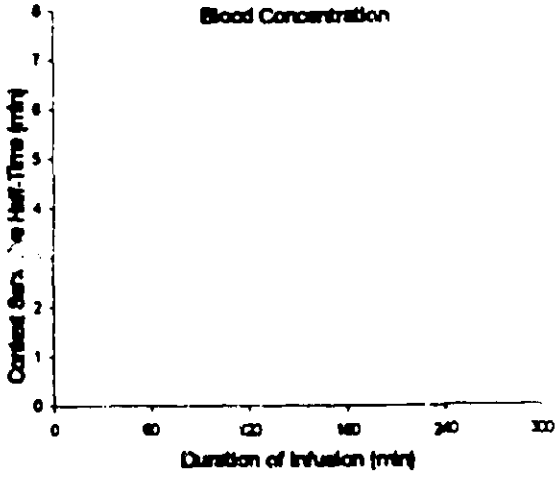




10.4. Context Sensitive Half-Time

The time for a 50% reduction in the effect site and blood concentration of remifentanil following a CACI-simulated infusion was determined for the young (UCP/94/018), middle-age, and elderly subjects. Figures 28 and 29 show the context sensitive half-time based on the concentration of drug in the effect site and the blood, respectively, for the young, middle-age, and elderly subjects (see below). The context sensitive half-time in blood is consistent among the three age groups, whereas an apparent increase in half-time with age is noted for concentration at the effect site





Study USA-219P (UCP/95/026)
Pharmacokinetic Summary

NDA # 20-6[illegible]0 Submission Date: 9/15/95 Volume 96/96

STUDY TYPE: Pediatric Population

Investigator:
Site

Single Dose: XXX Multiple Dose: ____

Subjects
Normal ___ Patients: XXX Young: ___ Elderly: ___

Impaired Hepatic ___ Renal ___

Cross-Over: ___ Parallel: XXX N= 23 M= 16 F= 7

Subject Type: Pediatric male and female patients

	Age Group	
	2-6yr	7-12yr
N	13	10
Gender male/female	7/6	9/1
Age (yrs)	3.7 ± 1.0 (2-6)	9.5 ± 1.8 (7-12)
Weight (kg)	15.2 ± 3.0 (11-21)	33.4 ± 12.5 (17-58)

Treatment Summary

Treatment
Remifentanil, Zero Order IV Infusion, Infused for 1 minute
Rate 5 µg/kg/min was administered to all patients

Lot # CS-USA10008

Sample Strategy

Arterial Blood Samples: Prior to dosing, at the end of infusion (1min), and at 2, 3, 5, 10, 20, 30, 45, 60, 90, 120, 180 and 240 minutes after the start of the infusion

Assay Method
Remifentanil (blood/urine): GC-High Resolution Mass Spectrometry-Selected Ion Monitoring
GR90291 (blood): GC with mass selective detection (GC-MSD)

Sample	Sensitivity	Site	%CV (QC Conc)	QC Range
Remifentanil Blood	0.1 ng/mL		4.9% (80ng/ml) -10.6% (0.25ng/ml)	0.25-80ng/ml
GR90291 Blood	1ng/mL		3.3% (180ng/ml) - 8.3% (4.0ng/ml)	4.0-180ng/ml

Labeling Claims From Study: The pharmacokinetics of remifentanil were similar in children aged 2-6 and 7-12 years old and consistent with previous studies in adults

Study 219P - Pediatric Pharmacokinetic Study

Conclusions: The mean clearance and volume of distribution of remifentanil were similar between 2-6 year old and 7-12 year old patients (55.7±20.2mL/min/kg and 550±808mL/kg in 2-6 year olds and 37.6±13.4mL/min/kg and 339±217mL/kg in 7-12 year olds, respectively). No differences were observed in elimination half-lives (19.7±36.2 and 13.71±12.1 min in 2-6 and 7-12 year olds, respectively) between the two groups. AUC_{∞}, C_{max} and elimination half-life for GR90291 were also similar between the two groups. Mean systolic and diastolic blood pressure and heart rate showed a noticable drop below baseline during and immediately following remifentanil infusion but rapidly returned to baseline within 10-20 minutes.

Investigators:

Purpose: 1) to determine the pharmacokinetics of remifentanil in pediatric patients; 2) to evaluate the safety of remifentanil in these patients.

Study Design: Two-center, open-label, parallel study in two age groups (2-6 years and 7-12 years) of pediatric patients. Remifentanil was administered as an single dose intravenous infusion over one minute.

Demographics: 23 patients (2-6 year olds:13; 7-12 year olds:10), male and female, ASA status I-III, scheduled for elective inpatient surgery. While the study was initially designed to recruit 16 patients (8 patients per group), the protocol was amended to allow enrollment of additional patients due to technical difficulties with sample analysis.

Anesthesia Protocol: *Premedication:* Oral diazepam (0.1-0.2mg/kg), oral midazolam (0.3-1mg/kg), intranasal midazolam (0.2-0.4mg/kg) or intravenous midazolam (0.02-0.1mg/kg) administered within 75 min of induction of anesthesia, as necessary. *Induction:* Patients received halothane and nitrous oxide in oxygen or intravenous thiopental (50-300mg/kg) for induction. Pancuronium or vecuronium (0.1mg/kg) were administered intravenously to facilitate intubation. Following intubation, remifentanil (5μg/kg/min) was infused over one minute. *Maintenance:* Isoflurane and nitrous oxide. Ventilation was adjusted to maintain a $PaCO_2$ of 35-40mmHg and body temperature of ≥35°C.

Table of Principle PK and Safety Results, All Patients (N = 23)
Values are N (% Total) or Mean ± SD

	2-6 Year Olds	7-12 Year Olds
Pharmacokinetics		
Remifentanil	N=8	N=5
CL (mL/min/kg)	55.73 ± 20.28	37.63 ± 13.38
Vd_{ss} (mL/kg)	550 ± 808	339 ± 217
λ_z $t_{1/2}$ (min)	19.72 ± 36.19	13.71 ± 12.08
GR90291	N=11	N=8
AUC_∞ (ng•mL/min)	740 ± 220	1068 ± 673
C_{max} (ng/mL)	8.14 ± 3.89	9.54 ± 4.07
λ_z $t_{1/2}$ (min)	90.46 ± 25.93	106.6 ± 49.75
Safety	N=13	N=10
Any adverse event	8 (62%)	8 (80%)

Seven 2-6yr old patients and eight 7-17 yr old patients experienced mild/moderate adverse events. One patient (three year old) experienced two serious adverse events post-operatively (decreased post-operative brain stem function and a perforated duodenal ulcer) that were unrelated to study drug.

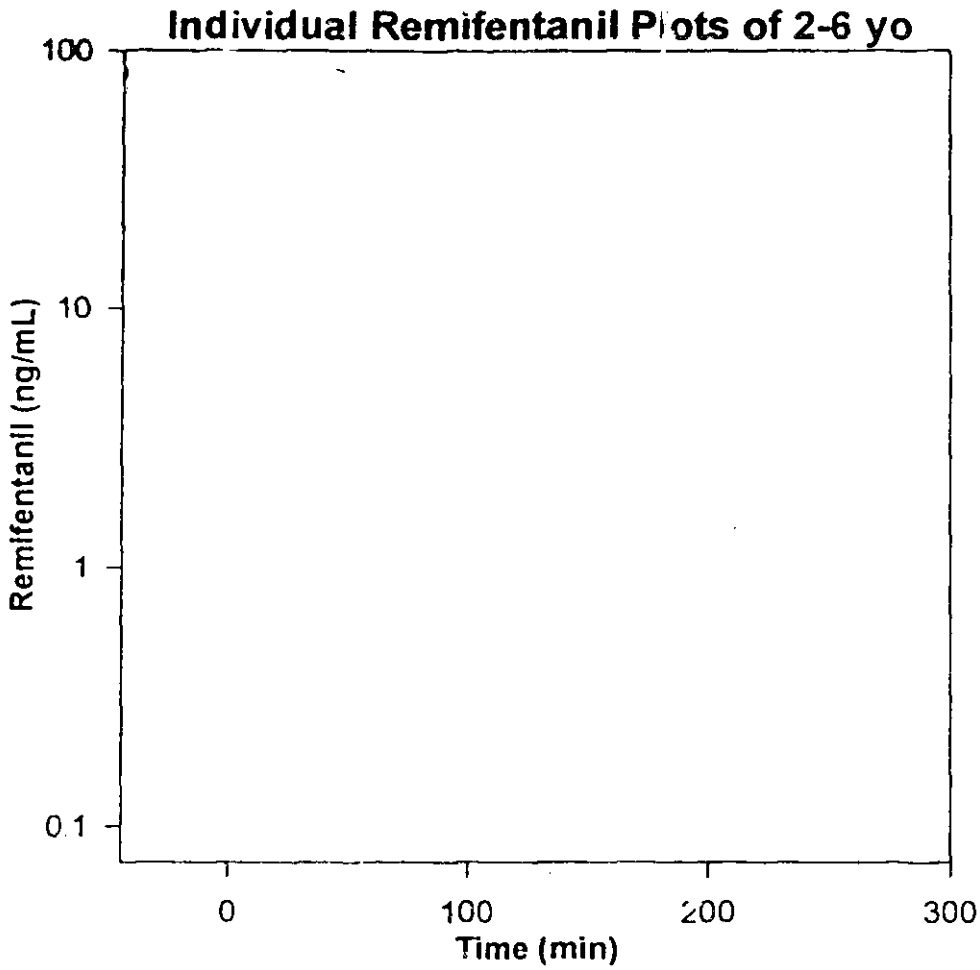
Table 23. Pharmacokinetic Parameters of Remifentanil (Model Dependent Analysis)

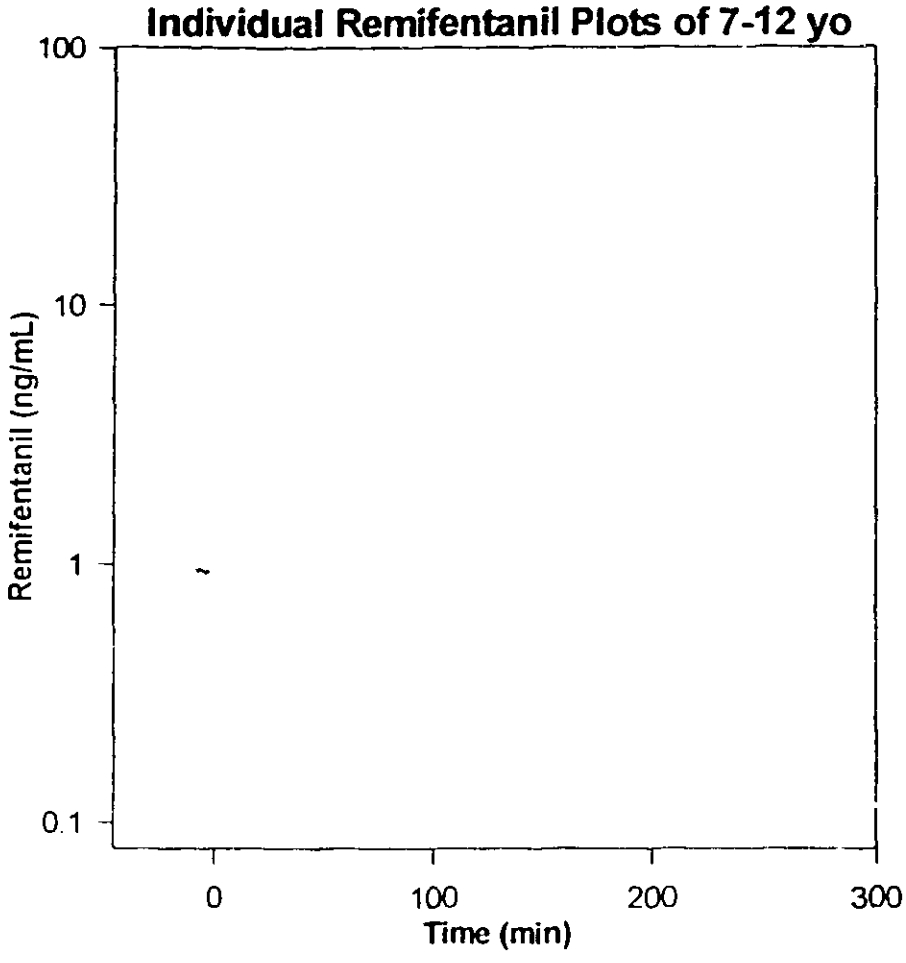
Parameters	2-6yr Old Patients												
	6	9	10	11	106	107	109	110	Mean	SD	CV%	Median	Harmonic Mean
Body Wt (kg)									15.48	3.43	22	15.60	---
Dose (mcg/min)									77.36	17.19	22	78.00	---
K_{10} (1/min)									0.54	0.24	44	0.54	---
K_{12} (1/min)									0.38	0.28	75	0.31	---
K_{21} (1/min)									0.18	0.11	61	0.21	---
$t_{1/2}\lambda_1$ (min)									0.83	0.38	46	0.79	0.69
$t_{1/2}\lambda_2$ (min)									19.72	36.19	183	6.16	6.56
V_1 (L)									1.69	0.66	39	1.57	---
V_1 (ml/kg)									109.2	33.97	31	107.85	---
V_{ss} (L)									7.51	9.07	121	4.16	---
V_{ss} (ml/kg)									550.2	808.30	147	246.94	---
Cl. (L/min)									0.87	0.36	42	0.85	---
Cl. (mL/min/kg)									55.73	20.28	36	56.13	---
	7-12yr Old Patients												
	7	8	108	111*	112				Mean	SD	CV%	Median	Harmonic Mean
Body Wt (kg)									33.76	16.82	50	27.20	---
Dose (mcg/min)									168.8	84.11	50	136.0	---
K_{10} (1/min)									0.49	0.10	21	0.43	---
K_{12} (1/min)									0.33	0.25	76	0.25	---
K_{21} (1/min)									0.13	0.08	59	0.13	---
$t_{1/2}\lambda_1$ (min)									0.90	0.31	35	0.97	0.81
$t_{1/2}\lambda_2$ (min)									13.71	12.08	88	8.60	8.72
V_1 (L)									2.39	0.54	23	2.16	---
V_1 (ml/kg)									82.78	33.90	41	77.83	---
V_{ss} (L)									12.34	13.07	106	7.56	---
V_{ss} (ml/kg)									339.0	216.8	64	247.8	---
Cl. (L/min)									1.15	0.45	39	1.05	---
Cl. (mL/min/kg)									37.63	13.38	36	38.60	---

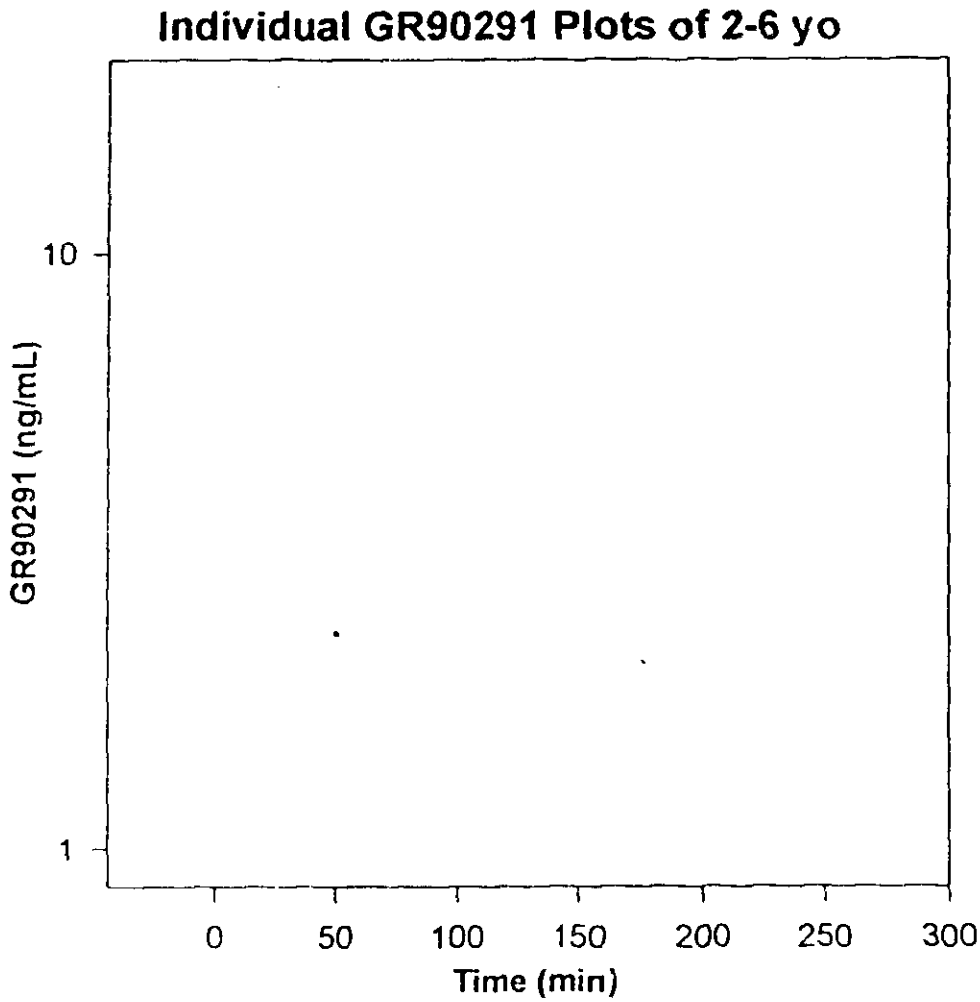
*Model estimated T-lag of 0.46min

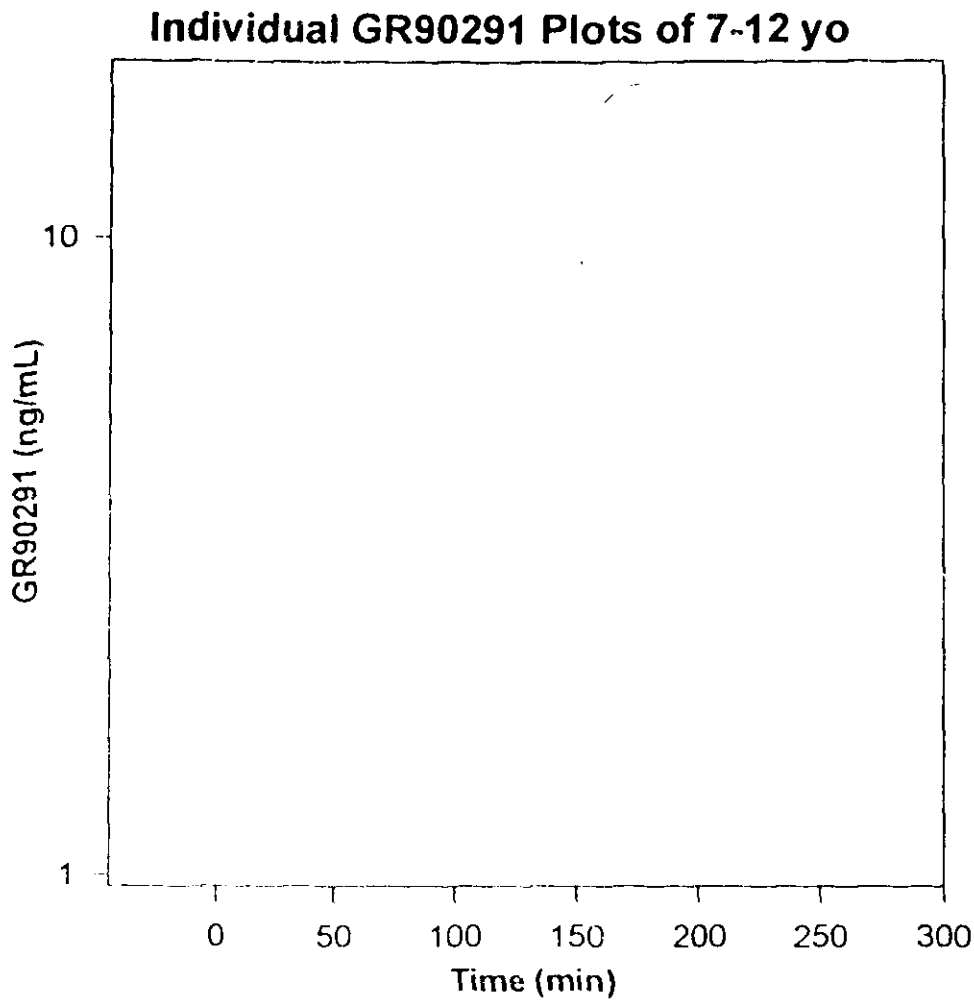
Table 33. Pharmacokinetic Parameters of Remifentanil (Model Independent Analysis)

Parameters	2-6yr Old Patients												
	6	9	10	11	106	107	109	110	Mean	SD	CV%	Median	Harmonic Mean
Body Wt (kg)									15.48	3.43	22	15.60	---
Dose (mcg/min)									77.36	17.19	22	78.00	---
C_{max} (ng/ml.)									35.77	9.51	27	32.28	---
$t_{1/2}\lambda_z$ (min)									16.74	32.47	194	5.52	5.59
AUC_{last} (ng*min/ml.)									103.6	38.17	37	93.87	---
AUC_{inf} (ng*min/ml.)									114.5	63.52	55	95.45	---
$AUMC_{inf}$ (ng*min^2/ml.)									5745	15024	262	435.6	---
MRT (min)									23.71	55.64	235	4.10	---
V_{ss} (L)									7.58	11.30	149	3.68	---
V_{ss} (mL/kg)									572.9	1000	175	213.1	---
Cl. (L/min)									0.81	0.33	41	0.76	---
Cl. (mL/min/kg)									51.35	17.50	34	52.39	---
	7-12yr Old Patients												
	7	8	108	111	112				Mean	SD	CV%	Median	Harmonic Mean
Body Wt (kg)									33.76	16.82	50	27.20	---
Dose (mcg/min)									168.8	84.11	50	136.0	---
C_{max} (ng/ml.)									47.15	15.98	34	47.24	---
$t_{1/2}\lambda_z$ (min)									17.53	23.16	132	7.40	8.00
AUC_{last} (ng*min/ml.)									150.6	51.44	34	136.0	---
AUC_{inf} (ng*min/ml.)									154.7	56.13	36	137.5	---
$AUMC_{inf}$ (ng*min^2/ml.)									3459	5971	173	859.5	---
MRT (min)									16.02	23.53	147	5.87	---
V_{ss} (L)									18.30	28.43	155	6.81	---
V_{ss} (mL/kg)									420.0	446.3	106	213.5	---
Cl. (L/min)									1.10	0.43	39	0.99	---
Cl. (mL/min/kg)									35.57	11.79	33	36.37	---


Individual Remifentanil Plots of 2-6 yo
100
10
1
0.1
Remifentanil (ng/mL)
0
100
200
300
Time (min)


Individual Remifentanil Plots of 7-12 yo
100
10
1
0.1
Remifentanil (ng/mL)
0
100
200
300
Time (min)


Individual GR90291 Plots of 2-6 yo
10
1
GR90291 (ng/mL)
0
50
100
150
200
250
300
Time (min)


Individual GR90291 Plots of 7-12 yo
10
1
GR90291 (ng/mL)
0
50
100
150
200
250
300
Time (min)

Study USA-227 (UCP/95/025)
Pharmacokinetic Summary

NDA # 20-630 Submission Date: 9/15/95 Volume 102-104

Investigator:
Site

Single Dose: XXX Multiple Dose: ____

Subjects:
Normal: ___ Patients: XXX Young: ___ Elderly: ___
Impaired Hepatic: ___ Renal: ___

Cross-Over: ___ Parallel: XXX N= 24 M= 8 F= 16

Subject Type: Obese Males and Females, and Matched Controls

	Obese	Control
N	12	12
Gender male/female	4/8	4/8
Age (yrs)	38.2 ± 8.2 (29-54)	38.3 ± 6.7 (30-53)
Weight (kg)	15.2 ± 3.0 (11-21)	33.4 ± 12.5 (17-58)

Treatment Summary

Treatment
Remifentanil, Zero Order IV Infusion, Infused for 1 minute.
Rate 10 µg/kg/min was administered to first 3 obese patients then dose was reduced to 7.5 µg/kg/min)

Lot # CS-USA10008

Sample Strategy

Arterial Blood Samples: Prior to dosing, at the end of infusion (1minute), and at 2, 3, 4, 5, 7, 8, 10, 12, 15, 20, 25, 30, 40, 60, 90, 120, 180, 240, 300 and 360 minutes after the start of the infusion.

Assay Method
Remifentanil (blood/urine): GC-High Resolution Mass Spectrometry-Selected Ion Monitoring
GR90291 (blood): GC with mass selective detection (GC-MSD)

Sample	Sensitivity	Site	%CV (QC Conc)	QC Range
Remifentanil Blood	0.1 ng/mL		4.8% (5ng/ml) -11.9% (0.25ng/ml)	0.25-80ng/ml
GR90291 Blood	1ng/mL		4.8% (75ng/ml) - 10.1% (3.0ng/ml)	1.5-75ng/ml

Labeling Claims From Study TBW-corrected CL, V_1 and V_{ss} were significantly different in the obese patients compared to the matched control patients; however, IBW-corrected CL, V_1 and V_{ss} for the two groups were similar Remifentanil should be dosed based on IBW rather than TBW in obese patients

Study 227 - Pharmacokinetics in Obese Patients

Conclusions: The mean clearance and volume of distribution (corrected for total body weight, TBW) for remifentanil were significantly different between obese and control patients (27.7mL/min/kg and 146mL/kg in obese patients and 42.4mL/min/kg and 217mL/kg in matched controls, respectively). Pharmacokinetic parameters showed better correlation with ideal body weight (IBW) than TBW in obese patients, suggesting that dosing based on IBW may be more appropriate in grossly obese patients. No differences were observed in elimination half-lives (6.97-7.50 min) between the two groups. Dose-normalized AUC_∞ and C_{max} for GR90291 were higher in obese patients than controls. Systolic and diastolic blood pressure and heart rate showed a noticable drop below baseline during and immediately following remifentanil infusion. Values rapidly returned to baseline in control patients but showed a more gradual return to baseline in obese patients.

Investigators:

Purpose 1) to compare the pharmacokinetics of remifentanil in obese surgical patients to control, non-obese surgical patients; 2) to evaluate the safety of remifentanil in these patients.

Study Design: Single-center, open-label, parallel study in obese versus control patients. Remifentanil was administered as an single dose intravenous infusion over one minute.

Demographics: 24 patients (12 obese and 12 control patients), aged 29-54 years, male and female, ASA status I-III, scheduled for elective inpatient surgery. Obese patients were defined as >80% over ideal body weight (IBW), while control patients were defined as within 25% of IBW. Obese and control patients were matched for age, height, race, gender and ASA status.

Anesthesia Protocol: *Premedication:* Midazolam (0.5-3mg IV) was administered within 2 hours prior to surgery, as necessary. *Induction:* Patients received intravenous thiopental (3-7mg/kg) for induction. Vecuronium (0.075-0.1mg/kg) was administered intravenously to facilitate intubation. Following intubation, glycopyrrolate (up to 0.5 mg) was administered intravenously followed by remifentanil as a 1-minute infusion. Three obese patients received a dose of 10mcg/kg remifentanil and the remaining patients received 7.5mcg/kg. *Maintenance:* 66% nitrous oxide in oxygen with supplementation with isoflurane as needed

Results: Table of Principle PK and Safety Results, All Patients (N = 24)

	Obese Patients (N = 12)	Control Patients (N = 12)
Pharmacokinetics Mean ± SD		
Remifentanil		
CL (TBW) (mL/min/kg)	27.7 ± 7.2	42.4 ± 7.5
CL (IBW) (mL/min/kg)	56.4 ± 12.7	49.4 ± 9.2
V_{ss} (TBW) (mL/min/kg)	146 ± 55	217 ± 66
V_{ss} (IBW) (mL/min/kg)	294 ± 99	257 ± 93
λ_z $t_{1/2}$ (min)	7.50 ± 1.39	6.97 ± 1.40
GR90291		
C_{max} (ng/mL)[1]	17.1 ± 3.2	11.1 ± 1.7
AUC_∞ (ng•min/mL)[1]	276 ± 53	214 ± 39
Safety N (% Total)	N = 12	N = 12
Any adverse event	10 (83%)	12 (100%)

[1] Normalized to a dose of 1 µg/kg

Table 42. Pharmacokinetic Parameters of Remifentanil (Model Independent Analysis)

Parameters	*Obese Patient*								
	1	2	3	5	6	7	8	9	12
C_{max} (ng/mL)									
DN-C_{max} (ng/mL)									
AUC_{last} (ng*min/mL)									
AUC_{inf} (ng*min/mL)									
DN-AUC_{inf} (ng*min/mL)									
$AUMC_{inf}$ (ng*min^2/mL)									
MRT (min)									
$t_{1/2}\lambda_z$ (min)									
CL (L/min)									
CL (mL/min/kg)									
V_{ss} (L)									
V_{ss} (mL/kg)									
	Control Patients								
	4	10	11	13	15	18	19	20	21
C_{max} (ng/mL)									
DN-C_{max} (ng/mL)									
AUC_{last} (ng*min/mL)									
AUC_{inf} (ng*min/mL)									
DN-AUC_{inf} (ng*min/mL)									
$AUMC_{inf}$ (ng*min^2/mL)									
MRT (min)									
$t_{1/2}\lambda_z$ (min)									
CL (L/min)									
CL (mL/min/kg)									
V_{ss} (L)									
V_{ss} (mL/kg)									

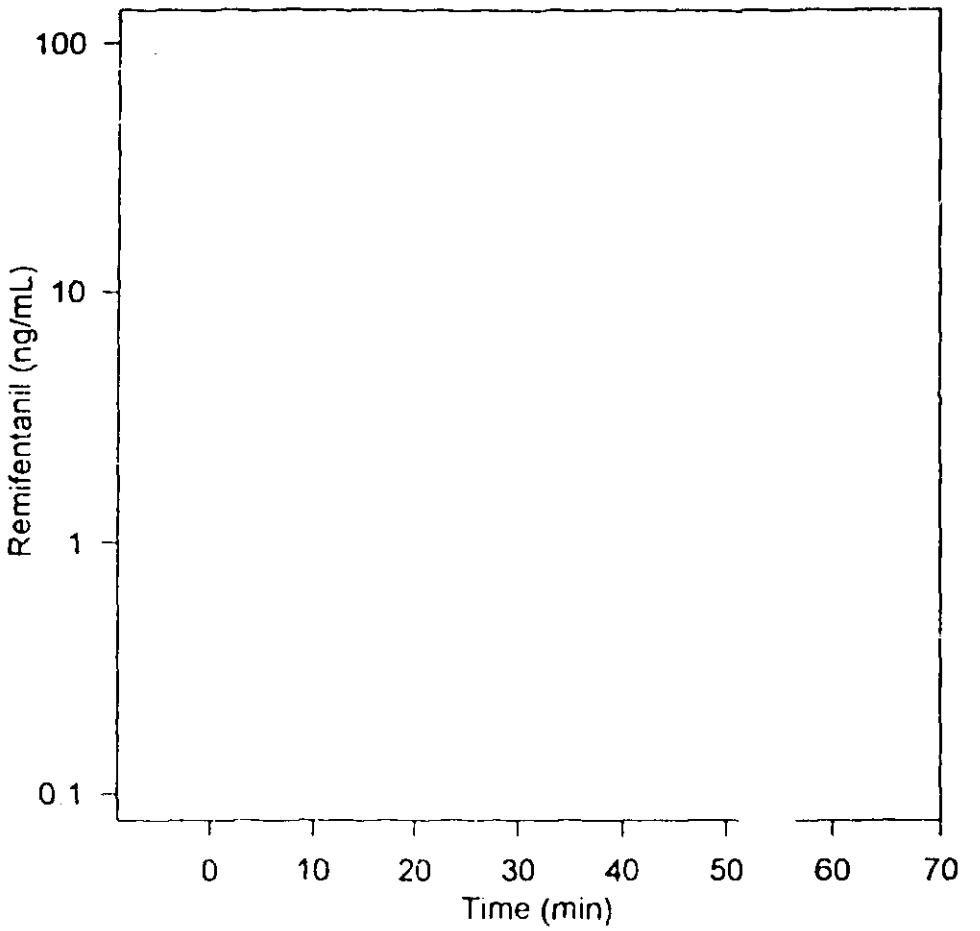
DN = Dose normalized to 1mcg/kg

Table 42. (Contd.) Pharmacokinetic Parameters of Remifentanil (Model Independent Analysis)

Parameters	*Obese Patients*							
	14	16	17	Mean	SD	CV%	Median	Harmonic Mean
C_{max} (ng/mL)				54.87	17.07	31	50.17	—
DN-C_{max} (ng/mL)				6.77	1.87	28	6.52	—
AUC_{last} (ng*min/mL)				222.57	44.85	20	221.69	—
AUC_{inf} (ng*min/mL)				224.52	45.02	20	223.87	—
DN-AUC_{inf} (ng*min/mL)				27.81	5.39	19	28.59	—
$AUMC_{inf}$ (ng*min^2/mL)				1663	561.99	34	1540	—
MRT (min)				6.82	1.60	23	6.31	—
$t_{1/2}\lambda_z$ (min)				6.60	1.06	16	6.23	6.45
CL (L/min)				4.17	0.80	19	4.22	—
CL (mL/min/kg)				37.32	7.80	21	35.03	—
V_{ss} (L)				28.06	7.45	27	26.50	—
V_{ss} (mL/kg)				249.8	55.67	22	246.2	—
	Control Patients							
	22	23	24	Mean	SD	CV%	Median	Harmonic Mean
C_{max} (ng/mL)				31.74	8.40	26	28.52	—
DN-C_{max} (ng/mL)				4.22	1.10	26	3.82	—
AUC_{last} (ng*min/mL)				135.47	34.07	25	132.27	—
AUC_{inf} (ng*min/mL)				137.10	34.33	25	135.01	—
DN-AUC_{inf} (ng*min/mL)				18.19	4.28	24	17.59	—
$AUMC_{inf}$ (ng*min^2/mL)				969	385.58	40	852.90	—
MRT (min)				6.70	1.49	22	6.20	—
$t_{1/2}\lambda_z$ (min)				6.09	1.15	19	5.90	5.90
CL (L/min)				3.65	0.82	23	3.66	—
CL (mL/min/kg)				57.85	13.93	24	57.32	—
V_{ss} (L)				24.51	7.88	32	23.60	—
V_{ss} (mL/kg)				381.2	95.5	25	392.0	—

DN = Dose normalized to 1mcg/kg

Individual Remifentanil Plots of Obese Patients



Individual Remifentanil Plots of Control Patients

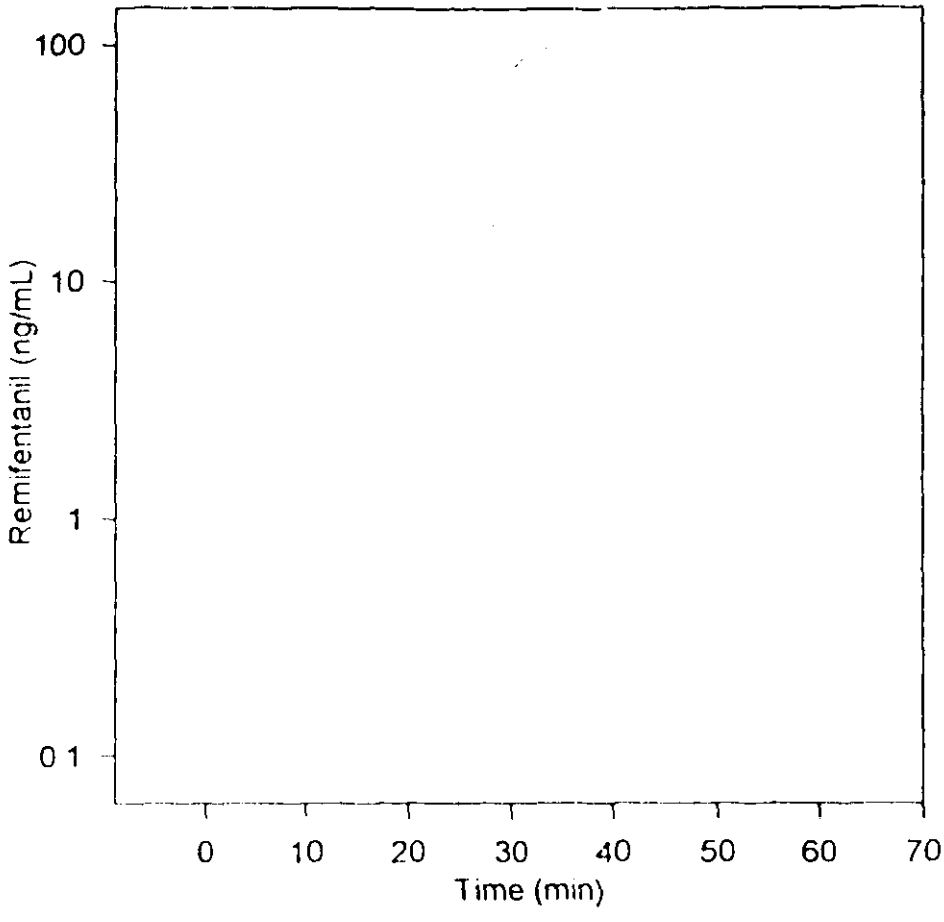


Table 50. Pharmacokinetic Parameters of GR90291 (Model Independent Analysis)

Parameters	*Obese Patients*								
	1	2	3	5	6	7	8	9	12
C_{max} (ng/mL)									
DN-C_{max} (ng/mL)									
Tmax (min)									
$AUC_{inf,90291}$ (ng*min/mL)									
DN-$AUC_{inf,90291}$ (ng*min/mL)									
$t_{1/2\lambda_z}$ (min)									
$AUC_{inf,Remi}$ (ng*min/mL)[a]									
Ratio (AUC_{90291}/AUC_{Remi})									
	Control Patients								
	4	10	11	13	15	18	19	20	21
C_{max} (ng/mL)									
DN-C_{max} (ng/mL)									
T_{max} (min)									
$AUC_{inf,90291}$ (ng*min/mL)									
DN-$AUC_{inf,90291}$ (ng*min/mL)									
$t_{1/2\lambda_z}$ (min)									
$AUC_{inf,Remi}$ (ng*min/mL)[a]									
Ratio (AUC_{90291}/AUC_{Remi})									

DN = Dose-normalized to 1mcg/kg Remifentanil

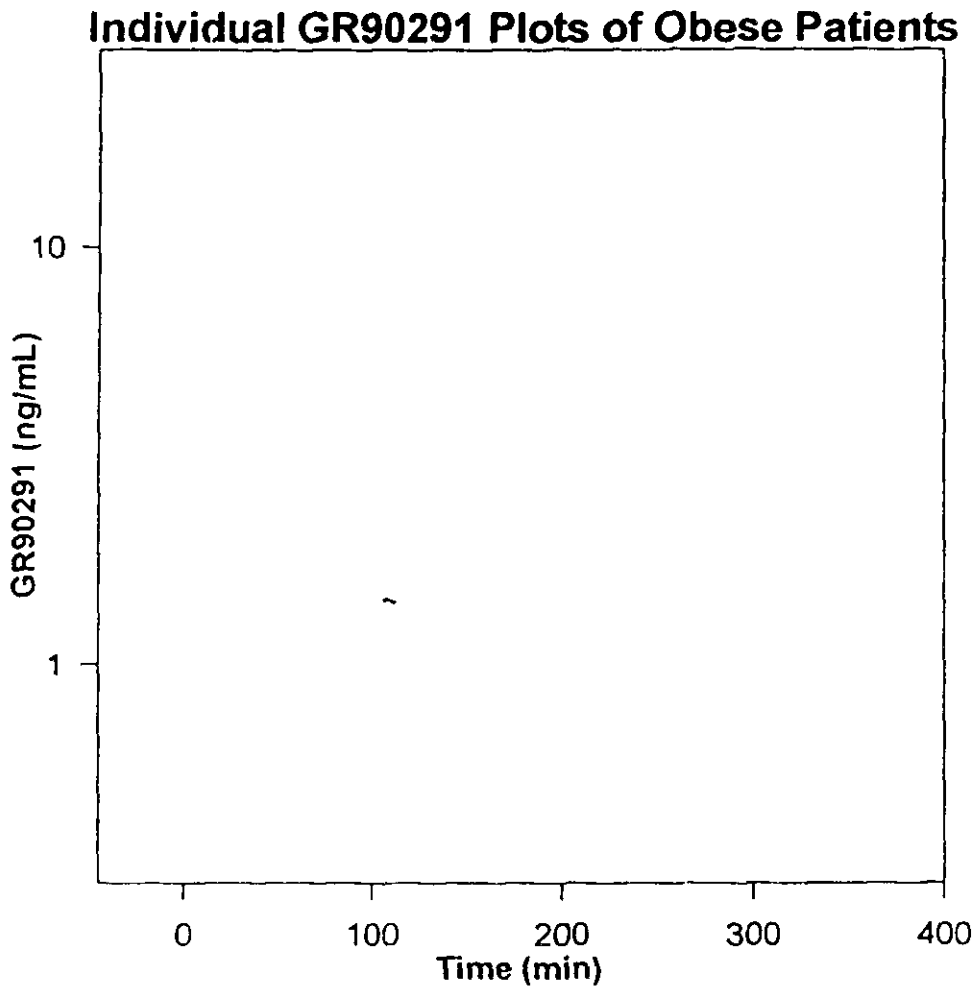
[a] Model dependent analysis

Table 50 (Contd.). Pharmacokinetic Parameters of GR90291 (Model Independent Analysis)

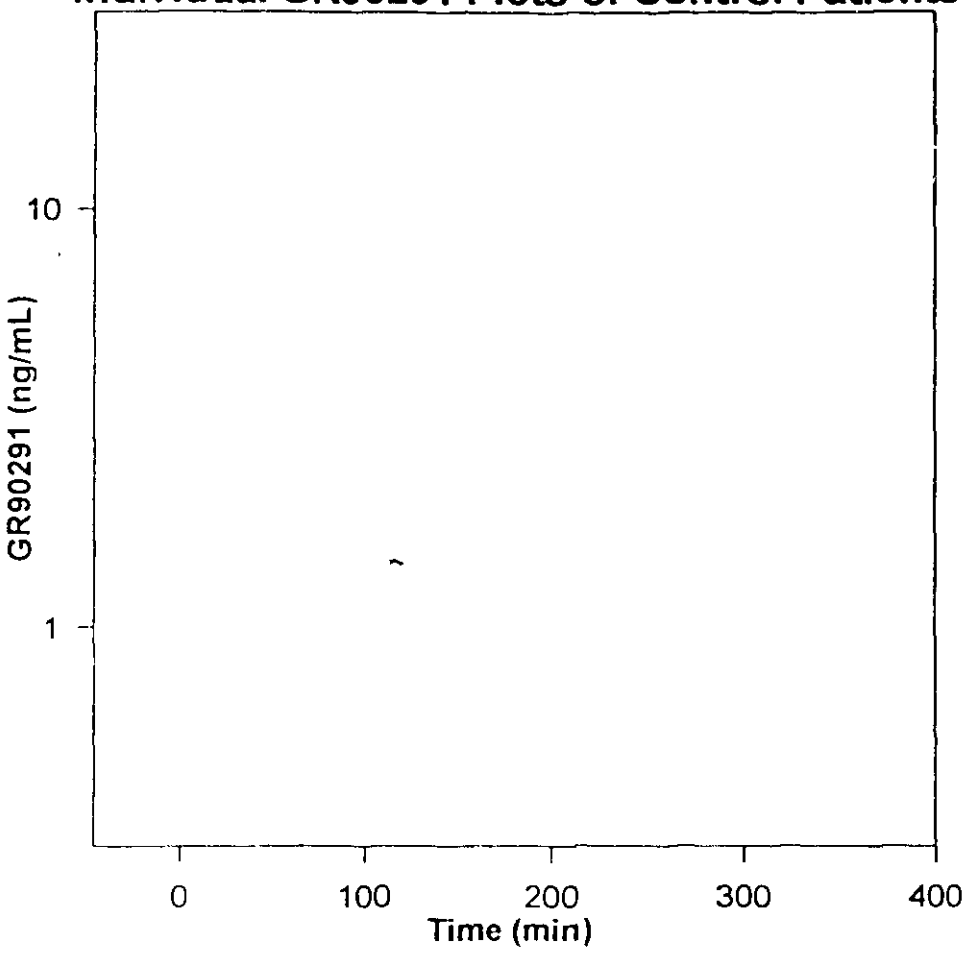
Parameters	*Obese Patients*							
	14	16	17	Mean	SD	CV%	Median	Marmonic Mean
C_{max} (ng/mL)				17.09	3.18	19	17.00	---
DN-C_{max} (ng/mL)				2.10	0.28	13	2.05	---
T_{max} (min)				25.17	9.31	37	27.50	---
$AUC_{inf,90291}$ (ng*min/mL)				2226	453.3	20	2171	---
DN-$AUC_{inf,90291}$ (ng*min/mL)				275.7	53.03	19	278.8	---
$t_{1/2\lambda_2}$ (min)				112.81	43.50	39	101.30	101.14
$AUC_{inf,Remi}$ (ng*min/mL)*				309.48	88.54	29	294.20	---
Ratio (AUC_{90291}/AUC_{Remi})				7.56	2.04	27	7.65	---
	Control Patients							
	22	23	24	Mean	SD	CV%	Median	Mean
C_{max} (ng/mL)				11.13	1.73	16	11.10	---
DN-C_{max} (ng/mL)				1.48	0.25	16	1.45	---
T_{max} (min)				29.58	11.17	38	27.50	---
$AUC_{inf,90291}$ (ng*min/mL)				1608	295.7	18	1577	---
DN-$AUC_{inf,90291}$ (ng*min/mL)				214.0	38.75	18	212.6	---
$t_{1/2\lambda_2}$ (min)				112.17	19.93	18	108.17	109.04
$AUC_{inf,Remi}$ (ng*min/mL)*				183.52	40.58	22	171.60	---
Ratio (AUC_{90291}/AUC_{Remi})				8.96	1.83	20	8.33	---

DN = Dose-normalized to 1mcg/kg of Remifentanil

* Model dependent analysis


Individual GR90291 Plots of Obese Patients
GR90291 (ng/mL)
10
1
0
100
200
300
400
Time (min)

Individual GR90291 Plots of Control Patients



Study USA-204 (UCR/94/026)
Pharmacokinetic Summary

NDA # 20-630 Submission Date: 9/15/95 Volume 117-122

Investigators:
Sites:

Single Dose:____. Multiple Dose: XXX.

Subjects:
Normal:___. Patients: XXX Young:___. Elderly:___.
Impaired Hepatic:___. Renal:___.

Cross-Over:___. Parallel: XXX. N= 118 M= 79 F= 39

Subject Type: Adult Inpatients

PART I	Investigator				Investigator			
	Remifentanil			Alfentanil	Remifentanil			Alfentanil
	Low (N=13)	Mid (N=8)	High (N=7)	(N=3)	Low (N=5)	Mid (N=11)	High (N=7)	(N=3)
Gender (M/F)	6/7	5/3	4/3	2/1	5/0	9/2	6/1	3/0
Age (yrs)	45.4 ± 13.7 21-65	43.3 ± 17.6 18-63	43.9 ± 16.2 20-63	39.0 ± 10.6 31-51	32.4 ± 8.2 21-40	37.5 ± 10.9 22-56	37.4 ± 13 27-63	33.7 ± 12 22-46
Weight (kg)	75.1 ± 15.5 55-100	73.5 ± 9.9 61.4-86.4	74.1 ± 15 51.4-93.2	76.8 ± 16.1 59-90.4	84.2 ± 18.7 64-112.8	78.5 ± 13.3 60-100	77.2 ± 9.4 64.5-93.1	85.6 ± 6.2 80-92.2

PART II	Remifentanil			Alfentanil
	Low (N=18)	Mid (N=9)	High (N=18)	(N=16)
Gender (M/F)	10/8	6/3	6/1	3/0
Age (yrs)	34.6 ± 8.8 19-53	40.8 ± 11.9 22-57	40.1 ± 13.9 23-63	38.9 ± 12.2 23-60
Weight (kg)	74.3 ± 18 46.8-109	82.5 ± 11.9 66.3-97.7	77.9 ± 14.0 54.5-100	73.5 ± 16.0 50-96.3

Treatment Summary
Remifentanil or Alfentanil, Zero Order IV Infusion, Infused for 1 minute plus continuous infusion:
Rate: Remifentanil
1mcg/kg bolus + 0.0125mcg/kg/min continuous infusion , 1mcg/kg bolus + 0.025mcg/kg/min continuous infusion, 1mcg/kg bolus + 0.05mcg/kg/min continuous infusion, 1mcg/kg bolus + 0.1mcg/kg/min continuous infusion, 1mcg/kg bolus + 0.3mcg/kg/min continuous infusion, 1mcg/kg bolus + 0.6mcg/kg/min continuous infusion, 1mcg/kg bolus + 1mcg/kg/min continuous infusion, 1mcg/kg bolus + 0.04mcg/kg/min continuous infusion. 1mcg/kg bolus + 1mcg/kg/min continuous infusion, 1mcg/kg bolus + 0.04mcg/kg/min continuous infusion, 1mcg/kg bolus + 0.1mcg/kg/min continuous infusion, or 1mcg/kg bolus + 0.4mcg/kg/min continuous infusion.
Alfentanil
40mcg/kg bolus + 0.5mcg/kg/min continuous infusion, 40mcg/kg bolus + 1mcg/kg/min continuous infusion, or 40mcg/kg bolus + 0.75mcg/kg/min continuous infusion,

Lot # CS-USA10008

Sample Strategy:
Arterial Blood Samples: Before intubation, skin incision, every 30 minutes post skin incision, at skin closure, spontaneous respiration and 10, 30, and 60 minutes post infusion.

Assay Method:
Remifentanil: GC-High Resolution Mass Spectrometry-Selected Ion Monitoring
GR90291: GC/Tandem Mass Spectrometry
Alfentanil: GC-High Resolution Mass Spectrometry-Selected Ion Monitoring

Sample	Sensitivity	Site	%CV (QC Conc)	QC Range
Remifentanil Blood	0.1 ng/mL	Triangle	4.5% (5ng/ml) -10.8% (0.2ng/ml)	0.2-80ng/ml
GR90291 Blood	0.5ng/mL	Oneida	4.8% (75ng/ml) -15.9% (3ng/ml)	1.5-75ng/ml
Alfentanil	1ng/mL	Triangle	4.2% (2500ng/ml) - 9.4% (2.5ng/ml)	2.5-2500ng/ml

Labeling Claims From Study: The pharmacokinetics of remifentanil in general surgical patients under nitrous oxide/oxygen anesthesia were the same as those in healthy conscious volunteers

Study USA-204 Dose Finding and Comparative trial of Remifentanil vs Alfentanil for Anesthesia Maintenance

Conclusions: Remifentanil was safely and effectively used in patients undergoing general anesthesia with N_2O 66%. The pharmacokinetics of remifentanil in general surgical patients were the same as those in healthy conscious volunteers. Potency ratios for intubation and skin incision based on the EC_{50} values of remifentanil and alfentanil were 49:1 and 52:1, respectively. However, because of the wide confidence intervals on the EC_{50}'s these values should be interpreted with caution.

Investigators:

Purpose: 1) To compare the efficacy and safety of remifentanil with alfentanil when used with nitrous oxide for maintenance of anesthesia and 2) To determine a dose response and blood concentration-response curve for remifentanil for intubation, skin incision, and skin closure.

Study Design: The study was conducted in two parts. Part I was an open-label, active-controlled, dose-escalation design; Part IA and Part IB were randomized, double-blind, parallel-group design; Part II was a randomized, double-blind, active controlled parallel-group design.

Demographics: One-hundred eighteen patients were enrolled in this study. Fifty-seven patients completed Part I, and 61 patients completed Part II (including one replacement patient). No patients were withdrawn from the study.

Anesthesia Protocol: *Premedication:* None

Induction: Propofol (2 mg/kg) was administered to produce loss of consciousness. After LOC was obtained, the patient was ventilated with 66% nitrous oxide in oxygen by mask. Vecuronium 0.07-0.08mg/kg was administered for tracheal intubation. A bolus dose of study medication was administered over a 1-minute period, immediately after which a continuous infusion was started at a rate described below:

Part	No.Patients	No.Patients	Study Medication	Initial Bolus (mcg/kg)	Infusion Rate (mcg/kg/min)
IB	4		remifentanil	1	0.0125
	4		remifentanil	1	0.025
I, IA, IB	5	5	remifentanil	1	0.05
	1	1	alfentanil	40	0.5
	5	6	remifentanil	.	0.1
	2	2	alfentanil	40	1.0
I, IA	3	5	remifentanil	1	0.3
	3	5	remifentanil	1	0.6
I	4	2	remifentanil	1	1.0

The following dose schedule was administered in Part II of the study:

Dose Tier	No.Patients	Study Medication	Initial Bolus mcg/kg	Infusion Rate mcg/kg/min
1	18	remifentanil	1	Low (0.04)
2	9	remifentanil	1	Medium (0.1)
3	18	remifentanil	1	High (0.4)
4	15	alfentanil	40	0.75

Maintenance: Following tracheal intubation, anesthesia was continued with N_2O 66% and the study opioid. Rescue anesthetics (propofol or isoflurane) were allowed if necessary.

Results: Table 1. Principal PK and PD Results

Values are Mean ± SD

	Part I	Part II
PK		
Remifentanil	N = 39	N = 40
CL (mL/min/kg)	40.04 (13.40)	33.66 (7.98)
V_1 (mL/kg)	101 (70.0)	86.99 (54.0)
V_{ss} (mL/kg)	395 (328)	227 (108)
λ_z $t_{1/2}$ (min)	15.11 (11.24)	9.94 (5.46)
	Combined Parts I and II	
Alfentanil	N=20	
CL (mL/min/kg)	7.21 (3.37)	
V_1 (mL/kg)	164 (120)	
V_{ss} (mL/kg)	722 (380)	
λ_z $t_{1/2}$ (min)	108 (87.78)	

	Investigator 2	
PD	Remifentanil (N=67)	Alfentanil (N=19)
$EC_{50,intubation}$ (ng/mL)	2.04	111
$EC_{50,S\ incision}$ (ng/mL)	1.50	86.71

No deaths occurred and no patient was withdrawn from the study. No patients had muscle rigidity. Three patients, two remifentanil and one alfentanil, had serious adverse events.

USA-220
Pharmacokinetic Study Summary

NDA # 20-630 Submission Date: 9/15/95 Volume 155-158

Investigator:
Site:

Single Dose:____ . Multiple Dose:_____.
Subjects: Normal: ____. Patients: X . Young: X. Elderly:____.
Hepatic:____. Renal: ___.
Cross-Over:____. Parallel: X. N= 83 M= 83 F= 137

Subject Type: ASA I-III patients for elective inpatient or outpatient surgery

	CACI Targeted Remifentanil Concentration Group (ng/ml)								
Category	Placebo (N=26)	0.5 (N=25)	1 (N=26)	1.5 (N=24)	2 (N=28)	4 (N=26)	8 (N=24)	16 (N=28)	32 (N=13)
Female Male	11(42%) 15(58%)	11(44%) 14(14%)	9(35%) 17(65%)	10(42%) 14(58%)	12(43%) 16(57%)	10(38%) 16(62%)	7(29%) 17(71%)	11(39%) 17(61%)	2(15%) 11(85%)
Age Mean (yrs) Range	38.5±12.6 (21-61)	37.2±11.6 (20-64)	36.7±11.5 (21-61)	43.5±14.2 (18-65)	42.5±13 (19-65)	39.9±13 (20-64)	39.4±13.1 (19-64)	40.9±12.1 (19-62)	36.1±13.5 (18-63)
Wt Mean (kg) Range	72.5±17.1 (44-109)	78±14.6 (54.2-120)	72.3±15 (51.4-107.3)	72.4±12.9 (52-104)	75.8±14.9 (51-120.9)	74.9±15.1 (51-112.9)	72.9±13.3 (50-96.3)	72.8±18.2 (47.4-106)	69±13.1 47.6-96.4)

Treatment Summary:

Remifentanil: Computer-assisted continuous infusion (CACI)
Target Remifentanil Concentrations: 0, 0.5, 1, 1.5, 2, 4, 8, 16, 32ng/mL
Lot # CS-USA1008

Sample Strategy:

Blood Samples: Arterial samples were collected at 5 minutes after stable end-tidal isoflurane concentration was achieved, just prior to skin incision, and 2 minutes after skin incision

Assay Method:

Remifentanil was assayed using GC-High Resolution Mass Spectrometry (Triangle Labs)
Assay sensitivity 0.1ng/ml; Interday CV = 2.4% (80ng/ml) - 8.2% (0.25ng/ml); QC range = 0.25-80ng/ml

Pharmacodynamic Measurements:

Response to endotracheal intubation and skin incision were recorded

Pharmacokinetic/Pharmacodynamic Analysis:

Logistic regression analysis was used to determine the concentration of remifentanil that produces a 50% reduction in isoflurane MAC for response to intubation and skin incision. Remifentanil clearance was estimated using the remifentanil infusion rate and steady-state concentration.

Labeling Claims From Study: Remifentanil and isoflurane show a synergistic interaction. The clearance of remifentanil is not altered in the presence of isoflurane.

Study USA-220 - Minimum Alveolar Concentration (MAC) Reduction of Isoflurane with Remifentanil

Conclusions: A synergistic interaction was observed bwteen remifentanil and isoflurane for responses to skin incision. A 50% reduction in the MAC of isoflurane was produced by a remifentanil concentration of 1.37ng/ml. The maximum MAC reduction over the concentrations studied (up to 32ng/mL) was 91%. The clearance of remifentanil was not altered by isoflurane.

Investigator:

Purpose:. (1) To determine the end-tidal isoflurane concentration which inhibits movement in 50% of patients (MAC) at steady-state remifentanil blood concentrations, and to quantitate the maximum reduction of the MAC of isoflurane with remifentanil

Study Design: Two-center, open-label, randomized study

Demographics: 220 ASA I-III male and female patients, ages 18-65, scheduled for elective inpatient or outpatient surgery

Anesthesia Protocol: *Premedication*: None. *Induction*: A computer assisted continuous infusion (CACI) device was used to achieve a target remifentanil blood concentrations. Patients were ventilated with oxygen/isoflurane to induce loss of consciousness (LOC). *Maintenance*: The initial patient in each treatment block received a targeted end-tidal isoflurane concentration up to the time of skin incision. For subsequent patients isoflurane was adjusted based on the previous patient's response to SKI using the Dixon Up/Down method. The patient was observed for 60 seconds and the response to incision noted. Two minutes after SKI the infusion of remifentanil was stopped.

Results: Table of Principal Pharmacokinetic and Efficacy Results

Remifentanil Target Concentration Group (ng/mL)	Isoflurane MAC (%)	%MAC Reduction	Clearance (mL/min/kg)
0	1.30	–	
0.5	1.16	10	34.7 (7.7)
1	0.79	39	34.6 (9.9)
1.5	0.63	52	34.0 (10.6)
2	0.54	59	34.2 (7.2)
4	0.36	72	30.8 (6.2)
8	0.25	81	28.0 (5.1)
16	0.17	87	34.5 (10.4)
32	0.11	91	34.29 (9.4)

Study USA-205 (GGN/94/008)
Pharmacokinetic Summary

NDA # 20-630 Submission Date: 9/15/95 Volume 123-126

Investigator:
Site:

Single Dose: ____ Multiple Dose: XXX

Subjects:
Normal: ___ Patients: XXX Young: ___ Elderly: ___
Impaired Hepatic: ___ Renal: ___

Cross-Over: ___ Parallel: XXX N= 120 M= 55 F= 65

Subject Type: Male and Female Patients Scheduled for Elective Inpatient Surgery

	Remifentanil Treatment Group (Premed.=Temazepam)					Remifentanil Treatment Group (Premed.=Placebo)				
	A	B	C	D	E	A	B	C	D	E
N	12	11	11	12	12	14	11	12	12	13
Gender (M/F)	7/5	3/8	2/9	6/6	7/5	8/6	5/6	5/7	6/6	6/7
Age (yrs)	44 ± 11.1 27-62	51 ± 9.0 37-64	46 ± 10.1 29-61	43 ± 10.1 29-64	48 ± 11.3 19-65	46 ± 10.3 25-63	50 ± 7.4 42-65	43 ± 8.1 27-56	46 ± 11.6 22-58	40 ± 11.2 21-59
Weight (kg)	60 ± 9.52 46-75	69.6 ± 14.8 51.4-102	66 ± 9.94 53-84	71 ± 12.13 47.8-86	73.7 ± 14.5 54-96	73.9 ± 10.7 55-92	64 ± 10.8 48.5-100	71.7 ± 16 48.5-100	69 ± 8.73 57-100	68.7 ± 9.09 55-88

Treatment Summary

Treatment

Each patient was randomised to receive either 20mg temazepam or placebo as premedication together with one of the following five remifentanil dose regimens:

Rate: Zero Order IV Infusion, Infused for 1 minute plus continuous infusion

2mcg/kg bolus + 0.05mcg/kg/min continuous infusion (Treatment Group = A)
4mcg/kg bolus + 0.1mcg/kg/min continuous infusion (Treatment Group = B)
6mcg/kg bolus + 0.25mcg/kg/min continuous infusion (Treatment Group = C)
8mcg/kg bolus + 0.50mcg/kg/min continuous infusion (Treatment Group = D)
10mcg/kg bolus + 1.0mcg/kg/min continuous infusion (Treatment Group = E)

Lot # CS-USA10007

Sample Strategy

Venous Blood Samples: Prior to induction (baseline), induction +2min, intubation, incision, termination of infusion, infusion termination + 1min, infusion termination + 2min, infusion termination + 4min, infusion termination + 6min and infusion termination + 10min.

Assay Method
Remifentanil: HPLC with UV absorbance detection

Sample	Sensitivity	Site	%CV (QC Conc)	QC Range
Remifentanil Venous Blood	1 ng/mL	Glaxo	2.58% (160ng/ml) -6.18% (3ng/ml)	3-160ng/ml

Labeling Claims From Study: Temazepam premedication had no effect on the venous pharmacokinetics of remifentanil when assessed by nonlinear mixed effects modeling. However, temazepam was found to increase the sensitivity of remifentanil by 2-3 fold for loss of consciousness

Study USA-205 (USA-P05, GGN/94/008) Double-blind - Remifentanil with Pre-operative Benzodiazepines

Conclusions: Loss of consciousness (LOC) was achieved in some, but not all patients with remifentanil boluses and continuous infusions from 4mcg/kg + 0.1mcg/kg/min to 10mcg/kg + 1mcg/kg/min. Remifentanil 6mcg/kg + 0.25mcg/kg/min or greater in combination with 0.5MAC isoflurane in oxygen provided stable anesthesia during intubation, skin incision and maintenance. Temazepam (20mg) premedication did not significantly affect responses to skin incision but increased the sensitivity to remifentanil by approximately 2.5 fold for LOC. All patients achieved adequate respiration and were extubated and responding to command within 13 minutes following remifentanil discontinuation. Temazepam had no effect on the pharmacokinetics of remifentnail.

Investigators:

Purpose: To investigate the effect of benzodiazepine premedication on induction, maintenance and recovery from anesthesia with remifentanil.

Study Design: Double-blind, randomized study in patients having elective inpatient surgery.

Demographics: 120 patients, aged 19-65 years, ASA status I and II, male and female

Anesthesia Protocol: *Premedication*: Temazepam 20mg or placebo. *Induction*: Patients received a bolus dose of remifentanil followed by a continuous infusion for five minutes to assess LOC. Propofol and succinylcholine were then given and intubation performed. *Maintenance:* 0.5MAC isoflurane plus remifentanil infusion, isoflurane adjusted to patient need. Remifentanil doses: 2mcg/kg (bolus) + 0.05mcg/kg/min (infusion), 4mcg/kg + 0.1mcg/kg/min, 6mcg/kg + 0.25mcg/kg/min, 8mcg/kg + 0.5mcg/kg/min and 10mcg/kg + 1mcg/kg/min.

Results: **Table 1. Principal PK and PD Parameters (N=88)**

Values are Population Mean (Based upon venous blood sampling)

	Premedication: Placebo	Premedication: Temazepam
Remifentanil		
CL (mL/min/kg)	58.3	No Change
V_1 (mL/kg)	68	No Change
V_{ss} (mL/kg)	983	No Change
$EC_{50\,LOC}$ (ng/mL)	23.4	8.60

All patients showed a rapid recovery of respiratory function following discontinuation of the remifentanil infusion. In the placebo groups 100% of patients achieved adequate respiration (>8 breaths/min) with 10 minutes of discontinuation of remifentanil infusion. In the temazepam patients, the percentage of patients achieving adequate respiration within 10 minutes decreased with increasing remifentanil dose. The most common adverse events were bradycardia, hypotension, muscle rigidity and nausea. Six serious adverse events were reported.

USA-226
Pharmacokinetic Study Summary

NDA # 20-630 Submission Date: 9/15/95 Volume 168/169

Investigator:
Site:

Single Dose:____ . Multiple Dose: X
Subjects: Normal: ___. Patients: X . Young: X.
Elderly:___.
Hepatic:___. Renal: ___.
Cross-Over:___. Parallel: X. N= 55 M= 34 F= 21

Subject Type: ASA I-II patients scheduled for elective orthopedic arthroscopic surgery; age 18-50 years

	Target Propofol Concentration Group		
Category	1 mcg/mL	2 mcg/mL	4 mcg/mL
Gender: Female	6	8	7
Male	15	9	10
Age- Years Mean	34.2 ±8.5	33.8 ± 8.3	37.5 ± 8.1
Range	(19-49)	(23-50)	(23-50)
Weight- Kg Mean	82.3 ± 12.5	83.1 ± 16.1	83.7 ± 13.2
Range	(57-104)	(54-122)	(60-104)

Treatment Summary:

Propofol: Computer-assisted continuous infusion (CACI) to a target concentration of 1, 2, or 4μg/mL
Remifentanil administered based on Dixon Up/Down Method (Lot # CS-USA10008)

Sample Strategy:

Blood Samples: Arterial samples were collected immediately before intubation and skin incision, for each response occurring after skin incision, and every 10min intraoperatively before each infusion rate decrease.

Assay Method:

Remifentanil was assayed using reversed phase HPLC with UV detection at Glaxo Research Institute
Interday QC %CV ranged from 8.6% (0.3ng/mL) to 4.17% (160ng/mL); QC range = 0.3-160ng/ml
Propofol was assayed using HPLC at Triangle Laboratories (as a result of sample stability, no propofol concentrations were evaluable)

Pharmacodynamic Measurements:

Response to endotracheal intubation, skin incision, and intraoperative stress

Pharmacokinetic/Pharmacodynamic Analysis:

Logistic regression analysis was used to evaluate the interaction between propofol and remifentanil for ablating the response to intubation, skin incision, and intraoperative stress. Remifentanil clearance was estimated using the remifentanil infusion rate and steady-state concentration

Labeling Claims From Study: Remifentanil and propofol show a synergistic interaction The clearance of remifentanil is not altered in the presence of propofol

Study USA-226 - Interaction of Remifentanil and Propofol During Intubation and Skin Incision/Arthroscope Insertion for Orthopedic Outpatient Surgery

Conclusions: The combination of propofol and remifentanil showed a synergistic interaction. Increasing doses of remifentanil from 0.05mcg/kg/min to 0.2mcg/kg/min achieved four-fold reductions in propofol requirements to blunt patient response to trocar insertion and skin incision. The clearance of remifentanil (25-35mL/min/kg) was consistent with results from previous studies and was not altered by the infusion of propofol.

Investigator:

Purpose: 1) to determine ED_{50}/EC_{50} of remifentanil for lack of response to intubation and skin incision at three target propofol concentrations; and 2) to determine safety and efficacy for analgesic infusion rates of remifentanil in the postanesthesia care unit setting.

Study Design: Formal study (Part 2): open label, randomized, parallel-group, controlled study using the Dixon up/down method to determine remifentanil infusion rates.

Demographics: The safety population was 55 male and female patients (10 pilot patients, 45 patients in the randomized study) who were ages 18-50 years, ASA status I/II, and had elective orthopedic arthroscopic surgery. Two patients withdrew from the study due to CACI pump malfunction (one patient in part 1 and one in part 2 of the study).

Anesthesia Protocol: *Premedication*: None. *Induction:* Patients were randomized to receive one of three target propofol concentrations. After a bolus dose of 2mg/kg, propofol was administered by a computer assisted continuous infusion (CACI) device to obtain target propofol concentrations of 1, 2, or 4μg/mL. Patients were assigned a starting remifentanil infusion rate within each propofol group based on the Dixon up/down method. *Maintenance:* After stabilization following intubation, the remifentanil infusion was discontinued for 1 minute, then restarted at a lower infusion rate and maintained for at least 8 minutes before skin incision.

Results: **Table of Principal Efficacy and Pharmacokinetic Results**

Values are Mean (sd)

	Target Propofol Concentration		
	1μg/mL	2μg/mL	4μg/mL
ED_{50} (mcg/kg/min) Intubation	0.44	0.18	0.07
EC_{50} (ng/mL) Intubation	14.3	4.5	1.4
ED_{50} (mcg/kg/min) Incision	0.19	0.11	0.06
EC_{50} (ng/mL) Incision	8.8	4.2	2.0
EC_{50} (ng/mL) Intraoperative Stress	10.9	5.7	2.3
Clearance (mL/min/kg)	25.5 (8.2)	34.2 (10.9)	29.2 (6.6)

Report No. UCR/94/007
Protocol USA-203

USA-203
Pharmacokinetic Study Summary

NDA # 20-630 Submission Date: 9/15/95 Volume 113-116

Investigator:
Site:

Single Dose: X Multiple Dose: ____
Subjects: Normal ___ Patients: X Young: X Elderly: ___
Hepatic ___ Renal ___
Cross-Over: ___ Parallel: X N = 47 M = 28 F = 19

Subject Type: Patients, ASA I-II, scheduled for elective inpatient surgery

	Remifentanil Dose Group (mcg/kg)								
	2 (N=5)	3 (N=5)	4 (N=5)	5 (N=5)	6 (N=5)	8 (N=5)	10 (N=5)	15 (N=5)	20 (N=5)
Male Female	2 (40%) 3 (60%)	4(80%) 1(20%)	3(60%) 2(40%)	3(60%) 2(40%)	2(33%) 4(67%)	4(80%) 1(20%)	3(60%) 2(40%)	4(67%) 2(33%)	3(60%) 2(40%)
Age Mean (yrs) Range	49.4±10.6 (38-64)	51.2±12.8 (34-63)	42.4±7.4 (33-52)	37.8±13.7 (21-56)	47.8±17.2 (22-64)	48±13 (34-60)	51.6±7.5 (45-63)	50±13 (37-64)	44.4±22.1 (20-65)
Wt Mean (kg) Range	70.6±23.1 (51-97.5)	75.4±10.9 (64.6-88.8)	73.8±15.2 (50.5-89.3)	74.3±16.1 (59.4-97.7)	77.8±6.7 (67.3-87.7)	86.7±10.5 (68.9-96.8)	77.8±16.7 (54.6-91)	84.5±11.7 (70.5-100.4)	66.9±5.7 (60.4-75)

	Alfentanil Dose Group (mcg/kg)						
	40 (N=5)	60 (N=5)	80 (N=5)	100 (N=5)	120 (N=5)	160 (N=5)	200 (N=10)
Male Female	2 (40%) 3 (60%)	4(80%) 1(20%)	2(40%) 3(60%)	4(67%) 2(33%)	3(40%) 2(60%)	4(80%) 1(20%)	6(60%) 4(40%)
Age Mean (yrs) Range	37.2±9.8 (28-51)	32.[illegible]±12.4 (22-52)	52.6±13.9 (30-65)	45.5±12.7 (23-59)	52.8±6.3 (48-63)	44.2±19.3 (20-61)	40.6±13.8 (20-65)
Wt Mean (kg) Range	74±14.4 (60.5-91)	79.2±9.3 (70-93)	66.9±9.7 (57.3-80)	79.2±10.1 (69.3-94.6)	75.7±9.4 (64-86)	70.6±17.9 (47.1-95.4)	76±15.4 (41.4-96.9)

Treatment Summary

Remifentanil, 2-minute IV Infusion at 2, 3, 4, 5, 6, 8, 10, 15, and 20µg/kg/min x 2 minutes
Lot # CS-USA10008

Alfentanil, 2-minute IV Infusion at 40, 60, 80, 100, 120, 160, and 200µg/kg/min x 2 minutes

Sample Strategy

Blood samples for remifentanil, its principle metabolite GR90291, and alfentanil were obtained prior to study drug administration, 30 seconds after the end of the study drug infusion, immediately prior to endotracheal intubation, at 3, 5, 10, 20, 30, 45, 60 minutes post endotracheal intubation, and at skin incision.

Assay Method
Remifentanil: GC-High Resolution Mass Spectrometry-Selected Ion Monitoring
GR90291: GC/Tandem Mass Spectrometry
Alfentanil: GC-High Resolution Mass Spectrometry-Selected Ion Monitoring

Sample	Sensitivity	Site	%CV (QC Conc)	QC Range
Remifentanil Blood	0.1 ng/mL		2.4% (20ng/ml) -10.9% (0.2ng/ml)	0.2-80ng/ml
GR90291 Blood	0.5ng/mL		7.7% (100ng/ml) -17.9% (2ng/ml)	1.5-75ng/ml
Alfentanil	1ng/mL		4.9% (500ng/ml) - 9.6% (25ng/ml)	2.5-2500ng/ml

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Labeling Claims From Study: Remifentanil produced synergistic, dose-related reductions in thiopental dosage requirements for loss of consciousness. Thiopental did not alter the pharmacokinetics of remifentanil.

Study USA-203 - Remifentanil vs Alfentanil for Anesthesia Induction

Conclusions: The ED_{50} and EC_{50} values for loss of consciousness (LOC) for remifentanil and alfentanil were 12μg/kg and 169μg/kg, and 54ng/mL and 1012ng/mL, respectively. Both remifentanil and alfentanil produced a high incidence of muscle rigidity at the doses required for LOC. Remifentanil and alfentanil demonstrated a dose-relationship with the thiopental dose required for LOC. The clearance and volume of distribution of remifentanil and alfentanil were independent of patient demographics (weight, gender, age, ASA status) in this study and were similar to values previously reported.

Investigators:

Purpose: (1) To compare R and A as primary anesthesia induction agents and (2) to establish a dose-response curve for remifentanil in the induction of anesthesia.

Study Design: Two-center, randomized, double-blind, dose escalation study of remifentanil and alfentanil in patients scheduled for elective inpatient surgery.

Demographics: 88 male and female patients, ages 18-65 years, ASA status I/II.

Anesthesia Protocol: *Premedication*: None. *Induction:* Two-minute infusion of R (2, 3, 4, 5, 6, 8, 10, 15 or 20mcg/kg) or A (40, 60, 80, 100, 120, 160, or 200mcg/kg) after preoxygenation and administration of D-tubocurarine. If no LOC occurred within 30 seconds after the infusion, thiopental 2mg/kg/min was given until LOC. If LOC occurred with study drug alone, a nasopharyngeal airway (NAI) was inserted. Responses to NAI were treated with thiopental. Succinylcholine was given after the study drug infusion and intubation was done 1 minute later. *Maintenance:* 66% nitrous oxide in oxygen and isoflurane.

Results: Principal Pharmacokinetic, Efficacy, and Safety Results

Parameter	Remifentanil	Alfentanil
ED_{50} LOC (μg/kg)	12 (9-22)	169 (122-434)
EC_{50} LOC (ng/mL)	54 (35-118)	1012 (712-9149)
V_1 (L)	2.05	1.65
V_2 (L)	3.69	6.89
V_3 (L)	7.48	18.3
CL (L/min)	2.46	0.415
CL_2 (L/min)	1.41	2.21
CL_3 (L/min)	0.380	0.781

The most common adverse events were muscle rigidity, nausea, and vomiting. Muscle rigidity was dose-related in both R and A groups. The median times to muscle rigidity were 1.0 to 5.0 min after starting the study opioid infusion. No serious adverse events or deaths occurred during the study treatment period.

Study USA-207 (GGN/93/006)
Pharmacokinetic Summary

NDA # 20-630 Submission Date: 9/15/95 Volume 74/75

Investigator:
Site:

Single Dose: XXX . Multiple Dose: ____.

Subjects:
Normal: ___. Patients: XXX Young: ___. Elderly: ___.
Impaired Hepatic: ___. Renal: ___.

Cross-Over: ___. Parallel: ___. N= 16 M= 12 F= 4

Subject Type: Male and Female Patients Scheduled for Elective Cardiopulmonary Bypass Surgery

	Remifentanil (mcg/kg)	
	2	5
N	9	8
Gender male/female	7/2	6/2
Age (yrs)	55 ± 6.3 (48-62)	60 ± 6.93 (48-70)
Weight (kg), Males	77.86 ± 10.84 (68-98.4)	80.85 ± 5.7 (73-90.5)
Weight (kg), Females	72.2 ± 8.2 (66.4-78)	69.25 ± 15.2 (58.5-80)

Treatment Summary

Treatment
Remifentanil, Zero Order IV Infusion, Infused for 1 minute.
Rate: 2 µg/kg/min or 5 µg/kg/min remifentanil was administered over one minute to 8 patients prior to bypass, during bypass and during rewarming.

Lot # CS-USA10007

Sample Strategy:

Arterial Blood Samples: Prior to dosing, at the end of infusion (1min), and at 2, 3, 4, 5, 10, 15, 20, and 30, minutes after the start of the infusion prior to bypass and during rewarming. During hypothermic bypass, an additional sample was drawn at 40 minutes after the start of the infusion.

Assay Method:
Remifentanil (blood/urine): GC-High Resolution Mass Spectrometry-Selected Ion Monitoring
GR90291 (blood): GC with mass selective detection (GC-MSD)

Sample	Sensitivity	Site	%CV (QC Conc)	QC Range
Remifentanil Blood	0.1 ng/mL		4.6% (80ng/ml) -10.1% (0.25ng/ml)	0.25-80ng/ml
GR90291 Blood	0.5ng/mL		5.7% (75ng/ml) - 9.0% (1.5ng/ml)	1.5-75ng/ml

Labeling Claims From Study: The clearance of remifentanil was reduced by approximately 20% during hypothermic cardiopulmonary bypass when compared to pre-bypass (normothermic) values.

Study USA-207 (USA-P07, GGN/93/006) - Pharmacokinetics in Cardiac Bypass Patients

Conclusions: The pharmacokinetics of remifentanil during hypothermic cardiopulmonary bypass (CPB) showed reduced clearance (20%) compared to normothermic (pre-bypass) values. This observation was consistent with the expected effects of hypothermia. Falls in arterial blood pressure (14-25% from baseline) occurred during periods A (pre-bypass) and C (on bypass normothermia). No clinically relevant changes in blood pressure occurred during hypothermic bypass (Period B). There were no clinically relevant changes in heart rate at either the 2mcg/kg or 5mcg/kg doses. Dose escalation was halted after the completion of the 5mcg/kg dose group due to hypotension.

Investigators:

Purpose: 1) To evaluate the effect of cardiopulmonary bypass and/or hypothermia on the pharmacokinetics of remifentanil and GR90291 (major metabolite). 2) To assess the haemodynamic effects of remifentanil in patients undergoing coronary artery bypass graft surgery.

Study Design: Two center, open-label, dose escalation study in patients undergoing elective coronary artery bypass surgery.

Demographics: 17 male and female patients, ages 18-70 years

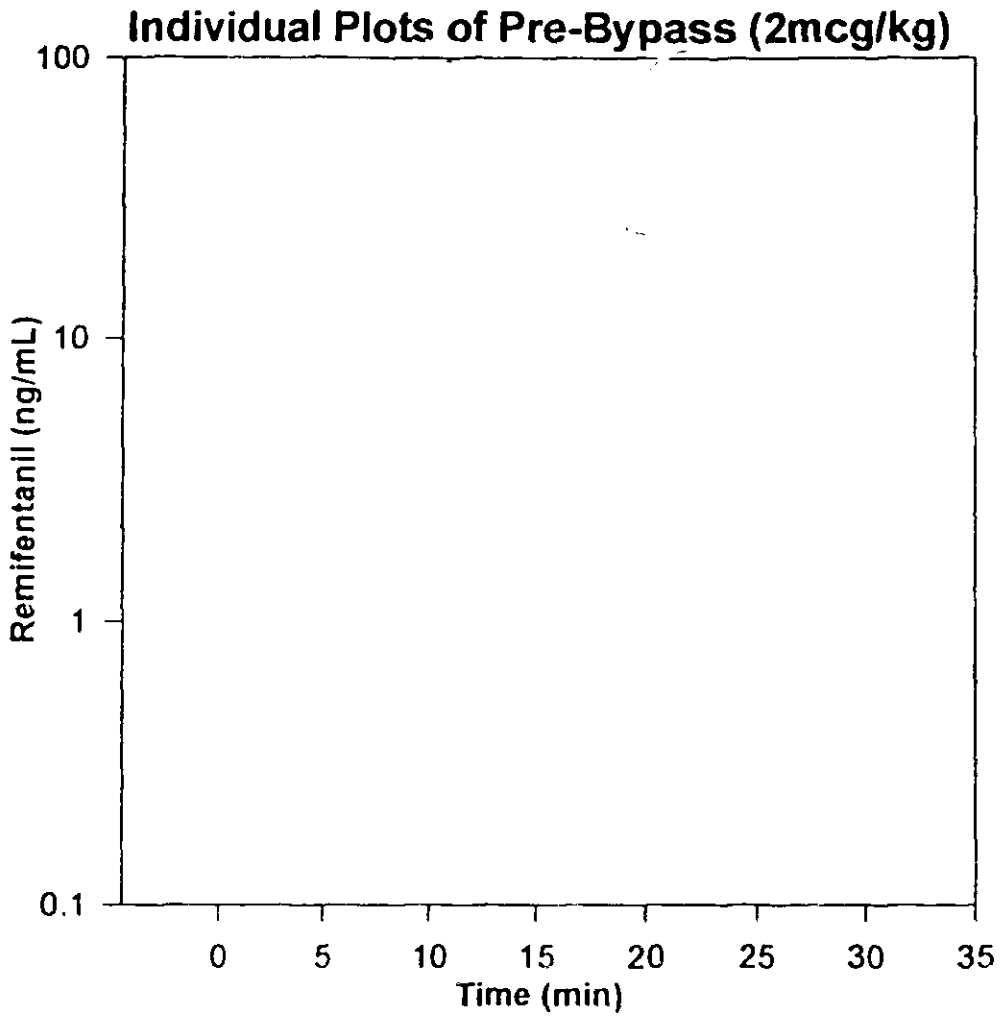
Anesthesia Protocol: Patients were given a standard anesthetic for CABG. Each received three IV remifentanil boluses over one minute: 1) pre-bypass and at normothermia (Period A), 2) on bypass at hypothermia (28°C) (Period B) and 3) on bypass at normothermia (Period C). Serial arterial blood samples were taken up to 40 minutes post-dosing. Four dose tiers of eight patients each were planned: 2mcg/kg, 5mcg/kg, 10mcg/kg, 20mcg/kg. Escalation to the next dose tier took place only if pre-defined safety parameters (blood pressure <30% below baseline, heart rate <45 beats/minute, or major safety issue, eg., ischemia) were not exceeded. The 2mcg/kg and 5mcg/kg dose tiers were the only dose tiers completed.

Results: Table 1. Principal Combined PK Parameters of 2 μg/kg and 5 μg/kg Remifentanil

Values are Mean ± SD

	Prior to Bypass	During Bypass	During Rewarming
Pharmacokinetics	N = 16	N=14	N = 10
Remifentanil			
CL (mL/min/kg)	31.48 (13.39)	25.17 (9.09)	34.79 (17.22)
V_1 (mL/kg)	60.59 (49.35)	86.27 (113.9)	88.70 (96.32)
V_{ss} (mL/kg)	176.6 (96.1)	328.8 (443.4)	246.1 (224.6)
λ_z $t_{1/2}$ (min)	6.43 (1.76)	11.86 (7.51)	7.23 (2.40)

Nausea and lymphopenia were the most commonly reported adverse events, however none were assessed as drug related. Two patients experienced a serious adverse event (cardiac failure and post-operative myocardial infarction). Both patients died, however, neither event was drug-related. No patient was withdrawn from the study.


Individual Plots of Pre-Bypass (2mcg/kg)
100
10
1
0.1
Remifentanil (ng/mL)
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5
10
15
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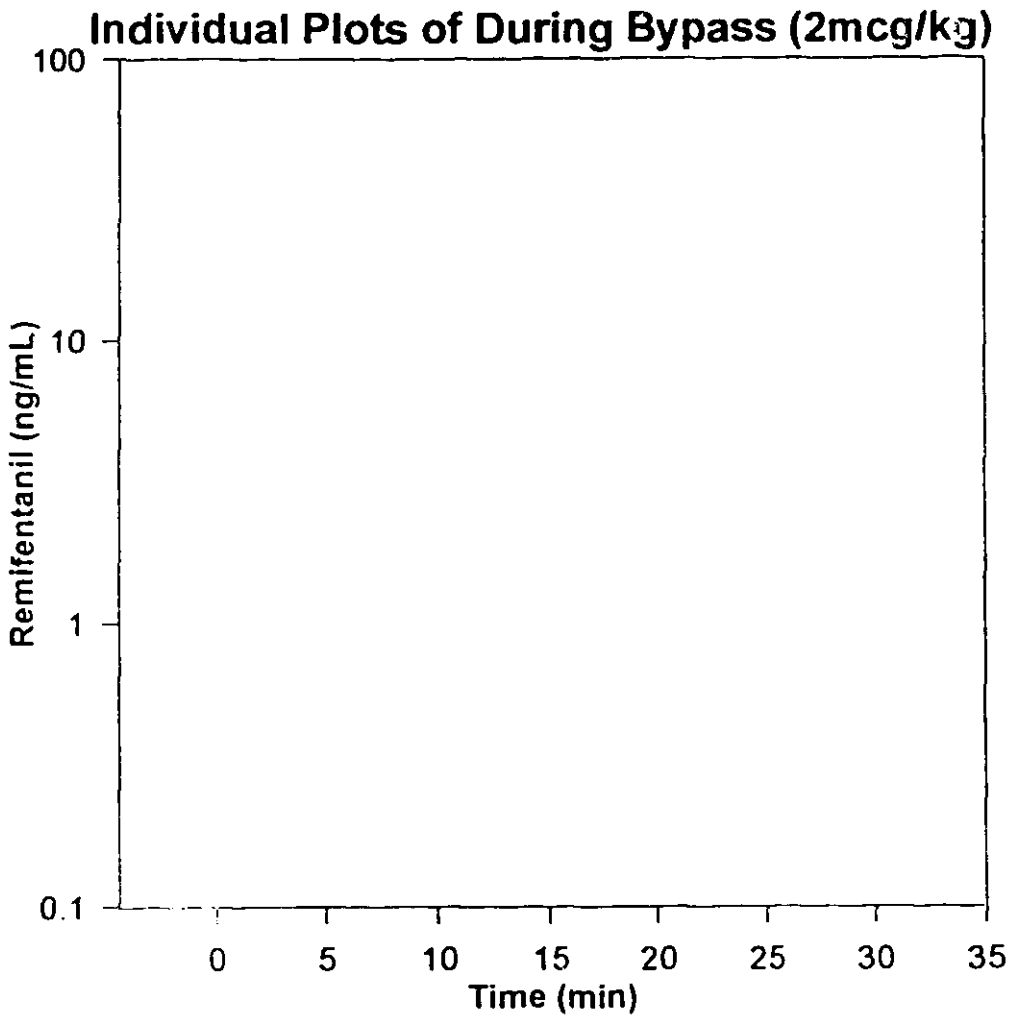
25
30
35
Time (min)


Individual Plots of During Bypass (2mcg/kg)
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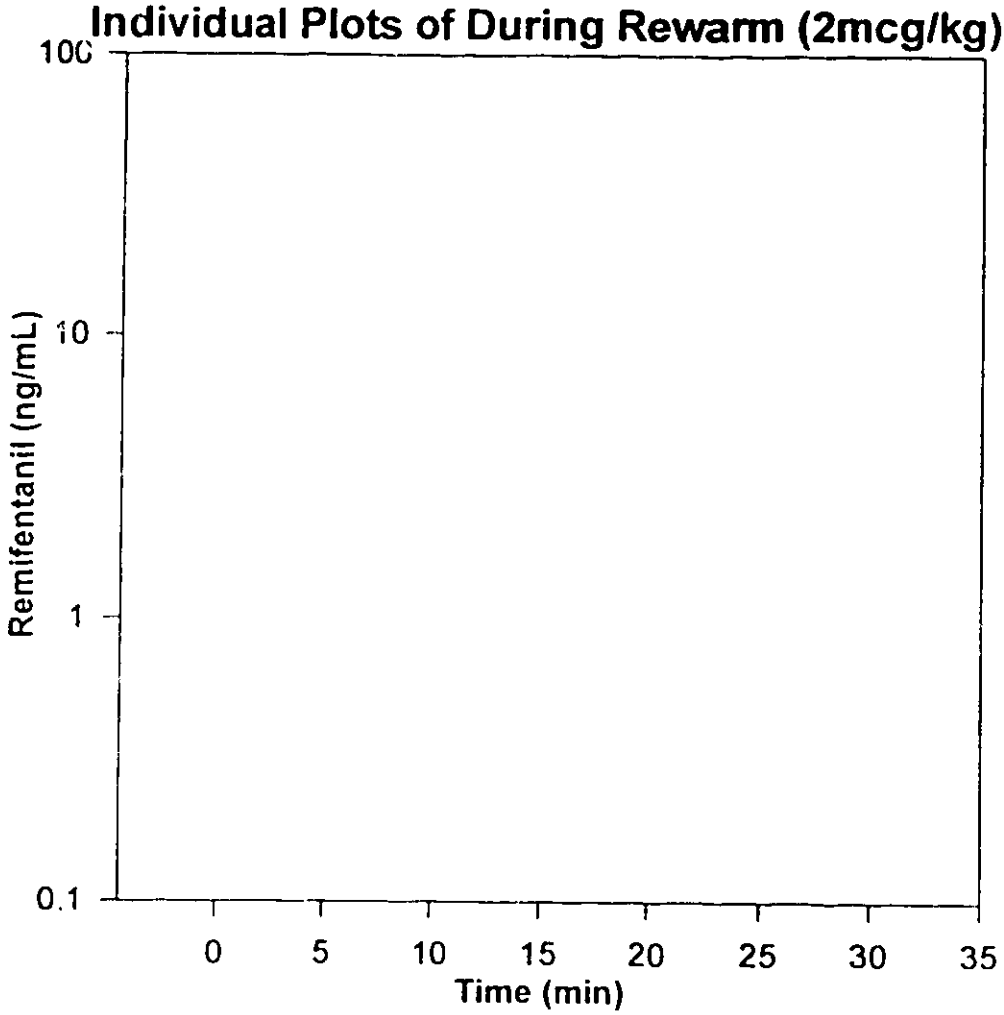
Remifentanil (ng/mL)
0
5
10
15
20
25
30
35
Time (min)


Individual Plots of During Rewarm (2mcg/kg)
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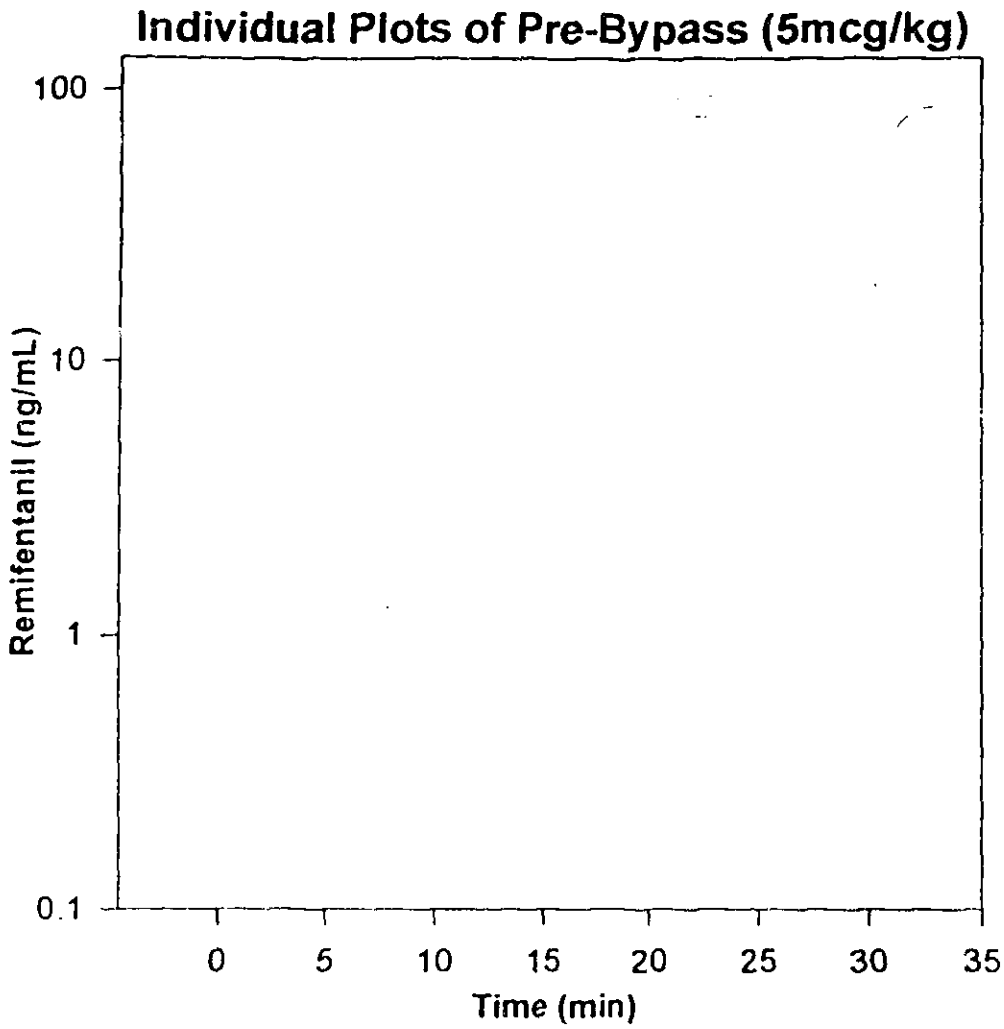
10
1
0.1
Remifentanil (ng/mL)
0
5
10
15
20
25
30
35
Time (min)


Individual Plots of Pre-Bypass (5mcg/kg)
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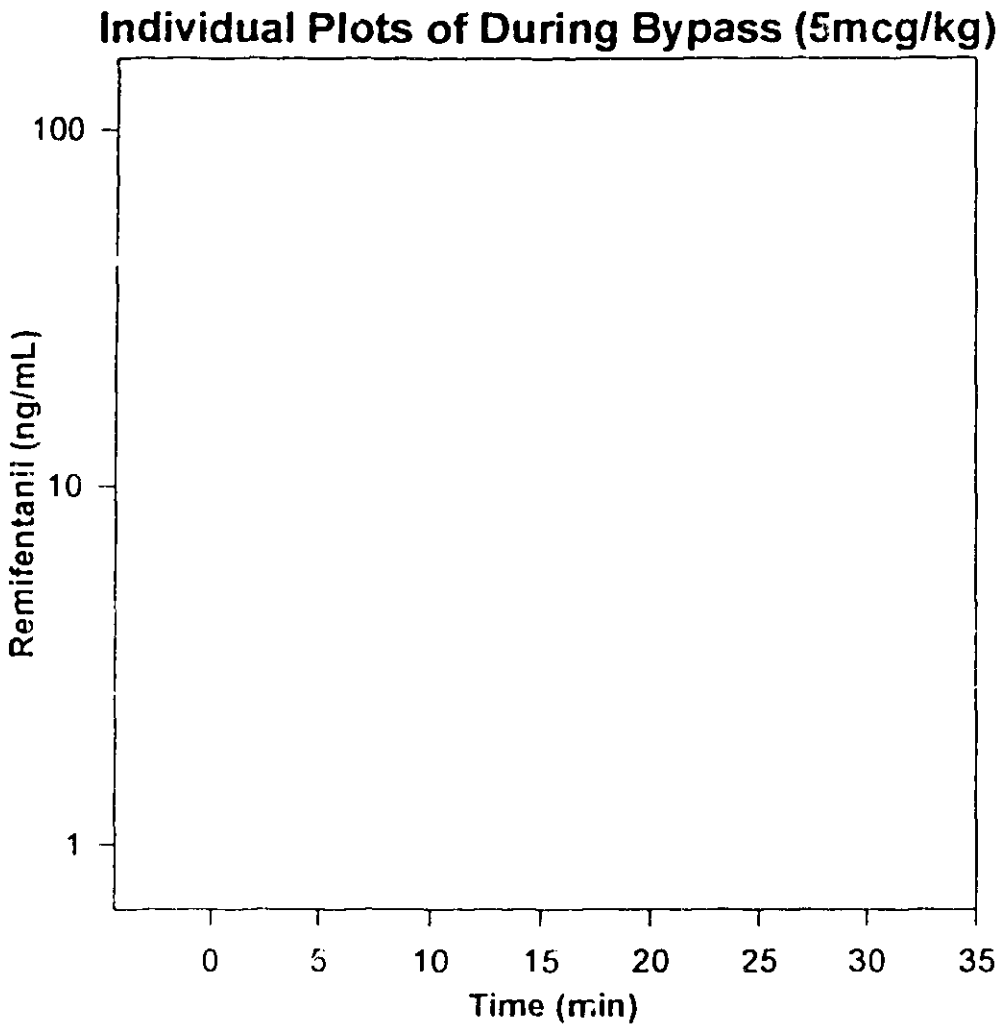
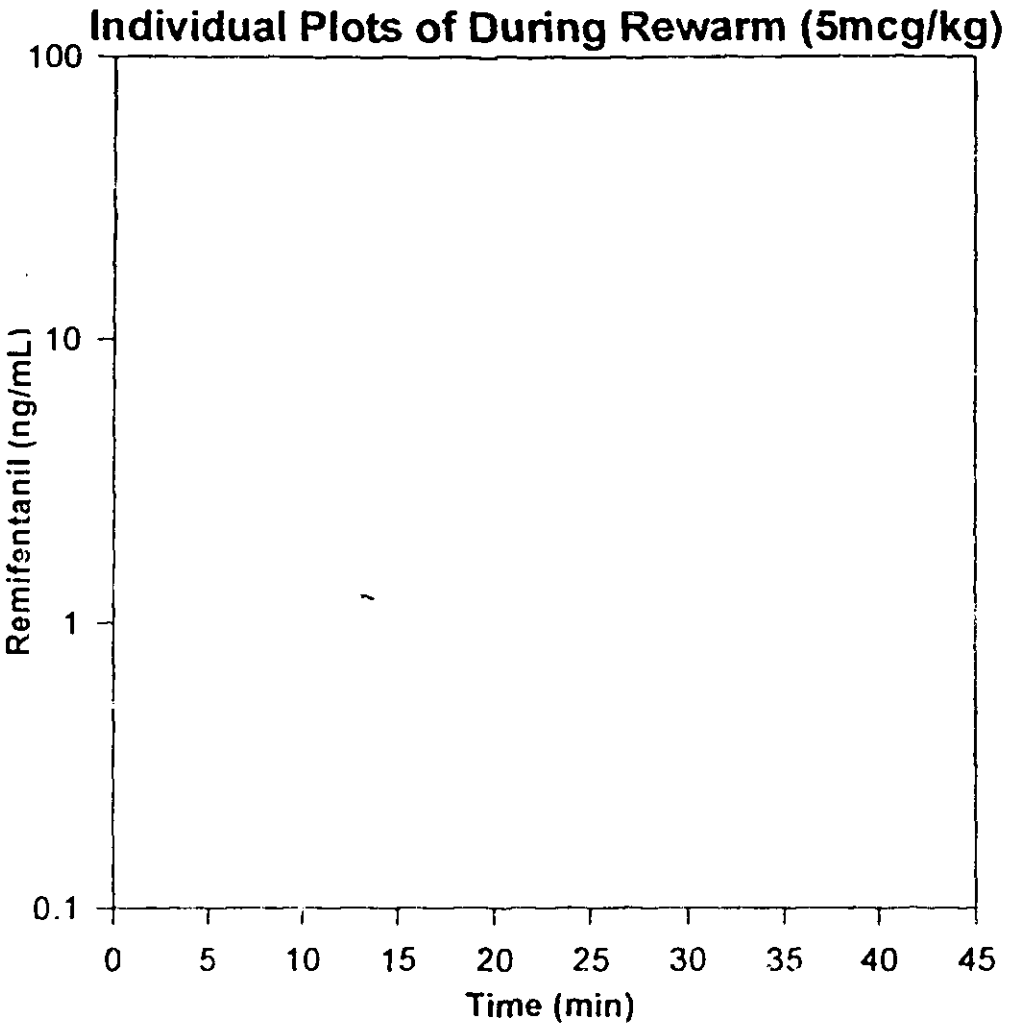
0.1
Remifentanil (ng/mL)
0
5
10
15
20
25
30
35
Time (min)


Individual Plots of During Bypass (5mcg/kg)
100
10
1
Remifentanil (ng/mL)
0
5
10
15
20
25
30
35
Time (min)


Individual Plots of During Rewarm (5mcg/kg)
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10
1
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Remifentanil (ng/mL)
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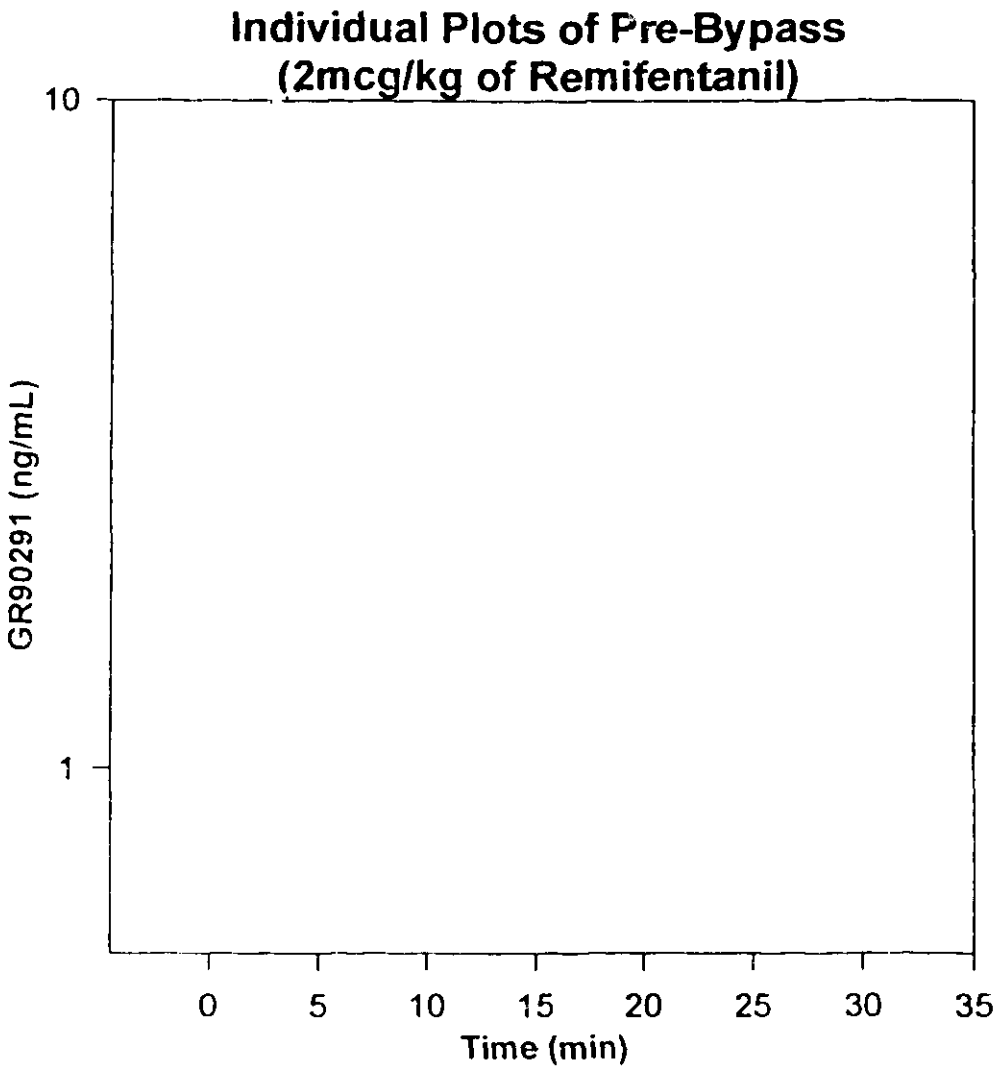
45
Time (min)


Individual Plots of Pre-Bypass
(2mcg/kg of Remifentanil)
10
1
GR90291 (ng/mL)
0
5
10
15
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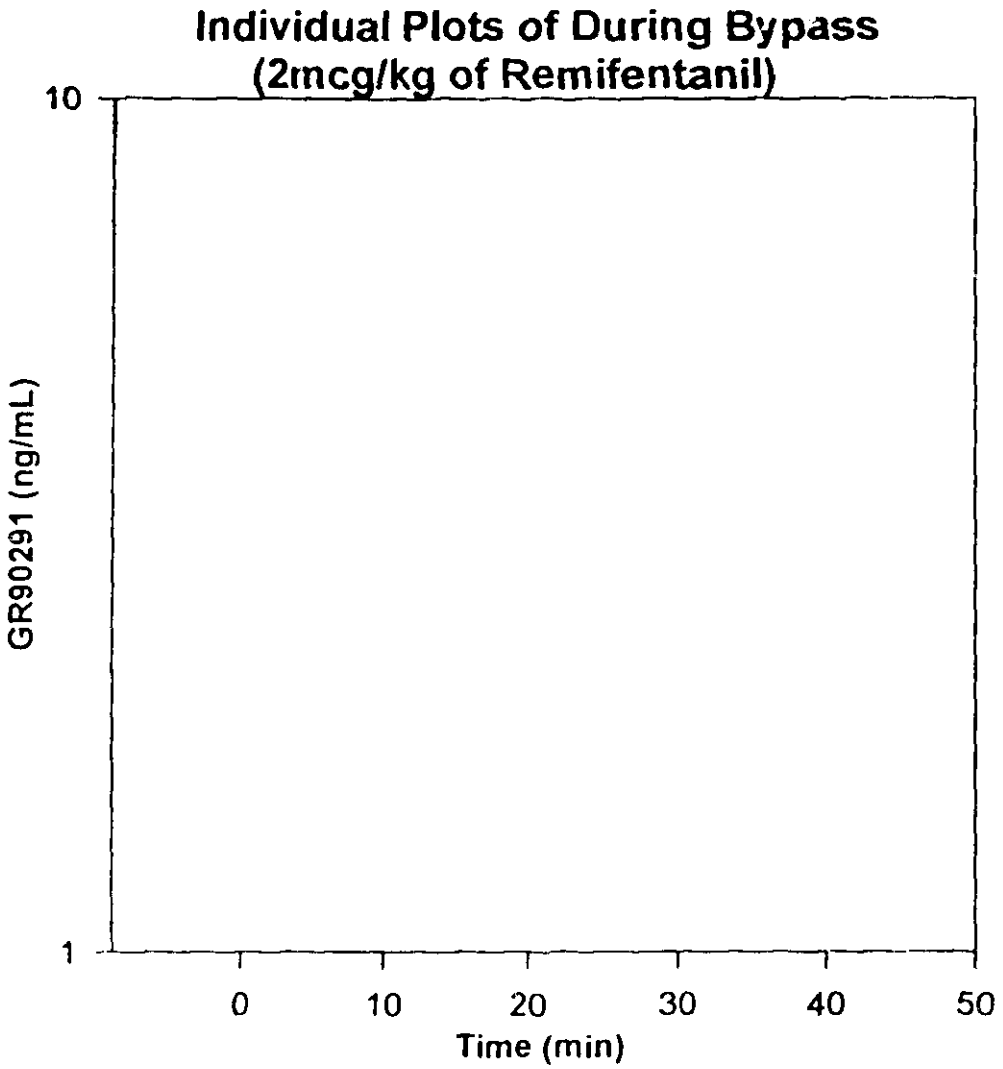
25
30
35
Time (min)


Individual Plots of During Bypass
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10
1
GR90291 (ng/mL)
0
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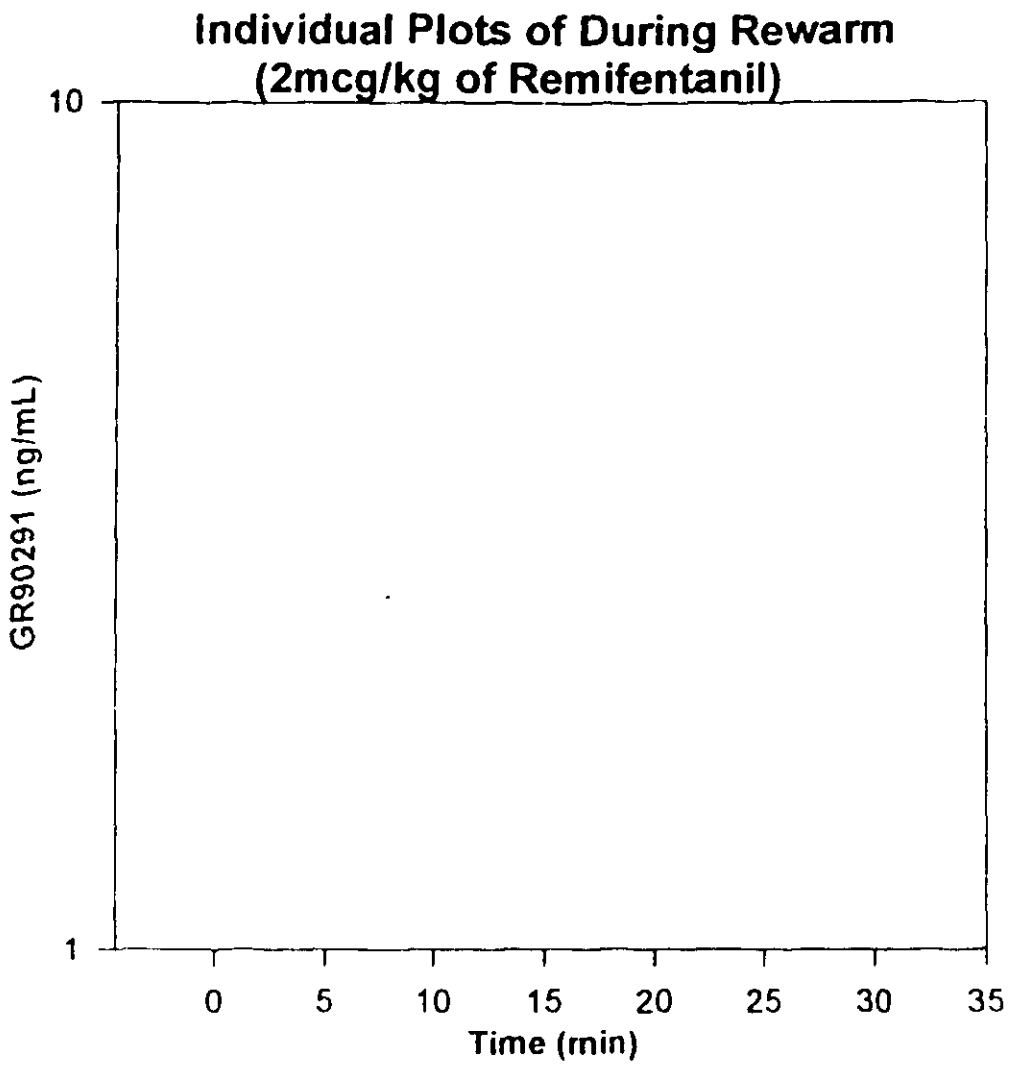
40
50
Time (min)


Individual Plots of During Rewarm
(2mcg/kg of Remifentanil)
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1
GR90291 (ng/mL)
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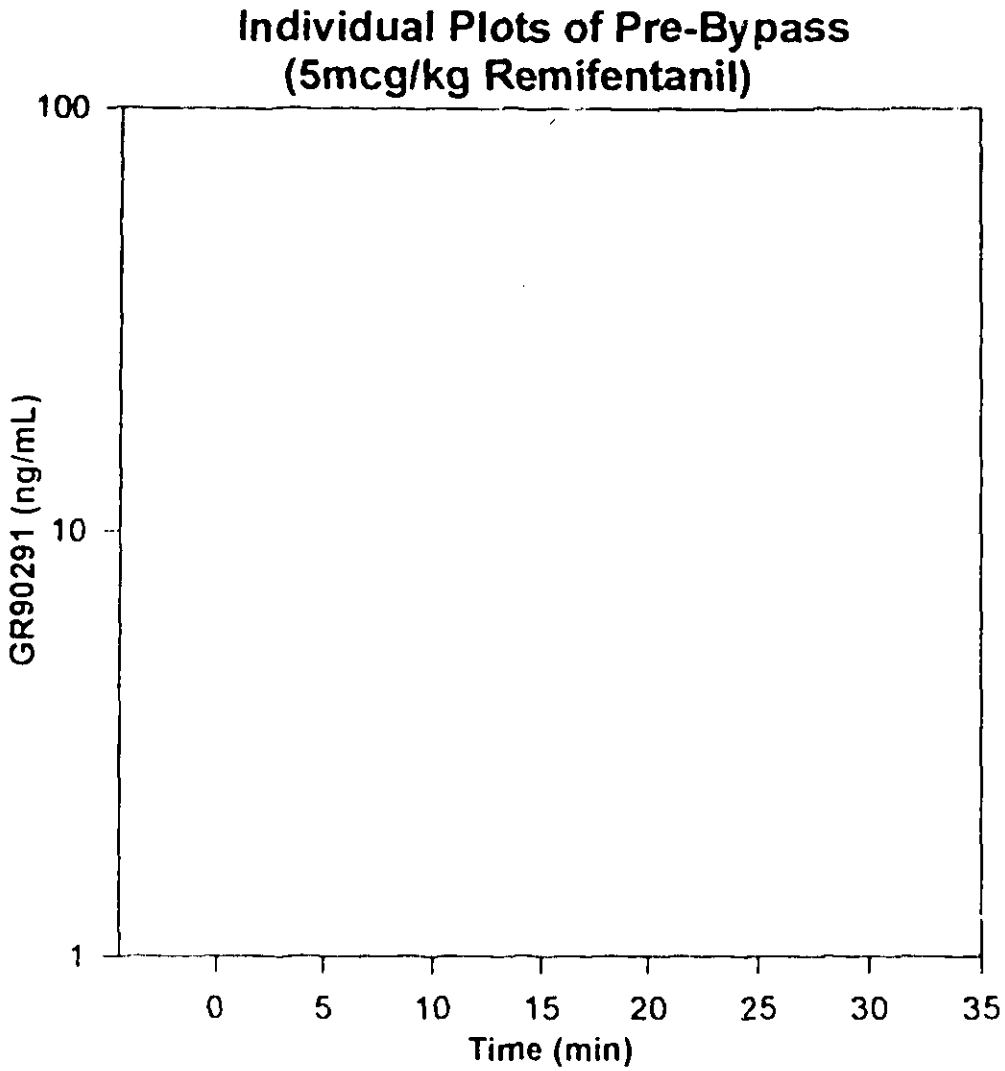
35
Time (min)


Individual Plots of Pre-Bypass
(5mcg/kg Remifentanil)
100
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GR90291 (ng/mL)
0
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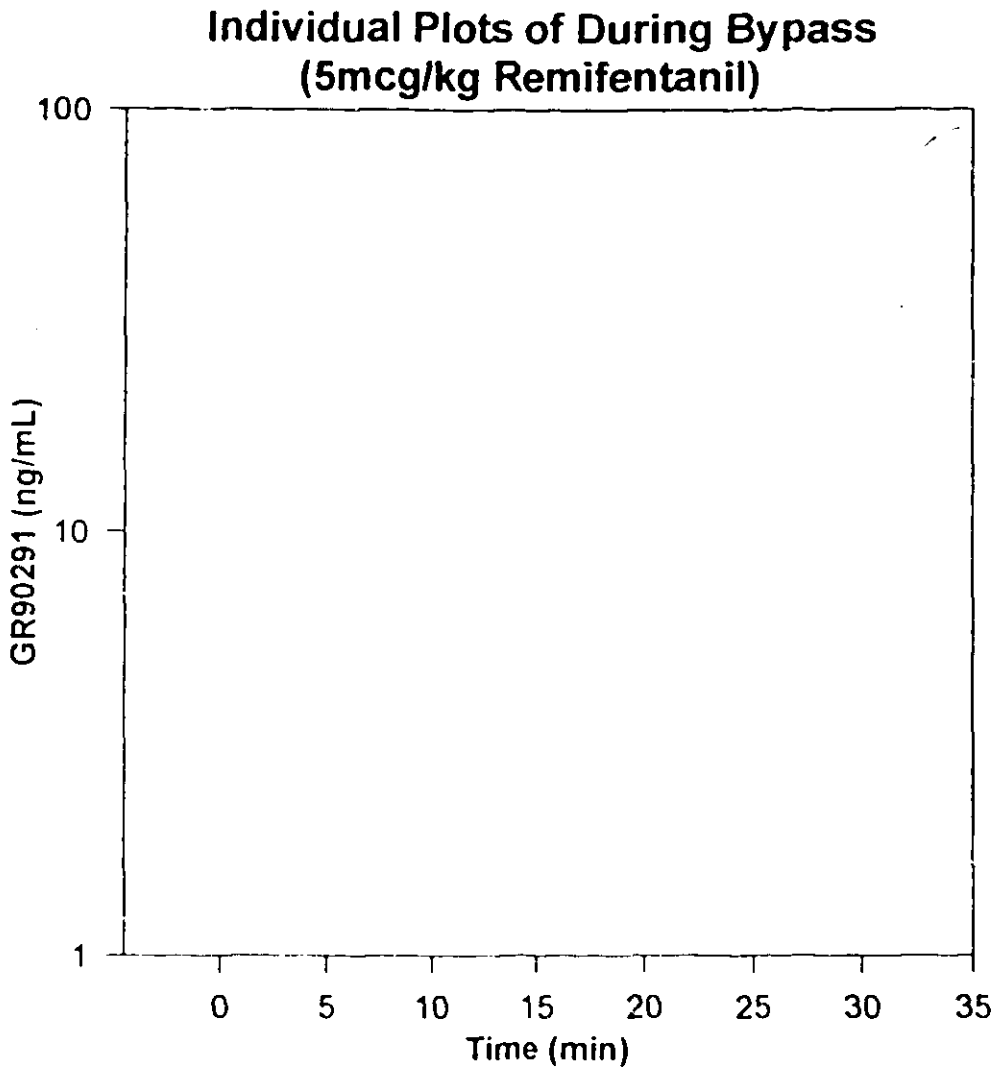
35
Time (min)


Individual Plots of During Bypass
(5mcg/kg Remifentanil)
100
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1
GR90291 (ng/mL)
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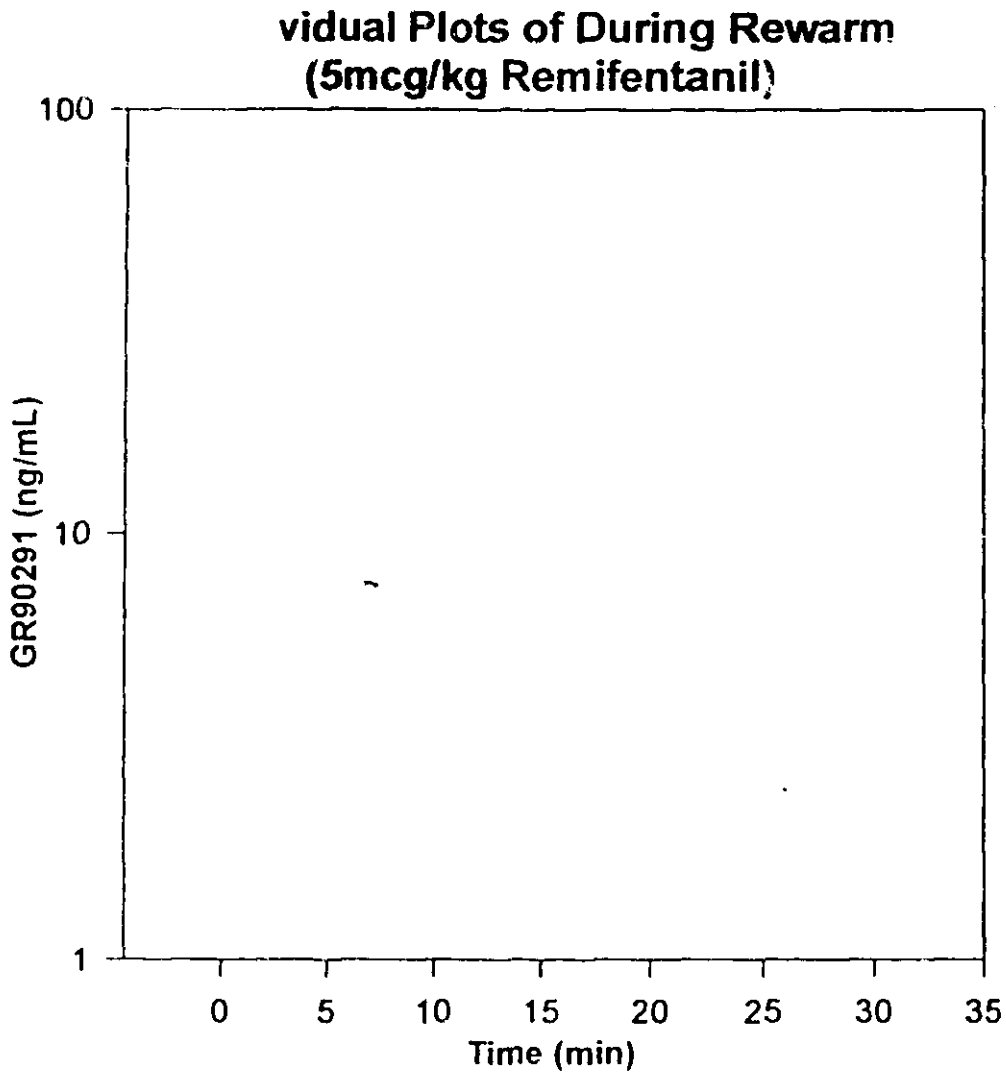
Time (min)


vidual Plots of During Rewarm
(5mcg/kg Remifentanil)
100
10
1
GR90291 (ng/mL)
0
5
10
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20
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30
35
Time (min)

USA-106
Pharmacokinetic Study Summary

NDA # 20-630 Submission Date: 9/15/95 Volume 69/70

Investigator:
Site:

Single Dose: X Multiple Dose: ___
Subjects: Normal: X Patients: ___ Young: X Elderly: ___
Hepatic: ___ Renal: ___
Crossover: X Parallel: ___ N= 26 M= 26 F= 0

Subject Type: Healthy Volunteers

N	26
Gender: male/female	26/0
Age (yrs)	23.4± 4.5 (19-35)
Weight (kg)	76.2 ± 10.6 (45-97)

Treatment Summary

Remifentanil Zero Order IV Infusion: 0.2mcg/kg/min x 10min

Pilot Phase: Route 1 synthesis given on two separate occasions (n=6)
Comparative Phase: Routes 1 and 2 given in a crossover fashion (n=20)

Route 1 Lot #: A92L559
Route 2 Lot #: A93L675

Sample Strategy:

Arterial blood samples were collected at baseline and at 2, 4, 6, 8, and 10 minutes during remifentanil administration. After the infusion, samples were collected at 1, 2, 4, 6, 8, 10, 15, 20, 25, 30, 35, 40, 50, and 60 minutes.

Assay Method

GC-High Resolution Mass Spectrometry

Sensitivity	Site	%CV (QC Conc)	QC Range
0.1 ng/mL	Triangle	4.5% (80ng/ml) - 7.4% (0.25ng/ml)	0.25 - 80 ng/ml

Labeling Claims From Study:

The pharmacokinetics of remifentanil prepared by route 1 and route 2 sythesis were equivalent.

Study 106 - Remifentanil Route 1 and Route 2 Comparative Pharmacokinetics Study

Conclusions: The geometric least squares mean ratio (and 90% confidence intervals) for AUC_∞, 0.92 (0.88-0.95) and C_{max}, 0.92 (0.86-0.98), were within the range of 0.80-1.2, indicating that the pharmacokinetics of route 1 and route 2 remifentanil were equivalent. Changes in mean systolic blood pressures, diastolic blood pressures, heart rate, respiratory rate and peripheral oxyhemoglobin saturation were similar between route 1 and 2 remifentanil. The dose of remifentanil administered produced respiratory slowing (less than 8 breaths per minute) in conscious, unstimulated voluteers.

Investigators:

Purpose: 1) to determine if the pharmacokinetics of remifentanil manufactured using route 2 synthesis were equivalent to that of remifentanil manufactured using route 1 synthesis.

Study Design: Open-label, randomized, two-period crossover study in 20 healthy, young, male subjects. Subjects received a 0.2mcg/kg/min infusion of route 1 (reference) or route 2 remifentanil over 10 minutes in a randomized fashion, with a 2-14 day washout period between treatments. The study also included a pilot phase (performed before the actual study, in order to estimate intra-subject variability for calculation of sample size) in which six subjects were administered route 1 remifentanil on two separate occasions.

Demographics: 26 healthy male subjects, ages 19-35 years

Anesthesia Protocol: Remifentanil (route 1 and/or route 2 formulation) was administered to conscious subjects as a 0.2mcg/kg/min intravenous infusion over ten minutes, via a syringe pump.

Results: **Table of Principle PK and Safety Results, All Subjects (N = 20)**
Values are N (% Total) or Geometric least squares means (95% confidence intervals)

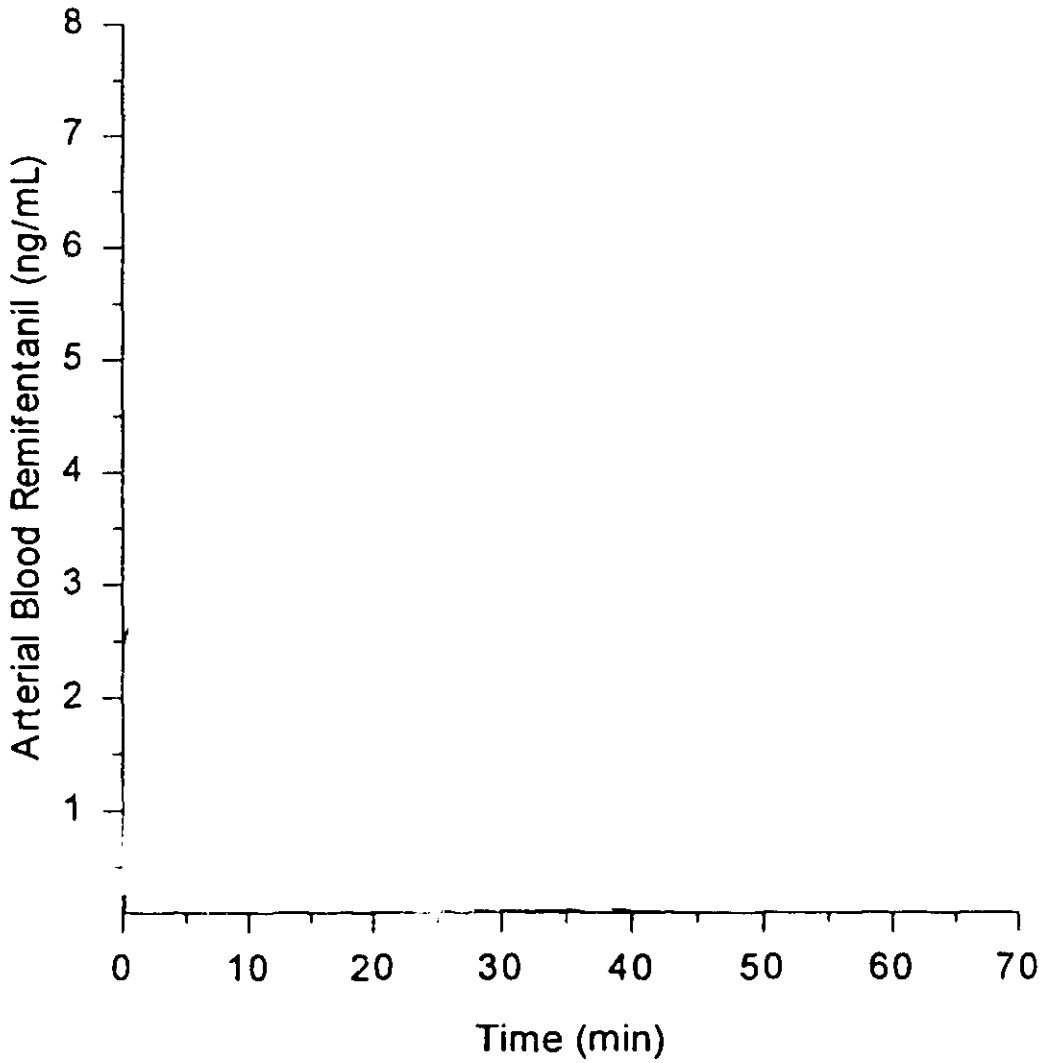
	Route 1 Remifentanil	Route 2 Remifentanil	P-Value
AUC_∞ (ng•min/mL)	55.6 (53.7 - 57.5)	50.9 (49.1 - 52.8)	0.0017
C_{max} (ng/mL)	5.14 (4.87 - 5.43)	4.72 (4.45 - 4.99)	0.0335
CL (mL/min/kg)[1]	36.4 (5.8)	39.9 (5.8)	-
Vd_{ss} (mL/kg)[1]	345 (45)	392 (93)	-
k_e $t_{1/2}$ (min)	6.58 (6.31 - 6.87)	6.77 (6.47 - 7.08)	0.3544
Safety	N=26	N=20	-
Any Adverse Event	25 (96%)	18 (90%)	-

[1] Mean (SD)

USA-106

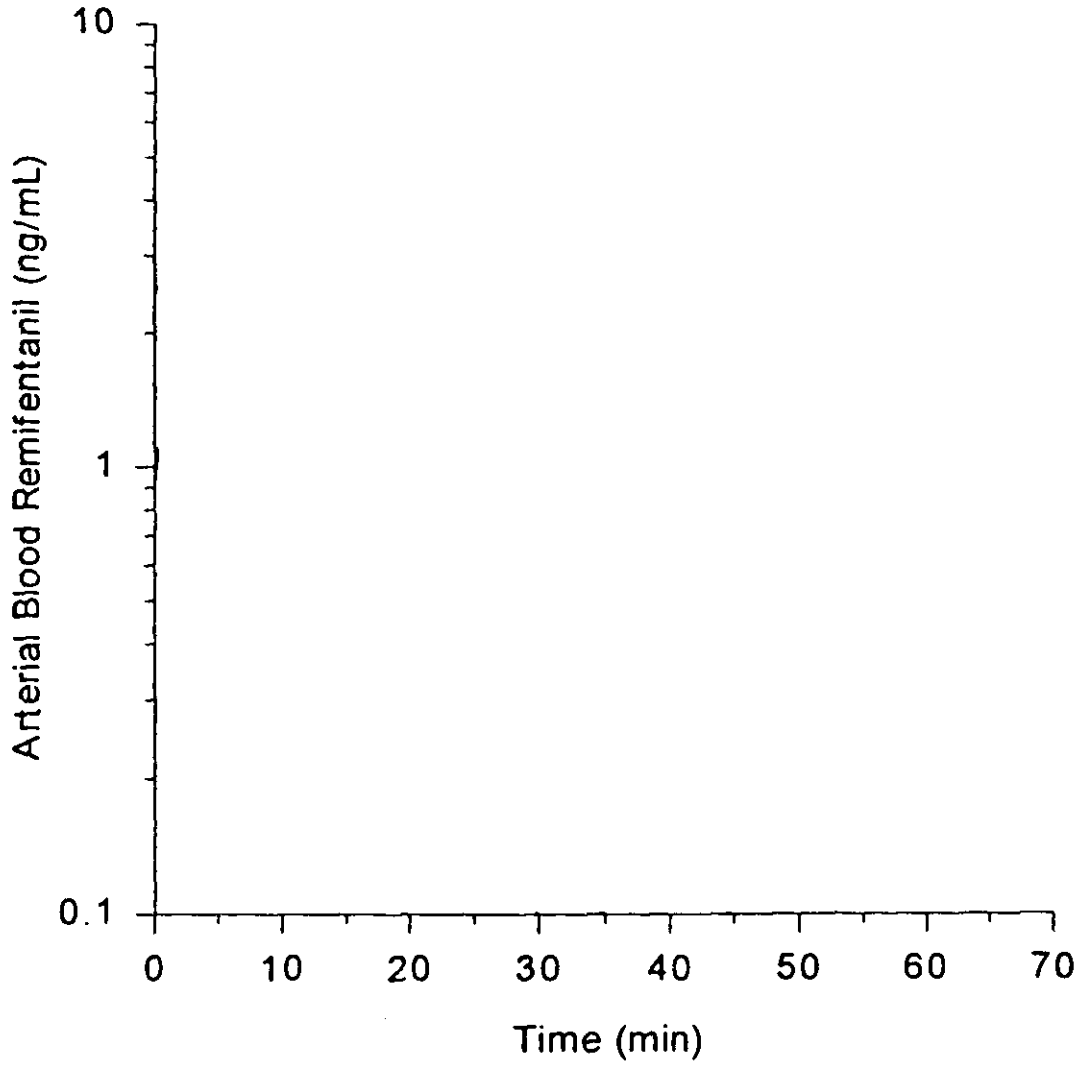
Route 1

Individual Arterial Blood Remifentanil Concentration-Time Profiles



USA-106

Route 1
Individual Arterial Blood Remifentanil
Concentration-Time Profiles



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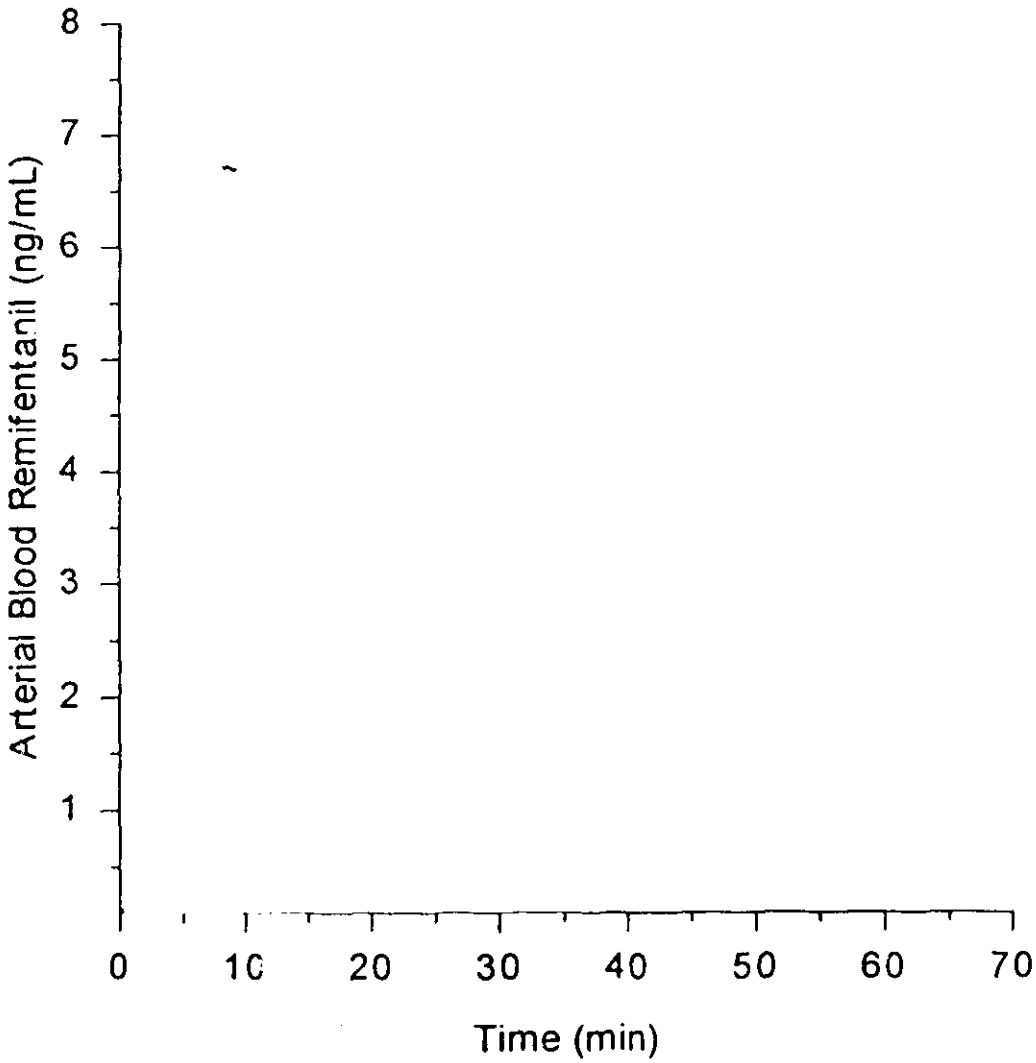
Route 2

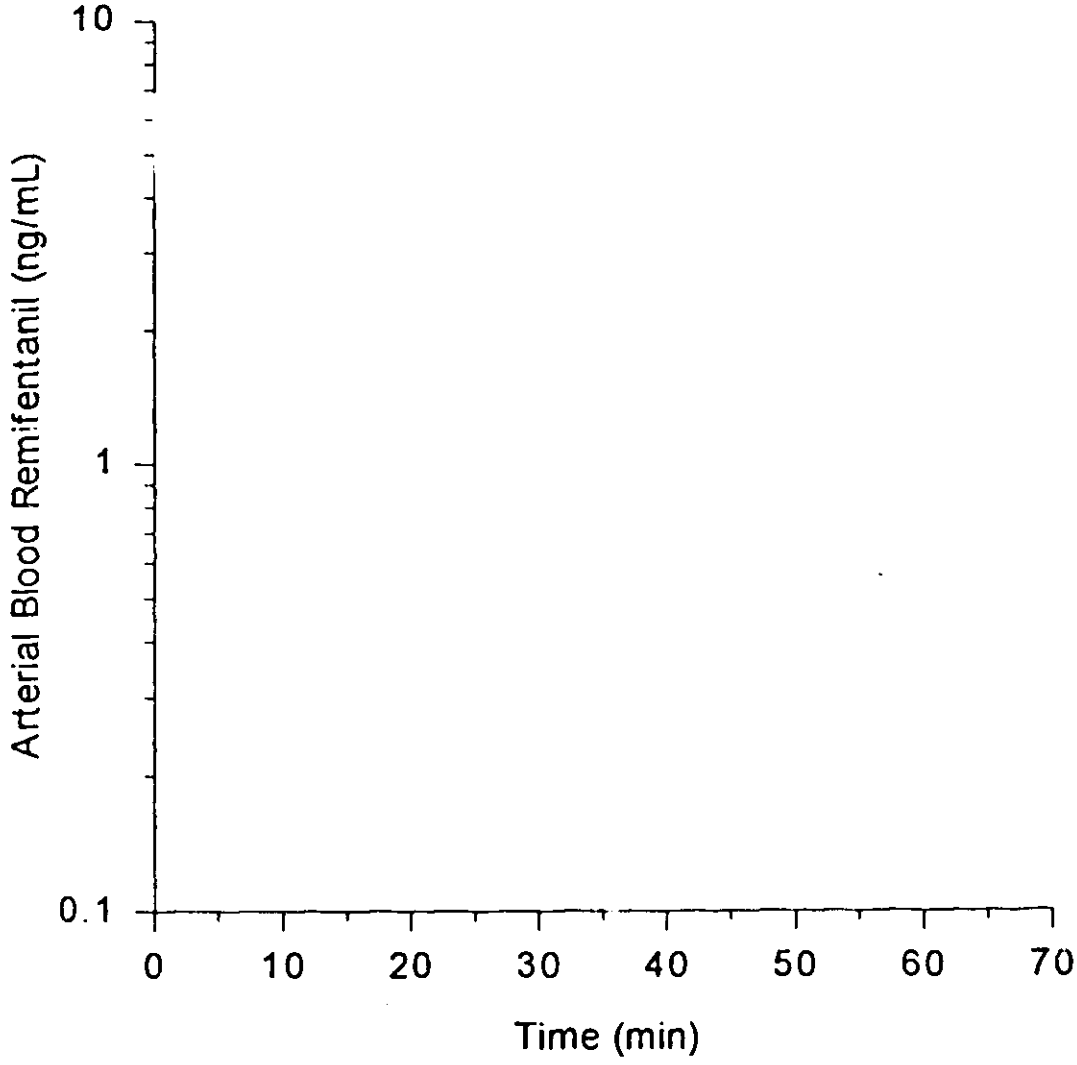
Individual Arterial Blood Remifentanil Concentration-Time Profiles



USA-106

Route 2

Individual Arterial Blood Remifentanil Concentration-Time Profiles



Pharm/Tox.

NDA #20-630

Division of Anesthetics, Critical Care and Addiction Drug Products

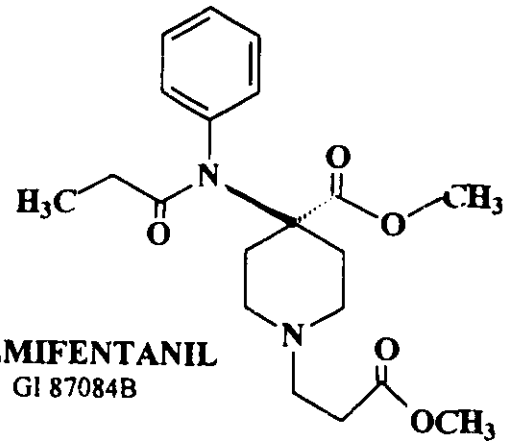
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY

Sponsor: Glaxo Wellcome Inc.

Trade Name: Ultiva™

Generic Name: remifentanil

Structure:



REMIFENTANIL
GI 87084B

3-[4-methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine] propanoic acid methyl ester, hydrochloride salt

mw 412.9

Pharmacologic Class: Narcotic Analgesic

Indication: Surgical analgesia/anesthesia

Dosage Form: lyophilized powder for injection (remifentanil hydrochloride + glycine)

NDA #20-630

Table of Contents

PHARMACOLOGY STUDIES

GI87084B, A SHORT-ACTING μ-OPIOID AGONIST: SIDE EFFECT PROFILE IN THE MOUSE (NDA V3/p100)

STUDY/REPORT NUMBER: WNP/89/026

STUDY SITE: unknown

GLP SPECIFICATIONS: unknown

SPECIES/NUMBER OF SUBJECTS/SEX: ♂ mice, CRH Glaxo-bred, 6 mice per dose group.

DOSES / ROUTE OF ADMINISTRATION: GI87084B (U540/157/3) was administered by subcutaneous injection, 1,2 or 5 minutes prior to determination of tail-flick latencies; 2 or 5 minutes prior to measurement of respiratory rate or esophageal temperature. The doses used were not stated although extrapolation from the graphs suggest the doses were 0.5, 1.0, 5, 10, 50, and 100 mg/kg in the tests of respiratory depression and body temperature.

RESULTS:

Table 1

TAIL-FLICK LATENCY (ED_{50}=DOSE INCREASE LATENCY X2)

Pretreatment time(min)	ED_{50} (95% confidence limits) mg/kg s.c.
1	1.9 (1.3-2.9)
2	4.3 (3.1-5.8)
5	12.2 (8.7-16.4)

Table 2

EFFECTS ON RESPIRATORY RATE AND BODY TEMPERATURE

Pretreatment time (min)	Respiration rate ED$_{25}$ (dose = -25%) mg/kg s.c.	esophageal temperature decrease ED$_{50}$ (dose = -2°C) mg/kg s.c.
2	16.4 (9.5-31.9) [19.4 (1.6-370)i.v.]	171.1(110-411)
5	37.9(22.1-100.8)	40.4(28.8-67.8)

The report did state that 2 of 6 dosed at 100 mg/kg i.v. died.

DISCUSSION:

The results indicate that GI87084B is a very short-acting analgesic with respiratory depression evident at doses greatly exceeding the effective analgesic dose by a factor of 3 to 4 fold. Lethality was observed at 100 mg/kg i.v.

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OPIOID ACTIVITY AND SUPPRESSION OF OPIATE WITHDRAWAL BY GI87084B (remifentanil)

(NDA V3/p110)

STUDY/REPORT NUMBER: UPC/94/009

STUDY SITE: :

GLP SPECIFICATIONS: unknown

SPECIES/NUMBER OF SUBJECTS/SEX:

A: Opioid receptor, ^{3}H-etorphine, binding to rat, Sprague Dawley, brain membranes. An *in vitro* test, number of rats unknown.

B: Mouse vas deferens assay: *in vitro* test with electrically stimulated vas deferens, number of mice

unknown.

C: Mouse tail-flick assay: Male Swiss-Webster mice, 6-10/dose, subcutaneous administration.

D: Mouse hot-plate test: Male Swiss-Webster mice, 6-10/dose, subcutaneous administration.

E: Mouse paraphenylquinone abdominal stretching test: Male Swiss-Webster mice, 6-10/dose, subcutaneous administration.

F: Monkey single dose substitution test: Rhesus monkeys (maccaca mulatta), 2.5-7.5 kg, 3 monkeys per group, subcutaneous administration.

METHODS, DOSES AND RESULTS:

A. Opioid receptor, ^{3}H-etorphine, binding. The method was as described by Medzihradsky, *et al* Life Sci. 34:2129-2138(1984). The EC_{50} of GI87084B was 117 nM as compared with historical values in this assay for fentanyl, 36.2 nM, and morphine, 23.6 nM.

B. The electrically evoked contractions of the mouse vas deferens was inhibited by GI87084B with an ED_{50}=107 nM as compared with historical values for fentanyl, 37 nM, and morphine, 395 nM. The inhibition of contraction by GI87084B was antagonized by the μ-receptor antagonist naltrexone but not by κ-antagonist nor-binaltorphimine or δ-antagonist ICI-174864.

C,D,E. The mouse tail-flick, hot-plate and paraphenylquinone tests did not demonstrate any effects of GI87084B when evaluated 20 minutes after s.c. injections of 1, 10 or 30 mg/kg. However, the classic μ-opioid signs of Straub tail and increased locomotion were observed after GI87084B administration but were gone by the time of testing. These signs were prevented by naloxone.

F. The monkeys had been made morphine-dependent by repeated injection of morphine for at least 3 months. On test days, 14 - 15 hours after the last morphine injection, the monkeys were injected with GI87084B at 0.25 or 1.0 μg/kg, morphine at 3.0 mg/kg or saline and observed for withdrawal signs for the

following 2.5 hours. The observers were blinded as to which treatment the monkeys received. The withdrawal signs were incompletely suppressed by GI87084B in a dose dependent manner. The onset of suppression was immediate for both morphine and GI87084B.

DISCUSSION:
The effectiveness of GI87084B as a μ-agonist were evident in the *in vitro* tests and the suppression of withdrawal in the monkeys, and the signs, Straub tail etc., seen in the mice in the analgesic tests. The lack of analgesic effects in the mice was probably due to the very short duration of action of GI87084B *in vivo*.

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ANESTHETIC POTENCY OF REMIFENTANIL IN DOGS

STUDY/REPORT NUMBER: MAC 1

STUDY SITE:

GLP/QA SPECIFICATIONS: not stated, also without data tables.

SPECIES/NUMBER OF SUBJECTS/SEX:
Mongrel dogs, N=25, sex not stated, body weights 19.9 ± 3.3kg.

PROCEDURE:
The dogs were divided into three treatment groups, all anesthetized with 5% enflurane in O_2, intubated and artificially ventilated. Tail pinch was the stimuli used to judge depth of anesthesia:

A. Incremental infusion rates of GI87084B at 0 055 to 5.5 μg/kg/min.

B. Constant infusion rate of 0.6 or 1.0 μg/kg/min for 6 to 8 hours. Enflurane minimal alveolar concentration (EMAC) was measured before and at hourly intervals after remifentanil administration. Naloxone was injected at the end of the experiment.

C. Alternating infusions of 0.5 and 1.0 μg/kg/min with MAC

determined 30 minutes after each rate change. Heart rate, mean arterial pressure and blood sample for remifentanil concentrations were taken during MAC determination.

RESULTS:
EMAC was reduced up to 63% in a dose dependent manner. The ED_{50} for EMAC reduction was calculated at 0.72µg/kg/min and corresponding blood concentration was 9.2 ng/ml. Naloxone prevented the MAC reduction by remifentanil. At constant infusion rates, no evidence of tolerance development were observed. The authors stated that the recovery was very rapid, even after prolonged administration however, there was no data presented.

Remifentanil decreased heart rate, as do other opioids, and this was prevented by naloxone.

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EFFECTS OF GI87084B (REMIFENTANIL HYDROCHLORIDE) ON CEREBRAL BLOOD FLOW, INTRACRANIAL PRESSURE AND ELECTROENCEPHALOGRAM IN ANESTHETIZED DOGS (V3/p161)

STUDY/REPORT NUMBER: UPC/94/010

STUDY SITE:

GLP/QA SPECIFICATIONS: unknown

SPECIES/SEX: Male mongrel dogs, 22-31 kg, divided into four treatment groups. All treatment groups were anesthetized and maintained on 2% end-tidal isoflurane and 50% nitrous oxide in oxygen through instrumentation. Neuromusculature blockade was induced by vecuronium (0.01 mg/kg/hr, i.v.). Femoral veins and arteries were cannulated on both sides and after a thoracotomy a catheter was placed in the left atrium for cerebral blood flow (CBF) measurements by injections of radiolabeled microspheres. After completion of instrumentation the isoflurane was reduced to 1%, nitrous oxide remained at 50% in oxygen and the animals were

allowed to equilibrate for one hour.

The CBF was measured four times for each dog using the microspheres. The microspheres were suspended in saline and injected at the end of the equilibrium period, at the end of each of the two infusion rates and at the end of the 30 minute recovery period.

The CBF volume (CBFV) was measured continuously by ultrasonic probe placed on the left temporal bone. A burr hole was drilled over the sagittal sinus and a catheter was inserted for blood samples. A catheter was also placed in the lateral ventricle for measurement of intracranial pressure. Five EEG electrode were placed, one central, two occipital and two frontal.

Brain electrical activity was measured bilaterally and a squared function of the electrical amplitude was determined within each of four frequency bands (Hz): Alpha (8.1-12.0); beta (12.1 - 30.0); delta (0.5-3.0) and theta (3.1-8.0).

PROCEDURE:

Group

#1. N=4; saline infusion at 0.5 and 1.0 ml/kg/min. These flow volumes were also used for drug administration.

#2. N=7; alfentanil infusion at 1.6 and 3.2 μg/kg/min.

#3. N=7; GI87084B at μg/kg/min (lot #541/47/1). Cerebral autoregulation was tested during the high dose infusion by injection of phenylephrine, 4 μg/kg, 20 minutes after the start of the higher infusion rates. CBFV was measured prior the phenylephrine and at the peak hypertensive response.

#4. N=4; GI87084B at μg/kg/min as with Group #3, but blood pressure was maintained by infusion of phenylephrine, 8 to 20 μg/kg/min.

RESULTS:

Electroencephlagram:

The results of remifentanil alone (Group 3) were initial found to be the same as those with remifentanil with phenylephrine (Group

4) and the groups were combined in subsequent analysis. Both remifenanil and alfentanil produced similar changes in the EEG spectrum. The fraction of total activity increased significantly in the alpha, delta and theta ranges and decreased in the beta fraction. The drug differences were both significantly different for saline controls, but not from each other. The principle difference between remifenanil and alfentanil was the return of EEG fractions to saline control levels during the 30 minute recovery phase by the remifentanil group. The EEGs in the alfentanil group remained outside the control values at all frequencies throughout the 30 minutes recovery period.

The 50% spectral edge frequency was significantly decreased by both remifentanil and alfentanil, nearly immediately after the start of infusion. However, only the remifentanil spectral edge returned to control levels within the 30 minute recovery phase.

There were differences between high and low doses effects within either the alfentanil or remifentanil groups at most EEG fractions but they were not evaluated statistically .

Intracranial Pressure (ICP) and Flow Velocity:
The effect of GI87084B with or without phenylephrine was a drop in ICP mmHg pressure of 42% (-10mmHg) and 29%, respectively, at the low dose and only 13% and 12% at the high dose. Alfentanil reduced ICP 35% and 29% at the low and high doses respectively. Of interest were the effects during the 30 minute recovery period; In the remifentanil group an increased in the ICP of 21% (5mmHg above baseline) was observed and 41% in the group with phenylephrine. The alfentanil group had ICP reduced only 1 mmHg (-6% below baseline) and the saline controls were reduced 3 mmHg during this time period.

The flow velocities were decreased at all time points and in all treatment groups including saline. During both high and low dose infusions, the flow rates (cm/sec) were reduced 34 to 45% in the treated groups and 5% in the saline controls. During the recovery period, the alfentanil group remained reduced (-26%), while both remifentanil groups returned to within 7% of the original control.

Cerebral Blood Flow (CBF ml/100g/min):
Remifentanil, with and without phenylephrine (PE) and alfentanil all reduced CBF in all brain areas measured, although this did not reach statistical significance in the cerebellum in any treatment group. There was not a dose-response relationship as the changes during high dose infusion were always less than low dose effects in all treatment groups. This was probably due to the sequence of administration, for in all three treatment groups the high dose always followed the low dose and physiological or pharmacological tolerance could have developed. Alternatively, the "low dose" may have produced the maximum effect.

The effects of remifentanil were very similar to alfentanil with two exceptions: 1) no dose of alfentanil significantly decreased CBF in the hypothalamus, brainstem or medulla although remifentanil did at the low dose without PE and in the hypothalamus with PE. 2) Remifentanil groups, with and without PE, did not show any significant CBF changes during the recovery phase while the CBF of the alfentanil group remained significantly depressed in the cortex, hippocampus and caudate during recovery.

Mean Arterial Pressure (MAP mmHg) and Heart Rate (HR):
MAP was significantly reduced in both the remifentanil group, without PE, and the alfentanil group. During the recovery phase, the remifentanil group rebounded, to greater than baseline, the alfentanil group did not rise to baseline values, but neither were significantly different from baseline. The remifentanil plus PE did not, by definition, show any significant change from baseline MAP. This was true except for the last ten minutes of recovery when this group had significantly higher MAP than baseline.

The HR was significantly reduced in all treatment groups throughout the treatment periods. Both remifentanil groups demonstrated reversal during all three 10 minute measurements during the recovery phase. The alfentanil group showed significantly reduced HR during the initial two 10 minute segments.

DISCUSSION:

The effects of remifentanil and alfentanil were very similar in all parameters measured, with the exception of the duration of action. Remifenanil effects were greatly reduced or reversed during the 30 minute recovery period after stopping of infusions. The effects of alfentanil appeared to last longer and are merely reduced during the recovery period.

The effects of both compounds were unrelated to dose. This may reflect the order of presentation as the low dose always preceded the high dose and this gave time for physiological and/or pharmacologic tolerance development. The low dose may also have produced the maximum effect, a pharmacological/physiological "floor" or "ceiling".

The EEG results demonstrated a drug induced shift of low amplitude fast waves to high amplitude slow waves. The spectral edge frequency was therefore decreased as activity in the beta fraction decreased and activity in the delta fraction increased.

The decrease of intracranial pressure (ICP) was similar with both remifentanil and alfentanil <u>during infusion</u>. However, during the recovery phase, alfentanil effects were merely reduced to near control values and remifentanil effects appeared to reverse, producing an increased ICP. This was not reported as statistically significant and was not mentioned in the report. The group receiving both phenylephrine (PE) and remifentanil appeared to have an exacerbated increase in ICP and also were significantly hypertensive in relation to baseline, during this recovery phase.

The mean blood flow velocity in the middle cerebral artery was reduced 35 to 45% during infusion in all treated groups. This was statistically significant for remifentanil without PE and alfentanil. The cerebral blood flow (CBF) was reduced in all measured areas, in all treatment groups during the infusion phases. The effects on systolic blood pressure, cerebral blood flow velocity and CBF was consistent with data in the literature by Werner *et al* 1991[A] with sufentanil. However, sufentanil was reported not to change the ICP, as was observed with alfentanil and remifentanil.

NDA #20-630

[A] Werner C, Hoffman WE, Baughman VL, Albrecht RF and Schulte J "Effects of sufentanil on cerebral blood flow, cerebral blood flow velocity, and metabolism in dogs" Anesth-Analg. 72(2): 177-81. 1991

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BINDING OF GI87084B (REMIFENTANIL) AND GL90291A TO VARIOUS MEMBRANE RECEPTORS AND ION CHANNELS

(4/200)

STUDY/REPORT NUMBER: UPC/94/007

STUDY SITE:

SPECIES:
In vitro studies: cell cultures (PC-12 cells); rat (whole brain, frontal cortex membranes, striatal membranes); Bovine cerebellar membranes and guinea pig cerebellar membranes.

PROCEDURE: The measurement of various membrane receptors and ion channels were performed with standard assay techniques and cell or membrane preparations were standard for the specific assay.

The assays were performed with GI87084B (remifentanil) and GI90291A, the major metabolite of remifentanil. Both compounds were tested at concentrations of 10^{-9}M, 10^{-7}M and 10^{-5}M.

RESULTS:
Neither remifentanil or GI90291 produced as much as 20% inhibition of ligand binding at 10^{-5}M to the following receptor/ion channels:

Adenosine (ns)
Alpha$_1$ (ns)
Alpha$_2$ (ns)
Beta (ns)
Dopamine (ns)
GABA$_A$
GABA$_B$
Histamine$_3$
Serotonin (ns)
Muscarinic (ns)
Purinergic P_{2Y}
K^+ (ATP-mod.)
K^+ (low cond.)
K^+ (voltage dep)
Na^+ site 1
Na^+ site 2

(ns) = non-specific for subtypes of receptor.

In contrast, both compounds were active on at least two of the three opioid receptors:

Compound	μ-opioid receptor EC_{50}	Sigma-opioid receptor EC_{50}	kappa-opioid receptor EC_{50}
remifentanil	2.6 ± 0.6 nM	66 ± 19 nM	6.1 ± 0.5 μM
GR90291	1.4 ± 0.48 μM	1.2 ± 0.4 μM	(<10% @ 10^{-5})

DISCUSSION:
The receptor binding of remifentanil and its primary metabolite, G190291, were limited to the receptors of the opioid system, with emphasis on the μ-receptor. The sigma and kappa-opioid receptor binding of remifentanil, GI87084B, were relatively weak and the sponsor states that the effects are of no practical significance.

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OPIOID RECEPTOR SUBTYPE SELECTIVITY OF GI87084B IN ISOLATED TISSUES (NDA 4/249)

STUDY/REPORT NUMBER: UPC/92/001

STUDY SITE: unknown

GLP/QA SPECIFICATIONS: unknown

COMPOUNDS: GI87084B, remifentanil hydrochloride (lots #U391/48/1, U541/4/1); G187084A, the oxalate salt (lot# U391/20/3); G187084C, the fumarate salt (lot# U391/50/1); and sufentanil (G187771A); naloxone hydrochloride and fentanyl citrate
Alfentanil hydrochloride (Alfenta™ from

SPECIES/TISSUE: Guinea pig ileum: rat and mouse vas deferens

PROCEDURE:
Tissues were mounted on tissue holders with tissue resting inside platinum ring electrodes. The mounted segments were placed in 10cc tissue baths filled with Krebs Henseleit buffer at 37°C.

The ileum tissue was electrically stimulated by a Grass S88 Stimulator at 0.1 HZ with a supramaximal voltage at 0.5 msec duration. Tissue contractions, electrically evoked, were recorded on a Gould physiological recorder.

A concentration-response inhibition of electrically induced ileum contractions was obtained with different salts of GI87084, fentanyl, sufentanil and alfentanil.

Remifentanil, GI87084B, was also tested in both rat and mouse vas deferens preparations. For Schild analysis two cumulative concentration-response curves were generated. A control dose-response curve was obtained with untreated tissue and then the tissue was incubated with naloxone (10 - 100 μM) for one hour. A second concentration-response curve was obtained with in the presence of naloxone.

RESULTS:
The inhibitory effects of the opioid agonists are presented in the following table:

INHIBITION OF ELECTRICALLY INDUCED
CONTRACTION OF THE GUINEA PIG ILEUM

Compound	guinea pig ileum EC_{50} - nM
GI87084A	3.6 ± 0.2 (n=8)
GI87084B	2.4 ± 0.6 (n=27)
GI87084C	3.9 ± 0.5 (n=4)

Compound	guinea pig ileum EC_{50} - nM
fentanyl	1.8 ± 0.4 (n=14)
sufentanil	approx. 3.0 (n=4)
alfentanil	20.1 ± 1.2 (n=8)

The concentration-response curves of GI87084B in both rat and mouse vas deferens yielded inhibitory ED_{50} values of 387 ± 44 nM and 39.5 ± 7.4 nM, respectively. The naloxone antagonism of GI87084B inhibitory effects was dose-related in the guinea-pig ileum and mouse vas deferens. The dose-response shift to the left in the ileum was somewhat incomplete as naloxone at greater than 30 nM reduced the maximum response to GI87084B. In the rat vas deferens preparation, GI87084B enhanced contraction when in doses greater than 10 μM. Naloxone antagonism in the preparation varied between no effect at 10 and 1000 nM to inhibition at 30 and 300 nM.

DISCUSSION:

Schild analysis of the GI87084B data in both ileum and mouse vas deferens produced pK_B, negative log of antagonist dissociation constant, of about 8.2. This is consistent with reported values for μ-opioid receptors(Takemori and Portoghese, 1985). The biphasic nature of GI87084B responses in the rat vas deferens preparation were not discussed extensively by the authors, and since this was primarily an effect at very high doses, it may have no physiological/toxicological effect.

The μ-agonist activity of GI87084B, remifentanil is comparable to those of fentanyl, sufentanil and alfentanil.

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NDA #20-630

DEPENDENCE STUDY ON GI87084B IN RHESUS MONKEYS AND RATS (NDA 4/400)

STUDY/REPORT NUMBER: NTX/95/007

STUDY SITE:

GLP/QA SPECIFICATIONS: compliance statement NDA 4/401.

PROCEDURE: Five separate experiments:

A1. Observation of gross behavior in Rhesus monkey
Five male and five female Rhesus monkeys: gross behavioral observation after; iv GI87084B at 0.25, 1, 4, 8, and 60 µg/kg and sc at 8, 30, 45 and 60 µg/kg.

A2. Suppression test of morphine withdrawal signs in Rhesus monkeys physically dependent on morphine
A total of 17 monkeys were treated with saline, GI87084B (45 or 60 µg/kg s.c.), or codeine (16 or 24 µg/kg s.c.). This treatment was 19 hours after the last s.c. morphine dose and the monkeys are displaying withdrawal signs.

A3. Continuous i.v. self-administration in Rhesus monkeys
GI87084B, pentazocine and saline were evaluated for self-administration performance in 4 experienced monkeys. Two naive monkeys were tested for self-administration of GI87084B followed by saline.

A4. Observation of gross behavior effects upon acute administration to rats
Thirteen male rats, 231 to 253 g, were used. Six received saline, one at 60 µg/kg and 2 each at 4, 8, and 15 µg/kg. They were observed prior to administration, immediately after administration 0.25 hrs, 0.5, 1.0, 2.0, 3.0, and 4.0 hours after administration,

A5. Repeated infusion for physical dependence production in rats
1. Three day infusion - 7 male rats per group. GI87084B,

remifentanil, at 8 or 15 μg/kg or saline at 2 cc/kg, every 10 minutes (432 infusions). Pentazocine at 4 mg/kg, hourly. Thirty minutes after the last infusion, naloxone, 1 mg/kg, was administered subcutaneously and the withdrawal signs were observed for one hour.
2. Seven day infusion: 7 male rats per group. GI87084B, remifentanil, at 8 or 15 μg/kg or saline at 2 cc/kg, every 10 minutes (1008 infusions). Pentazocine at 4 mg/kg, hourly.

RESULTS:

A1. A single dose of GI87084B produced ataxia, hypoactivity, hyporeactivity, prone position and asthenic positions in monkey after 8 μg/kg i.v. and 45 and 60 μg/kg s.c. and some respiratory depression was also observed. One monkey at 60μg i.v. immediately post injection was supine and had apnea. The animal recovered after administration of naloxone at 0.6 mg/kg s.c..

A2. GI87084B at 45 and 60 μg/kg and codeine at 16 and 24 mg/kg suppressed morphine-withdrawal signs in monkeys. At the low dose of both drugs, the suppression was rated as "intermediate" in 2 of 2 monkeys with each drug. The high dose of each drug was graded as "marked" suppression.

A3. The rate of self-administration of GI87084B was greater than saline in both experienced and naive monkeys. The vehicle control saline average for a week was 1.6 to 5 lever-presses per day while GI87084B administration produced high rates of >700 to >1000.

A4. GI87084B was tested at 4, 8, 15, and 60 μg/kg, in rats. The observations recorded behavioral depression at 15 and 60 μg/kg and muscle rigidity and respiratory depression was also observed at these doses.

A5. In the group of rats receiving GI87084B every 10 minutes for three days, the naloxone challenge produced only mild withdrawal signs. In contrast, the rats receiving

pentazocine demonstrated clear withdrawal signs including body weight loss.

In the 7-day infusion study with GI87084B at 8 and 15 µg/kg, one subject in each dose group died, possibly of mis-dosing. Significant body weight loss was observed in the 15 µg/kg group and in the pentazocine group.

DISCUSSION:
GI87084B produced opioid-like CNS depression and respiratory depression in both rats and monkeys after acute administration. This opioid characterization included reduction of morphine withdrawal signs in the monkey and production of mild withdrawal signs in the rat that were less than the pentazocine effects. GI87084B was also reinforcing in the self-administration test with both experienced and naive monkeys.

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EX-VIVO INTERACTION STUDY BETWEEN REMIFENTANIL AND ATRACURIUM, MIVACURIUM, ECHOTHIOPHATE, ESMOLOL, MIDAZOLAM, PHYSOSTIGMINE, AND NEOSTIGMINE

(NDA V6/256)

STUDY/REPORT NUMBER: UTX/94/015

STUDY SITE: Glaxo Inc. Research Institute

GLP/QA SPECIFICATIONS: unknown

PROCEDURE:
The blood sample of a drug-free volunteer was used for *in vitro* testing of the changes in $t_{1/2}$ of remifentanil in the presence of common intra-operative medications at clinically relevant concentrations. The compounds were mixed in blood aliquots and incubated at 37°C for various time intervals.

RESULTS:
Atracurium, mivacurium, echothiophate, esmolol, Midazolam, physostigmine, and neostigmine were tested. There was no significant change from control, remifentanil alone, in the presence of echothiophate, midazolam, physostigmine or neostigmine. However, atacurium, mevacurium and esmolol changed the $t_{1/2}$ by -22%, -10% and +10%, respectively, with statistical significance. A repeat of these mixtures produced the following respective changes; -10%, -5% and -3%, also all statistically significant. The *in vitro* $t_{1/2}$ for remifentanil was 1.18 hrs and 1.57 hrs on the repeat.

DISCUSSION:
The sponsor does not feel these changes are of biological or pharmacological significance and this reviewer agrees as the biological $t_{1/2}$ is only 3 to 10 minutes in the clinic. This *in vitro* test has limited value. The compound was referred to as remifentanil an no lot number was given and it is assumed this was the hydrochloride salt (G187084B), the compound to be marketed.

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Summary:
Remifenanil, GI87084B, is a potent, ultra-short acting opiate. The analgesic effects are typical of other opiates and principally due to mu-agonist activity. The short $t_{1/2}$ of about 6 minutes requires intravenous infusion to maintain analgesia and sedation and allows for rapid titration of the depth of anesthesia. When used with enflurane anesthesia in dogs, it reduced the MAC by as much as 63%. Use during anesthesia decreased intracranial pressure (ICP) similar to alfentanil but during recovery the ICP rebounded to greater than control levels.

As an opiate, remifentanil produced withdrawal after repeated administration, it suppresses respiration and withdrawal symptoms in morphine dependant monkeys. The monkeys, drug naive and drug experienced, will self-administer remifenanil.

As with other opioids, remifentanil produced some cardiac depressant effects, decreased HR, LV dp/dt, systolic and

diastolic BP, and this was naloxone reversible. However, no direct effects were observed in isolated tissue and in conscious dogs it produced a dose-dependant hypertensive response.

The main metabolite, GI90291, is the hydrolysis product by RBC esterases. *In vitro* assays did not show hydrolysis by human pseudo-, butyl-, or acetyl- cholinesterases or by carbonic anhydrases I or II.

Remifentanil is a weak histamine releaser *in vivo*, but not *in vitro*. Remifentanil and GI90291 do not significantly bind to non-opioid receptors. i.e. adrenergic, cholinergic, dopaminergic, serotonergic, gabaminergic, adenosine or calcium channels.

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The following studies were reviewed previously upon submission and the reviews are included in appendix as noted:

appendix I

UPC/93/011	Effects of GI87084 3 (remifentanil) on the electroencephalogram and systemic hemodynamics in anesthetized dogs: Comparison of drug substance synthesized via two different routes

appendix II

UMP/90/009	Antinociceptive activity of GI87084 in the rat tail withdrawal assay
UAP/91/006	In vitro and in vivo opioid effects of GR90291, the primary metabolite and degradation product of GI87084
UMP/90/011	Analgesic and cardiovascular effects of GI87084B in conscious dogs
UMP/90/007	Opioid effects of GI87084B in isolated tissues
UMP/88/002	Hemodynamic effects of GI87084B in anesthetized dogs

UMP/90/002 Hemodynamic effects of low dose infusion and bolus doses of GI87084B in anesthetized dogs

UAP/91/003 Assessment of the potential interaction of GI87084B with succinylcholine and hemodynamic effects of prolonged GI87084B infusion in anesthetized dogs

UAP/91/004 Electroencephalographic and cardiovascular effects of high doses of GI87084B in anesthetized dogs

UMP/90/010 Cardiovascular effects of GI87084B in urethane anesthetized rats

UMP/90/001 Effects of GI87084 1 on renal excretory function in conscious rats

UMP/90/006 Effects of GI87084A, GI87084B, GI87084C on histamine release in rats (in vivo) and human peripheral mononuclear leukocytes (in vitro)

UMP/90/004 The effect of GI87084B in spontaneously beating guinea pig atria and in rat anococcygeus muscle

UMP/90/005 Effects of GI87084 3 on isolated rabbit aortic rings

UMP/90/003 Direct effects of GI87084A and effects on H1 histamine and M2 muscarinic receptors in guinea pig ileum longitudinal muscle

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The following studies were read, but not formally reviewed. However, selected data is presented in summaries:

UTX/93/060 Gl106769A (midazolam hydrochloride): Acute intravenous lethality study in Sprague Dawley rats 6/124

UTX/93/062 Gl106768X (thiopental sodium): Repeat acute intra

venous toxicity study in Sprague Dawley rats 6/169

UTX/93/061 GI87084B (opioid agonist), G1106768X (thiopental sodium) and G1106769A (midazolam): Acute intravenous lethality toxicity study in Sprague Dawley rats 6/211

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TOXICITY - ACUTE STUDIES

GI87084B (OPIOID AGONIST): ACUTE ORAL TOXICITY STUDY IN RATS (UP AND DOWN PROCEDURE) (V34/p176)

STUDY/REPORT NUMBER: UTX/93/034

STUDY SITE:

GLP/QA SPECIFICATIONS: In accordance V34/183,188,213

SPECIES/NUMBER OF SUBJECTS/SEX: Wistar rats 1/sex/dose and 5/sex/single dose of 2000mg/kg of GI87084B.

DOSES/ROUTE OF ADMINISTRATION: All single oral doses by gavage. Doses of 50, 65, 84.5, 200, 400, 800, 1600 and 2000 mg/kg in pairs of rats and 2000mg/kg to 5/sex for Maximum Non-Lethal Dose (MNLD). Dose volume of 10 ml/kg and the pH of solution/suspensions ranged for 4.6 to 5.0.

PROCEDURE: Animals were dosed once, observed for 12 days and sacrificed and necropsy performed on day 15.

RESULTS: No deaths occurred at any dose. Decreased motor activity was noted in 1/2 at 84.5, 400 and 800 mg/kg and 2/2 at 1700 and 2/2, 10/10 at 2000 mg/kg. The other signs of opioid intoxication; prostration, rigid body, low carriage, impaired righting reflex, all started within 15 minutes to 4 hours post dosing and were gone by 24 hours. Convulsions were observed in both animals at 1600 mg/kg.

Although the animals were necropsied, no data are presented and in the text there is only the statement that no macroscopic abnormalities were observed. The MNLD would exceed the 2000 mg/kg dose tested.

DISCUSSION:
GI87084B appears to be very safe upon oral administration as no deaths occurred at 2gm/kg and significant effects were not observed below 400 mg/kg.

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GI87084B (opioid agonist): Industrial toxicology evaluation acute in tracheal inhalation toxicity study in albino rats (V34/214)

STUDY/REPORT NUMBER: UTX/94/009

STUDY SITE:

GLP/QA SPECIFICATIONS: none cited

SPECIES/NUMBER OF SUBJECTS/SEX: rats, male; 4 groups of 4 = additional group of 4 larger males for repeat of high dose.

DOSES/ROUTE OF ADMINISTRATION: 0, 2.5, 5 or 10 µg/kg GI87084B aerosol into trachea of methoxyflurane anesthetized animals only.

PROCEDURE: The anesthetized rats each received one dose of GI87084B were observed for symptoms and mortality. Due to difficulties in the aerosol administration in small rats, 246 to 270 grams, the high dose was repeated with rats 311 to 357 gms. At he end of 14 days all survivors were euthanized and examined.

RESULTS:
The 2.5 µg/kg dose produced no mortalities or body rigidity. The 5 µg/kg dose produced 1/4 deaths shortly after dosing and the remaining 3 rats had body rigidity but recovered from anesthesia without obvious abnormalities.

At 10 µg/kg in the smaller rats, one died during administration and 2 shortly thereafter. The fourth had body rigidity but recovered. A repeat of this with the larger rats 1 died during and a second shortly after. The remaining 2 rats developed

hindlimb rigidity but appeared normal thereafter.

The deaths were all attributed to hypoxia from cessation of breathing and no macroscopic lesions were seen upon necropsy. The acute intratracheal LD$_{50}$ was 8 μg/kg GI87084B and the safe exposure limit was set at 1 μg/kg G187084B/M^3.

DISCUSSION:
This was an internal safety determination for the synthesis facilities.

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SUMMARY:
The acute toxicity of remifentanil is characteristic of opioid overdose with sedation, respiratory depression, cyanosis, body rigidity, excess salivation and convulsions as the primary symptoms. In rats the oral LD$_{50}$ is greater than 2 grams/kg; intravenous, 17 mg/kg and by aerosol inhalation, 8μg/kg. Mice and dogs are more tolerant of iv administration with LD$_{50}$ of 100 mg/kg and >80 mg/kg, respectively.

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The following studies were read but not formally reviewed, although selected data is presented in summaries:

UTX/93/059	GI87084B (opioid agonist): Acute intravenous lethality study in Sprague Dawley rats	6/076
UDM/89/008V2	G187084 blood concentrations in rats immediately after intravenous administration of doses used in LD50 determination	48/026

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The following studies were reviewed previously and the reviews are included in appendix as noted:

Appendix II

UMP/90/008 Direct myocardial effects of GI87084B

UTX/90/002 GI87084B (opioid): Acute intravenous toxicity study in the rat

UTX/90/003V2 GI87084B (opioid agonist): Acute intravenous toxicity study in the dog

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TOXICITY
SUBCHRONIC / CHRONIC STUDIES

GI87084B (opioid agonist): Pilot continuous intravenous infusion toxicity study in rats
(NDA V14/001)

STUDY/REPORT NUMBER: UTX/94/024

STUDY SITE:

GLP/QA SPECIFICATIONS: In concordance, V14/pg007.

SPECIES/NUMBER OF SUBJECTS/SEX:
Wistar rats. Control, saline injection, 10/sex; treated groups, 25/sex, (10/sex toxicity, 15/sex pharmacokinetics.

DOSES/ROUTE OF ADMINISTRATION: All rats had indwelling jugular catheters: iv dosing escalated from 0.01 µg/kg/min GI87084B (days 1,2 and 3); 0.05 µg/kg/min GI87084B (days 4,5,6 and 7); 0.1 µg/kg/min GI87084B (days 8, 9 and 10); 0.5 µg/kg/min GI87084B (days 11,12,13 and 14); 1.0 µg/kg/min GI87084B (days 15,16 and 17).

PROCEDURE:
The animal were observed twice daily and had food and water available *ad libitum*. Saline infusion started approximately 3 days prior to test initiation. Food consumption was recorded daily and body weight were taken at the start of each dose escalation phase.

Toxicokinetic samples were taken by cardiac puncture on days 1, 4, 8, 11 and 15 of testing after pentobarbital anesthesia and no necropsy was done on these animal from the toxicokinetic group.

On day 18 the toxicity group was euthanized, bled for hematology and clinical tests and necropsied. Organs were weighed and microscopic examination of selected tissues was performed on all animals.

RESULTS:

No compound related effects were observed in terminal body or organ weights or any macro- or microscopic changes, according to the investigators summary.

The body weights of the toxicity male subjects appeared to be significantly different pre-test (V14/56), controls 4 to 9% heavier than remifentanil animals, and during the treatment phase, this difference remained, 3.3 to 4.3%, but lost significance. The table of terminal body weights (V14/70) indicates that, with the loss of an animal per treatment group, the difference became statistically significant again with the controls 8.4% heavier. Although the absolute organ weights did not differ between groups, except for a pituitary weight 16.6% greater in controls, organ weights per body weight percentages appeared significantly elevated in the treated group. i.e. left and right adrenals, +29.4% and +29.85, and thyroid/parathyroids by 25% and liver weights by 11%. The latter effect correalities with the lack of remarkable macroscopic changes in the controls (0/9) and the presences of macroscopic changes in the treated group of males (3/9). The microscopic changes also appeared to support a different effect with remifentanil. The macroscopic and possibly microscopic thymic abnormalities were also more prevalent in both male and female treatment groups (3/9 & 4/9), than in the controls (1/10 & 2/9).

The effects were not severe, however nothing was noted by the sponsor.

DISCUSSION:

Although the sponsor does not consider any treatment related effects are present, the elevated liver and adrenal weights / body weight and accompanying increased macro and microscopic changes may indicate a compound induced change. The stress of remifentanil administration to conscious animals could be the foundation of the increased relative adrenal weights.

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GI87084B (OPIOID AGONIST): REPEAT PILOT CONTINUOUS INTRAVENOUS INFUSION TOXICITY STUDY IN RATS

(NDA 14/280)

STUDY/REPORT NUMBER: UTX/94/033

STUDY SITE:

GLP/QA SPECIFICATIONS: Glaxo Research Institute did the toxicokinetic analysis. In concordance, Vol.14/pg 287.

SPECIES/NUMBER OF SUBJECTS/SEX:
Wistar rats. Control, saline injection, 10/sex; treated groups, 23/sex, (5/sex toxicity, 18/sex pharmacokinetics).

DOSES/ROUTE OF ADMINISTRATION: All rats had indwelling jugular catheters: iv dosing escalated from 1 μg/kg/min GI87084B (days 1 and 3); 5 μg/kg/min GI87084B (days 3 and 4); 10 μg/kg/min GI87084B (days 5 through 8).

PROCEDURE:
The animal were observed twice daily and had food and water available *ad libitum*. Saline infusion started approximately 3 days prior to test initiation. Food consumption was recorded daily and body weight were taken at the start of each dose escalation phase.

Toxicokinetic samples were taken from 3 animals/sex by cardiac puncture on days 1, 3, 5 and 8 of testing after pentobarbital anesthesia and no necropsy was done on these animal from the toxicokinetic group.

On day 9 the surviving toxicity group was euthanized, bled for hematology and clinical tests and necropsied. Organs were weighed and microscopic examination of selected tissues was performed on all animals.

RESULTS:

The changes that appeared to differ significantly between control and treatment groups are presented in the following table:

organ system	absolute weights		wgt relative to BW	
	♂	♀	♂	♀
LF ADRENAL	NS -8.8%	P<.01 - 24%	NS -1%	P<.01 -19%
RT ADRENAL	NS + 9%	NS -18%	NS +19%	NS -12%
SPLEEN	NS -26.5%	P<.01 - 19%	NS -21%	NS -16%
LF KIDNEY	P<.05 -19%	P<.01 - 19%	P<.05 -13%	NS -13%
RT KIDNEY	P<.05 -21%	P<.01 - 20%	P<.05 -15%	NS -14%
PROSTATE	P<.01 -44%		P<.02 -39%	
LF OVARY		P<.01 - 35%		P<.02 -31%
RT OVARY		NS -23%		NS -19%
UTERUS/CERVIX		P<.05 - 44%		NS (p<.1) - 40%

Clinical Chemistry	terminal concentrations	
	♂	♀
Blood Glucose	$p<.001$ +55%	$p<.001$ +70%
Total protein	$p<.01$ +6.8%	$p<0.02$ +11.9%
Alkaline phosphatase	$p<.001$ -47.9%	$p<.02$ -46.4%

DISCUSSION:

The drug effects in this second pilot study were not severe and were generally in the opposite direction from the trends in the initial pilot study. i.e. reduced adrenal weights versus increased weights in the initial pilot. This difference may also reflect the increased doses of remifentanil. The increased dose may also have induced a decreased kidney weights and sex organs in both sexes.

The clinical chemistry changes in blood glucose and alkaline phosphatase were noted by the sponsor. The increase protein content was not noted and none of the changes were explained in context of drug administration.

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GI87084B: TWO WEEK CONTINUOUS INTRAVENOUS INFUSION TOXICITY STUDY IN RATS

(NDA 15/001)

STUDY/REPORT NUMBER: UTX/94/050

NDA #20-630

STUDY SITE:

GLP/QA SPECIFICATIONS: In concordance at
and at Glaxo Research Institute for pharmacokinetic analysis (NDA 15/9).

SPECIES/NUMBER OF SUBJECTS/SEX/DOSE:
Wistar rats, Crl(WI)BR. Control, saline injection, 15/sex; treated groups: high dose (5 µg/kg/min), 21/sex, (15/sex toxicity, 6/sex pharmacokinetics); Low and Medium doses (0.1 and 1.0 µg/kg/min), 16/sex (10/sex toxicity and 6/sex pharmacokinetics). In the control and high dose toxicity groups of 15/sex, 5/sex were treated for the 15 days and then observed for 2 weeks post-treatment.

PROCEDURE:
All rats had indwelling jugular catheters implanted about three weeks prior to study initiation. The infusion of sterile saline started two days prior to the start of testing at the infusion rate used for drug administration, 1 ml/kg/hour.

At initiation of testing, the animals were infused continuously with saline or remifentanil at 0.1, 1.0 or 5 µg/kg/min, in volume of 1 ml/kg/hour as calculated from body weights on days 1, 8 and 15. The pharmacokinetic blood samples were collected by cardiac puncture 4 hours after start of infusion on day 1 (3/sex) and during infusion on day 15 (3/sex). No necropsy followed blood collection.

Clinical Hematology screens evaluated the following parameters: Red blood cell count, Hemoglobin, Hematocrit, Mean corpuscular volume, Mean corpuscular hemoglobin, Mean corpuscular hemoglobin concentration, Platelet count, Prothrombin time, Activated partial thromboplastin time, White blood cell count, Nucleated red blood cell count, Corrected white blood cell count, Segmented neutrophil count, Band neutrophil count, Lymphocyte count, Monocyte count, Eosinophil count, Basophil count.

Clinical Chemistry parameters measured were:
Glucose, Urea nitrogen, Creatinine, Total protein, Albumin,

Globulin, Total bilirubin, Direct bilirubin, Indirect bilirubin, Cholesterol, triglycerides, Total lipids
Aspartate aminotransferase, Alanine aminotransferase, Alkaline phosphatase, Calcium, Inorganic phosphorus, Sodium, Potassium, Chloride.

Clinical Urinalysis measured parameters were: Urine volume, Specific gravity, Urine pH.

RESULTS:
Three male rats were found dead or euthanized during the study. One high dose rat was found dead on day 8 and probably died of respiratory depression. One medium dose subject died on day 8 and one on day 26, both of systemic bacterial infections.

The test solutions were sampled before and after use and all solutions did not reach the criteria of ±20%. The only high dose solution not reaching criteria was found to contain only 62 percent of the desired concentration in the predosing solution, but 84% postdosing sample. This was used in the dosing days 11-14. Of the five solution failing pre or post dosing concentration, no solution failed both pre and post.

Toxicokinetic analyses showed that blood concentrations of GI87084 (at doses up to and including 5.0 μgGI87084B/kg/minute were all below 1ng/ml (the limit of quantification). The blood levels of GR90291 were similar both between sexes and sampling occasions (Days 1 and 15) and increased in an approximate dose-related manner as shown below:

Summary of Mean Blood Concentrations of GR90291 (ngGR90291X/ml) Approximately Four Hours after Start of infusion on Days 1 and 15

Group	Dose*	Sex	Day 1	Day 15
1	0	M	BQL (n=3)	BQL (n-3)
	0	F	BQL (n=3)	BQL (n=1)
2	0.1	M	4.18 (n=3)	1.88 (n=3)
	0.1	F	2.13 (n=3)	1.36 (n=3)
3	1.0	M	16.2 (n=3)	18.9 (n=3)
	1.0	F	15.4 (n=3)	27.9 (n=2)
4	5.0	M	176 (n=3)	87.9 (n=3)
	5.0	F	77.3 (n=3)	70.8 (n=3)

*(ngGI87084B/kg/min)

Cumulative exposures to GI87084 could not be determined because all blood concentrations of GI87084 were below the limit of quantification. Cumulative exposures to GR90291 over the course of the study, taking the duration of dosing as approximately 360 hours (15 days x 24 hours), were as follows:

Cumulative Exposure to GR90291

Sex	Dose (µgGI87084/kg/min)	Mean conc. ng GR90291/ml*	Estimate total exposure (h.ngGR90291/ml)
Male	0.1	3.03	1091
Female	0.1	1.75	630
Male	1.0	17.6	6336
Female	1.0	21.7	7812
Male	5.0	132	47520
Female	5.0	74.1	26676

* Average of blood concentrations Day 1 and Day 15

The major behavioral changes during treatment were irregular respiration in the high dose group. Remifentanil infusion did not induce bodyweight changes at any dose in the female rats. However, the high dose group of male rats was 7.5% lighter at one week, 7.9% lighter at two weeks and 3.3% lighter after the first week of non-treatment for the 5 recovering males. The bodyweight gain decrease was significantly different the first week and the total two week treatment segment. The differences in bodyweights were less than 10% and the high dose group gained 35.6% less during the two week treatment. Although statistically significant these decreased weight gains probably have no bearing on the acute use of remifentanil. The differences in bodyweight gains reversed during recovery and at the end of two weeks, the bodyweight gains were only an insignificant 6% less for the high dose group. The food consumption of the groups paralleled the bodyweight gains.

The results in Hematology screens did not indicate any significant treatment related changes at the end of the 15 days of treatment. However, in the Clinical Chemistry screens, the serum glucose levels were elevated on Day 16 with both the mid and high dose groups. The effect was reversed in the recovery animals after 2 weeks without remifentanil. The reversal was not only the lowering of the glucose level in the treated animals, but glucose levels in the control group were higher than either the controls at Day 16 or the high dose group. This requires further clarification. The results are presented in the following table:

Mean Serum Glucose (mg/dl)				
Dose[a]	Day 16		Day 31	
	male	female	male	female
0	99 (76-130)	76 (55-123)	151 (133-164)	133 (109-165)
0.1	92 (74-112)	84 (67-113)	-	-
1.0	115 (95-137)	105* (80-130)	-	-
5.0	141* (111-163)	117* (48-153)	128* (115-135)	129 (110-148)

* statistically significant [a]G187084B/kg/min

The histology of the pancreas in the mid and high dose groups indicated moderate to severe decreases in acinar cell zymogen granules which are involved in proteolytic enzyme production rather than insulin. The sponsor stated that the changes in zymogen granule number were of no pathological significance as they were not different from control after the two week recovery in addition to the fact that the number of granules shows considerable variation in normal conditions. However, there was no pancreas weights reported and no suggestions as to what caused the increased blood glucose and if this was related to any decreased pancreatic insulin production or release.

Other Clinical Chemistry parameters which after two week of dosing were: Urea nitrogen, Creatinine, Total Protein, cholesterol, sodium and potassium as presented in the following table:

Sex	Day	Dose	glu	urea Nitro	creat	T prot	chol	Na^+	K^+
♂	16	low	↓	↓	↓*	↓	↑	±	↓
♀			↑	↑	±	±	±	±	±
♂		med	↑	↓	↓	↑	↑	±	±
♀			↑*	↑	±	↑	↑	±	±
♂		hi	↑*	↓*	↓*	↑	↑*	↓*	↑*
♀			↑*	↓	±	↑*	±	±	↑
♂	31	hi	↓*	↑	±	±	±	±	±
♀			↓	↓*	±	↓*	↑	±	↓*

* significantly different from control

The Urinalysis did not demonstrate any treatment induced changes in the parameters measured; urine volume, specific gravity or pH.

The absolute organ weights did not differ significantly to any degree except for kidney, lung and liver weights in the high dose

males and the relative organ to body weight did not differ from control groups. This indicates decreased organ weights merely reflected the decreased body weights observed in the high dose group males.

DISCUSSION:
The major treatment related changes appeared to be the increased blood glucose levels, the decreased pancreatic acinar cell zymogen granules, decreased body weight and food consumption.

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GI87084B (opioid agonist): Pilot continuous intravenous infusion toxicity study in dogs

(V21/001)

STUDY/REPORT NUMBER: UTX/94/052

STUDY SITE:

GLP/QA SPECIFICATIONS: accordance 21/16

SPECIES/NUMBER OF SUBJECTS/SEX: Beagle Dogs 4/sex in control and treatment groups.

DOSES/ROUTE OF ADMINISTRATION: Escalating dose by indwelling iv catheter inserted 1 to 2 weeks prior to study initiation. On days 1-3, 0.01 µg G187084B/kg/min; Days 4-7, 0.05 µg; Days 8-10, 0.1 µg; Day 11, 0.5 µg for 5 hours and severe clinical signs seen and dose was reduced to 0.1 µg through Day 14; Days 15-18/19, 0.25 µg.

PROCEDURE:
The infusion pumps were set to deliver solutions at 1ml/kg/hour and the control group received normal saline. The animals were observed at least twice daily and an additionally at 30 minutes and 1 hour after the start of a new concentration.

Clinical Hematology screens evaluated the following parameters:

Red blood cell count, Hemoglobin, Hematocrit, Mean corpuscular volume, Mean corpuscular hemoglobin, Mean corpuscular hemoglobin concentration, Platelet count, Prothrombin time, Activated partial thromboplastin time, White blood cell count, Nucleated red blood cell count, Corrected white blood cell count, Segmented neutrophil count, Band neutrophil count, Lymphocyte count, Monocyte count, Eosinophil count, Basophil count.

Clinical Chemistry parameters measured were:
Glucose, Urea nitrogen, Creatinine, Total protein, Albumin, Globulin, Total bilirubin, Direct bilirubin, Indirect bilirubin, Cholesterol, Triglycerides, Total lipids,
Aspartate aminotransferase, Alanine aminotransferase, Alkaline phosphatase, Calcium, Inorganic phosphorus, Sodium, Potassium, Chloride.

Clinical Urinalysis measured parameters were: Urine volume, Specific gravity, Urine pH.

RESULTS:
No animals died during the study and although about 50% of the dogs had some interruption of the infusion due to mechanical problems, all received 95% to 105% of the intended dose.

No significant changes were observed in the Clinical hematology, Clinical Chemistry or Urinalysis screens. The absolute organ weights did sometimes differ significantly, but when expressed as percent body weight, there was no significant difference. The results were used as a basis for the following study UTX/94/056.

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GI87084B: TWO-WEEK CONTINUOUS INTRAVENOUS INFUSION TOXICITY STUDY IN DOGS (V21/242)

STUDY/REPORT NUMBER: UTX/94/056

STUDY SITE:

GLP/QA SPECIFICATIONS: concordance V21/249,263

SPECIES/NUMBER OF SUBJECTS/SEX:
Beagle dogs, 6/sex in control and high dose groups, 4/sex in low and mid dose groups. Two/sex were used as recovery groups from both the control and high dose groups.

DOSES/ROUTE OF ADMINISTRATION:
Intravenous administration through indwelling jugular catheters implanted 1 to 2 weeks prior to test initiation. The low dose was 0.01 µg/kg/min GI87084B, the mid dose 0.05 and the high dose 0.25 µg/kg/min GI87084B. The control was sterile saline and the infusion rate for all was 1 ml/kg/hour.

PROCEDURE:
The animals were observed at least twice daily and electrocardiograms were taken for each dog prior to initiation and after at least 14 days of treatment. Blood samples were taken for toxicokinetics 4 hours after the initiation of infusion and while still infusing on day 15. Animals not designated as recovery dogs were euthanized on days 16/17 and the recovery animals on day 34.

Clinical Hematology screens evaluated the following parameters: Red blood cell count, Hemoglobin, Hematocrit, Mean corpuscular volume, Mean corpuscular hemoglobin, Mean corpuscular hemoglobin concentration, Platelet count, Prothrombin time, Activated partial thromboplastin time, White blood cell count, Nucleated red blood cell count, Corrected white blood cell count, Segmented neutrophil count, Band neutrophil count, Lymphocyte count, Monocyte count, Eosinophil count, Basophil count.

Clinical Chemistry parameters measured were:
Glucose, Urea nitrogen, Creatinine, Total protein, Albumin, Globulin, Total bilirubin, Direct bilirubin, Indirect bilirubin, Cholesterol, Triglycerides, Total lipids,
Aspartate aminotransferase, Alanine aminotransferase, Alkaline phosphatase, Calcium, Inorganic phosphorus, Sodium, Potassium, Chloride.

Clinical Urinalysis measured parameters were: Urine volume,

Specific gravity, Urine pH.

RESULTS:
The following three tables present the exposure of the dogs to remifentanil (Gl87084B) and the major metabolite GR90291.

Mean Blood Concentrations ngGl87084B/ml			
Sex	Dose (μgGl87084/kg/min)	Day 1	Day 15
Male	0	BQL (N=6)	BQL (N=6)
Female	0	0.1[a]	BQL (N=6)
Male	0.01	BQL (N=4)	BQL (N=4)
Female	0.01	BQL (N=4)	BQL (N=4)
Male	0.05	0.19 (N=4)	0.36 (N=3)
Female	0.05	0.19 (N=4)	0.15 (N=4)
Male	0.25	1.20 (N=6)	0.59 (N=6)
Female	0.25	0.94 (N=6)	0.68 (N=6)

BQL - below quantification level
[a] n=1 other 5 dogs BQL

Mean Blood Concentrations ngGR90291x/ml			
Sex	Dose (μgGI87084/kg/min)	Day 1	Day 15
Male	0	BQL (N=6)	BQL (N=6)
Female	0	BQL (N=6)	BQL (N=6)
Male	0.01	0.70 (N=4)	1.49 (N=4)
Female	0.01	0.59 (N=4)	0.65 (N=4)
Male	0.05	3.19 (N=4)	6.38 (N=4)
Female	0.05	3.48 (N=4)	3.13 (N=4)
Male	0.25	11.6 (N=6)	8.81 (N=6)
Female	0.25	13.5 (N=6)	14.5 (N=6)

BQL - below quantification level

Sex	Dose GI87084B (μg/kg/min)	Mean concentration ng/ml[a]		Estimate total exposure (h.ng/ml)	
		GI87084B	GR90291	GI87084B	GR90291
Male	0.01	BQL	1.01	BQL	435.6
Female	0.01	BQL	0.62	BQL	245.5
Male	0.05	0.28	4.79	110.9	1896.8
Female	0.05	0.17	3.31	67.3	1310.8
Male	0.25	0.90	10.21	356.4	4043.2
Female	0.25	0.81	14.0	320.8	5544.0

The bodyweight gains were less for the high dose animals and significant weight loss occurred with both male and females in the initial week. The overall two week weight gain was also less

but only statistically significant for the males of the high dose group, 0.25μg Gl87084B/kg/minute. The food consumption was parallel the weight profile. No significant differences from control bodyweight gain were observed in the low and mid dose groups.

Upon analysis of the EKG records, one veterinary cardiologist detected T-wave reversal in 3 of the high dose dogs however, a second cardiologist found these changes in all groups and the sponsor concludes there is no difference induced by the compound.

No significant differences involving remifentanil treatment were observed in the Hematology screens either after dosing or in the recovery group.

In the Clinical Chemistry data, there was significant reduction in Total blood proteins in both mid and high dose males, but not females. No elevated levels of glucose or cholesterol or changes in electrolytes were observed in the treated groups.

The organ-to-body weights ratios suggested a greater relative adrenal weight with both the low and high dose group males although only the right adrenal ratio was statistically significant. The difference was not evident in the females.

DISCUSSION:
The data shows very few effects attributable to the drug treatment, except for some possible T-wave polarity reversal and body weight loss. The sponsor concludes the NOEL is 0.01 μg/kg/min of GI87084B although the high dose was 1/20th, by body weight, that used in rats.

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GI87084B: Bolus intrathecal maximum repeatable dose (MRD) toxicity study in dogs (V30/001)

STUDY/REPORT NUMBER: UTX/94/058

NDA #20-630

STUDY SITE:

GLP/QA SPECIFICATIONS: In compliance V30/10,19 Batch 37126

SPECIES/NUMBER OF SUBJECTS/SEX: Beagle dogs, 2/sex/treatment group.

DOSES/ROUTE OF ADMINISTRATION and **PROCEDURE:**
The dogs were implanted with intrathecal catheters at L3-4 and the catheters exited in the dorsal neck region. Increasing bolus doses, starting at 100 μg GI87084B + 750 μg glycine and doubled daily until side effects, respiratory depression or seizures occurred. The daily intrathecal injections were given over a 20 to 40 second interval. All administrations were in the volume of 0.3 ml followed by 0.3 ml of saline to clear the catheters. A glycine vehicle control was used and also a 0.9% Saline control.

When the maximum repeated dose (MRD) was ascertained the dogs were infused daily with this dose for a minimum of 14 days. The dogs were observed for overt evidence of hind limb dysfunction, pain and analgesia was determined by skin twitch response latencies. The heart and respiratory rates and blood pressure measurements were recorded prior to daily administrations and 10 minutes post-administrations. On day 18, after two week of the MRD, the animals were euthanized and tissue sections macroscopic examined and preserved. The brain and section of spinal cord were sent to the sponsor for processing. Blood and CSF samples were also sent to sponsor for assay of GI87084B. The measured parameters on Days -3 and 18, were as follows:

Clinical Hematology :
Red blood cell count, Hemoglobin, Hematocric, Mean corpuscular volume, Mean corpuscular hemoglobin, Mean corpuscular hemoglobin concentration, Platelet count, White blood cell count, Nucleated red blood cell count, Corrected white blood cell count, Segmented neutrophil count, Band neutrophil count, Lymphocyte count, Monocyte count, Eosinophil count, Basophil count.

Clinical Chemistry:

Glucose, Urea nitrogen, Creatinine, Total protein, Albumin, Globulin, Total bilirubin, Direct bilirubin, Indirect bilirubin, Cholesterol, Triglycerides, Total lipids, Aspartate aminotransferase, Alanine aminotransferase, Alkaline phosphatase, Calcium, Inorganic phosphorus, Sodium, Potassium, Chloride.

RESULTS:

The adverse effects happened at 1600 μg GI87084B when one dog seized after administration. The maximum repeated dose was determined to be 800 μg and this was repeated daily for 14 days. No dogs died due to administration of GI87084B and all solution were within the ±20% of intended dose.

Starting with the lowest dose used, 100μg, the twitch skin response was completely blocked by GI87084B and this persisted throughout the 18 study. The twitch response returned to normal within 24 hours of each administration. The glycine solvent group demonstrated an increased twitch latency, most prominent days 13 and 17, and the saline control group demonstrated no effect.

The remifentanil group demonstrated typical symptoms of μ-agonist activation; sedation, suppression of motor activity, loss of hindlimb weight bearing and loss the ability for coordinated limb movement. This returned to normal within 24 hours. The heart rate was reduced after injection. Depression of arousal occurred within 1.3 to 4.3 minutes of injection and reversed within 18 to 35 minutes.

The glycine group also demonstrated loss of hind limb coordination with complete recovery within 24 hours. This group also demonstrated agitation and exaggerated pain behavior when touched lightly on caudal portion of the body. This started upon each glycine injection, persisted for more than 10 minutes after completion and returned to normal within 24 hours. This agitation following injection could have been due to the glycine, the pH of the glycine solution (3.5), osmolarity of the solution or any combination. The saline group demonstrated no abnormal behavior. The heart rate increased both pre and post injection

and pre-injection was probably anticipatory to the increased pain response post injection. The post injection response included increased systolic, diastolic and mean blood pressures(V30/05).

On Day 18, the mean CSF concentrations of GI87084B were 16.2 ng/ml, range of 4.47 to 24.8 ng/ml, and exceeded the blood concentrations of 22.3 to 32.1 ng/ml, mean of 27.8 ng/ml. This was taken as indication that remifentanil is rapidly removed from the CSF.

No GI87084B was detected in the blood or CSF of the saline animals, however CSF of two dogs in the glycine control group did have GI87084B concentrations of 3.14 and 436 ng/ml respectively , but none in the blood. Because similar CSF concentrations in the remifentanil group resulted in detectable blood levels, the sponsor suggested the problem was in contamination of the samples rather than a mistake in dosing of the glycine animals. The increase in CSF protein concentration in dogs of the remifentanil and glycine groups was attributed to contamination with peripheral blood. Histopathology of the spinal cords revealed symptoms of chronic meningeal inflammation but no group specific changes.

No significant differences were evident in either the Clinical Chemistry or Hematology screens. The CSF samples on Day -3 and 18 did not differ significantly although the small sample size of 2/sex, the mix of some samples with blood and the evidence of sporadic meningeal inflammation did not make any comparison realistic. There were no test-related changes in systolic, diastolic or mean blood pressure over the 19 days of injection (V30/36).

DISCUSSION:

The Maximum Repeatable Dose (MRD) for bolus intrathecal administration with glycine excipient was 800μg GI87084B. The analgesic effects were evident at the lowest dose tested, 100μg and sedation, muscle weakness and ataxia progressed with increasing doses. No significant changes were evident in hematology or clinical chemistry screens and all dogs were normal in pain-response and awareness within 24 hours of administration.

Glycine, 12 mg in 0.3 ml of 0.9% saline, was found to induce pain response and hyperalgesia. This was not seen when 0.8 mg of GI87084B was in the solution an this probably is the result of μ-agonist activation inhibiting the pain sensation.

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Microhemorrhages in the brains of dogs:

Microhemorrhages were reported to occur in the brains of dogs treated with remifentanil. The hemorrhages were small, 20 to 200 microns, and could appear in any brain region although Hippocampus, Caudate, Substantia Nigra, Cerebellum and Thalamus/Hippocampus were the most affected sites. The following table presents the data of the animals from the largest dose group and both single and multiple administrations are combined:

DOGS WITH MICROHEMORRHAGES (6-8 studies)			
Dose (mg/kg)	N	N with hemorrhages	N with 2+ hemorrhages
0	49	5 (10%)	1 (2%)
0.1-0.12	23	12 (52%)	10 (43%)
1	31	26 (84%)	18 (58%)

These effects prompted a Clinical Hold on the studies until the sponsor submitted data which supported their contention that the microhemorrhages were due to the hypoxia produced by the remifentanil induced respiratory depression. The request was for both post- bolus and after prolonged infusion. The following table summarizes those results:

Dogs with Microhemorrhages - test studies			
Dose (mg/kg)	N	N with hemorrhages	N with 2+ hemorrhages
0	20	2 (10%)	1 (5%)
1 (UnVent)[1]	10	5 (50%)	4 (40%)
1 (V - bolus)[2]	5	0	0
0.2 (V - inf)[3]	5	1 (20%)	0

[1] Unventilated [2]ventilated - bolus injection

[3] ventilated - infusion 20 µg/kg/min X 4 hours

The results were considered adequate by the pharmacologist group from HFD-007, although this reviewer was not completely satisfied due to the small numbers and lack of statistical significance. The tissue slices were reviewed by CFSAN pathologists and they agreed with the microhemorrhage designations of the sponsor.

The pharmacologists reviews are attached in appendix 1 and the CFSAN pathologists in appendix III.

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SUMMARY:

The major alterations observed after chronic administration of remifentanil to rats were: reduced absolute and relative epididymal weights at 2.5 mg/kg/day and sloughed epithelial cells in epididymal tubules after 0.25, 1 and 3.5 mg/kg/day for four weeks. In addition, continuous infusion of remifentanil to rats lead to a reversible increase in serum glucose, upto 54%.

Cerebrovascular toxicity was observed in unventilated dogs but not rats. In the control dogs of 8 studies (N=49), 10% were observed with microhemorrhages and 2% with 2 or more. In the remifentanil groups with 0.1 to 0.12 mg/kg (N=23), the relative percentages were 52% and 43%. This increased to 84% and 58% after the dose of 1 mg/kg (N=31) and a Clinical Hold was imposed

until the sponsor demonstrated that ventilation reduced the hemorrhages to control levels. This was submitted and the effects emphasize the need for ventilation when using this compound.

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The following studies were reviewed previously upon submission, and the reviews are included in appendix as noted:

appendix II

UTX/90/004	GI87084B (opioid): A two-week intravenous toxicity study in the rat

appendix I

UTX/92/014	GI87084B (opioid agonist): 4-Week intravenous injection toxicity study in rats
UTX/92/015	GI87084B (opioid agonist): 4-Week intravenous injection toxicity study in dogs
UTX/93/027	GI87084B (opioid agonist): Intravenous maximum repeated dose (MRD) toxicity study in dogs with Route 1 synthetic material
UTX/92/024	GI87084B (opioid agonist): Intravenous maximum repeated dose (MRD) toxicity study in dogs
UTX/93/003	GI87084B (opioid agonist): Repeat 4-week intravenous injection toxicity study in dogs
UTX/93/058V2	Assessment of microhemorrhages in the brains of dogs following administration of GI87084B (opioid agonist)
UTX/94/021	GI87084B: Pilot acute bolus intravenous toxicity study in non-ventilated male dogs
UTX/94/022	GI87084B (remifentanil hydrochloride), Gl1

	17877A (alfentanil hydrochloride): Acute bolus intravenous toxicity study in non-ventilated male dogs
UTX/94/020	GI87084B (remifentanil hydrochloride) and GI1 17877A (alfentanil hydrochloride): 7-Day bolus intravenous toxicity study in non-ventilated dogs
UTX/94/047	GI87084B (opioid agonist): Acute bolus intravenous toxicity study in ventilated male dogs
UTX/94/049	GI87084B: Intravenous infusion toxicity study in ventilated male dogs

Appendix I

Collection of reviews of microhemorrhage studies.

Appendix III

CFSAN pathologists report of microhemorrhage studies.

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The following studies were read but not formally reviewed, although selected data is presented in summaries:

UDM/94/028	GI87084B (opioid agonist): Two week continuous intravenous infusion toxicity study in rats -- Drug Metabolism Report	48/016
UDM/90/003V2	Blood concentrations of GI87084B in male and female rats after the fourteenth daily intravenous dose of GI87084B	48/34
UDM/92/083	GI87084B (opioid agonist): A four-week intravenous injection toxicity study in rats -- Drug Metabolism Report	48/044

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SPECIAL TOXICITY STUDIES

GI87084B (OPIOID AGONIST): ACUTE PERIVASCULAR IRRITANCY STUDY IN MICE (V34/023)

STUDY/REPORT NUMBER: UTX/93/035

STUDY SITE:

GLP/QA SPECIFICATIONS: IN ACCORDANCE (V34/31)

SPECIES/NUMBER OF SUBJECTS/SEX: Mice, 3/sex/dose

DOSES/ROUTE OF ADMINISTRATION: 0.5, 5, or 50 μg G187084B/ml; .03 ml/mouse; single subcutaneous injection into tail adjacent to vein. Thiamyl sodium, 5%, as the positive control.

PROCEDURE: A single injection of GI87084B in sterile water and 5% dextrose(D5W), the vehicle control was sterile water and D5W and the positive control was Thyiamyl sodium in sterile water. On the fourth day, the animals were euthanized and the tail examined macroscopically and microscopically.

RESULTS: No irritation signs, red or tan discolorations or red depressions at the injection site, were seen in either vehicle control or any GI87084B dose group. In the positive control, discoloration was evident in 2/3 male and depressed reddened areas in 1/3 male and 3/3 female.

DISCUSSION: The use of D5W and instead of the HCl acidified glycine-mannitol solvent makes this test of limited utility.

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NDA #20-630

GI87084B INJECTION *IN VITRO* HEMOLYSIS AND PLASMA COMPATIBILITY TESTS (V34/001)

STUDY/REPORT NUMBER: WPT/90/107

STUDY SITE: Glaxo Research Ltd - Ware - Herts U.K.

GLP/QA SPECIFICATIONS: inspection V34/14.

SPECIES/NUMBER OF SUBJECTS/SEX: Human volunteer blood, 2 male/ 2 female.

DOSES/ROUTE OF ADMINISTRATION: GI87084B for injection, 0.5mg/ml, complete with mannitol, glycine, and HCl.

PROCEDURE: One ml blood + 1 ml GI87084B solution, 1% saponin solution was the positive control and saline was the negative control. The samples were incubated at 37°C for 45 minutes and centrifuged at 1200g for 10 minutes. The hemoglobin content of the supernatant was measured by spectrophotometer.

The plasma potassium levels were measured as sign of RBC membrane leakage and for plasma compatibility; 1 ml of plasma + 1ml of GI87084B solution were incubated at 37°C and examined for any signs of flocculation, precipitation or coagulation.

RESULTS:
There was no significant difference in hemoglobin content of the supernatants. Although the 16.8% increase in potassium levels were statistically significant ($P<0.01$), the sponsor did not think this was biologically significant and it did not compare to the 1200% increase of the positive control. In the compatibility test a slight precipitate formed but completely dissolved when mixed with another 1ml sample of plasma.

DISCUSSION:
GI87084B has no hemolytic potential and the chances of precipitate formation *in vivo* is very slight.

GI87084B (OPIOID AGONIST): ACUTE INTRA-ARTERIAL IRRITANCY STUDY IN RABBITS (V34/124)

STUDY/REPORT NUMBER: UTX/90/017

STUDY SITE:

GLP/QA SPECIFICATIONS: V34/131, 138

SPECIES/NUMBER OF SUBJECTS/SEX: Three groups of 2 ♀ rabbits.

DOSES/ROUTE OF ADMINISTRATION: 0.5, 5 or 50 μg/ml, 1 ml/ear, single intra-arterial administration.

PROCEDURE:
A single dose of GI87084B was given into the left ear and a single dose of solvent was given in the right ear. Four days later, the animals were euthanized and the ear tissue prepared for histological examination.

RESULTS:
Behavioral depression was observed at the 50μg dose and some hemorrhages were observed in both ears. The latter was attributed to the injection stress and not compound related.

The macro- and microscopic examinations of the ear tissue did not demonstrate any intra-arterial irritation at doses to 50μg/ml of GI87084B in the rabbit.

DISCUSSION:
No intra-arterial irritation was observed at doses to 50μg/ml of GI87084B in the rabbit.

Hydrolysis

The rate of *in vitro* hydrolysis was determined in dog and human blood. The $t_{½}$ was 56.7 and 65.4 minutes, respectively and very short in the rat, 0.5 minutes. (V48/121)

The $t_{½}$ was twice as long in human plasma than in whole blood and if the blood had been previously heated, the $t_{½}$ was like plasma. This supports the idea that hemolysis is by esterases in the RBCs not plasma. Remifentanil was not hydrolyzed by human cholinesterase (pseudocholinesterase), butyrylcholinesterases, acetylcholinesterase, carbonic anhydrases I or II. The hydrolysis rate in human blood was not affected by the addition of the main metabolite GR90291, however, addition of human serum albumin did delay hydrolysis in serum. (V48/403).

Protein-binding

In human and canine blood, protein-binding was found to be concentration dependent:

Protein-Binding of Remifentanil in Blood			
concentration ng/ml	Dog	Human	
	%GI87084B bound	%GI87084B bound	%GI90291 bound
1	40.4	92.2	100.0
10	32.4	84.8	98.2
100	34.2	82.2	33.5
1000	25.0	86.4	46.4
10000	23.4	66.6	30.2

Protein binding in human blood (V49/84) UDM/95/002			
GI87084 ng/ml	average percent bound (N=6)	percent bound to albumin (N=2)	% bound to α-1-acid glycoprotein
2	72	16	44
10	72	14	38
25	71	15	42
50	71	15	47

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SUMMARY:

Remifentanil was not found to be irritating to the rabbits skin or upon intra-arterial administration. Intravenous and extravascular dose produced only slight irritation in the rabbit and none in the mouse. While remifentanil did not cause irritation to the rabbits eyes, it was absorbed.

Remifentanil did not cause hemolysis in human blood samples and although a slight precipitate formed, this was re-dissolved upon addition of more blood.

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The following studies were reviewed previously upon submission, and the reviews are included in appendix as noted:

appendix II

WPT/90/107	GI87084B injection: In vitro haemolysis and plasma compatibility tests
UTX/90/006	GI87084B (opioid): Acute intravenous irritation study in the rabbit

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NDA #20-630

The following studies were read but not formally reviewed, although selected data is presented in summaries:

UTX/93/012	GI87084B (opioid agonist): Dermal sensitization study in the guinea pig -- Buehler method	34/232
UTX/93/050	GI87084B (opioid agonist): Acute dermal toxicity study in rabbits	34/271
UTX193/049	GI87084B (opioid agonist): Acute dermal irritation study in rabbits	35/001
UTX/93/016	GI87084B (opioid agonist): Ocular irritation study in rabbits	35/037
UDM/94/037	GI87084B: Intravenous infusion toxicity study in ventilated male dogs	48/177
UDM/94/005	GI87084B (opioid agonist): Comparison of pharmaco kinetics of route 1 material and route 2 material administered by intravenous injection (0.05mg/kg) to male beagle dogs	48/244
UDM/94/030	GI87084B (remifentanil hydrochloride), GI117877A (alfentanil hydrochloride): Acute bolus intravenous toxicity study in non-ventilated male dogs -- Drug Metabolism Report	48/289
UDM/94/036	Acute bolus intravenous toxicity study in ventilated male dogs -- Drug Metabolism Report	48/304
UDM/94/031	GI87084B (remifentanil hydrochloride), Gl1 17877A (alfentanil hydrochloride): 7-Day bolus intravenous toxicity study in non-ventilated dogs -- Drug Metabolism Report	48/329

NDA #20-630

MUTAGENICITY STUDIES

GI87084B (OPIOID AGONIST): SALMONELLA/MAMMALIAN MICROSOME REVERSE MUTATIONAL ASSAY (LOT C1762/263/2) WITH A CONFIRMATORY ASSAY (V46/060)

STUDY/REPORT NUMBER: UTX/92/021

STUDY SITE:

GLP/QA SPECIFICATIONS: V46/08,09

SPECIES: *Salmonella typhimurium*. Strains: TA1535, TA1537, TA1538, TA98, TA100. TA98 and TA100 were tested in the presence of pKM101 plasmid.

DOSES: 5, 10, 50, 100, 500, 1000, 2500 and 5000 µg/plate, with and without S-9 fraction from Arochlor treated rat livers.

METHODS: The method were as described by Ames et.al..., Mutation Research 31:347-64(1975). The number of revertant colonies were determined after 48 to 72 hours of incubation with compounds at 37°C.

RESULTS:
All specimens had normal lawns and none had precipitate. The relative cloning efficiency was from 88% to 114% with no dose relationship and all positive controls, 2-NF, 2-AA, NaAz and 9-AAc, were active in creating mutant reversals.

No concentration of GI87084B produced any significant increase in revertant colonies over the respective solvent control.

DISCUSSION:
GI87084B was non-toxic to 5000μg/plate and not mutagenic in the *Salmonella typhimurium* Gene mutation assay.

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GI87084B (OPIOID AGONIST): L5178Y/TK± MOUSE LYMPHOMA IN VITRO MAMMALIAN CELL MUTAGENESIS ASSAY (V46/218)

STUDY/REPORT NUMBER: UTX/94/048

STUDY SITE:

GLP/QA SPECIFICATIONS: V46/234

PROCEDURE:
L5178Y/TK$^{+/-}$ mouse lymphoma were exposed to test solutions for four hours both with and without S9, a post-mitochondrial enzyme fraction. The cells were then washed and incubated at 37°C for 14 days. The positive control mutagens were hycanthone and cyclophosphamide.

The doses tested on the initial assay were from 382 μg GI87084B/ml to 1216 with S9 activation and 1175 to 4510 μg GI87084B/ml without S9. The assay was repeated and the dose range was from 20 to 716 with S9 and 1734 to 5000 without S9. These doses were calculated from analysis of the dosing solution by the sponsor.

RESULTS:
In the initial testing, no increase in mutations were detected without S9 activation and the relative total growth (RTG) of the cell cultures was 70 to 45% without S9. With S9, mutation rates increase about three-fold from the lowest dose tested, 382 μg GI87084B/ml to the sixth dose 852 μg GI87084B/ml. The RTG was 54% to 13% of control. The three higher dose also resulted in similar increases in mutation rate but the relative total growth was below 10%. The mutations appeared more in the small colonies than in the large ones. The positive controls produced 3 to 4-

fold increases in mutations.

There was no dose-response relationship in the initial testing and test was repeated, 22 months later. Again, no increased mutation rate was observed in the non-activated group to the highest dose of 5000 µg GI87084B/ml. In the S9 activated groups, there was a significant dose-related increase in mutations as counted by the Artek Automatic Colony Counter and presented in the following table:

Dose (µg GI87084B/ml)	Relative Total Growth (%)	Total Mutation Frequency ($x10^{-6}$)
solvent control	87	93
solvent control	114	91
20	108	93
39	100	78
113	69	99
203	62	132
308	52	179*
421	36	275*
527	18	299*
602	7	349*
716	5	287*
cyclophosphamide @2µg/ml	30	261*
cyclophosphamide @3µg/ml	31	257*

*induced mutant frequency ≥70 x 10^{-6} over solvent control

Based on colony size, the mouse lymphoma assay can detect two types of mutations. The large colony mutants, usually growing at a normal rate, are presumed to have small alteration of the

thymidine kinase gene; pair substitutions, frame shifts or small deletions. The small colony mutatants usually grow at a slower rate and are cytogenetically abnormal with large alterations such as chromosomal trans locations, rearrangements or very large deletions.

The positive controls produced increased mutant frequencies mainly in the small colonies. GI87084B produced increases in both the large and small colonies and when the plates were recounted manually, GI87084B produced a very large number of very small colonies, <0.3 mm, that were not counted by the machine. These results are presented in the following table:

Dose (μg GI87084B/ml)	Mutant Frequencies x 10^{-6}			
	Tiny Colonies	Small Colonies	Large Colonies	Total
solvent control	39	33	55	127
solvent control	47	25	61	133
20	45	29	59	133
39	60	29	45	134
113	68	26	68	162
203	89	42	83	214
308	476	71	98	645
421	943	133	127	1203
527	1129	152	131	1412
602	1064	154	176	1394#
716	1452	149	123	1724#
cyclophosphamide @2μg/ml	343	144	103	580
cyclophosphamide @3μg/ml	898	144	99	1141

RTG <10%

DISCUSSION:
The increase in tiny and small colonies indicates that GI87084B may be inducing large-scale chromosomal mutations. The sponsor, not the testing laboratory, suggests that this is drug-class specific and stated that due to the inactivity of GI87084B in the micronucleus assay and CHO/chromosomal aberration tests, that the effect is specific to the mouse lymphoma test.

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GI87084B: ASSAY FOR UNSCHEDULED DNA SYNTHESIS (UDS) IN RAT PRIMARY HEPATOCYTE CULTURES OBTAINED FROM MALE CRL:(WL)BR WISTAR RATS TREATED IN VIVO WITH A SINGLE INTRAVENOUS INJECTION

(V47/078)

STUDY/REPORT NUMBER: UTX/94/055

STUDY SITE:

GLP/QA SPECIFICATIONS: In accordance V47/87

SPECIES/NUMBER OF SUBJECTS/SEX: Male Wistar rats 4/dose

DOSES/ROUTE OF ADMINISTRATION: The doses were 1.6, 3.3 and 6.6 mg/kg by intra[illegible]ous injections of about 60 seconds duration in the volume 1[illegible].

Group	Number of rats	
	2-4 hour	15-16 hour
vehicle control	4	4
DMN @ 10 mg/kg	4	-
DMN @ 15 mg/kg	-	4
GI87084B 1.6 mg/kg	4	4
GI87084B 3.3 mg/kg	4	4

Group	Number of rats	
	2-4 hour	15-16 hour
GI87084B 6.6 mg/kg	4	4

DMN = dimethylnitrosamine - positive control

PROCEDURE:
Primary hepatocytes were prepared from the livers extracted 2-4 hours post injection and 15-16 hours after injection. The hepatocytes were attached to coverslips and cultured with ^{3}H-thymidine for 4 hours. The mono-layer cultures were then washed of radioactivity and non-labeled thymidine was added for 18-19 hours and the cells were prepared for analysis of nuclear labeling.

The cells were fixed to the coverslip, dipped into emulsion and dried. The covered slides were stored for 8 days in a light-tight box and the emulsions were then developed and fixed. Under a microscope at 1500X power, the nuclear grains were counted and from this number, the average number of grains observed in three nuclear-sized areas of the cytoplasm (cytoplasmic count) was subtracted. The remainder, the net nuclear grain count, was averaged from the triplicate coverslips (150 total nuclei) for each animal and averaged for each treatment.

The UDS activity is not relative to the magnitude of DNA damage, but is dependent upon the type of DNA damage and the available mechanisms of repair. Some DNA repair occurs without incorporation of new nucleic acids.

RESULTS:
All animals dosed with GI87084B stiffened and were deeply anesthetized. The side-effects noted were increased salivation at all doses, muscular twitching of one animal at the high dose and convulsions in one at the mid-dose. The recovery time, from loss to regaining of righting reflex, varied from 5 to 43 minutes and averaged 8.2, 14.5 and 11.7 for the low, mid and high doses respectively.

Ranges of hepatocyte viability, attachment efficiency and viability of attached cells were considered adequate. The data was presented as both Mean Net Nuclear Grains (NNG) and percent of cells with NNG ≥ 5 as presented in the following table:

Treatment dose	2-4 hour group		15-16 hour group	
	NNG	%NNG>5	NNG	%NNG>5
Vehicle Control	0.11	4.00	0.40	4.33
GI87084B @ 1.6mg/kg	0.31	3.00	-0.09	3.00
GI87084B @ 1.6mg/kg	0.09	2.78	0.21	5.17
GI87084B @ 1.6mg/kg	-0.12	3.17	-0.27	2.83
dimethylnitrosamine	23.11	96.33	12.61	86.05

NNG = mean Net Nuclear Grains
%NNG>5 = percent of cells with NNG>5.

DISCUSSION:
There were no indications of increased unscheduled DNA synthesis (repair) when pretreated with GI87084B. The positive control induced very significant increases in DNA repair.

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SUMMARY:

Remifentanil was not mutagenic in the *in vitro Salmonella typhimurium* gene mutation assay (Ames test), with or without S9 activation or CHO chromosome aberration test. *In vivo* micronucleus test and Unscheduled DNA Synthesis test were also negative.

In the sensitive mouse lymphoma assay, remifentanil was a mutagen in the presence of the S9 activator and not without. The S9 liver microsome fraction could have altered the route

remifentanil metabolism. The lack of any effects in other mutagenic assays indicates that remifentanil has little mutagenic potential.

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The following studies were reviewed previously upon submission, and the reviews are included in appendix as noted:

appendix II

UTX/90/007	GI87084B (opioid): Evaluation in the Salmonella typhimurium plate incorporation mutagenesis assay in the presence and absence of Aroclor induced rat liver S-9
UTX/90/008	GI87084B (opioid): Test for chemical induction of chromosome aberrations using monolayer cultures of Chinese hamster ovary (CHO) cells with and without S-9 metabolic activation
UTX/91/032V2	GI87084B (opioid agonist): In vivo test for chemical induction of micronucleated polychromatic erythrocytes in mouse bone marrow cells

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NDA #20-630

REPRODUCTIVE TOXICITY

EFFECTS OF GI87084B (REMIFENTANIL HYDROCHLORIDE) IN PREGNANT RHESUS MONKEYS AT PARTURITION: PHARMACOKINETICS, NEONATAL OUTCOME, AND MORPHOMETRIC ANALYSIS OF NEONATES AFTER CESAREAN SECTION
(NDA 5/053)

STUDY/REPORT NUMBER: UPC/94/011

STUDY SITE:

GLP/QA SPECIFICATIONS: Within GLP regulation and audited by GRI Quality Assurance Unit. (NDA 5/66; 5/85; 5/459)

SPECIES/NUMBER OF SUBJECTS/SEX:
Female Rhesus Macaques (Macaca mulatta) Maternal-fetal test procedures were initially to be done on 33 pregnant females. The maternal subjects were 5 to 15 years of age and their body weights were between 6.1 and 9.7 kg.. The gestational age was estimated by ultrasonography and they were scheduled for caesarean delivery on day 163 of the normal 166 day gestation. However, due to an unacceptable rate of spontaneous deliveries prior to term, 16/33, the operation was done on day 156 by protocol change. The remaining 17 pregnant females were reduced to 15 due to the death of one fetus prior to testing and cardiac arrhythmia found in another after halothane anesthesia and prior to remifentanil administration. The 10 remifentanil dams were delivered 7 surviving infants and the 5 control dams delivered 4 surviving infants.

PROCEDURE:
The pregnant dams were preanesthetized with ketamine (10 mg/kg) and subsequently anesthetized with Halothane and nitrous oxide, given atropine and prepared for surgery. The dams were

administered remifentanil by bolus injection of 30 μg/kg i.v., five minutes after Halothane was turned off - This was injected quickly in the first two monkeys, but the one monkey died and subsequently bolus injections were given over a 60 sec period. Neither fetus survived.

Immediately after remifentanil injection, the dams underwent ventral midline abdominal incision and fundic uterotomy to expose the fetus and umbilical cord. Mechanical respiratory support was supplied as needed and arterial blood samples were obtained immediately prior to remifentanil and 1, 2, 3, 5, 7, 15, 20, 30, 45, and 60 minutes after dosing. Arterial blood samples were obtain from the umbilical cord 1, 3, 5, and 10 minutes post drug administration.

The dams were only on-study, for data collection, the day of surgery and they were released to the colony on the following day. However, they were observed for one week for any possible complications.

Each infant that survived the prenatal blood collection was delivered immediately after the 10 minute blood collection and resuscitation was attempted. Two of the fetuses, subject to high volume sampling schedule, succumbed during blood collection and the sampling procedure was modified. Two additional fetuses aspirated amniotic fluid during blood sampling, prior to umbilical severing. The remaining 11 infants were maintained in the infant nursery and hand-reared until six months of age. These infants were tested in standard behavioral test batteries four hours after delivery, on days 1 through 7 and day 17. They were videotaped the first three nights and the tape was rated for sleep-wake patterns and spontaneous behavior by observers blind to the treatment. Hematology was examined on days 4 and 11 and morphometric measurements were taken weekly for the first 26 weeks.

The planned EEG and blood pressure measurement during surgery was found to be impractical due to the need for aseptic conditions.

RESULTS:

Dams

Nine of the ten remifentanil animal ceased breathing within seconds of injection and the eight surviving dams required mechanical assisted ventilation for 15 to 40 minutes (mean = 25 minutes). None of the control dams needed assisted ventilation. The heart rate of the dames was also significantly suppressed; 15% immediately after administration, 20% after 5 minutes and 14% after 10 minutes. At delivery, there was no statistically significant difference in heart rate between treated and control.

Infants

The hematological variables were not different between remifentanil treated and control animal in any measured on either Day 4 and on Day 11: WBC, RBC, hemoglobin, hemocrit, Mean Corpuscular Volume, Mean Corpuscular Hemoglobin and Mean Corpuscular Hemoglobin concentration.

The intake of infant formula was less for the remifentanil group than controls by 32% the first day, 22% the second, 11% the third and 4.4 to 11% on days 4 through 7 post-birth. However, this difference did not reach statistical significance.

Simian Apgar scores were taken only at the 10 minute time post birth as resuscitation activities superseded earlier protocol planned readings. No significant difference was observed between treatment groups.

Morphometric measurements were taken on a weekly basis and no significant differences were observed between treatment groups in deltas of crown to rump length or thigh circumference. The skin-fold thickness difference was statistically significant but the study director concluded that this was of no biological significance due to variation in examiner experience and the practice of subcutaneous liquid injects to prevent overnight dehydration during the first month of life.

The mean birth weight of the infants in the control group were about 4% greater than the remifentanil group. Although this is of course not treatment related, it does influence weight gain and formula intake. The sponsor stated that none of these variable were significant at the $p<0.05$, however some tables

indicate the difference is statistically significant.

On the second day, the remifentanil group had significantly fewer motor abilities ($p<0.01$) and significantly less rooting behavior ($p<0.05$) during the second night. It is conceivable that these two behaviors are related as they both involve motor activity. The mean Motor ability scores were greater in the control group for the initial 4 days and the Rooting behavior scores were less in the remifentanil group on all nights videotaped, the initial three nights.

The pharmacokinetic evaluations indicated that the fetal (umbilical) concentrations of remifentanil were approximately one-half the maternal concentrations. However, the variability was high and the peak fetal concentrations were observed in the last sampling period and could have increased further. In some cases the fetal concentration was as high as the maternal concentration, or higher. (NDA 5/41")

DISCUSSION:
The behavioral testing was extensively examined and with 70+ variables examined, five statistically significant differences did appear. However, none of the significant effects were found on either previous or subsequent measurement and were considered by sponsor to be due to chance occurrences without biological significance. The reviewer definitely agrees in the cases of Moro response on the third day, and Nystagmus and General Activity scores on day 17. The motor ability on the second day and Rooting behavior on the second night were both significantly less for the remifentanil than the control group and this may reflect a transient effect of remifentanil.

As noted by the report author, the number of subjects in the experimental groups were very small and this limited the power of the statistical analysis.

In a subsequent analysis (UCP/95/043)of maternal and umbilical blood concentrations, the fetal levels were approximately 50% of the maternal blood levels of remifentanil. However, the within the range of values obtained, some infants had umbilical concentrations as high and the maternal arterial blood. The

infant concentrations of the metabolite GI90291 were about 71% of the maternal level, but were as high as maternal levels in one of 5 pairs tested.

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SUMMARY:

Segment I

Doses of 0.5, 0.75 and 1.0 mg/kg/day in rats: Males; GI87084B at all doses decreased testicular and epididymis weights and reduced the Fertility Index. Females; slight increase in days of cohabitation prior to impregnation and days of gestation.

Segment II

In rats: 1, 2, 4 and 6 mg/kg/day of GI87084B; No fetal toxicity was observed and no teratogenesis; no developmental impairments.

In rabbits: 0.1, 0.5 and 0.8 mg/kg/day or GI87084B; produced no teratogenic changes.

Segment III

In rats: 0.5, 1.5, 5.0 mg/kg/day of GI87084B; No treatment related effects were observed in the F1 generation development; physical, reflexive and reproductive capacities.

In monkeys, the single bolus administration of remifentanil to pregnant females at term in combination with anesthesia did not seriously affect the neonates; Simian Apgar scores same in treated as untreated but possibly some decreased weight gain and motor behavior on the second day and decreased rooting behavior on the second night.

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The following studies were reviewed previously upon submission, and the reviews are included in appendix II:

Appendix II

UTX/93/002V2 GI87084B (opioid agonist): Second repeat intravenous segment II developmental toxicity

study in New Zealand White rabbits

UTX/91/029 Peri-natal and post-natal reproduction study of GI87084B administered intravenously to Crl:CD BR VAF/Plus female rats (segment III evaluation) -

Appendix I

UTX/91/027 Dosage-range study of GI87084B administered intravenously to Crl:CD (SD)BR VAF/Plus rats (pilot study for segment I evaluation)

UTX/92/006 Fertility and general reproduction study of GI87084B administered intravenously to Crl:CD (SD)BR VAF/Plus male rats (segment I evaluation)

UTX/91/028 Fertility and general reproduction study of GI87084B administered intravenously to Crl:CD (SD)BR VAF/Plus female rats (segment I evaluation) (includes postnatal "behavioral/functional" evaluation)

UTX/91/017 Dosage-range developmental toxicity (embryo fetal toxicity and teratogenic potential) study of GI87084B administered intravenously to presumed pregnant Crl:CD (c D)BR rats

UTX/91/018 Developmental toxicity (embryo-fetal toxicity and teratogenic potential) study of GI87084B administered intravenously to Crl:CD (SD)BR presumed pregnant rats

UTX/91/015 Dosage-range developmental toxicity (embryo fetal toxicity and teratogenic potential) study of GI87084B administered intravenously to presumed pregnant New Zealand White rabbits

UTX/91/016 Developmental toxicity (embryo-fetal toxicity and teratogenic potential) study of GI87084B administered intravenously to pregnant New Zealand White rabbits

UTX/91/029 Peri-natal and post-natal reproduction study of GI87084B administered intravenously to Crl:CD BR VAF/Plus female rats (segment III evaluation)

UTX/91/027 Dosage-range study of GI87084B administered intravenously to Crl:CD (SD)BR VAF/Plus rats (pilot study for segment I evaluation)

UTX/92/006 Fertility and general reproduction study of GI87084B administered intravenously to Crl:CD (SD)BR VAF/Plus male rats (segment I evaluation)

UTX/91/028 Fertility and general reproduction study of GI87084B administered intravenously to Crl:CD (SD)BR VAF/Plus female rats (segment I evaluation) (includes postnatal "behavioral/functional" evaluation)

UTX/91/017 Dosage-range developmental toxicity (embryo fetal toxicity and teratogenic potential) study of GI87084B administered intravenously to presumed pregnant Crl:CD (cD)BR rats

UTX/91/018 Developmental toxicity (embryo-fetal toxicity and teratogenic potential) study of GI87084B administered intravenously to Crl:CD (SD)BR presumed pregnant rats

UTX/91/015 Dosage-range developmental toxicity (embyro fetal toxicity and teratogenic potential) study of GI87084B administered intravenously to presumed pregnant New Zealand White rabbits

UTX/91/016 Developmental toxicity (embryo-fetal toxicity and teratogenic potential) study of GI87084B administered intravenously to pregnant New Zealand White rabbits

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NDA #20-630

The following studies were read but not formally reviewed. The majority of the results were reported previouly in reviewed studies and selected data is presented in summaries:

UDM/90/009V2	Developmental toxicity (embryo-fetal toxicity and teratogenic potential) studies of GI87084B administered intravenously to Crl:CD(SD)BR rats -- Drug Metabolism Report	48/061
UDM/90/014V2	Placental transfer of [3H]-GI87084 in Sprague Dawley rats and New Zealand White rabbits	48/085
UDM/94/054	GI87084B: Milk transfer in rats	48/095
UDM/90/008V2	Dosage-range developmental toxicity (embryo fetal toxicity and teratogenic potential) studies of GI87084B administered intravenously to New Zealand White rabbits -- Druq Metabolism Report	48/170
UCP/95/043	Maternal/fetal distribution of G187084 in rhesus monkeys and effects on infant outcome	49/043

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PHARMACOKINETICS

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION (ADME)

THE PHARMACOKINETIC AND PHARMACODYNAMIC INTERACTIONS OF REMIFENTANIL IN A RAT EEG MODEL (V3/223)

STUDY/REPORT NUMBER: UCP/95/016

STUDY SITE:

GLP/QA SPECIFICATIONS: in compliance (3/224)

SPECIES/NUMBER OF SUBJECTS/SEX: Wistar rats/male/3 groups of 8

DOSES/ROUTE OF ADMINISTRATION: In right jugular vein infusion of decreasing doses of remifentanil (Batch #U541/47/1, 50 to 2 μg/kg/min); GR90291 (Batch #C1809/206/1, 4 to 0.16 mg/kg/min); saline (40 to 1.6 μl/min). The volume of injection was the decreasing volume of the saline controls.

PROCEDURE:
GR90291 is the major metabolite of remifentanil and it has *in vitro* μ-binding activity. This experiment was designed to evaluate any *in vivo* opioid effects.

The rats had 7 EEG electrodes surgically implanted in the skull, one week prior to start of the experiment. One day prior to the experiment, four indwelling polyethylene cannula were implanted under light anesthesia; one in right femoral artery, one in right femoral vein and two in right jugular vein. In all experiments, medazolam was infused at 5.5 mg/kg/hr to prevent narcotic induced seizures. Bolus doses of vecuronium bromide 0.15 mg, were used when muscle rigidity appeared and the rats were then artificially

ventilated with a rodent face mask until spontaneous breathing returned. The arterial blood was sampled during 20 time points after the start of opioid infusion, 0.1 ml, for pharmacokinetic analysis.

Thirty minutes after the initiation of the medazolam, remifentanil and GR90291 infusion were started at 50 and 4000 μg/kg/min, respectively. The first infusion dose lasted 30 minutes and for the following two hours, dose was decreased every 10 minutes. The last dose was 2 μg/kg/min of remifentanil and 160 μg/kg/min for GR90291.

The arterial blood pH, pCO_2 and pO_2 were monitored in the spontaneously breathing rats, saline controls, and in ventilated rats.

RESULTS:

Pharmacokinetic:

Because of the complex administration paradigm, it was not possible to construct a compartmental pharmacokinetic model. The results were limited to AUC and clearance measurements.

The AUC ratios of GR90291:remifentanil ranged from 13.1 to 33.2 within the eight rats receiving remifentanil and the mean was 20.5 ± 7.3. The AUC for the GR90291 group averaged 82.0 ± 13.6 10^3 μg/ml/min and for the remifentanil group, 4.43 ± 1.55 μg/ml/min.

Pharmacodynamic:

The amplitude of the delta frequency band was significantly increased in the power spectrum compared to placebo, of both remifentanil and its primary metabolite GR90291. The concentration-EEG effect relationships of both remifentanil and GR90291 were both characterized by the sigmoidal E_{max} pharmacodynamic model. The concentration range of remifentanil covered the entire range of E_0 to E_{max} (109 μV) however GR90291 concentrations did not reach E_{max} and the authors assumed equal intrinsic activity and fixed the E_{max} at the remifentanil level for both compounds.

The EC_{50} values for remifentanil and GR90291 were 9.4 ± 2.6 ng/ml and 103 ± 25 µg/ml, respectively. The Hill factor was 2.2 ± 0.8 for remifentanil and 2.5 ± 1.0 for the metabolite. An unexplained variable was the use of results for only 6/8 of the rats in the GR90291 group for pharmacodynamic calculations.

The arterial blood pH, pCO_2 and pO_2 of the spontaneously breathing rats, saline controls, did not differ significantly from ventilated rats. However, there was more spread of values in the ventilated groups and some did have periods of respiratory depression after the pump was turned off and acidosis and decreased pO_2 were visible on the graphics provided.

DISCUSSION:

The power spectrum shift to the delta range was observed with both remifentanil and its metabolite, GR90291. This was also an EEG effect of both remifentanil and alfentanil in dogs as presented in the above study UPC/94/010.

The GR90291 doses did not cover the E_0 to E_{max} in the pharmacodynamic analysis and subsequently the remifentanil E_{max} was used for both compounds. This leaves open the possibility that there is bias in the calculations, but never-the-less, there is a large difference in potency between remifentanil and its first metabolite, GR90291. The difference may be less than the 10,000 fold stated by the sponsor in this study, but the contribution of the metabolite to the opioid effects of the parent compound remain minimal.

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PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENT OF GI87084B (REMIFENTANIL HYDROCHLORIDE), GR90291A, AND ALFENTANIL IN ANESTHETIZED DOGS (V4/001)

STUDY/REPORT NUMBER: UPC/94/016

STUDY SITE:

GLP/QA SPECIFICATIONS: unknown

SPECIES/SEX:
Male mongrel dogs, 26-34 kg (N=11), randomly assigned to rotation through four treatment groups with one week separation between treatments.

PROCEDURE:
Group

#1. 5 minute infusion of remifentanil at 0.5 μg/kg/min.
#2. 5 minute infusion of GR90291A at 500 μg/kg/min.
#3. 5 minute infusion of alfentanil at 1.6 μg/kg/min.
#4. 5 minute infusion of saline (solvent).

On the first treatment day the dogs were anesthetized and implanted with bilateral femoral vein and artery catheters which were threaded subcutaneously to an exit through an incision in the back of the neck. These catheters remained in place throughout the four treatments.

Needle electrodes were placed in the skin over the scalp for EEG measurement. Brain electrical activity was measured and delta frequency (0.5-3.0) and the spectral edge were used as the EEG variables. $PaCO_2$ was maintained at 35-40 mmHg and mean arterial blood pressure (MAP) and heart-rate were measured continuously.

Arterial blood samples (5cc divided into four 1 cc vials with citric acid) were obtained each minute, from 0 to 10 minutes, each two minutes from 10 to 20 minutes and in some experiments at 30 minutes. The samples were frozen and sent to Glaxo for analysis.

RESULTS:
Hemodynamic Effects:
Hemodynamic data was only collected in dogs 1-7 and EEG data was unavailable for some dogs due to technical problems. The MAP was stable during the saline treatment, a 5 mmHg increase by the end of testing. Remifentanil produced a 52 ± 18 mmHg decrease about one minute after the peak blood level was measured at 5 minutes. GR90291 produced a 59 ± 19 mmHg drop in blood pressure at about same time relationship. Alfentanil produced a 29 ± 7 mmHg drop

about 2 minutes after the peak blood level at 5 minutes.

The HR was reduced about 9 beats in control animals. The effects of Remifentanil, GR90291 and alfentanil were -51, -72 and -35 beats/minute, respectively.

Pharmacokinetic/Pharmacodynamic Effects:
EEG and plasma concentration data was obtained in 7 dogs infused with remifentanil at 0.5 μg/kg/min for 5 minutes. Because data from 4/7 dogs indicated a small but significant lag-time in the onset of measurable concentrations, an additional lag-time factor was incorporated in the pharmacokinetic calculations.

The pharmacokinetic/pharmacodynamic data with GR90291 was collected from 8 dogs dosed at 500 μg/kg/min. Alfentanil data at 1.6 μg/kg/min was evaluated in a total 9 dogs. The results are presented in the following two tables for all three compounds.

Pharmacokinetic Parameters

Compound	Volume of distribution at steady-state V_{ss} (ml/kg)	Total Clearance Cl (ml/kg/min)	Half-life $t_{½}$ (minutes)
remifentanil	222 ± 102	63 ± 18	5.7 ± 0.7
GR90291	293 ± 130	11 ± 3.9	26 ± 17
alfentanil	558 ± 230	30 ± 15	27 ± 21

[a] mean ± SD

Pharmacodynamic Parameters				
Compound	Delta Wave EC_{50} (ng/ml)[a]	Spectral Edge EC_{50} (ng/ml)[a]	Keo Delta Wave (/min)	Keo Spectral Edge (/min)
remifentanil	0.97 ± 0.41	0.64 ± 0.18	.29 ± .38	.13 ± .12
GR90291	4515 ± 1876	2930 ± 2415	1.8 ± 1.8	1.7 ± 2.4
alfentanil	7.7 ± 4.3	5.0 ± 2.5	.22 ± .10	.19 ± .10

[a] mean ± SD
Keo = equilibrium rate constant

The relative potencies was calculated by a computer program (PROC MIXED, SAS version 6.0) and are presented in the following table:

Potency Ratios Based on EC_{50} Values

Pharmacodynamic Measure	Remifentanil :	
	GR90291	alfentanil
Delta Wave Activity	1:4632	1:8.5
Spectral Edge	1:4251	1:7.7

DISCUSSION:
The data again demonstrates that the major metabolite of remifentanil has only a small fraction of the activity of the parent compound. In this case, the characteristic opioid EEG effects of the metabolite, GR90921, required about 4500 times the dose as did the parent compound and alfentanil required about 8 times the dose.

The effects on the cardiovascular system suggest that the difference between the parent and the metabolite may be less than

4500X. The maximum fall in systolic blood pressure was similar in the same dogs, -52 and -59 mmHg, respectively, and the mean maximum blood concentrations of remifentanil and GR90921 were 7.63 and 15,140 ng/ml, respectively, a difference of nearly 2000X. The difference remains sufficient to indicate that the metabolite plays a very minor role in action of remifentanil, either peripherally or in the central nervous system.

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SUMMARY:

Remifentanil is rapidly metabolized to the carboxylic acid GI90291 (GR90291) and does not accumulate in any animal species tested. The pharmacokinetics upon infusion in dog is liner between 0.4μg/kg/min and 40μg/kg/min.

The elimination of GI87084B is primarily by by non-specific esterases with about 18% occuring in muscle, liver, kidney, blood, brain and lung. The muscle contributes 8% and the other organs 0 to 3% of the total clearance.

Remifentanil related compounds were found to cross the placental membrane in rats, rabbits and monkeys. In rabbit and monkeys the fetal blood concentrations averaged 40 to 50% of the maternal levels and some reached the maternal level in the monkey umbilical blood. Remifentanil related compounds are excreted in the dams mild of lactating rats.

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The following studies were reviewed previously upon submission, and the reviews are included in appendix:

Appendix II

UDM/89/019V2 GI87084 blood concentrations in mice immediately after intravenous administration of doses used in LD50 determination

UDM/89/031 Metabolism, distribution, and excretion of

GI87084B in male mice

UDM/89/027V2 Blood concentrations of GI87084B in beagle dogs given a single dose of the compound

UDM/89/029 Preliminary pharmacokinetics, metabolism, and excretion of GI87084B in male beagle dogs

UDM/90/001 Estimation of protein binding of GI87084B in plasma of beagle dogs and humans

UDM/89/008V2 GI87084 blood concentrations in rats immediately after intravenous administration of doses used in LD50 determination

UDM/90/003V2 Blood concentrations of GI87084B in male and female rats after the fourteenth daily intravenous dose of GI87084B

UDM/89/030 Metabolism, distribution, and excretion of GI87084B in male and female rats

UDM/89/033 Determination of the rates of ester hydrolysis of the short-acting opioid GI87084 in rat, dog, and human blood

Appendix I

UDM/90/014V2 Placental transfer of [3H]-GI87084 in Sprague Dawley rats and New Zealand White rabbits

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The following studies were read or the data was presented and reviewed in toxicity or reproductive studies and are not formally reviewed again. However, selected data is presented in summaries:

UDM/89/030 Metabolism, distribution, and excretion of GI87084B in male and female rats 48/068

NDA #20-630

UDM/89/033 Determination of the rates of ester hydrolysis of the short-acting opioid Gl87084 in rat, dog, and human blood 48/121

UDM/94/053 GI87084B: Pharmacokinetics in pregnant New Zealand White rabbits 48/131

UDM/94/003 GI87084B (opioid agonist): Pharmacokinetics after intravenous infusion of 0.36 or 36.0 pg free base/kg/ min in male beagle dogs 48/191

UDM/94/029 GI87084B: Two-week continuous intravenous infusion toxicity study in dogs -- Drug Metabolism Report 48/212

UDM/93/055 GI87084B (opioid agonist): 4-Week intravenous injection toxicity study in dogs -- Drug Metabolism Report 48/350

UDM/93/054 Gl87984B (opioid agonist): Repeat 4-week intra venous injection toxicity study in dogs -- Drug Metabolism Report 48/377

UCP/94/016 Chemical and enzymatic hydrolysis of GI87084 48/401

UDM/94/001 Metabolism of GI87084B in beagle dogs 49/001

UDM/94/004 GI87084B (opioid agonist): Tissue clearance of anesthetized male beagle dogs during intravenous infusion of 0.36 or 36.0pg free base/kg/min 49/018

UDM/92/083 GI87084B (opioid agonist): A four-week intravenous injection toxicity study in rats -- Drug Metabolism Report 48/044

UDM/90/009V2 Developmental toxicity (embryo-fetal toxicity and teratogenic potential) studies of GI87084B administered intravenously to Crl:CD(SD)BR rats -- Drug Metabolism Report 48/061

UDM/94/053 GI87084B: Pharmacokinetics in pregnant New

	Zealand White rabbits	48/131
UDM/90/008V2	Dosage-range developmental toxicity (embryo fetal toxicity and teratogenic potential) studies of GI87084B administered intravenously to New Zealand White rabbits -- Drug Metabolism Report	48/170
UDM/94/037	GI87084B: Intravenous infusion toxicity study in ventilated male dogs	48/177
UDM/94/003	GI87084B (opioid agonist): Pharmacokinetics after intravenous infusion of 0.36 or 36.0pg free base/kg/min in male beagle dogs	48/191
UDM/95/002	GI87084B: Binding to human plasma proteins	49/084
UDM/90/007	Determination of the rate of hydrolysis of G187084 in human blood	49/099
UCP/95/018	Hydrolysis of remifentanil in pseudocholinesterase deficient patient blood	49/106
UCP/95/030	Remifentanil as a substrate for nonspecific esterases preliminary report	49/259

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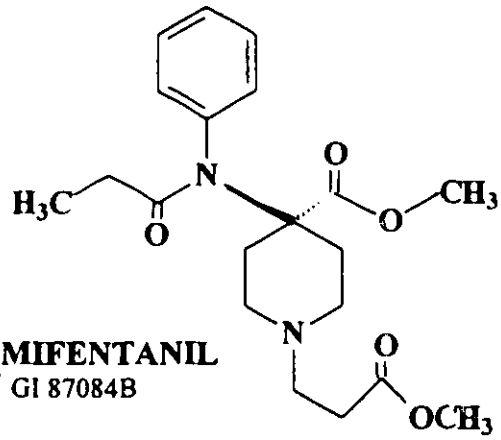
S U M M A R Y



REMIFENTANIL
GI 87084B

3-[4-methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]
propanoic acid methyl ester, hydrochloride salt

mw 412.9

Pharmacology

Remifentanil is a potent 4-anilidopiperidine, selective for the μ-opioid receptor and similar to other compounds of this class. The fast hydrolysis of this compound by blood and tissue esterases provides an ultrashort duration of action and rapid adjustment of blood levels by modification of the perfusion rate. The rapid non-hepatic metabolism also provides for predictable elimination in patients with compromised hepatic function. As with others of this class, remifentanil (GI87084) should reduce

minimum alveolar concentration (MAC) for volatile anesthetics and not cause histamine release.

Analgesia - μ-opioid receptors

in vitro -

- guinea pig ileum, rat and mouse vas deferens electrical stimulation = blocked by remifentanil (GI87084) and fentanyl and reversed in both by naloxone.

- opioid μ-receptor etorphine binding, EC_{50} = 117 nM, fentanyl = 36.2nM and morphine = 23.6 nM

- remifentanil and its primary metabolite (GR90291) are active primarily at mu-opioid sites - Although GR90291 is only 1/1857 x as potent as remifentanil:

Compound	μ-opioid receptor EC_{50}	Sigma-opioid receptor EC_{50}	kappa-opioid receptor EC_{50}
remifentanil	2.6 ± 0.6 nM	66 ± 19 nM	6.1 ± 0.5 μM
GR90291	1.4 ± 0.48 μM	1.2 ± 0.4 μM	(<10% @ 10^{-5})

in vivo -

- rat tail-flick assay - ED_{50} value comparable to alfentanil and fentanyl and more than sufentanil with duration of analgesia comparable to alfentanil and less than the others. Analgesia was naloxone reversible.

- mouse tail-flick assay - demonstrates short duration of action, after subcutaneous administration the ED_{50} was 1.9 mg/kg @ 1 minute, 4.3 mg/kg at 2 minutes and 12.2 mg/kg at 5 minutes.

- Dog paw pinch - duration of analgesia = 10 minutes.

- Narcotic withdrawal symptoms in morphine-dependant monkeys suppressed by GI87084B and codeine.

- GI87084 is self-administered in naive and experienced monkeys

Other *in vitro* receptors / ion channels

- H_1 histamine receptors and M_2 cholinergic receptors in the guinea pig ileum were only weakly effected by remifentanil.

- In isolated rabbit aorta rings, GI87084B did not have α_1-adrenergic or 5-HT receptor blocking activity or voltage dependent Ca^{++} channel blocking effects.

- GI87084B and GR90291 produced less than 20% inhibition at 10^{-5}M on the following receptors/ion channels:

Adenosine (ns)	$Alpha_1$(ns)	$Alpha_2$(ns)
Beta (ns)	Dopamine (ns)	$GABA_A$
$CABA_B$ (ns)	$Histamine_3$	Serotonin
Muscarinic (ns)	Purinergic P_{2Y}	K^+ (ATP-mod.)
K^+ (low cond.)	K^+ (voltage dep)	Na^+ site 1
		Na^+ site 2

(ns) = non-specific for subtypes of receptor.

<u>Cardiovascular</u>

- In dogs, 0.038 to 0.113 μg/kg/min significantly reduced heart rate, dp/dt, systolic and diastolic blood pressure. The effects were reversed by naloxone.

- In dogs i.v., remifentanil (0.5, 1.0 μg/kg/min), remifentanil + phenylephrine to maintain BP were compared with alfentanil (1.6 and 3.2 μg/kg/min):

  EEG: The 50% spectral edge was reduced by both compounds

nearly immediately but only remifentanil animals returned to control levels in the 30 minute recovery period.

Intracranial pressure (ICP) and flow velocity: both compounds reduced ICP 30% to 40% during infusion, but during recovery, ICP increased in remifentanil group, 21% alone and 41% in remifentanil group + phenylephrine. ICP of alfentanil group approached control levels. Flow velocity in the middle cerebral artery was reduced in all groups and during recovery, flow rate returned toward control in remifentanil animals but remained reduced in alfentanil animals.

Cerebral Blood Flow (CBF): the reduction was similar with both treatment except: 1) no dose of alfentanil significantly reduced CBF in the hypothalamus, brainstem or medulla, while low dose remifentanil did and 2) remifentanil groups returned to control during the recovery while CBF of the alfentanil group remained depressed in the cortex, hippocampus and caudate during recovery.

INTERACTIONS

- succinylcholine - no interaction on potency or duration - (dogs)

- midazolam - rats: additive toxicity, but given when recording EEG in both rats and dogs to stop cerebral convulsions with remifentanil

- thiopental - rats: additive toxicity

Pharmacokinetics

- Pharmacokinetic Parameters (anesthetized dogs)

Compound	Volume of distribution at steady-state V_{ss} (ml/kg)	Total Clearance Cl (ml/kg/min)	Half-life $t_{½}$ (minutes)
remifentanil	222 ± 102	63 ± 18	5.7 ± 0.7
GR90291	293 ± 130	11 ± 3.9	26 ± 17
alfentanil	558 ± 230	30 ± 15	27 ± 21

[a] mean ± SD

- Pharmacodynamic Parameters (anesthetized dogs)

Compound	Delta Wave EC_{50} (ng/ml)[a]	Spectral Edge EC_{50} (ng/ml)[a]
remifentanil	0.97 ± 0.41	0.64 ± 0.18
GR90291	4515 ± 1876	2930 ± 2415
alfentanil	7.7 ± 4.3	5.0 ± 2.5

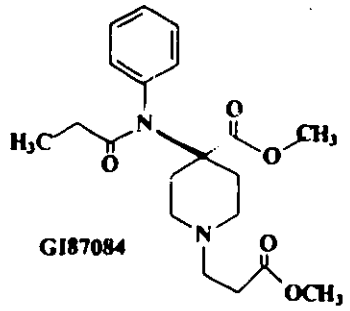
[a] mean ± SD

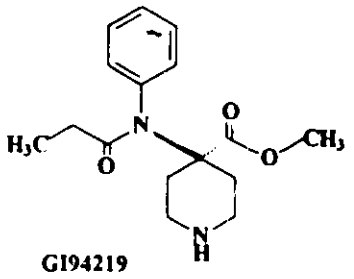
- Potency Ratios Based on EC_{50} Values

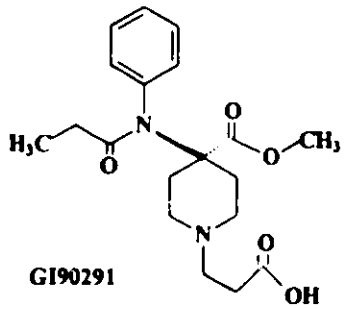
Pharmacodynamic Measure	Remifentanil :	
	GR90291	alfentanil
Delta Wave Activity	1:4632	1:8.5
Spectral Edge	1:4251	1:7.7

ADME Studies

The following structures are of remifentanil(GI87084B) and the major metabolites:







- Remifentanil is mainly metabolized to GI90291, the hydrolysis product of blood and tissue esterases.

  Humans = 100%; rats = 88%; mice = 91%; dogs = 60%

- Other identified metabolite, GI94219, is <2% in all species, when present.

- Remifentanil is highly protein-bound: 67 to 92% in human, (16% albumin, 45% α-1-glycoproteins): 33% protein-bound in dog

- Excretion mainly urinary; human = 100%
  dog, rat, mice = 70-80%

The following are points of interest in an ADME study in rats (V48/68):

- 92% of the radioactivity was recovered, 70% in urine, 22% in feces and 95% of this was recovered within 24 hours of dosing.

- Radiolabel was detected in every tissue examined and kidney and liver tissue had the highest concentrations at 30 minutes after injection.

- Principal metabolite, GR90291 the hydrolysis product, accounted for about 70% of the dose in the urine and 17% in the feces. In rats as well as dog, the second measurable metabolite GI94219, amounted to <2% of the dose in urine and <1% in feces. The parent compound, GI87084B, was <1% of the dose excreted.

- There was no sex difference in metabolism or excretion.

ACUTE TOXICITY

The toxicity of remifenanil is characteristic of opioid over-dose with sedation, respiratory depression, cyanosis, body rigidity, excess salivation and convulsions are the primary symptoms.

LD_{50}

- In rats: oral LD_{50} >2000 mg/kg
  i.v. = 17 mg/kg
  aerosol inhalation = 8μg/kg.

- In mice: i.v. = 100 mg/kg

- In dogs: i.v. >80mg/kg

Cerebrovascular

- brain microhemorrhages were found after acute doses as low as 0.1 mg/kg and as high as 160 mg/kg to unventilated dogs. However, bolus injections, 1 mg/kg, to ventilated, anesthetized dogs resulted in no observed microhemorrhages.

Renal-Urinary

Urinary retention with μ-agonists - reduced urinary sodium excretion and increased osmolarity in rats like alfentanil.

Chronic Toxicity

- reduced epididymal weights in male rats after 4-weeks of 2.5 mg/kg/day of remifentanil. Sloughed epithelial cells in epididymal tubules at 0.25, 1.0 and 2.5 mg/kg/day for 4-weeks.

- increased blood glucose after 16 days of venous infusion at (♂) 1 and (♂+♀) 5 μg GI87084B/kg/min. There was also a significant reduction in zymogen granule count in pancreatic acinar cells that was reversible.

- brain microhemorrhages were present in some dogs after continuous dosing of GI87084B at doses of 0.01 mg/kg and higher. When anesthetized dogs were infused with remifentanil at 20μg/kg/min for 4 hours, microhemorrhages in unventilated controls (2/5) were greater than ventilated remifentanil dogs (1/5).

  The brain microhemorrhages were attributed to the hypoxic conditions that remifentanil can produce as it suppresses respiration. The microhemorrhages were very small and the identification on the slides was verified by veterinary pathologists at the FDA.

Genetic Toxicology

Remifenanil was active in the *in vitro* mouse lymphoma test only with S9 activation and was inactive in two other *in vitro* test with and without activation and in both *in vivo* tests.

- *in vitro* - *Salmonella typhimurium*, GI87084B was inactive with or without S9 activation.
- *in vitro* - Chromosome aberration in CHO cells; GI87084B was inactive with or without S9 activation.
- *in vitro* - Mouse lymphoma cells, L5178Y/tk±; GI87084B induced significant mutagenic activity on after S9 activation. Increases in small colonies was significant, greater than positive control cyclophosphamide and was dose related.
- *ex vivo* - Unscheduled DNA synthesis (UDS) in rat hepatocytes; GI87084 inactive at doses to 6.6 mg/kg i.v.
- *in vivo* - Mouse micronucleus test; GI87084 did not induce an increased number of micronuclei in polychromatic erythroids after i.v. administration of 80, 100 or 120 mg/kg.

Reproductive Toxicology

Segment I - *Reproductive performance and effects on fertility*
Doses of 0.5, 0.75 and 1.0 mg/kg/day in rats: Males; GI87084B at all doses decreased testicular and epididymis weights and reduced the Fertility Index. Females; slight increase in number of days of cohabitation prior to impregnation and days of gestation.

Segment II - *teratology*
In rats: 1, 2, 4 and 6 mg/kg/day of GI87084B; No fetal toxicity was observed and no teratogenesis; no developmental impairments.

In rabbi 0.5 and 0.8 mg/kg/day of GI87084B; produced no teratoge nges.

Segment III - perinatal and postnatal development
In rats: No treatment related effects were observed in the F1 generation growth or development; physical, reflexive and reproductive capacities.

Cesarean delivery, Rhesus monkey: remifentanil, 30μg/kg bolus in anesthetized pregnant dams near term. Fast injection in first two, but death of one changed bolus administration to 60 seconds. Nine of 10 required intubation after injection and first Apgar score was at 10 minutes and no differences were observed between controls and neonates from remifentanil-treated dams. The mean umbilical blood had ¼ the remifentanil concentration of maternal blood.

CONCLUSIONS

Remifentanil produces a potent antinociceptive effect of short duration and does not accumulate in the body. It is selective for the μ-opioid receptor and does not induce histamine release. The attendant effects, respiratory suppression, reduced heart-rate and blood pressure, and sedation are characteristic of opioids.

The induction of brain microhemorrhages in dogs was prevented by adequate ventilation and did not appear in rats. No specific organ toxicity was observed upon chronic administration. The compound is mutagenic in only one of 5 test systems. Remifentanil has no significantly-adverse effects on reproduction at doses below maternal toxicity although after repeated administration, male rats had decreased testicular and epididymal weight and decreased fertility.

The main metabolite of remifentanil, the hydrolysis product GR90291, has opioid effects only at doses 210 to 4500 times that of the parent molecule and therefore no significant influence on the pharmacology/toxicology effects.

The review of the effects of remifenanil HCl in animal studies has provided no pharmacology/toxicology basis to prohibit its use in humans and it is recommended for approval.

Harry M. Geyer, III Ph.D.

In concurrence: _____ 5/13/96
Peer Leader: Anwar Goheer, Ph.D. date

cc
NDA #20-630
HFD-170/Div. File
HFD-170/HMGeyer
HFD-170/DMorgan
HFD-345

NDA #20-630

F/T by HMGeyer 04/29/96
WP#remidone.002

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date: December 20, 1995

From: Staff Pathologist
Diagnostic Pathology Section, HFS-716

Subject: Remifentanil (Pathology Project Number PR-168): A Microslide Review of Brain and Spinal Cord Sections From Five Dog Studies (Glaxo Report Numbers UTX/93/003, UTX/94/022, UTX/94/020, UTX/94/047 and UTX/94/049)

To: Harry Geyer, III, Ph.D., Pharmacologist
Pilot Drug Evaluation Staff
Office of Drug Evaluation II/CDER (HFD-007)
Through: Chief, Pathology Branch, HFS-716 _____
Leader, Diagnostic Pathology Section, HFS-716 _____

REFERENCES:

1. Memorandum dated November 22, 1994 from Harry Geyer, III, Ph.D., Pilot Drug Evaluation Staff (HFD-007) to Ronald Moch, D.V.M., Chief, Pathology Branch (HFS-716); subject: Remifentanil (GI87084B): Request for Pathology Support to Drug Review.

2. Memorandum dated February 10, 1995 from Prem Dua, D.V.M., Ph.D., Pathology Branch (HFS-716) to Harry Geyer, III, Ph.D., Pilot Drug Evaluation Staff (HFD-007); subject: Request for Information/Microslides.

SUMMARY:

During a review of the Investigational New Drug IND Remifentanil, a short-acting opioid, members of the Pilot Drug Evaluation Staff (PDES) of the Office of Drug Evaluation II, Center for Drug Evaluation and Research were concerned about hemorrhages occurring in the brains of dogs administered Remifentanil intravenously. After the Pathology Branch (PB) of the Office of Scientific Analysis and Support, Center for Food Safety and Applied Nutrition was contacted about this concern (Reference 1), the PB prepared a memorandum to PDES requesting the relevant microslides and pertinent information be obtained from the petitioner (Reference 2). The PB subsequently received brain microslides from five Glaxo studies along with two volumes of data containing the toxicology and pathology reports from these studies.

The Pathology Branch has reviewed the brain and spinal cord microslides submitted to the Agency by the petitioner as well as the pertinent correspondence and pathology/toxicology reports.

Essentially, the PB agreed slide-by-slide with the petitioner's report on whether hemorrhages were present or absent. The PB used strictly morphological terms to diagnose a particular lesion (i.e., "perivascular or extravascular" hemorrhage) whereas the petitioner's report used the terms artifactual hemorrhage or acute hemorrhage which is acceptable nomenclature.

According to the PB, the major findings from these five studies included:

1) An increase in the incidence of non-ventilated Remifentanil (and Alfentanil) treated dogs with brain hemorrhage when compared to the corresponding control dogs;

2) The most affected brain level was BR2 (Hippocampus) followed by BR0 (Caudate Nucleus), BR4 (Substantia Nigra), BR5 (Cerebellum) and BR1 (Thalamus/ Hypothalamus).

3) A reduction in the incidence of ventilated Remifentanil-treated dogs with brain hemorrhage to the incidence of control ventilated dogs with brain hemorrhage.

That is, unventilated Remifentanil-treated dogs have a higher incidence of brain hemorrhage when compared to the corresponding control groups of dogs with brain hemorrhage, but ventilating the dogs did prevent this apparent test-material related effect from occurring.

The PB has also recently reviewed data from two different HMG CoA reductase inhibitor studies in dogs in which it was reported that the test materials caused brain hemorrhage. Hypoxia was speculated to be the mechanism causing hemorrhages due to HMG CoA reductase inhibitors by the submitting petitioner, but no definitive studies were requested or performed to test the hypothesis. In the attached pathology report, the PB offers its opinion on possible mechanism(s) for the possible etiology of these hemorrhages.

If we can be of further help, please contact me by phone at 202-205-4123 or e-mail at fah@vm.cfsan.fda.gov.

Fred A. Hines, D.V.M.

Fred A. Hines, D.V.M.

Toxicologic Pathologist

ATTACHMENT: PR-168 Pathology Report

Pathology Report

Remifentanil (Pathology Project Number PR-168):

A Microslide Review of Brain and Spinal Cord

Sections From Five Dog Studies

(Glaxo Report Numbers UTX/93/003, UTX/94/022, UTX/94/020,

UTX/94/047 and UTX/94/049)

Pathology Project Officer : Fred A. Hines, D.V.M.

Date of Completion : December 20, 1995

BACKGROUND INFORMATION:

Remifentanil is a short-acting opioid being developed by Glaxo, Inc. as an anesthetic in man. It has analgesic and cardiovascular effects similar to the currently available short-acting opioid Alfentanil, but Remifentanil has a plasma half-life even shorter than Alfentanil[1]. As reported by the sponsor, high dosages of Remifentanil to rats and dogs (up to 5.0 mg/kg in rats and up to 160 mg/kg in dogs) cause clinical signs of hypoxia and convulsions in both rats and dogs and "in many of these animals, neuronal lesions characteristic of anoxia/ischemia and convulsions were identified.... At lower doses, brain [lesions] were restricted to a few, minimal, microscopic hemorrhages in brain sections of some dogs. These hemorrhages were characteristic of those produced by hypoxia ... Hemorrhages did not occur in brains of rats at any dose."[2] Glaxo, Inc. designed a series of studies to investigate a possible mechanism for these brain hemorrhages in dogs. One study was a repeat of the study in which non-ventilated dogs were given Remifentanil once a day intravenously at dose levels of 0, 0.01, 0.03 and 0.05 mg/kg/day (UTX/93/003) and the remaining studies dealt with either comparing findings of Remifentanil to Alfentanil (UTX/94/022 and UTX/94/020) in non-ventilated dogs or comparing findings from giving Remifentanil to non-ventilated versus ventilated dogs (UTX/94/047 and UTX/94/049). During the review of these studies for an Investigational New Drug (IND the Pilot Drug Evaluation Staff (PDES) of the Office of Drug Evaluation II, Center for Drug Evaluation and Research was concerned about the reported Remifentanil-induced hemorrhages occurring in the brains of dogs. After the Pathology Branch (PB) of the Division of General Scientific Support, Office of Scientific Analysis and Support, Center for Food Safety and Applied Nutrition was contacted about this concern[3], the PB prepared a memorandum to PDES in which it was suggested that additional information be obtained from the petitioner in order for the PB to complete its review.[4] Subsequently, PDES requested Glaxo, Inc. to provide the information requested by the PB. Glaxo, Inc. responded to this request for further information and the PB was provided a copy of two volumes of material containing toxicology and pathology reports from all five studies mentioned above. In addition, all available brain and spinal cord microslides from all five studies of both male and female dogs from control and treated groups, arranged by sex and dosage groups in increasing animal and/or accession numbers were submitted to the Agency and subsequently sent to the PB.

This pathology report by the PB, CFSAN, presents the PB's findings from its review of the petitioner's submission.

MATERIALS AND METHODS:

The brain and spinal cord sections from UTX/93/003, UTX/94/022, UTX/94/020, UTX/94/047 and UTX/94/049) were submitted in 14 slideboxes containing a total of 914 hematoxylin and eosin (H&E) slides which consisted usually of seven step sections through the brain and one section of spinal cord for each animal. Each of these levels was identified on the slide as follows:

BR0 = Slide 1 (Caudate Nucleus)
BR1 = Slide 2 (Thalamus/Hypothalamus)
BR2 = Slide 3 (Hippocampus)
BR3 = Slide 4 (Occipital Cortex)
BR4 = Slide 5 (Substantia Nigra)
BR5 = Slide 6 (Cerebellum)
BR6 = Slide 7 (Pons/Brainstem)
SC = Slide 8 (Spinal Cord)

The test animals for all five studies were male or female (or both) purebred beagle dogs obtained from

The Pathology Branch (PB) assigned one in-house pathology petition-review number (PR-168) to this review, but the findings were recorded into the PB's pathology software application (Pathdata, Inc.) as five separate studies (i.e., 10168, 20168, 30168, 40168 and 50168). The computer-generated tables from this software are attached to this pathology report.

Since Glaxo, Inc. had contracted the studies to , each study has a designated Glaxo Report Number, a Glaxo Study Number, a and a Pathology Branch study number. The designated numbers of each study are as follows:

Glaxo Report No.	Glaxo Study No.		PB Pathdata No.
UTX/93/003	D13953		10168
UTX/94/022	40064		20168
UTX/94/020	40077		30168
UTX/94/047	40087		40168
UTX/94/049	40094		50168

A brief synopsis in table format (title, objective. experimental design) of each study is provided below:

UTX/93/003 *

GI87084B [Remifentanil] (Opioid Agonist): Repeat 4-Week Intravenous Injection Toxicity Study in Dogs (Glaxo Study Number D13953)

The purpose of this study was to evaluate the toxicity of Remifentanil when given to non-ventilated male and female dogs at dose levels of 0, 0.01, 0.03 and 0.05 mg/kg once a day by intravenous injection for four weeks.

Group #	Dose of Remifentanil in mg/kg body weight/day	Terminally Sacrificed		Recovery Animals	
		# of ♂	# of ♀	# of ♂	# of ♀
1	0	4	4	2	2
2	0.01	4	4	0	0
3	0.03	4	4	0	0
4	0.05	4	4	2	2

* Pathology Branch's Petition Review PR-168; Pathdata No. 10168.

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UTX/94/022 * GI87084B (Remifentanil Hydrochloride), GI117877A (Alfentanil Hydrochloride): Acute Bolus Intravenous Toxicity Study in Non-Ventilated Male Dogs (Glaxo Study Number 40064)		
The purpose of this study was to determine if microscopic brain hemorrhages (as seen in both male and female dogs of UTX/93/003) occur following a single intravenous dose of Remifentanil or Alfentanil in male dogs.		
Group	Dose and Drug	# of ♂
Phase 1		
1	Control (sterile saline)	1
2	0.1 mg/kg Remifentanil	1
3	0.1 mg/kg Alfentanil	1
Phase 2		
1	Control (sterile saline)	1
2	0.5 Remifentanil	1
3	0.5 Alfentanil	1
Phase 3		
1	Control (sterile saline)	1
2	1.0 mg/kg Remifentanil	1
3	1.0 mg/kg Alfentanil	1
* Pathology Branch's Petition Review PR-168; Pathdata No. 20168.		

In the PB's pathology software system the above study was organized in such as way that the three control dogs were placed in Group 1; the treated Remifentanil groups were designated groups 12, 22, and 32 (for phase 1, group 2; phase 2, group 2 and phase 3 group 2, respectively) and the treated Alfentanil groups were designated 13, 23, and 33 (for phase 1, group 3, phase 2, group 3 and phase 3, group 3, respectively). That is:

Group	Dose and Drug	# of ♂
1	Controls (sterile saline)	3
12	0.1 mg/kg Remifentanil	1
22	0.5 mg/kg/ Remifentanil	1
32	1.0 mg/kg Remifentanil	1
13	0.1 mg/kg Alfentanil	1
23	0.5 mg/kg Alfentanil	1
33	1.0 mg/kg Alfentanil	1

UTX/94/020 *
GI87084B (Remifentanil Hydrochloride), GI117877A (Alfentanil Hydrochloride:
7-Day Intravenous Toxicity Study in Non-Ventilated Dogs (Glaxo Study Number 40077)

The purpose of this study was to determine if microscopic brain hemorrhages occur in non-ventilated dogs following seven consecutive daily intravenous doses of Remifentanil or Alfentanil.

Group	Dose and Drug	# of ♂	# of ♀
1	Controls (sterile saline)	3	3
2	1 mg/kg/day Remifentanil	3	3
3	0.1 mg/kg/day Alfentanil	3	3
4	1.0 mg/kg/day Alfentanil	3	3

* Pathology Branch's Petition Review PR-168; Pathdata No. 30168.

UTX/94/047 * GI87084B [Remifentanil]: Acute Bolus Intravenous Toxicity Study in Ventilated Male Dogs (Glaxo Study Number 40087)				
The purpose of this study was to determine if microscopic brain hemorrhages occur in ventilated male dogs following a single intravenous dose of Remifentanil.				
Group	Dose Level	Isoflurane	Ventilation	# of ♂
1	1 mg/kg/day Remifentanil	Yes	Yes	5
2	Controls (sterile saline)	Yes	Yes	5
3	1 mg/kg/day Remifentanil	Yes	No	5
4	1 mg/kg/day Remifentanil	No	No	5
5	Controls (sterile saline)	No	No	5
* Pathology Branch's Petition Review PR-168; Pathdata No. 40168.				

UTX/94/049 * GI87084B [Remifentanil]: Intravenous Infusion Toxicity Study in Ventilated Male Dogs (Glaxo Study Number 40094).				
The purpose of this study was to determine if microscopic brain hemorrhages occur in ventilated male dogs following a 4-hour intravenous infusion of Remifentanil.				
Group	Dose Level / Dose Concentration	Isoflurane	Ventilation	# of ♂
1	20 μg/kg/minute Remifentanil / 1,200 μg/mL	Yes	Yes	5
2	Controls (sterile saline)	Yes	Yes	5
3	Controls (sterile saline)	No	No	5
* Pathology Branch's Petition Review PR-168; Pathdata No. 50168.				

RATIONALE FOR DEFINITION OF TERMS USED IN THE STUDY:

The PB recognized two different morphologic types of hemorrhages in the brain and spinal cords from the dogs of these studies. One type was a perivascular accumulation of erythrocytes within the Virchow-Robin space. This type of hemorrhage was designated "perivascular" hemorrhage (see Figures 1, 2 & 3).

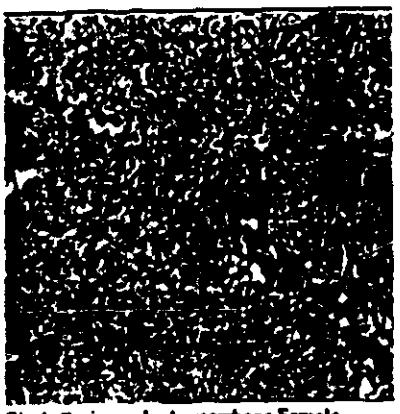


Fig 1: Perivascular hemorrhage Female Control 5591 of Study UTX/93/003 (596X)

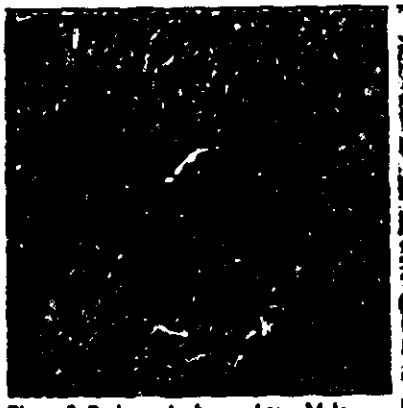


Figure 2: Perivascular hemorrhage: Male Control 7653 of Study UTX/94/007 (1172X).

Figure 3: Perivascular (arrow) and extravascular (arrowhead) hemorrhage: Male Control 5568 of Study UTX/93/003 (1172X).

The second type of hemorrhage in the brain was foci of small hemorrhages (20 to 200 microns at the widest width) which consisted of closely-packed to scattered, sometimes misshaped erythrocytes present extravascularly in the gray or white matter (Figures 3, 6, 7). This type of hemorrhage was designated "extravascular" hemorrhage.

The petitioner's pathologist used the terms "artifactual" and "acute hemorrhage" which is acceptable nomenclature. These terms were described quite well within the pathology report and essentially, the artifactual hemorrhages were of two types: one was the perivascular cuffing of erythrocytes about a blood vessel (as depicted in Figure 1) and the second was the presence of erythrocytes within the neuropil which was due to a putative mechanical disruption of tissues (Figures 4, 5 and 9).

Figure 4: "Mechanical Disruption" in BR6 of Female Control 5594 in Study UTX/93/003 (118X)

Figure 5: "Mechanical Disruption" in BR0 of Remifentanil-treated Animal 7797 of Study UTX/94/049 (297X)

Essentially, artifactual hemorrhage as defined by the petitioner's pathologist encompassed the two morphologic terms of perivascular and extravascular used by the PB, i.e., all perivascular hemorrhage was considered artifactual and extravascular hemorrhage in areas of mechanical

disruption of tissues was also considered artifactual. The other type of hemorrhage defined by the petitioner's pathologist was acute hemorrhage which was "focal extravascular smattering of erythrocytes within the gray matter .... The size of the microhemorrhages varied but generally were in the range of 20 to 200 microns in dimension. These foci were not closely associated with a recognizable blood vessel." All of the petitioner's diagnoses of "acute" hemorrhage encompassed the PB's term of extravascular hemorrhage.

The PB noticed that in some of these foci of "extravascular" hemorrhage, the erythrocytes tended to accumulate about a nidus of degenerating neurons or undetermined cellular components (see Figures 6 & 7).

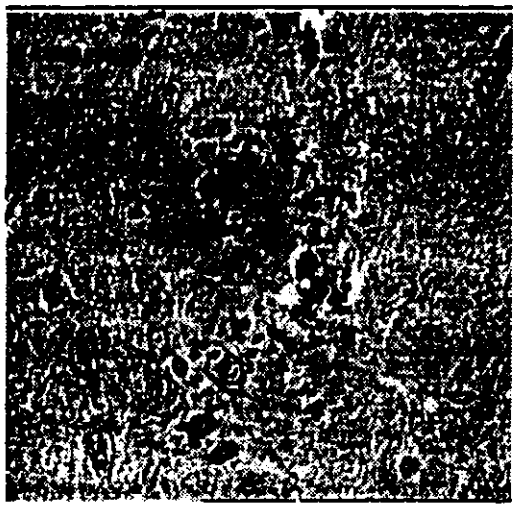


Figure 6: Hemorrhage about a nidus of undetermined cellular debris in BR0 section of High-dose Alfentanil Animal 6950 of Study UTX/94/022 (1172X).

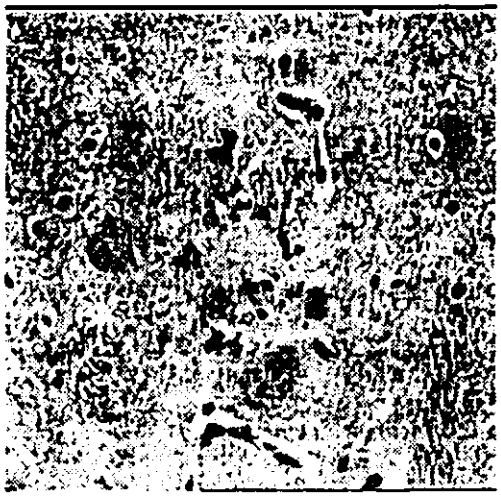


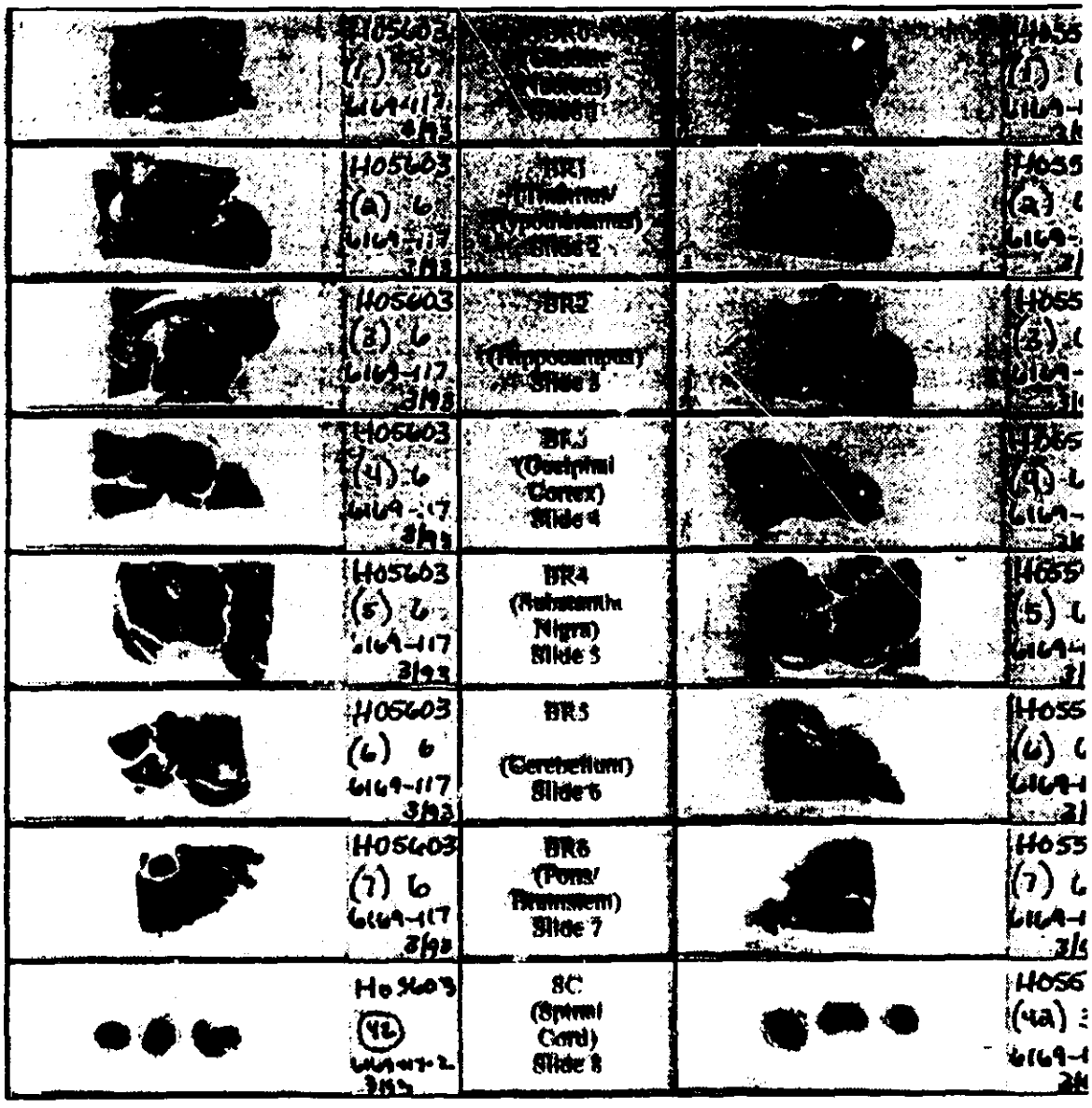
Figure 7: Perineuronal hemorrhage in BR1 section of Mid-dose Remifentanil animal 6942 of Study UTX/94/022 (596X).

Occasionally, brain sections were prepared so that both hemispheres were present on the microslide. Figure 8 represents the subgross of all eight microslides submitted by the petitioner for the female control animal 5591 of UTX/93/003 as well as the high-dose female animal 5603 for comparison. The object marker labels two slides for 5591 which shows multiple lesions (slides 3 and 5). Figure 9 magnifies slide 5 of BR4 which shows the bilaterally-symmetrical pattern of the perivascular hemorrhages in this portion of the brain.

Figure 8

Scanned images of the eight microslides from the brain and spinal cord sections from the Female Control 5591 and High-dose Remifentanil Animal 5603 of Study UTX/93/003. The 3 mm circles mark where a hemorrhagic lesion was present.

5603 **5591**



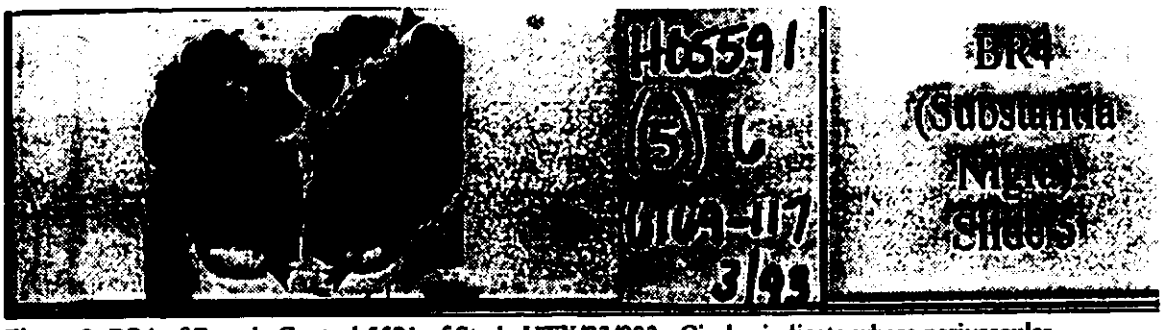


Figure 9: BR4 of Female Control 5591 of Study UTX/93/003. Circles indicate where perivascular hemorrhages were present. Note "mechanical disruption" (arrowheads) which is not associated with areas where hemorrhages were seen.

RESULTS:

The summary incidence of dogs with brain lesions as determined by the PB can be found on Pathdata pages 2-5, 57-58 and 87-88 for studies 10168, 20168 and 30168, respectively. Selected findings from those tables emphasizing the number of animals with either extravascular hemorrhage or perivascular hemorrhage by level of brain examined and the distribution and degree of severity of the two types of hemorrhage in the brain and spinal cord are summarized in Tables 1 - 5. The following page will list abbreviations or definition of terms used in Tables 1 - 5.

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Abbreviations used in the following Tables 1 through 5.

BR0 = Slide 1 = brain sectioned at about the level of the caudate nucleus.
BR1 = Slide 2 = brain sectioned at about the level of the thalamus/hypothalamus.
BR2 = Slide 3 = brain sectioned at about the level of the hippocampus.
BR3 = Slide 4 = brain sectioned at about the level of the occipital cortex.
BR4 = Slide 5 = brain sectioned at about the level of the substantia nigra.
BR5 = Slide 6 = brain sectioned at about the level of the cerebellum.
BR6 = Slide 7 = brain sectioned at about the level of the pons/brainstem.
SC = Slide 8 = spinal cord section

ANY = a merge of BR0 through BR6, i.e., if any brain section BR0 through BR6 was diagnosed with extravascular or perivascular hemorrhage, ANY would represent the lesion was present in at least one brain section for any particular dog.

P = Present

1 = Minimal degree of severity
2 = Mild degree of severity
3 = Moderate degree of severity
4 = Severe degree of severity

Alfen = Alfentanil
Remi = Remifentanil
Sac = sacrificed
SI = Summary incidence

TABLE 1

Pathology Petition Review PR-168 (Pathdata Report 10168); Glaxo Report Number UTX/93/003

MALE DOGS WITH EXTRAVASCULAR HEMORRHAGE																											
	Group 1 Male Controls								Group 2: 0.01 mg/kg/day Remifentanil					Group 3. 0.03 mg/kg/day Remifentanil					Group 4: 0.05 mg/kg/day Remifentanil							
Level	Terminally Sac * Dogs				SI	Recovery		SI	Terminally Sac. Dogs				SI	Terminally Sac. Dogs				SI	Terminally Sac. Dogs				SI	Recovery		SI
	5568	5570	5579	5580		5565	5569		5566	5575	5578	5581		5567	5573	5574	5577		5563	5564	5572	5576		5561	5571	
BR0	1														1	2	1		1	1		1				
BR1												1			1	3	1		1	1		1				
BR2															1	2			1	1	1	1				
BR3																										
BR4															1	1				1	1	1				
BR5						1			1							1	1		1	1	1				1	
BR6															1		1				1	1				
ANY	P				1/4	P			P			P	2/4		P	P	P	3/4	P	P	P	P	4/4		P	½
SC	1		1	1	3/4		1	½	1	1		1	3/4			1	1	2/4	1	1		1	3/4		1	½
MALE DOGS WITH PERIVASCULAR HEMORRHAGE																											
BR0									1						1	1				1	1				1	
BR1	1														1										1	
BR2							1			1					1											
BR3										1							1									
BR4										1					1							1		1		
BR5																	1				1	1				
BR6						1				1						1	1							1		
ANY	P				1/4	P	P	2/2	P	P			2/4		P	P	P	3/4		P	P	P	3/4	P	P	2/2
SC					0/4	1	1	2/2		1			1/4				1	1/4		1	1	1	3/4		1	

* See Page 11 for a list of abbreviations used in Tables 1 - 5.

TABI

Pathology Petition Review PR-168 (Pathdata Report 10168); Glaxo Report Number UTX/93/003

FEMALE DOGS WITH EXTRAVASCULAR HEMORRHAGE																										
	Group 1 Female Controls								Group 2: 0.01 mg/kg/day Remifentanil					Group 3: 0.03 mg/kg/day Remifentanil					Group 4: 0.05 mg/kg/day Remifentanil							
Level	Terminally Sac.* Dogs				SI	Recovery		SI	Terminally Sac. Dogs				SI	Terminally Sac. Dogs				SI	Terminally Sac. Dogs				SI	Recovery		SI
	5590	5591	5594	5595		5596	5601		5583	5586	5588	5598		5584	5587	5589	5599		5592	5602	5603	5604		5593	5600	
BR0																			1					1		
BR1															1				1							
BR2		1										1			1											
BR3																										
BR4		1										2			1				1							
BR5	1	1	1	1															1		1			1		
BR6			1									1		1			1				1			1		
ANY	P	P	P	P	4/4			0/2				P	1/4	P	P		P	3/4	P		P		2/4	P		½
SC					0/4			0/2	1		1	1	3/4	1	1	1		3/4	1	1	1	1	4/4	1		½
FEMALE DOGS WITH PERIVASCULAR HEMORRHAGE																										
BR0	1			1												1			1	1	1				1	
BR1						1																1		1		
BR2		2	1			1					1	2			1						1			1		
BR3																					1					
BR4		2										2			1					1				1		
BR5				1					1					1		1					1			1	1	
BR6	1	1	1				1				2	2				1			1	1	1			1		
ANY	P	P	P	P	4/4	P	P	2/2	P		P	P	3/4	P	P	P		3/4	P	P	P	P	4/4	P	P	2/2
SC		1	1		2/4	1	1	2/2	1	1		1	3/4	1	1		1	3/4	1	1	1	1	4/4	1	1	2/2

* See Page 11 for a list of abbreviations used in Tables 1 - 5.

TABLE 2

Pathology Petition Review PR-168 (Pathdata Report 20168); Glaxo Report Number UTX/94/022

Male Dogs with EXTRAVASCULAR HEMORRHAGE													
				Remifentanil Groups (mg/kg)					Alfentanil Groups (mg/kg)				
	Male Controls			0.1		0.5		1.0	0.1		0.5		1.0
	6943	6945	6946	6949		6942		6948	6944		6953		6950
BR0						1							1
BR1				1		1							
BR2													
BR3													
BR4													
BR5		1				1							
BR6	1												
ANY	P	P		P		P							P
SC			1					1	1				1
Male Dogs with PERIVASCULAR HEMORRHAGE													
BR0													
BR1													
BR2													
BR3			1										
BR4													
BR5													
BR6	1					1							1
ANY	P		P			P							P
SC			1			1			1				

* See page 11 for a list of abbreviations used in Tables 1 - 5.

TABLE 3

Pathology Petition Review PR-168 (Pathdata Report 30168); Glaxo Report Number UTX/94/020

Male Dogs with EXTRAVASCULAR HEMORRHAGE

Level	Group 1 Male Controls			SI	Group 2 1mg/kg Remi*			SI	Group 3 .1mg/kg Alfen			SI	Group 4 1mg/kg Alfen			SI
	7148	7155	7159		7160	7164	7168		7146	7154	7163		7149	7151	7157	
BR0	1				1	1	1						1	1		
BR1					2	1	1							1	1	
BR2					2	2			1					1	1	
BR3					1									1		
BR4					1	1								2	1	
BR5					2	1	1			1				2		
BR6			1		1	1	1		1	1	1		1			
ANY	P		P	2/3	P	P	P	3/3	P	P	P	3/3	P	P	P	3/3
SC	1			1/3	1	1	1	3/3	1		1	2/3	1	1	1	3/3
Male Dogs with PERIVASCULAR HEMORRHAGE																
		1			1	1			1							
BR1						1			1							
BR2									1		1			1	1	
BR3											1					
BR4											1				1	
BR5	1					1	1									
BR6		1	1							1			1			
ANY	P	P	P	3/3	P	P	P	3/3	P	P	P	3/3	P	P	P	3/3
SC				0/3				0/3			1	1/3				0/3

* See page 11 for a list of abbreviations used in Tables 1 - 5.

TABLE 3

Pathology Petition Review PR-168 (Pathdata Report 30168); Glaxo Report Number UTX/94/020

Female Dogs with EXTRAVASCULAR HEMORRHAGE

Level	Group 1 Female Controls			SI	Group 2 1mg/kg Remi*			SI	Group 3 .1mg/kg Alfen			SI	Group 4 1mg/kg Alfen			SI
	7171	7185	7188		7173	7178	7187		7170	7176	7183		7174	7177	7189	
BR0					3	1							1			
BR1					2		1								1	
BR2					2		1									
BR3																
BR4					2		1							1		
BR5					1		1						1			
BR6	1				2						1				1	
ANY	P			1/3	P	P	P	3/3			1	1/3	P	P	P	3/3
SC	1	1	1	3/3		1		1/3	1	1	1	3/3		1	1	2/3
Female Dogs with PERIVASCULAR HEMORRHAGE																
BR0	1	1					1									
BR1							1									
BR2							1									
BR3	1	1														
BR4																
BR5									1							
BR6		1				1										
ANY	P	P		2/3		P	P	2/3	P			1/3				0/3
SC				0/3		1		1/3	1		1	2/3		1	1	2/3

* See Page 11 for a list of abbreviations used in Tables 1 - 5.

Male Dogs with EXTRAVASCULAR HEMORRHAGE

	Group 1: 1 mg/kg/day Remifentanil Isoflurane + Ventilated						Group 2: Control (Sterile Saline) Isoflurane + Ventilation						Group 3: 1mg/kg/day Remifentanil Isoflurane/No Ventilation						Group 4: 1mg/kg/day Remifentanil No Isoflurane/No Ventilation						Group 5: Controls (Sterile Saline) No Isoflurane/No Ventilation					
	7635	7636	7638	7642	7651	SI	7640	7646	7650	7652	7653	SI	7627	7630	7643	7645	7647	SI	7625	7633	7637	7641	7648	SI	7631	7632	7639	7644	7649	SI
BR0					1						1																			
BR1														1					1				1						1	
BR2																	1													
BR3																														
BR4														1																
BR5	1			1					1	1	1			1			1		1	1	1	1			2		2	1		
BR6	1						1	1								1	1				1	1	1			1				
ANY	P			P	P	3/5	P	P	P	P	P	5/5		P		P	P	3/5	1	1	1	1	1	5/5	P	P	P	P	P	5/5
SC	1	2	1			3/5	1	1	1	1	1	5/5	2	1	1		1	4/5	1		1	1	2	4/5	1		2	2	1	4/5

Male Dogs with PERIVASCULAR HEMORRHAGE

BR0	1	1	1														1								1					
BR1		1									1					1														
BR2																	1													
BR3																														
BR4											1															1				
BR5	1	1	1								1			1	1	1	1		1	1	1				1					
BR6	1		1													1											1			
ANY	P	P	P			3/5					P	1/5		P	P	P	P	4/5	P	P	P			3/5	P	P	P		P	4/5
SC		1	1		1	3/5			1			1/5					1	1/5	1					1/5					1	1/5

• See Page 11 for a list of abbreviations used in Tables 1 - 5.

TABLE 5

Pathology Petition Review PR-168 (Pathdata Report 50168); Glaxo Report Number UTX/94/049

	Group 1. 20 μg/kg/min Remifentanil Isoflurane + Ventilation						Group 2: Control (Sterile Saline) Isoflurane + Ventilation						Group 3: Controls (Sterile Saline) No Isoflurane / No Ventilation					
	7785	7788	7790	7791	7797	SI	7781	7782	7783	7794	7795	SI	7786	7787	7789	7793	7796	SI
Male Dogs with EXTRAVASCULAR HEMORRHAGE																		
BR0					1													
BR1																1		
BR2																		
BR3																		
BR4													1					
BR5	1			1	1			1		1	2				1			
BR6	1		1	1	1			1			1		1		1			
ANY	P		P	P	P	4/5		P		P	P	3/5	P		P	P		3/5
SC	1			1		2/5		1			1	2/5	1	1		1	1	4/5
Male Dogs with PERIVASCULAR HEMORRHAGE																		
BR0				1	1					1	1						1	
BR1										1	1							
BR2			1							2						1		
BR3										1			1				1	
BR4				1						1						1	1	
BR5										1	1		1					
BR6										1				1		1		
ANY			P	P	P	3/5				P	P	2/5	P	P		P	P	4/5
SC		1		1	1	3/5		1		1	1	3/5			1	1	1	3/5

• See Page 11 for a list of abbreviations used in Tables 1 - 5.

COMMENTS:

Non-Ventilated Dog Studies 10168, 20168 and 30168

The purpose of 10168 (UTX/93/003) was to evaluate the toxicity of Remifentanil when given to non-ventilated male and female dogs at dose levels of 0, 0.01, 0.03 and 0.05 mg/kg once a day by intravenous injection for four weeks. As can be seen in Table 1, there was an increase in the incidence of terminally-sacrificed treated male (but not female) dogs with either extravascular or perivascular hemorrhage when compared to the corresponding control group of males. Specifically, statistical significance of $p \leq 0.05$, as reported on page 16 of the Patadata Study 10168, was achieved at the following levels:

Slide 1 or Caudate nucleus (BR0) for treated male dogs with extravascular hemorrhage

Slide 2 or Thalamus/Hypothalamus (BR1) for treated male dogs with extravascular hemorrhage

Slide 3 or Hippocampus (BR2) for treated male dogs with extravascular hemorrhage

Slide 5 or Substantia Nigra (BR4) for treated male dogs with extravascular hemorrhage

Slide 6 or Cerebellum (BR5) for treated male dogs with extravascular hemorrhage

Slide 8 or Spinal Cord (SC) for treated male dogs with perivascular hemorrhage

These findings suggest that the test material related effect is an increase in the incidence of extravascular hemorrhage in the brain of the dogs of this study. According to the statistical calculations, the most affected brain level was BR2, followed by BR0, BR4, BR5 and BR1.

The statistical significance of the male treated dogs with perivascular hemorrhage in the spinal cord was probably not of biologic significance since in the other studies the incidence of control male dogs with spinal cord perivascular hemorrhage varied widely (range 0% - 60%).

In all sections, the location of the hemorrhagic lesions was predominantly in the gray matter.

Figure 10 represents an image of the two subgross microslides from the most affected male dog with extravascular hemorrhage in the 10168 study (it is the mid-dose Remifentanil-treated male animal 5574). The lesions have been marked with a 3mm object marker. The microslides represent those from the BR2 (Slide 3 or Hippocampus area) BR4 (Slide 5 or the Substantia Nigra area). The subgross depicts the number of lesions for the slide and the location of the lesions. The lesions are predominantly in the gray matter and in the BR4 sections where both hemispheres are present, there is a slight suggestion that the lesions may be bilaterally-

symmetrical in the gray matter. This point can not be confirmed since part of the tissue has been trimmed to accommodate the size of the slide which was common procedure for these studies).[a] Of the seven lesions marked in Figure 10 from the BR4 microslide, a typical one is presented in Figure 11. Figure 11 demonstrates just how small these lesions were - even in the most affected animal of the study. The increase in the degree of severity was based on number of lesions present - not an increase in the size of the lesions.

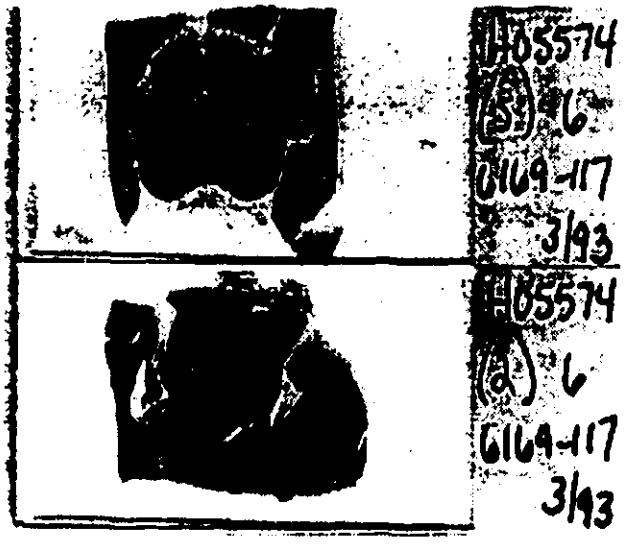

Figure 10: BR4 (top) and BR1 (bottom) from Group 3 male Animal 5574 receiving 0.03 mg/kg/day Remifentanil from Study UTX/93/003. Circles indicate where hemorrhages were present (most located in gray matter). Also note that hemorrhages can not be seen by gross examination of the tissues.

Figure 11: BR4 from Group 3 male Animal 5574 receiving 0.03 mg/kg/day Remifentanil from Study UTX/93/003 (1172X). Perineuronal hemorrhage demonstrating typical size of the hemorrhagic lesion.

[a] The point being that future studies to determine mechanisms for brain hemorrhages in dogs should use whole brain blocks and microslides to prepare the brain sections.

Even in the females a test-material related effect can be seen in Table 1 when looking at the population dynamics of the total incidence of extravascular hemorrhagic lesions among the various brain levels (as distinct from the incidence of dogs with the lesion). That is, there are more "hits" at the mid- and high-dose levels for both male and female on the study.

The incidence of terminally-sacrificed female dogs with both extravascular and perivascular hemorrhage was 100%. The bilaterally-symmetrical pattern of perivascular hemorrhages in the gray matter was demonstrated previously (Figure 9, page 10) for the terminally-sacrificed female control 5591. In a previous pathology report generated by the PB in which dogs with brain hemorrhage were evaluated, perivascular hemorrhages were designated "extravasation" since they could not be distinguished from the artifactual seepage of blood from the cut end of a vessel[b]. What persuaded the PB to change its nomenclature was the data from the female control animal 5591 of study UTX/93/003 (Figures 8 and 9 on pages 9 and 10). It would be unlikely that such a pattern would occur as a result of artifactual processes.

One of the perivascular hemorrhages from the microslide represented in Figure 9 was photographed at 596X and depicted in Figure 1 (page 7).

The data from the recovery group of male dogs did not duplicate the results from the terminally-sacrificed dogs, i.e., although there was no terminally-sacrificed male control dogs with perivascular hemorrhage, both male recovery high-dose dogs had the lesion and the incidence of recovery male control animals with any brain extravascular hemorrhage or spinal cord extravascular hemorrhage was identical to the high-dose treated male dogs with any brain extravascular hemorrhage or spinal cord extravascular hemorrhage, i.e., ½ or 50%.

The purpose of designing studies 20168 (UTX/94/022) and 30168 (UTX/94/020) was to determine if microscopic brain hemorrhages occur following a single intravenous dose (20168) or seven consecutive daily intravenous doses (30168) of Remifentanil and Alfentanil. Table 2 shows that similar lesions and incidence of lesions among the brain and spinal cord levels was similar in the Remifentanil and Alfentanil groups, but the difference from the control groups was more apparent in study 30168 (Table 3). That is, as expected, a test-material effect with Remifentanil and Alfentanil is more pronounced in the study in which the treated animals received daily intravenous doses for seven days than when dogs received a single intravenous dose.

As with the 10168 study, lesions in the 20168 and 30168 studies are predominantly confined to the gray matter and an increase in the degree of severity is due to an increase in the number of lesions per slide, not an increase in the size of the lesions.

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[b] This opinion was also the one provided by the petitioner's consultant pathologist on the present studies.

Ventilated Dog Studies (40168 and 50168)

The purpose of these studies was to determine if microscopic brain hemorrhages occur in ventilated male dogs after an acute intravenous bolus (40168) or following a 4-hour infusion of Remifentanil (50168). The findings from Tables 4 and 5 indicate that both kinds of hemorrhage are occurring in the ventilated Remifentanil groups (Group 1 of both 40168 and 50168); however, they can not be distinguished from the hemorrhages occurring in the ventilated control groups (see Figure 2, page 7 and Figure 12 for examples of control hemorrhages in these studies and Figure 13 for a typical example of hemorrhage occurring in a Remifentanil-treated dog). There was no pattern of lesions present among the brain sections of the ventilated Remifentanil-treated groups which would indicate an exacerbation of the type of hemorrhages seen in the ventilated control dogs.

Figure 12: BR5 of Male Control 7653 of Study UTX/94/047. Example of extravascular hemorrhage in a Isoflurane + and ventilated control animal (1172X).

Figure 13: BR5 of Remifentanil-treated Animal 7635 of Study UTX/94/047. Example of extravascular (perineuronal) hemorrhage in an Isoflurane + and ventilated Remifentanil-treated dog (1172X).

DISCUSSION:

This pathology review is the second one within the past two years that the PB has been requested to evaluate the significance of brain hemorrhage occurring in dogs. The other pathology review was with an HMG-CoA reductase inhibitor.[5] This review is similar to the previous HMG-CoA reductase inhibitor study in four aspects:

1) the test-material related lesion occurred primarily in the gray matter.

2) the sponsor hypothesized hypoxia as the mechanism for causing the hemorrhages; but a definitive study to confirm this hypothesis was not done.

3) the sponsor compared their HMG-CoA reductase inhibitor with one already on the market (Lovastatin®) and the latter did produce the same lesions and

4) brain hemorrhages did not occur in other animal species tested.

Two major differences in this present review from the HMG-CoA reductase inhibitor study review is that

1) the dogs in the HMG-CoA reductase inhibitor study developed a spectrum of lesions in the brain such as perivascular edema, neuropil edema, perivascular and extracelluar hemorrhage, formation of fibrinous plaques, polio- and leukomalacia and necrotizing vasculitis;

2) the test material related lesion was shown to be bilaterally-symmetrical in the gray matter of a specific location (the piriform lobe).

In the present study, each individual hemorrhagic lesion could not be distinguished from some type of postmortem artifact. In the few instances when both hemispheres were present, a bilaterally-symmetrical pattern of the hemorrhages may have been present in the gray matter. This kind of distribution and location would discount the lesions being artifact; however, control animals demonstrated this pattern as well as treated animals. When the hemorrhagic lesions were present in an area of "mechanical disruption", the petitioner's consultant pathologist regarded the hemorrhage as artifact. An alternative hypothesis to perivascular and extravascular hemorrhage occurring in mechanically-disrupted tissue is that the tissue is weakened by the presence of the hemorrhagic lesion and this predisposes the tissue to tearing and fractures. That is, the lesion is causing the disruption of the tissue and therefore the tearing may not be due to a mechanical disruption.

The spinal cord hemorrhages in the dogs from the present study were almost invariably located in the gray matter which implies the hemorrhages were real since the lesions were restricted to a specific area. However, the summary incidence data from the spinal cord does not suggest a test-material effect since control animals with extravascular hemorrhage in the spinal cord occurred in similar numbers to treated animals with spinal cord hemorrhage or the incidence of control animals with perivascular hemorrhage in the spinal cord varied widely (0 to 60%) among the five studies.

Treatment with Isoflurane and ventilation to dogs did reduce the levels of brain hemorrhage to control levels which would tend to support the sponsor's hypothesis that hypoxia may be a contributing factor in the mechanism of brain hemorrhage in the dogs.

Extravascular and perivascular hemorrhages were observed in brain sections of control dogs of the present study, but perivascular hemorrhages predominated. In the treated Remifentanil (and Alfentanil) dogs, extravascular hemorrhage predominated. It could not be determined from microscopic examination of these tissues whether the perivascular hemorrhage may have preceded the extravascular (or acute) hemorrhage, i.e., it could not be determined with certainty whether the test-material related lesions represented an exacerbation of cryptogenic (of unknown etiology) perivascular hemorrhages as seen in the control animals or whether the test material related lesion (extravascular hemorrhage) was due to a direct toxic effect on the vascular system although the PB favors the former explanation as explained below.

With the HMG-CoA reductase inhibitor studies in mind as well as the present review, the PB deduces that the laboratory beagle dog may have a pre-existing condition which manifests as subtle hemorrhages in the brain and spinal cord of control dogs which has been interpreted as artifact or lesions of little pathologic significance. These hemorrhages may instead signal a pre-existing condition in control beagle dogs which is confounding results from toxicity studies since an exacerbation of this pre-existing condition triggered by hypoxia may lead to a spectrum of lesions such as locally-extensive hemorrhage and necrosis, neuronal necrosis and leuko- or poliomalacia. This hypothesis could explain the apparent species specificity of apparent test-material related brain hemorrhagic effects in this study and in the HMG-CoA reductase inhibitor studies, but the "pre-existing" condition needs to be elucidated before the biologic significance of these exacerbated lesions in treated dogs are fully known.

CONCLUSION:

Essentially, the PB agreed slide-by-slide with the petitioner's report on whether hemorrhages were present or absent. The PB used strictly morphological terms to diagnose a particular lesion (i.e., "perivascular or extravascular" hemorrhage) whereas the petitioner's report used the terms artifactual hemorrhage or acute hemorrhage which is acceptable nomenclature.

According to the PB, the major findings from these five studies included

1) An increase in the incidence of non-ventilated Remifentanil (and Alfentanil) treated dogs with brain hemorrhage when compared to the corresponding control dogs;

2) The most affected brain level was BR2 (Hippocampus) followed by BR0 (Caudate Nucleus), BR4 (Substantia Nigra), BR5 (Cerebellum) and BR1 (Thalamus/ Hypothalamus).

3) A reduction in the incidence of ventilated Remifentanil-treated dogs with brain hemorrhage to the incidence of control ventilated dogs with brain hemorrhage.

That is, unventilated Remifentanil-treated dogs have a higher incidence of brain hemorrhage when compared to the corresponding control groups of dogs with brain hemorrhage, but ventilating the dogs did prevent this apparent test-material related effect from occurring.

The PB has also recently reviewed data from two different HMG CoA reductase inhibitor studies in dogs in which it was reported that the test materials caused brain hemorrhage. Hypoxia was speculated to be the mechanism causing hemorrhages due to HMG CoA reductase inhibitors by the submitting petitioner, but no definitive studies were requested or performed to test the hypothesis.

REFERENCES

1. Hoffman, WE *et al.* (1993). Effects of Remifentanil, a new short-acting opioid, on cerebral blood flow, brain electrical activity, and intracranial pressure in dogs anesthetized with Isoflurane and nitrous oxide. *Anesthesiology* 79: 107-113.

2. Tyler, R *et al.* (1993). Assessment of microhemorrhages in the brains of dogs following administration of GI87084B. Glaxo Inc. Report Number UTX/93/058.

3. Memorandum dated November 22, 1994 from Harry Geyer, III, Ph.D., Pilot Drug Evaluation Staff (HFD-007) to Ronald Moch, D.V.M., Chief, Pathology Branch (HFS-716); subject: Remifentanil (GI87084B): Request for Pathology Support to Drug Review.

4. Memorandum dated February 10, 1995 from Prem Dua, D.V.M., Ph.D., Pathology Branch (HFS-716) to Harry Geyer, III, Ph.D., Pilot Drug Evaluation Staff (HFD-007); subject: Request for Information/Microslides.

5. Memorandum dated August 8 from Dr. Fred A Hines, Toxicologic Pathologist, HFS-716 to Dr. Elizabeth K. Barbehenn, Review Pharmacologist, HFD-510; subject: Pravastatin (Pathology Petition Review PR-136): A Review of Microslides Containing Brain and Eye from a Two-Year oral Study in Dogs; Bristol-Myers-Squibb (BMS) Study Numbers 8601 and 8614. ATTACHMENT: Pathology Branch's Pathology Report of Above-cited Petition Review PR-136.

PATHOLOGY REPORT FINAL

UTX/93/003|D13953|6169-117

TEST ARTICLE : REMIFENTANIL
TEST SYSTEM : BEAGLE, 4 WEEKS,
SPONSOR : GLAXO INC.

PATHOL. NO.: 10168 FAH
DATE : 20-DEC-95
PATHDATA SYSTEM V3.5d

Fred A. Hines DVM

PREPARED BY: Dr. Fred A. Hines
Toxicologic Pathologist

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date February 10, 1995

From Diagnostic Pathology Section
Pathology Branch/DGSS/OSAS/CFSAN (HFS-716)

Subject Remifentanil (GI87084B): Request for Information/Microslides (Pathology Project No. PR-168)

To Harry Geyer, III, Ph.D., Pharmacologist
Pilot Drug Evaluation Staff
Office of Drug Evaluation II/CDER (HFD-007)
Through: Chief, Pathology Branch, HFS-716 Ronald W. Moch

Ref. Memorandum dated November 22, 1994 from Dr. Harry Geyer, III, Pilot Drug Evaluation Staff (HFD-007) to Dr. Ronald W. Moch, Pathology Branch (HFS-716); subject: Request for Pathology Support to Drug Review

This is in response to your request (Ref.) for the Pathology Support for review of slides and pathology data from different dog studies with Remifentanil, an Investigational New Drug (IND 34,847) that you are currently evaluating.

The materials you provided us, i.e., two volumes of data submitted on 12/12/94 and the previous summary materials of these studies, have been reviewed. The primary focus of our review is to assess the basis for the microhemorrhages reported in the brain and spinal cord of dogs in these studies. Please request that the microslides and other relevant information from the following studies be forwarded to your office for forwarding to the Pathology Branch:

Glaxo Report Nos.:

UTX/93/003	Four-week Intravenous Injection Toxicity Study in Dogs
UTX/94/022	Acute Bolus Intravenous Toxicity in Non-Ventilated Male Dogs
UTX/94/020	7-Day Bolus Intravenous Toxicity Study in Non-Ventilated Dogs
UTX/94/047	Acute Bolus Intravenous Toxicity Study in Ventilated Male Dogs
UTX/94/049	Intravenous Infusion Toxicity Study in Ventilated Male Dogs

The above listed studies should provide a comparison of lesions reported in the brain of dogs from both ventilated and non-ventilated group animals as well as from a study dealing with the recovery group animals and should suffice for assessing the reported lesions. The following materials/information should be obtained from the sponsor at this time:

1. All available brain and spinal cord microslides for each study listed above (arranged by study number, animal numbers and dosage groups). The slides should be accompanied by a listing of gross and microscopic observations, correlation of gross to microscopic lesions and be provided in the order corresponding to the arrangement of the slides for a designated study.

2. A glossary/description of the histopathologic terms used in describing lesions in the brain and spinal cord.

3. Information on the examination of brains and spinal cord including the scope of gross examination (external and cut surfaces), method and location of tissue sampling, and number of sections examined microscopically from each animal. Was any perfusion technique used for tissue preservation, e.g., whole body perfusion at time of necropsy? If so, please provide details on the methodology used.

4. The sponsor's explanation of the possible etiology of the observed hemorrhage.

5. Supporting references insofar as the etiology of the hemorrhage.

6. The results of any further studies, e.g, the use of electron microscopy to evaluate the observed hemorrhage.

7. Any additional information/material which might assist in the evaluation and interpretation of these lesions.

Some of the information requested above is contained in the volumes of the data already provided to us. It would expedite our review if the applicable information is extracted by the sponsor and submitted along with the microslides.

Once the requested materials are received by your Consumer Safety Officer (CSO), please notify me and I will work with your CSO to have the materials transferred to our office.

Should you have any questions/comments as to the information/materials requested in this memorandum, please contact me via phone (202-205-4123) or via E. Mail (PNDeVM.CFSAN.FDA.Gov.).

P N Dua

Prem N. Dua, D.V.M., Ph.D.

cc: HFS-700 (Falci)
HFS-715 (Moch, r/f)
HFS-716 (Dua, Hines)
HFS-716 (PB Central Files)

Prepared by: Prem N. Dua, DVM:2/7/95:205-4123
Reviewed by: CStevenson:205-4247 CMS 2/10/95
Cynthia Howard:205-4866 CKH 2/10/95

HFS-716:PNDua:cms:Doc. No.
PR168:RD:2/7/95:REDRAFTED:2/9/95:FT:2/10/95

STAT

Statistical Review and Evaluation

NDA 20-630

Date of review: 16 April 1996
By: Thomas Permutt

Name of drug: Ultiva (remifentanil)
Applicant: Glaxo Wellcome
Indication: Opioid analgesic component of anesthesia

Documents reviewed: volumes 2.1, 2.105-108, 15 September 1995
(received HFD-007 18 September 1995)
electronic data sets
study summaries submitted electronically

Project manager: David Morgan
Medical reviewer: Barbara Palmisano, M.D.

Introduction

Remifentanil is a new member of the fentanyl family of μ-opioids. It is proposed for the usual indications for these drugs, which are as an analgesic component of balanced anesthesia and for monitored anesthesia care and postoperative analgesia. Remifentanil differs from fentanyl and other fentanyl analogs in having a very rapid onset (but perhaps not more rapid than alfentanil) and an extremely short duration of action.

As discussed in the medical officer's review, the efficacy of remifentanil has been clearly established in clinical trials, and there are no special statistical problems with respect to efficacy. Also, the side effects appear to be typical of the class, and vary, along with the desired effects, according to the dose. The radically different kinetics of remifentanil, however, make it difficult to speak in terms of "equivalent" doses. An important question about the safety and utility of remifentanil is therefore whether side effects are more common or more severe than with similar drugs at therapeutic doses.

At the medical officer's request, this statistical review focuses on the relative incidence, in general anesthesia studies with an active comparator, of certain classic opioid side effects: hypotension, bradycardia, muscle rigidity, nausea and vomiting, pruritus, and headache. Hypotension occurred about twice as often remifentanil as with alfentanil. Bradycardia and

muscle rigidity were substantially more common with remifentanil than with alfentanil in one study. There were no clear differences between treatments in the other adverse effects.

All the tables in this review were made by the reviewer from the submission of electronic data. The sponsor's conclusions were generally similar.

Overall rates of typical opioid adverse events

Labeling typically includes a table with the number of patients experiencing adverse events expressed as a fraction of the total number exposed, often alongside similar information for comparators. Here is such a table for the typical opioid adverse events considered in this review, for all controlled studies in general anesthesia.

	Remifentanil (N = 1784)	Alfentanil (N = 522)
Hypotension	420 (24%)	43 (8%)
Bradycardia	172 (10%)	33 (6%)
Muscle rigidity (moderate or severe)	195 (11%)	43 (8%)
Nausea	863 (48%)	258 (49%)
Vomiting	369 (21%)	118 (23%)
Pruritus	70 (4%)	10 (2%)
Headache	45 (3%)	14 (3%)

On the whole, hypotension was about three times as common with remifentanil as with alfentanil, and bradycardia was nearly twice as common with remifentanil as with alfentanil.

Such a table is probably the best way to present data on rare adverse events, especially if they are not believed to be strongly related to the dose. It is desirable to capture as many as possible of such events to improve the reliability of the estimates of their frequency. The present case is rather different. The adverse events considered are typical of opioid drugs; they are not very rare; and their frequency is expected to depend strongly on the dose. Many of the studies used remifentanil at doses higher than what is proposed as the recommended

range. This comparison of rates of adverse events may therefore not correspond closely to what might be expected in clinical practice consistent with the label recommendations.

The rest of this review will therefore focus on three relatively large trials in which remifentanil was used at or near the recommended doses and in which it was directly compared to alfentanil.

Description of Studies

The three large, double-blind comparisons with alfentanil in general anesthesia are designated as Studies 3001, 3003, and 3008. The dosing regimes are rather complicated, and the dose (and possibly the use of other agents) is of central importance in interpreting the rates of adverse events. I therefore quote the sponsor's descriptions of the studies in detail.

Study 3001

> Study Design: A multicenter, multinational, randomized, double-blind, parallel group, comparative study of remifentanil and alfentanil for the maintenance of anesthesia using a balanced anesthetic technique in patients undergoing major abdominal surgery.
>
> Demographics: 234 patients aged 18-86 years, ASA I-III, male and female were treated. Most patients were caucasian (97%). Fifty-one females and 65 males (116 total) were treated with remifentanil and 47 females and 71 males (118 total) were treated with alfentanil.
>
> Anesthesia Protocol: After premedication of oral midazolam (7.5mg) or oral diazepam (5-10mg), induction was begun with either a bolus dose of remifentanil (1mcg/kg) plus a continuous infusion of 0.5mcg/kg/min or a bolus dose of alfentanil (25mcg/kg) plus a continuous infusion of 1mcg/kg/min. Immediately following the bolus dose of study drug, propofol was administered slowly (10mg every 10 seconds) until loss of consciousness occurred. Vecuronium (0.08-0.1mg/kg) was given to facilitate intubation. Anesthesia was maintained with 66% nitrous oxide and 0.5% end-tidal isoflurane. Five minutes after intubation, the study drug infusion was reduced by 50%. Alfentanil was discontinued 15 minutes before the end of surgery by changing the alfentanil maintenance infusion syringe to one containing placebo. Remifentanil treated patients continued to receive an analgesic infusion initially set at 0.05mcg/kg/min, but subsequently amended to 0.1mcg/kg/min for the provision of post-operative analgesia during the immediate post-operative period. Responses to surgical stimuli (primarily hemodynamic responses) were treated primarily with bolus doses or rate increases of study drug.

Study 3003

> Study Design: Randomized, multi-center, parallel group double-blind study comparing remifentanil and alfentanil during anesthesia for varicose vein surgery, knee arthroscopy or multiple wisdom tooth extraction.

Demographics: A total of 201 patients (103 male and 98 female), aged 18-65 years, ASA status I-II received treatment. The majority of patients were Caucasian.

Anesthesia Protocol: *Induction:* Glycopyrrolate was given followed by oxygenation of the patient. Remifentanil continuous infusion was started at 0.25mcg/kg/min or alfentanil at 0.5mcg/kg/min with simultaneous bolus of 1mcg/kg or 25mcg/kg, respectively. Propofol 10mg every 10 seconds was given until LOC. Isoflurane was started and vecuronium given for intubation. *Maintenance:* Anesthesia was maintained with 0.8% isoflurane. Signs of light anesthesia (SBP/HR increases, somatic or autonomic) were treated with bolus doses of remifentanil 1mcg/kg or alfentanil 5mcg/kg and the infusion rate was doubled. *Termination:* Prior to end of surgery, patients received a NSAID suppository for post-operative pain control. Isoflurane and study opioid infusion discontinued at end of surgery and neuromuscular block was reversed. *Recovery:* Times to response to verbal command, extubation, return of respiratory function and discharge were recorded. Trieger Dot Tests and Digit Symbol Substitution Tests were administered to assess quality of recovery (baseline was measured prior to start of study drug).

Study 3008

Study Design: Multi-center, randomized, double-blind, parallel group, active-controlled study for laparoscopic outpatient procedures greater than 30 minutes. Patients received a bolus (1mcg/kg remifentanil or 20mcg/kg alfentanil) followed by a continuous infusion (0.5mcg/kg/min remifentanil or 2mcg/kg/min alfentanil)

Demographics: 223 in the safety population (222 female, 1 male): 23 were pilot patients and the remainder of the patients (200) were randomly assigned to either the remifentanil/propofol regimen (134) or the alfentanil/propofol regimen (66). Patients aged 18-51, ASA status I-III, male and female, 70% of which were Caucasian.

Anesthesia Protocol: *Premedication:* midazolam 1 mg. *Induction:* Propofol bolus (2mg/kg) followed by 150mcg/kg/min infusion, followed by study drug. A priming dose of vecuronium (0.01mg/kg) and additional vecuronium (up to 0.1mg/kg) facilitated intubation. *Maintenance:* Five minutes after trocar insertion, the propofol infusion was decreased to 75mcg/kg/min and the opioid infusion was decreased (0.25mcg/kg/min for remifentanil or 1mcg/kg/min for alfentanil). Alfentanil was discontinued 10 minutes before the end of surgery. Remifentanil was discontinued at the end of surgery. Five minutes before end of surgery, the propofol infusion was stopped and patients were reversed with neostigmine (0.04-0.07mg/kg) and glycopyrrolate (0.01mg/kg).

Hypotension

study	drug	AE (%)	exposed	RR (95% C.I.)
3001	remi	42 (36%)	116	2.0 (1.3–3.2)
	al	21 (18%)	118	
3003	remi	8 (8%)	102	—
	al	0	99	
3008	remi	11 (7%)	157	0.9 (0.3–2.6)
	al	5 (8%)	66	

RR is the estimated relative risk. The confidence interval is the test-based interval as calculated by SAS Proc Freq.

Hypotension occurred twice as often in the remifentanil as in the alfentanil group in Study 3001. It also occurred in 8% of patients in the remifentanil group in Study 3003 but not at all in the alfentanil group. In the third study (3008) the rates were nearly equal for the two treatments. Note the differences in protocol among the studies. In particular, the infusion rate for alfentanil was twice that for remifentanil in Studies 3001 and 3003, but four times in Study 3008.

I have not calculated p-values for these comparisons. In general, I do not think significance testing is useful for describing adverse-event data. The main difficulty is the interpretation of negative results. It is not generally reasonable to suppose that tests are sufficiently powerful to detect any clinically meaningful effect. Therefore, a "nonsignificant" result does not reliably indicate the absence of a difference. There are also questions of multiplicity if the studies are considered separately, and of poolability if they are taken together. Still, it is desirable to indicate the extent of uncertainty in the data. I have done this by computing confidence intervals for the relative risk. While there is considerable uncertainty about the magnitude of the difference between remifentanil and alfentanil, there is little doubt about its direction. On the whole, hypotension occurred more frequently with remifentanil than with alfentanil.

Bradycardia

study	drug	AE (%)	exposed	RR (95% C.I.)
3001	remi	17 (15%)	116	2.2 (1.0–4.7)
	al	8 (7%)	118	
3003	remi	7 (7%)	102	0.8 (0.3–2.3)
	al	8 (8%)	99	
3008	remi	14 (9%)	157	0.6 (0.3–1.3)
	al	10 (15%)	66	

Study 3001, which showed a twofold relative risk of hypotension with remifentanil, produced a similar result with respect to bradycardia. In Study 3003, where glycopyrrolate was used, bradycardia, unlike hypotension, was about equally common in the two groups. In Study 3008 (fourfold rather than twofold ratio of infusion rates), the rate was somewhat lower with remifentanil. No overall conclusion can be drawn, but it seems prudent to observe that the incidence of bradycardia may be substantially higher with remifentanil than with alfentanil under some conditions.

Muscle rigidity

The table includes occurrences of muscle rigidity classified as moderate or severe, not mild.

study	drug	AE (%)	exposed	RR (95% C.I.)
3001	remi	12 (10%)	116	4.1 (1.3–13)
	al	3 (3%)	118	
3003	remi	1 (1%)	102	—
	al	0	99	
3008	remi	0	157	—
	al	0	66	

Except for one case, moderate or severe muscle rigidity was seen in only one of the three studies. In that one study (3001), it was four times as common in the remifentanil group. Note that the doses of both remifentanil and alfentanil were lower in Study 3003 than in Study 3001, and that a priming dose of vecuronium (a neuromuscular blocking agent) was used in Study 3008.

Nausea, vomiting and pruritus

These common, dose-related opioid side effects were not seen more often with remifentanil than with alfentanil in the comparative studies. Even in Study 3001, where hypotension, bradycardia, and muscle rigidity were more common with remifentanil, the rates appear comparable, or (for vomiting) perhaps slightly lower with remifentanil.

Nausea

study	drug	AE (%)	exposed	RR (95% C.I.)
3001	remi	55 (47%)	116	1.0 (0.7–1.3)
	al	56 (47%)	118	
3003	remi	19 (19%)	102	0.9 (0.5–1.5)
	al	21 (21%)	99	
3008	remi	81 (52%)	157	0.9 (0.7–1.1)
	al	40 (61%)	66	

Vomiting

study	drug	AE (%)	exposed	RR (95% C.I.)
3001	remi	12 (10%)	116	0.6 (0.3–1.3)
	al	19 (16%)	118	
3003	remi	8 (8%)	102	1.3 (0.5–3.6)
	al	6 (6%)	99	
3008	remi	41 (26%)	157	0.7 (0.5–1.0)
	al	25 (38%)	66	

Pruritus

study	drug	AE (%)	exposed	RR (95% C.I.)
3001	remi	1 (0.9%)	116	1.0 (0.06–16)
	al	1 (0.8%)	118	
3003	remi	0	102	—
	al	0	99	
3008	remi	4 (3%)	157	0.8 (0.2–4.5)
	al	2 (3%)	66	

Headache

study	drug	AE (%)	exposed	RR (95% C.I.)
3001	remi	0	116	—
	al	1 (0.8%)	118	
3003	remi	7 (7%)	102	3.4 (0.8–14)
	al	2 (2%)	99	
3008	remi	2 (1%)	157	0.2 (0.05–0.96)
	al	4 (6%)	66	

Headache occurred rather more with remifentanil than with alfentanil in Study 3003, rather less in Study 3008, and hardly at all in either group in Study 3001.

Conclusions and recommendations

The application is approvable from a statistical standpoint. The rates of certain adverse events, which are typical of opioids and related to dose, appear higher in the overall data base for general anesthesia with remifentanil than with alfentanil, its closest comparator. This appears to be partly because remifentanil was used at higher doses in earlier studies. At recommended doses in direct comparisons with alfentanil, remifentanil still appears to produce more hypotension, and more bradycardia and muscle rigidity under some conditions.

Thomas Permutt

Thomas Permutt, Ph.D.
Mathematical Statistician
Acting Team Leader,
Division of Anesthetic, Critical Care
and Addiction Drug Products

concur:
Nancy B. Smith, Ph.D. N Smith 4/17/96
Acting Director, Division of Biometrics III

archival: NDA 20-630
cc:
HFD-720/N. Smith
HFD-720/S. Moore (file copy, chron. copy)
HFD-170/D. Morgan
HFD-170/B. Palmisano
HFD-170/T. Permutt
HFD-170/division file

Chem

DIVISION OF ANESTHETICS, ANALGESIC, CRITICAL CARE AND SCHEDULED DRUG PRODUCTS, HFD-170

Review of Chemistry, Manufacturing, and Controls

NDA #: 20 - 630

REVIEW # 1 **DATE REVIEWED:**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	30-Jun- 95	3 -Jul-95	24 -Jul- 95
AMENDMENT	15-Sep- 95	15-Sep-95	-Sep-95
AMENDMENT	15-Jan- 96	16-Jan-96	23-Jan-96
AMENDMENT	17-May-96	8-May-96	10-May-96
AMENDMENT	11-Jun-96	11-Jun-96	12-Jun-96 (FAX)

NAME & ADDRESS OF APPLICANT: Glaxo Wellcome Company
Five Moore Drive
Research Triangle Park, N.C.
27709

DRUG PRODUCT NAME

Proprietary: ULTIVA (Remifentanil HCL) for Injection

Established: Remifentanil Hydrochloride

Code Name/#: G187084B

Chem.Type/Ther.Class: 1S

PHARMACOL. CATEGORY: Anesthetic/Analgesic

DOSAGE FORM: Lyophilized powder for injection

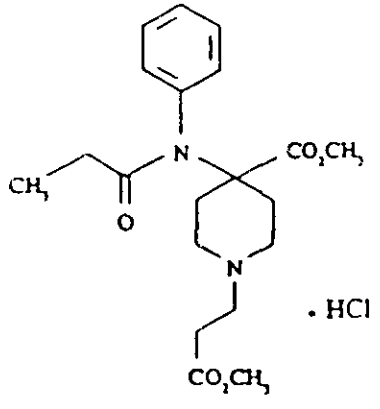
STRENGTHS: 5 mg/vial, 2 mg/vial, & 1 mg/ vial

ROUTE OF ADMINISTRATION: Intravenous

DISPENSED: X Rx ____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

1-(2-Methoxycarbonyl-ethyl)- 4-(phenyl-propionyl-amino)-piperidine-4-carboxylic acid methyl ester hydrochloride



Molecular Formula $C_{20}H_{28}N_2O_5.HCl$

Molecular Weight 412.9

SUPPORTING DOCUMENTS:

1. IND GLAXO, INC.
Five Moore Drive
Research Triangle Park, N.C. 27709

This is the investigational new drug application submitted by the applicant for this new drug application.

2. DMF

This company supplies the glass vials (10 mL, 5 mL, and 3 mL sizes)

3. DMF

The alternate company that supplies the 3 mL and 10 mL glass vials.

RELATED DOCUMENTS:

None

CONSULTS:

1. Microbiology Section : Sent: 01-Jan-96
Dr.Peter Cooney
Di . of Medical Imaging and
Radiopharmaceutical Drug Products

Status: In a report dated April 30,1996, our microbiologist recommended approval of NDA 20-630 for Ultiva (Remifentanil for Injection)

2. Environmental Assessment Report: Sent: 27-Sept-95-
Ms. Nancy Sager
HFD-357

Status: In a reported dated April 15,1996, our consultant indicated production of the drug product had no significant impact on the quality of the human environment.

REMARKS

Remifentanil Injection is a sterile, nonpyrogenic, preservative -free, white lyophilized powder for intravenous administration after reconstitution and dilution. There will be three formulations strengths, 5 mg, 2 mg, and 1 mg of remifentanil base per vial; which are reconsitituted with Sterile Water for Injection USP or 5% Dextrose Injection USP to give a solution of 1 mg/ml remifentanil base. The product will be packaged in Glass vials and stopperred with gray bromobutyl rubber stoppers and secured with aluminum overseals. The product is used for induction and maintenance of anesthesia/analgesia and provides immediate onset of action. Remifentanil has a short elimination half-life of less than 10 minutes because it is immediately metabolized to its principal metabolite, GR90291X, by hydrolysis of the propanoic acid methyl ester linkage, which is catalyzed by non-specific blood and tissue esterases.

The drug substance, remifentanil hydrochloride, is manufactured at Glaxo Operations UK Ltd., Montrose, United Kingdom. The dosage form is manufactured by The filled unlabeled vials will be shipped to Glaxo Wellcome Inc.,Zebulon, North Carolina facility where the vials will be labeled and cartoned.

REMARKS (continued)....

This application was reviewed and the substance of the review is found in the "Review Notes". The initial deficiencies are listed on pages 55-58. These questions were faxed to applicant on April 15,1996. The applicant responded in an amendment dated May 17,1996. A second set of deficiencies was faxed to the applicant on May 7,1996 and a response dated June 11,1996 was faxed to FDA.

The amendment dated Sept. 15,1996 contained an overall summary of the new drug application. The amendment dated Jan.15,1996 contained a correction with regard to a batch formulation, where an amount of remifentanil in various strengths was referred to as the hydrochloride salt when this amount should have been reported as the remifentanil free base.

We have received a satisfactory inspection report from our Office of Compliance for all the sites that were inspected. The analytical methods to be validated have been sent to two district laboratories, namely Atlanta and St. Louis.

CONCLUSIONS/RECOMMENDATIONS:

The applicant has satisfactorily responded to our deficiencies and from a chemist viewpoint, approval is recommended.

Juanita Ross
Juanita Ross
Review Chemist

M. Theodorakis for
Albinus D'Sa, Ph.D.
Acting Team Leader

cc:
Orig. NDA 20-630
HFD-170/Div. File
HFD-170/JRoss
HFD/170/DMorgan
HFD820/Dr, Y.Y. Chiu
F/T by: JRoss 3/5/56
Revised: 4/17/96
6/5/96
Filename: WP/NDA 20-630

micro

MICROBIOLOGY REVIEW

NDA 20-630

ULTIVA (remifentanil) Injection

Submitted date January 29, 1996

APR 30 19

REVIEW TO HFD-170
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW OF NDA

April 30, 1996

A. 1. **NDA 20-630** **APPLICANT:** Glaxo Wellcome Inc
5 Moore Drive
Research Triangle Park, NC 27709

2. **PRODUCT NAMES:** Remifentanil Hydrochloride
Utiva™ for Injection
GI87084B

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:**
Ultiva™ (Remifentanil HCl) for Injection in strengths of 1 mg/vial, 2 mg/vial, 5 mg/vial is a sterile, preservative-free, dry lyophilized powder for reconstitution. It is administered by intravenous injection/infusion.

4. **METHODS OF STERILIZATION:**
Aseptically filled and freeze-dried.

5. **PHARMACOLOGICAL CATEGORY:**

1 Induction and maintenance of general anesthesia in both the inpatient and outpatient setting.
2 Parenteral analgesic in post-operative and monitored setting.
3 Parenteral analgesic adjunct to local or regional anesthesia (monitored anesthesia care).

B. 1. **DATE OF INITIAL SUBMISSION:** September 15, 1996

2. **RELATED DOCUMENTS:** IND
DMF

3. **ASSIGNED FOR REVIEW:** February 2, 1996

C. **REMARKS:** The drug product Remifentanil for Injection and the primary package are manufactured by The finished vials are shipped to Glaxo's Zebulon Facility where secondary packaging and approval for release occurs.

D. CONCLUSIONS: The NDA 20-630 for Ultiva™(Remifentanil for Injection) is recommended for approval from the standpoint of microbiology Specific comments are provided

4/30/96

Patricia F. Hughes, Ph.D.
Reviewing Microbiologist

PAC 4/30/96

cc: Original NDA 20-630
HFD-160/Consult File
HFD-160/PFHughes
HFD-170/Division File
HFD-170/J.M. Ross

Drafted by P F.Hughes/04/30/96
R/D initialed by P. Cooney/04/30/96

EA + FONSI

ENVIRONMENTAL ASSESSMENT / FONSI

NDA 20-630

ULTIVA (remifentanil) Injection

Submitted date January 31, 1996

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

NDA 20-630

ULTIVA® Injection

(remifentanil HCL)

1, 2, and 5 mg Vials

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Division of Anesthetic, Critical Care, and Addiction Drug Products
(HFD-170)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-630

ULTIVA® Injection

(remifentanil HCL)

1, 2, and 5 mg Vials

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for ULTIVA®, Glaxo Wellcome, Inc. has conducted a number of environmental studies and prepared an abbreviated environmental assessment in accordance with 21 CFR 25.31(b)(3) (attached) which evaluates the potential environmental impacts of the manufacture of the product.

Remifentanil is a chemically synthesized drug which is administered intravenously at dosage strength of 1, 2, and 5 mg for the induction and maintenance of anesthesia and/or analgesia. The bulk drug substance will be manufactured by Glaxo Operations (UK) Limited in Montrose Scotland. The drug product (Remifentanil for Injection) will be manufactured and filled into vials at the Filled vials will be packaged at Glaxo Inc. in Zebulon, North Carolina. The finished drug product will be used in hospitals throughout the United States.

Disposal of the drug may result from out of specification lots and discarding of unused or expired product. Returned or out-of-specification drug substance and rejected or returned drug product will be disposed via high temperature incineration either on site or at off-site facilities approved by the respective governments. At U.S. hospitals, empty or partially empty packages will be disposed according to hospital regulations.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are

expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

4/16/96
DATE

Approved
Phillip G. Vincent, Ph.D
Environmental Scientist
Center for Drug Evaluation and Research

4/17/96
DATE

Concurred
Nancy Sager
Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

Attachments: Environmental Assessment
Material Safety Data Sheet (drug substance)

HFD-170/CSO copy to NDA 20-630
HFD-357/FONSI File 20630
HFD-357/Docket File 20-630
HFD-01~~9~~/FOI COPY
20

APPENDIX 6

FREEDOM OF INFORMATION (FOI) RELEASABLE ENVIRONMENTAL ASSESSMENT

ENVIRONMENTAL ASSESSMENT
Freedom of Information (FOI) Releasable Copy

GLAXO INC.

Five Moore Drive
Research Triangle Park, NC 27709

Remifentanil for Injection (5mg per vial, 2mg per vial, and 1mg per vial)

APPENDIX 6
TABLE OF CONTENTS

1. DATE

January 10, 1995

2. APPLICANT

Glaxo Inc.

3. ADDRESS

Five Moore Drive
Research Triangle Park, NC 27709

4. DESCRIPTION OF THE PROPOSED ACTION

4.1. Description of Requested Approval

Glaxo Inc. is requesting approval to formulate, package, and market Remifentanil for Injection for the induction and maintenance of anesthesia and/or analgesia. Each dose of Remifentanil for Injection will contain 5, 2, or 1 mg remifentanil hydrochloride drug substance which will be filled into vials. The marketed product will be dispensed only on order of a licensed physician.

4.2. Need for the Action

Remifentanil is a novel opioid analgesic that will be administered intravenously for the induction and maintenance of general anesthesia and/or analgesia. Remifentanil's immediate onset of action and short-elimination half-life (less than 10 minutes) allows easy titration to give the desired depth of anesthesia and/or analgesia and also minimizes the frequency or severity of postoperative adverse effects.

Remifentanil, therefore, is a novel agent that may provide a significant improvement over existing [illegible]tics used in surgical anesthesia.

4.3. Locations where Products will be Produced

The drug substance, remifentanil hydrochloride, will be manufactured in bulk by Glaxo Operations (UK) Limited in Montrose, Scotland. The drug product (Remifentanil for Injection) will be manufactured and filled into vials at [illegible]. Filled vials of Remifentanil for Injection will be packaged at Glaxo Inc. in Zebulon, North Carolina.

Drug Substance Manufacturing

Glaxo Operations (UK) Ltd.
10 Cobden Street
Montrose
Angus DD10 SE13
Scotland, United Kingdom

Glaxo Operations (UK) Limited's Montrose facility is located in Montrose, a small town in northeast Scotland between the cities of Aberdeen and Dundee. The town is mainly residential and commercial with a small amount of industry. Industries in the town include agriculture, fishing and oil field supply services in addition to pharmaceutical manufacturing. The facility itself is located adjacent to the North Sea at the mouth of the River South Esk. The site covers 45 acres and is approximately one mile due east of the Montrose Basin. The site is bounded to the east by the local beach and the North Sea, to the south by the estuary of the South Esk river and to the north by residential, commercial and industrial properties.

Drug Product Manufacturing and Packaging

facility is located in the northern portion of the City of approximately 140 miles equidistant from the cities of Chicago and Detroit. The facility is approximately 1.7 miles northeast of the center of and directly to the south of the . The facility is located on land allocated for heavy industry. The site has a total of approximately 810 hectares. The Sterile Products facility employs approximately 140 people. Normal production consists of two eight-hour shifts, five days per week.

Glaxo Inc.
1011 North Arendell Avenue
Zebulon, North Carolina 27597

Glaxo Inc.'s Zebulon, North Carolina facility is located about 25 miles east of Raleigh, North Carolina. The Town covers two square miles and has an approximate population of 2839. Other industries which are located in Zebulon include textile mills, metal finishers and a plastics manufacturer. The site has a total of 224 acres. The Zebulon facility employs approximately 750 people. Normal production consists of two ten-hour shifts, four days per week.

4.4. Sites of Product Use

Remifentanil for Injection will be prescribed for use in hospitals throughout the United States.

4.5. Sites of Disposal

Product that is introduced into the patient will be excreted in the urine and feces and distributed into wastewater treatment systems throughout the United States

Returned product disposal will occur at high-temperature commercial incinerator facilities that are permitted to dispose of such wastes by appropriate local, state and federal regulatory agencies. Currently, disposal of return product is contracted to:

holds permit number 1280-0021, issued on July 29, 1986 by the South Carolina Department of Health and Environmental Control (DHEC). The permit has an expiration date of March 31, 1991. DHEC confirms that applied for a permit renewal as required and is operating under the existing permit until DHEC issues a new permit.

An alternative solid waste incineration facility under consideration for the disposal of returned product is:

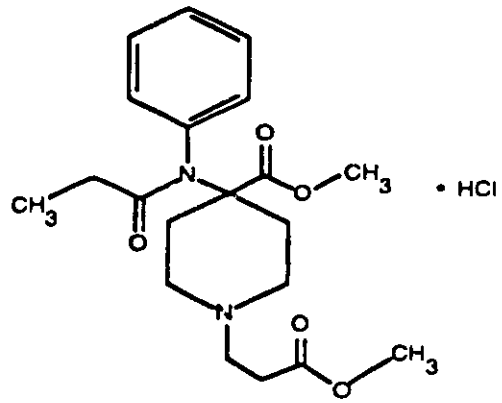
holds air permit number 5896R7 issued June 18, 1994 by the North Carolina Department of Environment, Health and Natural Resources (DEHNR). The permit has an expiration date of July 1, 1996. Rejected drug substance and drug product produced at manufacturing sites is disposed of via high temperature incineration either on site or at off-site facilities approved by the respective governments for this purpose. Information on incineration facilities used to destroy rejects can be found in Section 6.

5. IDENTIFICATION OF CHEMICAL SUBSTANCES

The chemical substances that are the subject of the proposed action can be divided into five categories: (1) drug substance, (2) drug substance impurities and degradation products, (3) drug product excipients, (4) drug substance and drug product manufacturing waste products, and (5) packaging materials and package disposal waste products. Information on the chemical substances identified in each of the categories is discussed in Sections 5.1 through 5.5.

5.1. Drug Substance Information

Approved Names remifentanil hydrochloride

Chemical Name	3-[4-Methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]propanoic acid methyl ester, hydrochloride salt
Code Name	GI87084B
Structural Formula	
Molecular Formula	$C_{20}H_{28}N_2O_5 \cdot HCl$
Molecular Weight	412.91
CAS Number	13539-07-2

5.2. Drug Substance Impurities and Degradation Products

A confidential list of impurities and degredants has been supplied to FDA.

5.3. Drug Product Excipients

A confidential list of impurities and degredants has been supplied to FDA.

5.4. Manufacturing Waste Products

Drug substance manufacturing wastes are those materials that can potentially be released during the manufacture of the drug substance or intermediates. Manufacturing wastes include a number of substances typically found in a pharmaceutical manufacturing facility, such as organic solvents, alcohols, and reagents as well as the drug substance and its intermediates. A confidential list of the chemicals used during the manufacture of remifentanil hydrochloride which could potentially become manufacturing waste products has been supplied to FDA.

5.5. Packaging Materials

The following materials will be used in packaging of the drug substance:

polyethylene bags
cardboard boxes
polypropylene drums

These packaging materials will enter the waste stream subsequent to manufacture of the drug product.

The following materials will be used in packaging the drug product:

Glass vials	Plastic trays
Aluminum caps	Rubber stoppers
Shrink wrap	

These packaging materials will enter the waste stream as a result of product use and when rejected or expired materials are returned. Information on chemical names, CAS numbers and chemical structures is not available for these widely used commercial packaging materials.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

site manufactures remifentanil hydrochloride for use at the facility where the material is filled into vials. These will then be packaged at Glaxo Inc. in Zebulon.

The drug substance and other substances associated with its manufacture can potentially enter the environment from four main sources: (1) the sites associated with the manufacture of the drug substance, remifentanil hydrochloride, or its intermediates; (2) the sites associated with the manufacture and packaging of the drug product; (3) the sites of use by patients; and (4) waste disposal sites for discarded or rejected product and packaging materials. Sections 6.1 through 6.5 discuss potential emissions from each of these sources.

6.1. Introductions Of Substances From Drug Substance Production

The substances expected to be emitted, emission controls, and compliance with relevant environmental and occupational laws for the drug substance manufacturing site is discussed below.

6.1.1. Substances Expected to be Emitted

The requested approval could potentially result in emissions to the environment from sites of production of starting materials, reagents and excipients used in the manufacture of the drug substance and the drug product. A confidential list of these materials has been supplied to the FDA.

6.1.2. Controls on Emissions

Montrose

Aqueous effluent generated in the remifentanil hydrochloride production areas is collected in any of four wooden vats. The contents are individually recirculated, brought into the required pH range with sodium hydroxide or hydrochloric acid, sampled and tested.

Pretreated wastewater is discharged to the tidal storage tank which collects all other process effluent streams from the site. Discharges of blended effluent are made into the estuary of the River South Esk one hour after high water to ensure maximum dilution and dispersion. There is no release of process wastewater into the storm water drainage system.

Two general purpose incinerators are used to dispose of waste solvents and aqueous streams produced during the manufacture of remifentanil hydrochloride. These incinerators operate under Her Majesty's Industrial Pollution Inspectorate (HMIPI) authorization number IPC/069/1993 which is valid until 8 September 1997.

All air emissions from the product finishing suite pass through prefilters and HEPA filters.

There are no on-site facilities for the disposal of solid wastes. Filter bags, HEPA filters, and filter aid materials used in the process and/or contaminated with trace amounts of remifentanil are bulked for disposal by high temperature incineration at the following licensed off-site facility:

Non-chemical wastes (e.g., used fiberboard kegs, general refuse) are also incinerated. The authorization number for this facility, issued by HMIPI is IPC/068/93. The authorization is valid until 30 September 1997.

A liquid waste stream is sent for disposal by high temperature incineration off-site. The address of the facility used is:

The authorization number for this facility, issued by HMIP, is AG82525. The authorization is valid until 31 July 1997.

6.1.3. Regulatory Controls and Compliance

This Section contains discussions of environmental regulatory requirements associated with the production of remifentanil hydrochloride and compliance with the requirements. Summaries of wastewater, air, solid waste and occupational requirements are included below.

Montrose

Table 1 contains a list of environmental regulations applicable to the Montrose manufacturing site.

Table 1. Overview of Environmental and Occupational Laws Applicable to the Glaxo Operations (UK) Ltd., Montrose Facility

WASTEWATER DISCHARGES	Water Act (1989) Control of Pollution Act (1974) Environmental Protection Act (1990)
AIR EMISSIONS	Health and Safety at Work Act (1974) Environmental Protection Act (1990)
COLLECTED WASTE	Control of Pollution Act (1974) Control of Pollution (Special Waste) Regulations (1980) Control of Pollution (Special Waste) Amendment Regulations (1988) Environmental Protection Act (1990)
OCCUPATIONAL	Health and Safety at Work Act (1974) Control of Substances Hazardous to Health Regulations (1988)

Up until the implementation of the Environmental Protection Act (1990) in Scotland in April, 1992, legislation controlled pollution to each medium separately (i.e., emissions to atmosphere, discharges to controlled waters and disposal of waste to licensed disposal sites). Part 1 of the Act and its subsequent regulations include the concept of Integrated Pollution Control (IPC) and is being implemented in a phased manner to replace the existing registration procedure.

The process for the manufacture of remifentanil hydrochloride has been authorized under the terms of the Environmental Protection Act (1990) since October 1994.

Discharges of effluent to the River South Esk comes under the jurisdiction of the local Tay River Purification Board (TRPB). The Water Act (1989), Control of Pollution Act (1974), and the Environmental Protection Act (1990) allow the discharge of effluent under the conditions of a consent, which specifies limits on the quantity and quality of the effluent

Disposal of solid wastes from the Montrose site is controlled by the local authorities under the Control of Pollution Act 1974 and, subsequently, the Control of Pollution (Special Waste) Regulations 1980, the Control of Pollution (Special Waste) Amendment Regulations 1988 and the Environmental Protection Act 1990. Under the legislation, the transporter and waste disposer are required to hold a relevant license and to operate their practices within the conditions of the license with all parties involved in the transport and disposal chain demonstrating a Duty of Care.

Solid waste from the site is collected and transported to the local municipal waste incinerator in Dundee, which is operated by the local authority. Control of the transport and disposal operations is exercised by Angus District Council and Dundee City Council. Each consignment of waste is notified to the authority and annual returns are presented to the local council officers.

Emissions to atmosphere are controlled by the Environmental Protection Act 1990. In addition, emissions in the workplace are controlled by the Health and Safety at Work Act (1974) and the subordinate Control of Substances Hazardous to Health Regulations (1988).

These are enforced by the Health and Safety Executive. Occupational emissions are assessed to ensure that exposure to substances hazardous to health are controlled and comply at least with the provisions of the Health and Safety at Work Act (1974) and its supporting regulations.

6.1.4. Effect of Requested Approval on Compliance

Remifentanil hydrochloride was manufactured at the Glaxo Montrose facility in short campaigns during 1993 and 1994. Monitoring data collected during the manufacture of remifentanil hydrochloride indicated that the facility was in compliance with applicable requirements. Therefore, the requested approval is not anticipated to have any impact on the compliance status of the facility.

6.2. Introductions Of Substances From Drug Product Manufacturing and Packaging

The substances expected to be emitted, emission controls, and compliance with relevant environmental and occupational laws associated with the production and initial packaging of Remifentanil for Injection are discussed below. Controls and compliance at the Glaxo Inc. facility are not discussed because the only emission that will result from the final packaging is a small amount of solid waste.

6.2.1. Substances Expected to be Emitted

The requested approval could potentially result in emissions to the environment from sites of production of starting materials, reagents and excipients used in the manufacture of the drug product. A confidential list of these materials has been supplied to the FDA.

6.2.2. Controls on Emissions

At the The Upjohn Company facility, aqueous waste streams resulting from the chemical processes will be disposed of to the municipal sewer for biological treatment at the City of Kalamazoo Water Reclamation Plant.

The process to manufacture Remifentanil for Injection does not use volatile organic compounds. Isopropyl alcohol is used during preparation and testing of filtration equipment. Particulate emissions are controlled by a wet dynamic precipitator or HEPA filtration in the aseptic manufacturing facility.
Off-specification solid materials (e.g., defective vials) will be incinerated on-site. The on-site incinerator is currently being operated as a Resource Conservation Recovery Act (RCRA) interim status treatment storage and disposal facility under permit # MID000820381 in compliance with 40 CFR 264, Subpart 0 requirements

6.2.3. Regulatory Controls and Compliance

This section contains discussions of environmental regulatory requirements associated with the production of Remifentanil for Injection and compliance with the requirements. Summaries of wastewater, air, solid waste and occupational requirements are included.

Emissions of substances into the environment from the The Upjohn Company production facility from all media (air, water and solid waste) are controlled by either the United States Environmental Protection Agency (EPA) Regulations or by more restrictive Michigan Department of Environment, Health and Natural Resources (MDEHNR) regulations.

Wastewater discharges from production facility are regulated under the Clean Water Act. The wastewater is discharged to the sanitary sewer system for biological treatment. A discharge permit in the form of a Industrial Control Document (ICD) was issued in response to Federal and State requirements governing the City of Industrial Pretreatment Program (IPP).

Air emissions at the facility are regulated under the Clean Air Act. is operating under an Air Consent Judgment issued by MDEHNR, Air Quality Division and dated March 15, 1991. Under this judgment all VOC emitting processes must have controls constituting Lowest Achievable Emission Rate (LAER). The sterile injectable operations were authorized by air permit #923-92 in September 1994.

The on-site incinerator is currently being operated as a Resource Conservation Recovery Act (RCRA) interim status treatment storage and disposal facility under permit # MID000820381 in compliance with 40 CFR 264, Subpart O requirements.

A hazardous waste permit application has been submitted to the Waste Management Division of MDEHNR in Lansing, Michigan under RCRA Part B/Act 64 . The facility also operates under Michigan State air permit #242-80 (issued July 15, 1980), which was revised to incorporate the Act 64 requirements and approved on May 26, 1993.

There are no specific permit requirements for the generation and disposal of solid waste.

has comprehensive programs and practices in place addressing all applicable OSHA requirements. In the case of occupational emissions, compliance with the general regulations is required and no specific permits are issued. Occupational emissions are controlled by either the United States Occupational Safety and Health Administration (OSHA) or the Michigan Department of Labor. In some cases, regulations are specifically applied to the facility via a permit. In other cases, compliance with only the general regulations is required.

6.2.4. Effect of Requested Approval on Compliance

It is not anticipated that the manufacture of Remifentanil for Injection will have any detrimental impact on the current compliance status of the site. None of the compounds expected to be emitted are specifically regulated for the facility.

No emissions except solid waste will result from the packaging process at Zebulon.

6.3. Statement of Compliance

By signing this Environmental Assessment report, Glaxo states that it is in compliance, or on an enforceable schedule to be in compliance, with all environmental laws and regulations applicable to the production of remifentanil hydrochloride or Remifentanil for Injection at its Montrose and Zebulon facilities, respectively.

6.4. Introductions From Product Use

Except for the drug substance, remifentanil hydrochloride, all components of Remifentanil for Injection are food or pharmaceutical grade substances that are not specifically regulated under any environmental legislation or regulations, and are discharged into the environment from a wide range of sources. Therefore, only remifentanil hydrochloride is considered in this discussion.

Administered remifentanil hydrochloride and its metabolites will enter the environment primarily through wastewater treatment facilities. The Maximum Expected Emitted Concentration (MEEC) of remifentanil hydrochloride from product use is estimated to be 5.3×10^{-7} mg/L (PMA, 1991). This estimate is based on a fifth year production estimate of 26.8 kg of drug substance needed to formulate 13.5 million injections.

$$\text{MEEC} = \frac{26.8\ \text{kg}}{\text{year}} \times \frac{1\ \text{year}}{365\ \text{days}} \times \frac{1\ \text{day-person}}{568\ \text{liters}} \times \frac{1}{246\ \text{mil. persons}} \times \frac{1000000\ \text{mg}}{\text{kg}}$$

$$\text{MEEC} \approx 5.3 \times 10^{-7}\ \text{mg/L}$$

6.5. Introductions From Product Disposal

It is estimated that there will be no emission to the environment from product disposal. All product in the United States that is returned is disposed of by high-temperature incineration at an off-site facility operated by a contract waste disposal firm. All of the drug substance, excipients, and packaging materials are destroyed in the incineration process.

The contractor used to transport and dispose of returned pharmaceuticals is:

holds permit number 1280-0021, issued on July 29, 1986 by the South Carolina Department of Health and Environmental Control (DHEC). The permit has an expiration date of March 31, 1991. DHEC confirms that Chambers Medical Technologies, Inc. applied for a permit renewal as required and is operating under the existing permit until DHEC issues a new permit.
An alternative solid waste incineration facility under consideration for the disposal of returned product is:

holds air permit number 5896R7 issued June 18, 1994 by the North Carolina Department of Environment, Health and Natural Resources (DEHNR). The permit has an expiration date of July 1, 1996

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

Not applicable to this class of drug for general anesthesia/analgesia.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

Not applicable to this class of drug for general anesthesia/analgesia.

9. USE OF RESOURCES AND ENERGY

Not applicable to this class of drug for general anesthesia/analgesia.

10. MITIGATION MEASURES

Not applicable to this class of drug for general anesthesia/analgesia.

11. ALTERNATIVES TO THE PROPOSED ACTION

Not applicable to this class of drug for general anesthesia.

12. LIST OF PREPARERS

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-Environmental Engineer, Glaxo Inc., 1994 - present
-Environmental Scientist, Glaxochem Ltd, 1987 - 1994
-Scientific Officer, Glaxo Operations (UK) Ltd, 1981 - 1987
- Bachelor of Science in Microbiology
University of Newcastle upon Tyne, 1980

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-Environmental Engineer, Glaxo Inc., 1992 - present
-Environmental Supervisor, North Carolina Division of Environmental Management 1985-1992
-Environmental Specialist, North Carolina Division of Environmental Management 1980-85
-Bachelor of Arts in Biology
University of North Carolina - Greensboro, 1979

13. CERTIFICATION

The undersigned official certifies that the information presented is true, accurate, and complete to the best of the knowledge of Glaxo Inc.

Thomas F. Cecich — February 17, 1995

Thomas F. Cecich — Date

Vice President, Safety & Environmental Affairs
Glaxo Inc.
Five Moore Drive
Research Triangle Park, NC 27709

14. REFERENCES

Council On Environmental Quality, -" Regulations On Implementing National Environmental Policy Act Procedures," Federal Register, Vol. 43, November 29, 1978, p. 55990.

Pharmaceutical Manufacturers Association, "Interim Guidance To The Pharmaceutical Industry For Environmental Assessment Compliance Requirements For The FDA v7," Semi r on Environmental Assessments, Rockville, Md., July 29-30, 1991.

U.S. FDA, "Environmental Assessment Technical Assistance Handbook", U.S. FDA, March 1987, NTIS PB87-175345.

U.S. FDA, "National Environmental Policy Act; Policies and Procedures: Final Rule," Federal Register, Vol. 50, April 26, 1985.

15. APPENDICES

Appendix 1 Substance Information Sheet

BLUE PAPER DIVIDER

APPENDIX 1

SUBSTANCE INFORMATION SHEET

MATERIAL SAFETY DATA SHEET

GI87084B
RESEARCH COMPOUND

Glaxo Inc.
Five Moore Drive
Research Triangle Park, NC 27709

Emergency Contact:
Environmental Safety
(919) 248-2100
(919) 248-2700 (24 hour contact)

Revision Date: 07/18/94

SECTION I -- General Information

Chemical Name:	3-[4-Methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine] propanoic acid, methyl ester, hydrochloride
Chemical Family:	Piperidine derivative
Agent Name/Synonyms:	GI87084B; Remifentanil
Molecular Weight:	412.92
Molecular Formula:	$C_{20}H_{28}N_2O_5.HCl$

SECTION II -- Hazardous Ingredients / Identity Information

Hazardous Components	%	Glaxo Limits	OSHA Limits	ACGIH Limits
GI87084B	100.00	1.0 mcg/m3 15 min TWA (STEL)	Not Established (PEL)	Not Established (TLV)

SECTION III -- Physical / Chemical Characteristics

Boiling Point:	Not Applicable (powder)
Vapor Pressure (mm Hg):	Not Applicable (powder)
Vapor Density (air = 1):	Not Applicable (powder)
Specific Gravity (H_2O = 1):	Not Applicable (powder)
Melting Point:	Melts with decomposition at 205 degrees C
Evaporation Rate:	Not Applicable (powder)
Solubility:	Soluble (>10%) in water
Appearance & Odor:	White powder; Odorless

SECTION IV -- Fire & Explosion Hazard Data

Flash Point (test method):	Not Applicable (powder)
LEL:	Unknown
UEL:	Unknown
Extinguishing Media:	Water Spray, Foam, Multi-purpose Dry Chemical.
Special Fire Fighting Procedures:	Wear full protective clothing and self-contained breathing apparatus.
Unusual Fire & Explosion Hazards:	As with any organic powder, there is potential for explosion when suspended in air in high concentrations as a fine dust.

SECTION V -- Reactivity Data

Stability:	Stable
Hazardous Polymerization:	NA
Conditions to Avoid:	Extreme heat - material partially decomposes above 100 degrees C.
Incompatibility (mat'ls to avoid):	No known incompatibilities
Hazardous Decomposition Products:	Thermal decomposition products can include toxic and/or corrosive vapor consisting of chlorides and nitrogen oxides.

SECTION VI -- Health Hazard Data

Glaxo Occupational Exposure Limits

For GI87084B, the Glaxo estimated safe working level is a short-term (15 min) exposure limit (STEL) of 1.0 mcg/m3.

Pharmacologic Activity

GI87084B is a potent, ultra short-acting narcotic analgesic of the fentanyl-like opioid class. Opioid analgesics are central nervous system depressants. When used medically for or during anesthesia, these compounds cause depression or arrest of respiration (slowed or stopped breathing). If respiratory support is not provided, death may result. Also, slowed heart rate, raised or lowered blood pressure, and muscular rigidity may occur. At lower doses, opioid analgesics may cause mental confusion, nausea, dizziness and paresthesias (a sensation of numbness or tingling). This class of compounds is capable of producing euphoria (a feeling of well-being or elation), as well as psychological and physical dependence (addiction). It should be assumed that absorption by any route may result in these effects.

SECTION VI -- Health Hazar . Data (Continued)

Signs and Symptoms of Occupational Exposure

There is limited experience with GI87084B in the occupational setting. However, it is likely that exposure could produce any of the effects described under "Pharmacologic Activity" (see page 2) including slowed or stopped breathing, slowed heart rate, and raised or lowered blood pressure.

Occupational Health Hazards

Skin: GI87084B does not cause skin irritation or allergic reactions of the skin in standard tests.

Eye Contact: GI87084B is not irritating to the eyes.

GI87084B can be absorbed by any route of exposure including through the skin, eyes, and by inhalation. It is relatively poorly absorbed following ingestion. GI87084B should be handled in a manner that prevents exposure by any route because of its pharmacological potency.

Medical Conditions Aggravated by Exposure

Unknown.

Toxicity Data

Acute Toxicity: GI87084B is a potent opioid analgesic of the fentanyl class. It is intended for medical use as an analgesic/anesthetic in patients undergoing surgery. Acute exposure may result in any of the pharmacological effects of this class of medications including slowed heart rate, slowed or stopped breathing, muscular rigidity, tremors, salivation, urination, body jerks, convulsions, and death (see "Pharmacologic Activity", p.2).

Chronic Toxicity: In reproductive toxicology studies, repeated treatment of male rats with high doses of GI87084B resulted in effects similar to those caused by other fentanyl-like narcotics. These included decreased male fertility, decreased sperm counts, and shrinkage of the epididymides. These effects occurred only in animals treated over a four week period with daily doses greater than the level causing loss of consciousness. Male reproductive effects were reversible, except in animals receiving extraordinarily high doses of GI87084B. GI87084B caused formation of extra ribs, a birth defect, in standard tests with pregnant rabbits. Extremely high doses of GI87084B also increased the number of fetal deaths in the few pregnant rabbits surviving treatment. Very high repeated doses caused subtle changes in the brain structure of dogs. These effects are believed to relate to depressed respiration, oxygen deprivation, and convulsions rather than direct toxicity of GI87084B to the brain.

SECTION VI -- Health Hazard Data (Continued)

Genotoxicity: Based on studies in bacteria, animals, and cell cultures, there is no indication that GI87084B causes mutations (heritable changes in genetic material) or chromosome breakage.

Emergency and First Aid Procedures

Eyes: Flush thoroughly with large amounts of water. Obtain medical attention.

Skin: Remove contaminated clothing. Wash all affected areas thoroughly with soap and water. Obtain medical attention.

Inhalation: If breathing is difficult or ceases, give oxygen or cardiopulmonary resuscitation. Remove to fresh air. Obtain medical attention.

Ingestion: Rinse mouth with water if conscious (awake). Do not give water if unconscious. Although GI87084B is not well absorbed after ingestion, overexposure may lead to cessation of breathing. Artificial respiration or mechanical ventilation may be required. Obtain medical attention.

Notes To Physician: An opioid antagonist, such as naloxone, as well as resuscitative equipment, including oxygen, may be necessary to treat overdosage. GI87084B produces narcosis rapidly, but the duration for this activity is short (about 10 min.). Therefore, supportive treatment for overexposure should be provided immediately; prolonged treatment will probably not be needed.

SECTION VII -- Precautions for Safe Handling and Use

Spill and Leak Procedures: Full protective equipment must be worn where there is potential for skin exposure or dust inhalation. Refer to Section VIII for more detailed guidance. Saturate spill area with water, unless material must be salvaged. Absorb liquid with paper towels or other absorbent material and package WHILE STILL WET in labeled, sealed container for disposal. If material must be salvaged, collect spillage by carefully sweeping or vacuuming with HEPA filtered vacuum and place in labeled, sealed container for reuse. Wash spill area (floor and other contact surfaces) with a suitable cleaning solvent, like soap and water, unless other standard operating procedures supercede these recommendations.

Waste Disposal Method: Incinerate at an approved facility in accordance with federal, state, and local regulations.

Handling and Storage Precautions: Use handling and storage practices that will minimize the generation of dust.

SECTION VIII -- Control Measures

Ventilation:	Provide local exhaust ventilation system at the source of dust generation.
Respiratory Protection:	Respiratory protective equipment must be worn when workers are potentially exposed to airborne dust. The respirator should be certified by NIOSH for dusts with a PEL <0.05 mg/m3. The minimum respiratory protection used should be a powered air purifying or supplied-air respirator that provides full head covering.
Eye Protection:	Suitable eye protection should be used to prevent dust contact.
Clothing:	It should be assumed that this compound can be absorbed through the skin. All skin contact should be avoided through proper protective clothing.
Gloves:	It should be assumed that this compound can be absorbed through the skin. Protective gloves must be worn at all times to avoid skin contact.
Work Practices:	Workers should wash hands or potentially exposed skin when leaving the work area. Workers exposed to dust should change clothes and shower at the end of the work assignment. Special care should be taken to ensure that contaminated clothing, equipment, and work surfaces are properly cleaned or disposed of after use. (See Section VII, Spill & Leak Procedures.)

*** End of MSDS ***