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NDA

19-353

NDA

19-353

AP/Ltr

NDA 19-353

DEC 29 1986

Janssen Pharmaceutica  
40 Kingsbridge Road  
Piscataway, NJ 08854

Attention: Carol D. Karp  
Manager, Regulatory Affairs

Gentlemen:

Please refer to your new drug application dated December 24, 1984, submitted pursuant to section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Alfenta (alfentanil hydrochloride) Injection.

We also acknowledge your additional communications dated April 2 and 9, May 8, 23 and 24, June 19, August 30, September 6 and 20, October 7 (2), 19 and 25 (2), November 5 and 26, and December 2 and 5, 1985; January 8, 15 and 24, April 2 and 7, November 18 and 24 and December 22, 1986 (2) amending this application.

We have completed our review of this application as amended and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on December 22, 1986. Accordingly, the application is approved, effective on the date of this letter.

Please submit one market package of the drug when available.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.91 for an approved NDA.

Sincerely yours,

*Paula Rotstein*

Paula Rotstein, M.D.  
Acting Deputy Director (Medical Affairs)  
Office of Drug Research and Review  
Center for Drugs and Biologics

cc NDA 19-353

HFN-83 w/ labeling

HFN-100/Botstein

HFN-160

HFN-160/Dassler/Stewart/Oberlander

Doc Room 160

R/D JPHannan 2228k/1072k 12/24/86

R/D Init by GBoyer 12/24/86; RMPatel 12/24/86; VFWhitehurst 12/24/86;

FT/MFatterson 12/24/86 JCKenealy 12/24/86

APPROVAL

SB 12/24/86

RI 12/24/86

RPatel 12/24/86  
(Acting sup. chemist)

DI by VFW 12/24/86  
V. Whitehurst 12-24-86

F P L

Labeling: Orig  
NDA No: 19-353 Rc'd. 12-23-86  
Reviewed by: James P. Hanna  
12-24-86

**ALFENTA®**  
(ALFENTANIL HCl)  
INJECTION

EXP. DATE

CONTROL

10 ml

PHARMACEUTICA

NDC 50458-060-10

5-10 ml ampoules

10 ml

**ALFENTA®**  
(ALFENTANIL HCl)   
INJECTION

Each ml contains: Alfentanil base 500 ug/ml  
Warning — May be habit forming.

Caution: Federal law prohibits dispensing  
without prescription.  
Not to be sold except as an unbroken box.  
FOR INTRAVENOUS USE

Usual dosage: For dosage and other  
information for use, see accompanying  
product literature.

Store at room temperature. Protect from light.  
(15° to 30°C / 59° to 86° F)

**ALFENTA®**  
(ALFENTANIL HCl)   
INJECTION

**ALFENTA®**  
(ALFENTANIL HCl)   
INJECTION

5-10 ml ampoules





\*+3504580601020\*

For your convenience in recording narcotic use

INITIAL/DATE

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**ALFENTA**  
(ALFENTANIL HCl)   
INJECTION

5-10 ml ampoules

49-57569-00

NDA No: 19-353 Rev'd. 12-23-86

Reviewed by: James P. Hanna  
12-29-82

2 ml ampoules

ALFENTA®  
(ALFENTANIL HCl)  
INJECTION

EXP. DATE CONTROL

2 ml

PHARMACEUTICA

# ALFENTA®

(ALFENTANIL HCl) INJECTION

Each ml contains: Alfentanil base 500 ug/ml

Warning — May be habit forming;

Caution: Federal law prohibits dispensing without prescription.

Not to be sold except as an unbroken box.

FOR INTRAVENOUS USE

Usual dosage: For dosage and other information for use, see accompanying product literature.

Store at room temperature. Protect from light.  
(15° to 30°C / 59° to 86° F)

2 ml

ALFENTA®  
(ALFENTANIL HCl)  
INJECTION

# ALFENTA®

(ALFENTANIL HCl) INJECTION

10-2 ml ampoules

NDC 50458-060-05

10-5 ml ampoules

ALFENTA®

5 ml

PHARMACEUTICA

# ALFENTA®

(ALFENTANIL HCl) INJECTION

Each ml contains: Alfentanil base 500 ug/ml

Warning — May be habit forming;

Caution: Federal law prohibits dispensing without prescription.

Not to be sold except as an unbroken box.

FOR INTRAVENOUS USE

Usual dosage: For dosage and other information for use, see accompanying product literature.

Store at room temperature. Protect from light.  
(15° to 30°C / 59° to 86° F)

5 ml

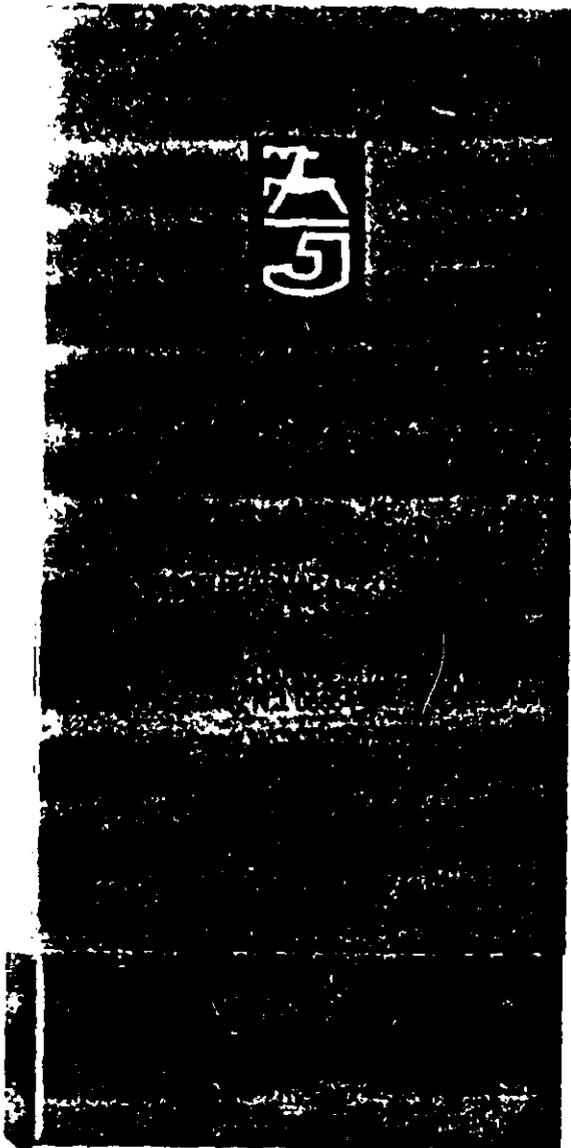
ALFENTA®  
(ALFENTANIL HCl)  
INJECTION

# ALFENTA®

(ALFENTANIL HCl) INJECTION

10-5 ml ampoules





\*++350458060052Y\*

For your convenience in recording narcotic use

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**ALFENTA<sup>®</sup>**  
(ALFENTANIL HCl)   
INJECTION

**10-5 ml ampoules**

49-57568-00



\*++350458060022V\*

For your convenience in recording narcotic use

INITIAL/DATE

INITIAL/DATE

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**ALFENTA<sup>®</sup>**  
(ALFENTANIL HCl)   
INJECTION

**10-2 ml ampoules**

49-57567-00

APPROVED 12-29-86

Labeling: Drug

NDA No: 19-353 hc. 12-23-86

Reviewed by: James P. Hanna  
12-24-86

NDC 50458-060-20

5-20 ml ampoules

20 ml

**ALFENTA<sup>®</sup>**  
**(ALFENTANIL HCl) **  
**INJECTION**

Each ml contains: Alfentanil base 500 ug/ml

Warning — May be habit forming;

Caution: Federal law prohibits dispensing without prescription.

Not to be sold except as an unbroken box.

FOR INTRAVENOUS USE

Usual dosage: For dosage and other information for use, see accompanying product literature.

Store at room temperature. Protect from light.  
(15° to 30°C / 59° to 86° F)

**ALFENTA<sup>®</sup>**  
**(ALFENTANIL HCl) **  
**INJECTION**

**ALFENTA<sup>®</sup>**  
**(ALFENTANIL HCl) ** 5-20 ml ampoules



**ALFENTA<sup>®</sup>**  
**(ALFENTANIL HCl)**  
**INJECTION **

EXP. DATE

CONTROL

20 ml

**JANSEN**  
**PHARMACEUTICA**

APPROVED 12-29-86

Labeling: Cruz

ND... No: 19-353 h.c. 12-23-85

Reviewed by: James P. Hanna  
12-24-86

NDC 50458-060-20

5-20 ml ampoules

20 ml

**ALFENTA<sup>®</sup>**  
**(ALFENTANIL HCl) **  
**INJECTION**

Each ml contains: Alfentanil base 500 ug/ml

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Caution: Federal law prohibits dispensing without prescription.

Not to be sold except as an unbroken box.

FOR INTRAVENOUS USE

Usual dosage: For dosage and other information for use, see accompanying product literature.

Store at room temperature. Protec. from light.  
(15° to 30°C / 59° to 86° F)

**ALFENTA<sup>®</sup>**  
**(ALFENTANIL HCl) **  
**INJECTION**

**ALFENTA<sup>®</sup>**  
**(ALFENTANIL HCl) ** 5-20 ml ampoules

**ALFENTA<sup>®</sup>**  
**(ALFENTANIL HCl)**  
**INJECTION **

EXP. DATE

CONTROL

20 ml

**JANSEN**  
**PHARMACEUTICA**





\*++350458060202V\*



For your convenience in recording narcotic use

INITIAL/DATE

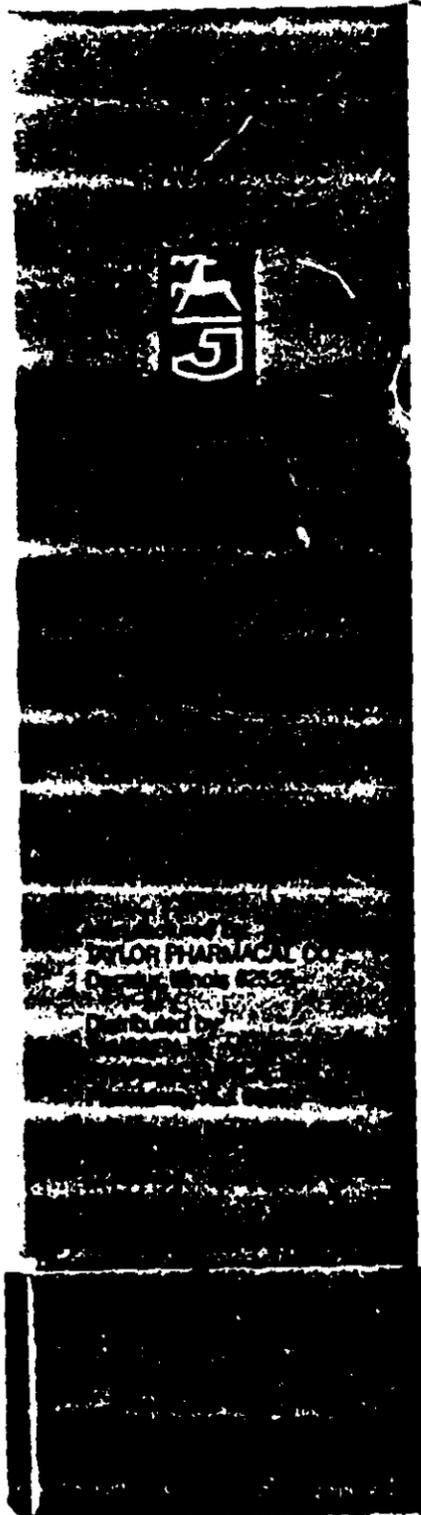
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TAYLOR PHARMACEUTICAL CO.  
2000 N. 1st St. Phoenix, AZ 85016  
Distributed by: \_\_\_\_\_

**ALFENTA<sup>®</sup>**  
(ALFENTANIL HCl)   
INJECTION

5-20 ml ampoules

48-57570-00



\*++350458060202V\*

For your convenience in recording narcotic use

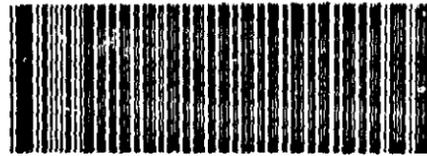
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**ALFENTA<sup>®</sup>**  
(ALFENTANIL HCl)   
INJECTION

5-20 ml ampoules

49-57570-00



\*++350458060202V\*

For your convenience in recording narcotic use

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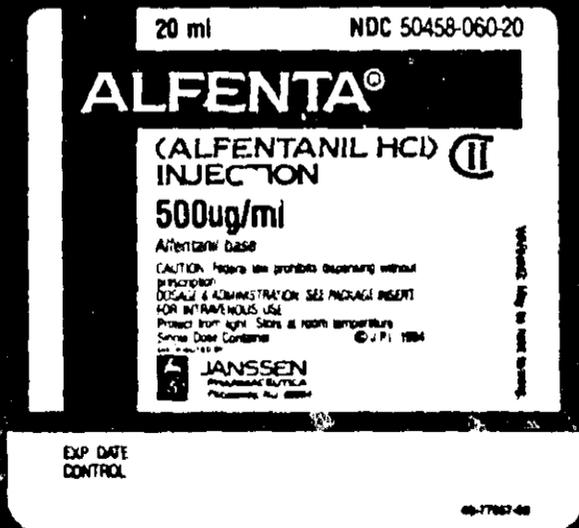
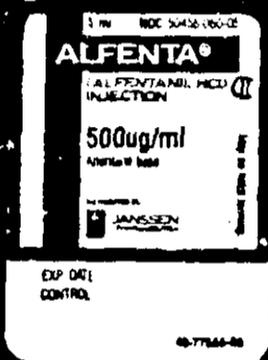
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49-57570-00

**ALFENTA<sup>®</sup>**  
(ALFENTANIL HCl)   
INJECTION

5-20 ml ampoules



**APPROVED** 12-29-86  
Labeling: Orig  
NDA No: 19-353  
Reviewed by: Jamel P Haman 12-23-86  
12/24/86

NDC 50458-060-20

5-20 ml ampoules

20 ml

# ALFENTA® (ALFENTANIL HCl) INJECTION

**Each ml contains:** Alfentanil base 500 ug/ml  
**Warning —** May be habit forming.  
**Caution:** Federal law prohibits dispensing without prescription.  
Not to be sold except as an unbroken box.  
**FOR INTRAVENOUS USE**

**Usual dosage:** For dosage and other information for use, see accompanying product literature.  
Store at room temperature. Protect from light.  
(15° to 30°C / 59° to 86° F)

ALFENTA®  
(ALFENTANIL HCl) INJECTION

ALFENTA®  
(ALFENTANIL HCl) INJECTION

... ml ampoules

ALFENTA®  
(ALFENTANIL HCl)  
INJECTION



CONTROL

20 ml

JANSSEN  
PHARMACEUTICA



NDC 50458-060-20

5-20 ml ampoules

20 ml

# ALFENTA® (ALFENTANIL HCl) INJECTION

Each ml contains: Alfentanil base 500 ug/ml  
Warning — May be habit forming;  
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Not to be sold except as an unbroken box.  
FOR INTRAVENOUS USE

Usual dosage: For dosage and other information for use, see accompanying product literature.

Store at room temperature. Protect from light.  
(15° to 30°C / 59° to 86° F)

ALFENTA®  
(ALFENTANIL HCl) INJECTION

ALFENTA®  
(ALFENTANIL HCl) INJECTION 5-20 ml ampoules

ALFENTA®  
(ALFENTANIL HCl) INJECTION

CONTROL

20 ml

JANSSEN  
PHARMACEUTICA



For your convenience in recording narcotic use

INITIAL/DATE

1. \_\_\_\_\_

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**ALFENTA<sup>®</sup>**  
(ALFENTANIL HCl)  5-20 ml ampoules  
INJECTION

ALFENTA<sup>®</sup>  
(ALFENTANIL HCl)   
INJECTION

EXP. DATE

CONTROL

2 ml

2

PHARMACEUTICA



NDC 50458-060-10

5-10 ml ampoules

**ALFENTA<sup>®</sup>**  
(ALFENTANIL HCl)   
INJECTION

**Each ml contains:** Alfentanil base 500 ug/ml

**Warning** — May be habit forming.

**Caution:** Federal law prohibits dispensing without prescription.

Not to be sold except as an unbroken box.

**FOR INTRAVENOUS USE**

**Usual dosage:** For dosage and other information for use, see accompanying product literature.

Store at room temperature. Protect from light.  
(15° to 30°C / 59° to 86° F)

**ALFENTA<sup>®</sup>**  
(ALFENTANIL HCl)   
INJECTION

5-10 ml ampoules

**ALFENTA<sup>®</sup>**  
(ALFENTANIL HCl)   
INJECTION

2 ml

**ALFENTA**  
(ALFENTANIL HCl)   
INJECTION

CONTROL

EXP DATE

3 31



**Pfizer**  
PHARMACEUTICA

NDC 50458-060-10

5-10 ml ampoules

**ALFENTA**<sup>®</sup>  
(ALFENTANIL HCl)   
INJECTION

Each ml contains: Alfentanil base 500 µg/ml

**Warning** — May be habit forming.

**Caution:** Federal law prohibits dispensing without prescription.

Not to be sold except as an unbroken box.

**FOR INTRAVENOUS USE**

**Usual dosage:** For dosage and other information for use, see accompanying product literature.

Store at room temperature. Protect from light.  
(15° to 30°C / 59° to 86° F)

**ALFENTA**<sup>®</sup>  
(ALFENTANIL HCl)   
INJECTION

5-10 ml ampoules

**ALFENTA**<sup>®</sup>  
(ALFENTANIL HCl)   
INJECTION

3 31

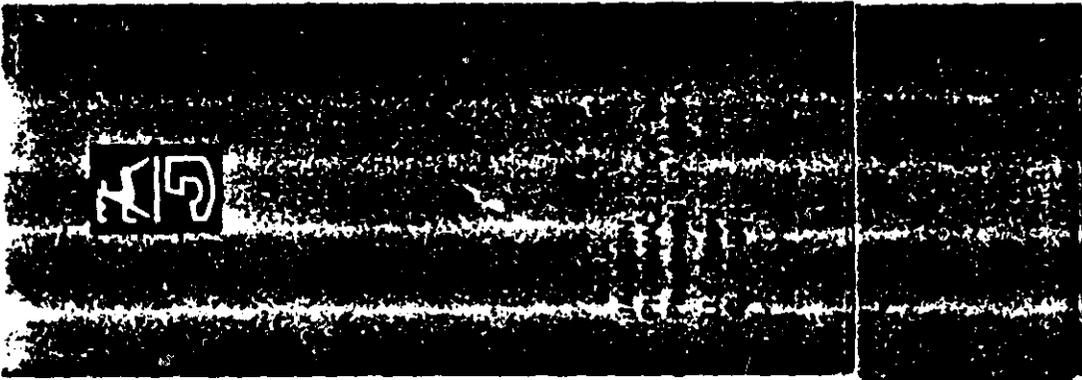
For your convenience in recording narcotic use

INITIAL/DATE

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**ALFENTA**  
(ALFENTANIL HCl)   
INJECTION

5-10 ml ampoules



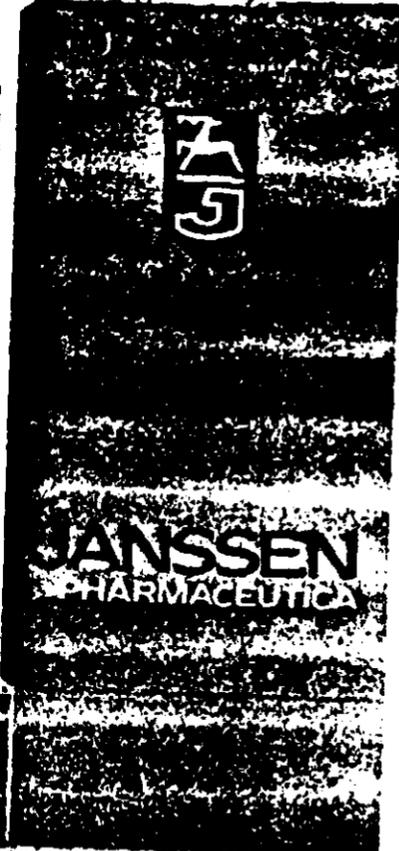


Reviewed by: James P. Hanna  
12-24-96

ALFENTA®  
(ALFENTANIL HCl)  
INJECTION

EXP. DATE  
CONTROL

2 ml



NDC 50458-060-02

10-2 ml ampoules

# ALFENTA®

(ALFENTANIL HCl) INJECTION

Each ml contains: Alfentanil base 500 ug/ml  
Warning — May be habit forming;  
Caution: Federal law prohibits dispensing without prescription.  
Not to be sold except as an unbroken box.  
FOR INTRAVENOUS USE

Usual dosage: For dosage and other information for use, see accompanying product literature.  
Store at room temperature. Protect from light.  
(15° to 30°C / 59° to 86° F)

2 ml  
ALFENTA®  
(ALFENTANIL HCl)  
INJECTION

# ALFENTA®

(ALFENTANIL HCl) INJECTION

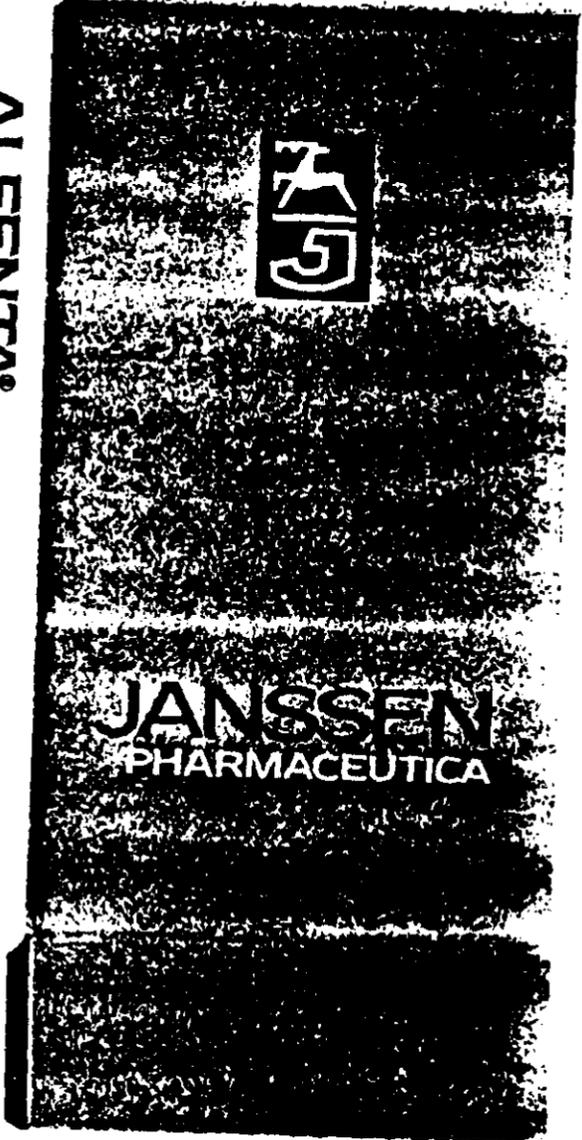
10-2 ml ampoules

NDC 50458-060-05

10-5 ml ampoules

ALFENTA®  
(ALFENTANIL HCl)

5 ml



# ALFENTA®

(ALFENTANIL HCl) INJECTION

Each ml contains: Alfentanil base 500 ug/ml  
Warning — May be habit forming;  
Caution: Federal law prohibits dispensing without prescription.  
Not to be sold except as an unbroken box.  
FOR INTRAVENOUS USE

Usual dosage: For dosage and other information for use, see accompanying product literature.  
Store at room temperature. Protect from light.  
(15° to 30°C / 59° to 86° F)

5 ml  
ALFENTA®  
(ALFENTANIL HCl)  
INJECTION

# ALFENTA®

(ALFENTANIL HCl) INJECTION

10-5 ml ampoules

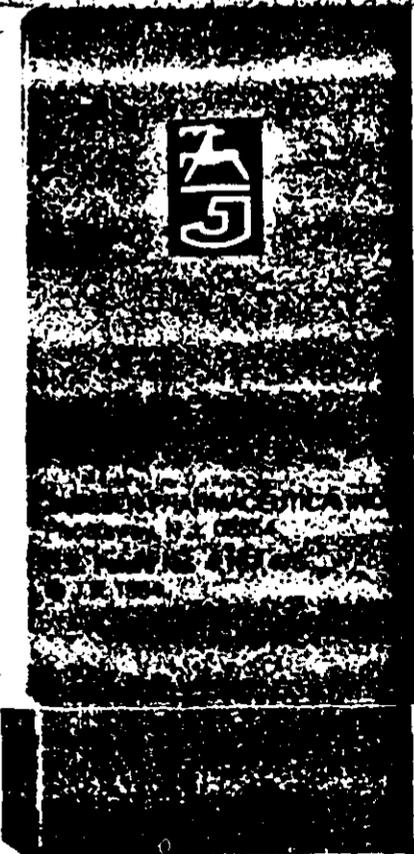


For your convenience in recording narcotic use

INITIAL/DATE	INITIAL/DATE
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3 _____	8 _____
4 _____	9 _____
5 _____	10 _____

**ALFENTA<sup>®</sup>**  
(ALFENTANIL HCl)   
INJECTION

**10-5 ml ampoules**



For your convenience in recording narcotic use

INITIAL/DATE	INITIAL/DATE
1 _____	6 _____
2 _____	7 _____
3 _____	8 _____
4 _____	9 _____
5 _____	10 _____

**ALFENTA<sup>®</sup>**  
(ALFENTANIL HCl)   
INJECTION

**10-2 ml ampoules**

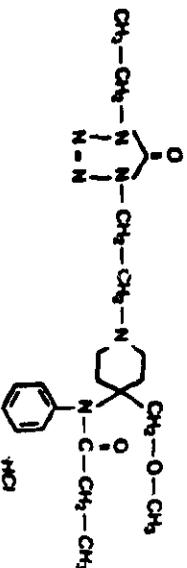
# ALFENTA®

(alfentanil hydrochloride)  
INJECTION



CAUTION: Federal Law Prohibits Dispensing Without Prescription

**DESCRIPTION**  
ALFENTA (alfentanil hydrochloride) injection is an opioid analgesic chemically designated as N-11-(2-(4-ethyl-5-dihydro-5H-tetrahydro-1,4-benzodiazepin-3-yl)propyl)-N-phenylpropionamide methanohydrochloride (1:1) with a molecular weight of 462.68. The structural formula of ALFENTA is:



ALFENTA is a sterile, non-pyrogenic, preservative free aqueous solution containing alfentanil hydrochloride equivalent to 500 µg per ml of alfentanil base for intravenous injection. The solution, which contains sodium chloride for isotonicity, has a pH range of 4.0-6.0.

### CHEMICAL PHARMACOLOGY

ALFENTA (alfentanil hydrochloride) is an opioid analgesic with a rapid onset of action. At doses of 8-40 µg/kg for surgical procedures lasting up to 30 minutes, ALFENTA provides analgesic protection against hemodynamic responses to surgical stress with recovery times generally comparable to those seen with equivalent fentanyl dosages. For longer procedures, doses of up to 75 µg/kg stimulate hemodynamic responses to laryngoscopy, intubation and extubation, with recovery time comparable to fentanyl. At doses of 50-75 µg/kg followed by a continuous infusion of 0.5-3.0 µg/kg/min, ALFENTA attenuates the cardiovascular response with more rapid recovery and reduced need for postoperative pharmacologic support of ALFENTA has been reported.

The pharmacokinetics of ALFENTA as determined in 11 patients given single bolus injections of 50 or 125 µg/kg, can be described as a three-compartment model; distribution half-life ranged from 0.4-3.1 minutes; redistribution half-life ranged from 4.8-21.6 minutes; and terminal elimination half-life ranged from 64.1-129.3 minutes (as compared to a terminal elimination half-life of approximately 218 minutes for fentanyl) and approximately 164 minutes for alfentanil. Linear kinetics have been described only with plasma concentrations up to 1000 ng/ml. Repeated or continuous administration of ALFENTA produces increasing plasma concentration and an accumulation of the drug, particularly in patients with reduced plasma clearance. The liver is the major site of biotransformation.

ALFENTA has an apparent volume of distribution of 0.6-1.0 L/kg, which is approximately one-fourth that of fentanyl, with a plasma clearance range of 1.7-17.6 ml/kg/min as compared to approximately 12.6 ml/kg/min for fentanyl. Approximately 81% of the administered dose is excreted within 24 hours and only 0.2% of the dose is eliminated as unchanged drug; urinary excretion is the major route of elimination of metabolites. Plasma protein binding of ALFENTA is approximately 82%.

In one study involving 15 patients administered ALFENTA with nitrous oxide-oxygen, a narrow range of plasma ALFENTA concentrations, approximately 310-540 ng/ml, was shown to provide adequate anesthesia for intra-abdominal surgery, while lower concentrations, approximately 180 ng/ml, blocked responses to skin closure. Plasma concentrations between 100-200 ng/ml provided adequate anesthesia for suprachloral surgery.

ALFENTA has an immediate onset of action. At dosages of approximately 105 µg/kg, ALFENTA produces hypnosis as determined by EEG patterns; an anesthetic ED<sub>50</sub> of 182 µg/kg for ALFENTA in unpremedicated patients has been determined, based upon the ability to block response to placement of a nasopharyngeal airway. Based on clinical trials, induction dosage requirements range from 130-245 µg/kg. For procedures lasting 30-60 minutes, loading dosages of up to 50 µg/kg produce the hemodynamic responses to endotracheal intubation and skin incision comparable to those from fentanyl. A pre-oxidation loading dose of 50-75 µg/kg prior to a continuous infusion attenuates the response to laryngoscopy, intubation and incision. Subsequent administration of ALFENTA infusion administered at a rate of 0.5-3.0 µg/kg/min with nitrous oxide/oxygen attenuates sympathetic responses to surgical stress with more rapid recovery than enflurane.

Requirements for volatile inhalation anesthetics were reduced by thirty to fifty percent during the first 60 minutes of maintenance in patients administered anesthetic doses (above 130 µg/kg) of ALFENTA as compared to patients given doses of 4-5 mg/kg fentanyl for anesthetic induction. At anesthetic induction dosages, ALFENTA provides a deep level of anesthesia during the first hour of anesthetic maintenance and provides attenuation of the hemodynamic response during intubation and incision.

Following an anesthetic induction dose of ALFENTA, requirements for ALFENTA infusion are reduced by 30 to 50% for the first hour of maintenance.

Patients with compromised liver function and those over 65 years of age have been found to have reduced plasma clearance and extended terminal elimination for ALFENTA, which may prolong postoperative recovery. Bradycardia may be seen in patients administered ALFENTA. The incidence and degree of bradycardia may be more pronounced when ALFENTA is administered in conjunction with non-vagolytic neuro-muscular blocking agents or in the absence of anticholinergic agents such as atropine.

Administration of intravenous diazepam immediately prior to or following high doses of ALFENTA has been shown to produce decreases in blood pressure that may be secondary to vasodilation; recovery may also be prolonged. Patients administered doses up to 200 µg/kg of ALFENTA have shown no significant increase in histamine levels and no clinical evidence of histamine release.

Skeletal muscle rigidity is related to the dose and speed of administration of ALFENTA. Muscular rigidity will occur with an intrathecal or epidural following anesthetic induction dosages. Prevalent masseters (see WARNINGS) may reduce the rate and severity.

The duration and degree of respiratory depression and increased airway resistance usually increase with dose, but have also been observed at lower doses. Although higher doses may produce apnea and a longer duration of respiratory depression, apnea may also occur at low doses.

### INDICATIONS AND USAGE

ALFENTA (alfentanil hydrochloride) is indicated: as an analgesic adjunct given in incremental doses in the maintenance of anesthesia with barbiturate/nitrous oxide/oxygen; as an analgesic administered by continuous infusion with nitrous oxide/oxygen in the maintenance of general anesthesia.

As a primary anesthetic agent for the induction of anesthesia in patients undergoing general surgery... which endotracheal intubation and mechanical ventilation are required.

SEE DOSAGE CHART FOR MORE COMPLETE INFORMATION ON THE USE OF ALFENTA.

### CONTRAINDICATIONS

ALFENTA (alfentanil hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.

### WARNINGS

ALFENTA SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS AND GENERAL ANESTHETIC AGENTS AND IN THE MANAGEMENT OF RESPIRATORY EFFECTS OF POTENT OPIOIDS.

AN OPIOID ANTAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND O<sub>2</sub> GEN SHOULD BE READY AVAILABLE.

BECAUSE OF THE POSSIBILITY OF DELAYED RESPIRATORY DEPRESSION, MONITORING OF THE PATIENT MUST CONTINUE WELL AFTER SURGERY.

ALFENTA (alfentanil hydrochloride) administered in initial dosages up to 20 µg/kg may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is usually dose-related. Administration of ALFENTA at anesthetic induction dosages (above 130 µg/kg) will consistently produce muscular rigidity with an immediate onset. The onset of muscular rigidity occurs earlier than with other opioids. ALFENTA may produce muscular rigidity that involves all skeletal muscles, including those of the neck and extremities. The incidence may be reduced by: 1) slower methods of administration of neuro-muscular blocking agents for balanced opioid anesthesia; 2) administration of up to 1/6 of the full paralyzing dose of a neuro-muscular blocking agent just prior to administration of ALFENTA at dosages up to 130 µg/kg, following loss of consciousness, a full paralyzing dose of a neuro-muscular blocking agent should be administered; or 3) intravenous administration of ALFENTA and a full paralyzing dose of a neuro-muscular blocking agent when ALFENTA is used in rapidly administered anesthetic dosages (above 130 µg/kg).

The neuro-muscular blocking agent used should be appropriate for the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered ALFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

### PRECAUTIONS

DELAYED RESPIRATORY DEPRESSION, RESPIRATORY ARREST, BRADYCARDIA, ASTYOTOLE, ARRHYTHMIAS AND HYPOTENSION HAVE ALSO BEEN REPORTED. THEREFORE, VITAL SIGNS MUST BE MONITORED CONTINUOUSLY. General: The initial dose of ALFENTA (alfentanil hydrochloride) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. In one clinical trial, the dose of ALFENTA required to produce anesthesia, as determined by appearance of delta waves in EEG, was 40% lower in geriatric patients than that needed in healthy young patients.

In patients with compromised liver function and in geriatric patients, the plasma clearance of ALFENTA may be reduced and postoperative recovery may be prolonged. Administration may produce loss of vascular tone and hypotension. Consideration should be given to fluid replacement prior to induction. Diazepam administered immediately prior to or in conjunction with high doses of ALFENTA may produce vasodilation, hypotension and result in delayed recovery.

Bradycardia produced by ALFENTA may be treated with atropine. Severe bradycardia and asystole have been successfully treated with atropine and conventional resuscitative methods.

The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuro-muscular blocking agent. Following an anesthetic induction dose of ALFENTA, requirements for volatile inhalation anesthetics or ALFENTA infusion are reduced by 30 to 50% for the first hour of maintenance.

Administration of ALFENTA infusion should be discontinued at least 10-15 minutes prior to the end of surgery. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by ALFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO<sub>2</sub> stimulation which may persist into or occur in the postoperative period. Intraoperative hyper-ventilation may further alter postoperative response to CO<sub>2</sub>. Appropriate postoperative monitoring should be employed, particularly after intubations and large doses of ALFENTA, to ensure that adequate spontaneous breathing is established and maintained in the absence of stimulation prior to discharging the patient from the recovery area.

Head injuries: ALFENTA may obscure the clinical course of patients with head injuries. Impaired Respiration: ALFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.

Impaired hepatic or renal function: In patients with liver or kidney dysfunction, ALFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of ALFENTA. Drug Interactions: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when ALFENTA is administered in combination with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or prolonged by these agents. In such cases of combined treatment, the dose of one or both agents should be reduced. Limited clinical experience indicates that requirements for volatile inhalation anesthetics are reduced by 30 to 50% for the first hour (60 minutes) following ALFENTA induction.

Preoperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma clearance and prolong recovery. Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of ALFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats and the dominant lethal test in female and male mice revealed that single intravenous doses of ALFENTA as high as 20 mg/kg (approximately 40 times the upper human dose) produced no structural chromosome mutations or induction of dominant lethal mutations. The Ames Salmonella typhimurium mutagenicity assay also revealed no mutagenic activity.

Pregnancy Category C: ALFENTA has been shown to have an embryocidal effect in rats and rabbits when given, in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects has been observed after administration of ALFENTA in rats or rabbits.

There are no adequate and well-controlled studies in pregnant women. ALFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Labor and Delivery:** There are treatment data to support the use of ALFENTA in labor and delivery. Physical transfer of the drug has been reported; therefore, use in labor and delivery is not recommended.

**Neonatal Outcome:** In one study of three women undergoing post-partum labor, significant levels of ALFENTA were detected in colostrum four hours after administration of 60 µg/kg of ALFENTA, with no detectable levels present after 28 hours. Caution should be exercised when ALFENTA is administered to a nursing woman.

**Adverse Reactions:** The most common adverse reactions, respiratory depression and skeletal muscle rigidity, are extensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity.

Delayed respiratory depression, respiratory arrest, bradycardia, apnea, arrhythmias and hypotension have also been reported.

The reported incidence of adverse reactions listed in the following table are derived from controlled and open clinical trials involving 1183 patients, of whom 785 received ALFENTA. The controlled trials involved treatment comparisons with bupivacaine, ropivacaine, etidocaine, saline placebo and heparin. Incidences are based on disturbing and non-disturbing adverse reactions reported. The comparative incidence of certain side effects is influenced by the type of use, e.g., chest wall rigidity has a higher reported incidence in clinical trials of skeletal induction, and by the type of surgery e.g., nausea and vomiting have a higher incidence in patients undergoing gynecologic surgery.

	ALFENTA (N=785) %	Fentanyl (N=243) %	Thiopental (N=86) %	Etidocaine (N=55) %	Bupivacaine (N=18) %	Saline Placebo* (N=18) %
<b>Gastrointestinal</b>						
Nausea	28	44	14	5	0	22
Vomiting	18	31	11	9	13	17
<b>Cardiovascular</b>						
Bradycardia	14	7	8	0	0	0
Tachycardia	12	12	39	36	31	11
Hypotension	10	8	7	7	0	0
Hypertension	10	13	30	20	6	0
Arrhythmia	2	2	5	4	6	0
<b>Max. Dilated Chest Wall Rigidity</b>	17	12	0	0	0	0
<b>Skeletal Muscle Movements</b>						
Rigidity	6	2	6	2	0	0
<b>Respiratory</b>						
Apnea	7	0	0	0	0	0
Postoperative Respiratory Depression	2	2	0	0	0	0
<b>CNS</b>						
Dizziness	3	5	0	0	0	0
Sleazehead/Postoperative Sedation	2	8	2	0	0	9
<b>Blurred Vision</b>	2	2	0	0	0	0

\*From two clinical trials, one involving supplemented balanced barbiturate/halothane oxide anesthesia and one in healthy volunteers who did not undergo surgery.

In addition, other adverse reactions less frequently reported (1% or less) were:

Laryngospasm, bronchospasm, postoperative confusion, headache, shivering, postoperative euphoria, hyperparathy, pain on hipion, uremia, and itching.

Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA.

**DRUG ABUSE AND DEPENDENCE:** ALFENTA (alfentanil hydrochloride) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

**OVERDOSEAGE:** Overdosage would be manifested by extension of the pharmacological actions of ALFENTA (alfentanil hydrochloride) (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. No experience of overdosage with ALFENTA was reported during clinical trials. The intravenous LD<sub>50</sub> of ALFENTA is 43.0-50.9 mg/kg in rats, 72.2-73.6 mg/kg in mice, 71.8-81.9 mg/kg in guinea pigs and 59.5-87.5 mg/kg in dogs. Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression.

The duration of respiratory depression following overdosage with ALFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude immediate establishment of a patent airway, administration of oxygen, and assisted or controlled ventilation as indicated for hypoventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents may be required to manage hemodynamic instability.

**DOSEAGE AND ADMINISTRATION:** The dosage of ALFENTA (alfentanil hydrochloride) should be individualized in each patient according to body weight, physical status, underlying pathological condition, use of other drugs, and type and duration of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. The dose of ALFENTA should be reduced in elderly or debilitated patients (see PRECAUTIONS).

Vital signs should be monitored routinely.

See Dosage Chart for the use of ALFENTA: 1) by incremental injection as an analgesic adjunct to anesthesia with barbiturate/halothane overdosage for short surgical procedures (suggested duration of use less than one hour); 2) by continuous infusion as a maintenance analgesic for short surgical procedures for general surgical procedures; and 3) by intravenous injection in anesthesia doses for the induction of anesthesia for general surgical procedures with a minimum expected duration of 45 minutes.

**Use in Children:** Clinical data to support the use of ALFENTA in patients under 12 years of age are not presently available. Therefore, such use is not recommended.

**Premedication:** The selection of preanesthetic medications should be based upon the needs of the individual patient. Neuro-muscular blocking agents: The neuro-muscular blocking agent selected should be compatible with the patient's condition, taking into account the hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required (see CLINICAL PHARMACOLOGY WARNINGS and PRECAUTIONS sections).

In patients administered anesthetic induction doses of ALFENTA, it is essential that qualified personnel and adequate facilities be available for the management of respiratory and postoperative respiratory depression.

Also see WARNINGS and PRECAUTIONS sections.

For purposes of administering small volumes of ALFENTA accurately, the use of a tuberculin syringe or equivalent is recommended.

The physical and chemical compatibility of ALFENTA have been demonstrated in solution with normal saline, 5% dextrose in normal saline, 5% dextrose in water and Lactated Ringers. Clinical studies of ALFENTA infusion have been conducted with ALFENTA diluted to a concentration range of 25 µg/ml to 80 µg/ml.

As an example of the preparation of ALFENTA for infusion, 20 ml of ALFENTA added to 200 ml of diluent provides a 40 µg/ml solution of ALFENTA.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

**DOSEAGE RANGE CHART**

Indication	Approximate Duration of Anesthesia (Final Dose)	Induction Period (Initial Dose)	Maintenance Period (Continuous Infusion)	Total Dose	Effects
Incremental Injection	5-30 min	6-20 µg/kg	3-5 µg/kg or 0.5-1 µg/kg/min	6-40 µg/kg	Spontaneously breathing or assisted ventilation when required
Continuous Infusion	30-60 min	20-50 µg/kg	5-15 µg/kg	up to 75 µg/kg	Assisted or controlled ventilation required. Administration of response to hypoxia and reflexion.
Continuous Infusion	> 45 min	50-75 µg/kg	0.5-1.0 µg/kg/min	dependent duration of procedure	Assisted or controlled ventilation required. Some administration of response to reflexion and reflexion with respiratory stability.
See Guidelines Below			Average Infusion Rate: 1-1.5 µg/kg/min		
Anesthetic Induction	> 45 min	120-240 µg/kg	0.5 to 1.0 µg/kg/min or general anesthetic procedure	dependent duration of procedure	Assisted or controlled ventilation required. Administer slowly (over three minutes). Concentration of infusion agents reduced by 30-50% for final dose.

**INFUSION DOSAGE**

Continuous infusion: 0.5-1.0 µg/kg/min administered with nitrous oxide/oxygen in patients undergoing general surgery following an anesthetic induction dose of ALFENTA. Infusion rate requirements are reduced by 30-50% for the first hour of maintenance.

Changes in vital signs that indicate a response to surgical stress or hyperventilation of anesthesia may be controlled by increasing the rate up to a maximum of 4.0 µg/kg/min (total administration of total doses of 7 µg/kg). If changes are not controlled after three total doses given over a two minute period, a barbiturate, vecuronium, or other relaxation agent should be used. Infusion rates should always be adjusted down 25% in the absence of vital signs over three to four responses to surgical stimulation.

Rather than an increase in infusion rate, 7 µg/kg bolus doses of ALFENTA or a potent relaxation agent should be administered in response to signs of hyperventilation at anesthesia when the last 15 minutes of surgery. Administration of ALFENTA infusion should be discontinued at least 10-15 minutes prior to the end of surgery.

**NOW SUPPLIED:** Each ml of ALFENTA (alfentanil hydrochloride) injection for intravenous use contains alfentanil hydrochloride equivalent to 500 µg of alfentanil base. ALFENTA injection is available as:

- NDC 50458-080-02, 2 ml ampoules in packages of 10
- NDC 50458-080-05, 5 ml ampoules in packages of 10
- NDC 50458-080-10, 10 ml ampoules in packages of 5
- NDC 50458-080-20, 20 ml ampoules in packages of 5

Protect from light. Store at room temperature 15°-30°C (59°-86°F). U.S. Patent No. 4,167,475 December, 1986

Manufactured by Janssen Pharmaceutica Co. for



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NDA 19-353

MEDICAL REVIEW OF SAFETY UPDATE  
(Amendment)

Sponsor: Janssen Pharmaceutica  
40 Kingsbridge Road  
Piscataway, NJ 08854

Name of Drug: Trade: ALFENTA  
Generic: Alfentanil Hydrochloride

Pharmacologic Category of Drug: Synthetic narcotic, short-acting analgesic

Dosage Form: Sterile, preservative free, aqueous solution containing  
alfentanil HCl equivalent to 500 ug/ml alfentanil base

Route of Administration: Intravenous

Date of Submission: November 18, 1986  
Date Received for Review: November 20, 1986  
Review Completed: November 21, 1986

Related IND: - originally submitted January 9, 1981

Background:

The amendment provides for an updated safety report to cover the period from October 25, 1985 through November 18, 1986 for 3 distinct areas.

Evaluation:

1. A table listing new patients entered into seven ongoing studies by individual investigators for the time period of this update. No adverse reactions have been reported for any of these 80 patients.

In addition, a list of 36 investigators and the number of patients entered into this open multicenter study (protocol JRD 39,209/500) by investigator and for each of the four parts of the study has been submitted. From the total of 1057 participating patients 4 adverse drug experience reports had been submitted during the reporting period. Of these 4 ADR's two were too sketchy (February 18, 1986 - Peter Glass, M.D. and March 4, 1986 - S. Gelman, M.D.) for a meaningful evaluation. Additional information was required. This information has now, November 20, 1986 been requested by telephone since the information provided with the safety up-date does not include additional data. The December 23, 1985 (M. Dubois, M.D.) ADR report has been reviewed by me previously (January 13, 1986) and considered not study drug related. In addition it appeared unlikely that the ADR represented a true case of malignant hyperthermia. Finally, the May 2, 1986 (John Mahaffey, M.D.) report has been considered as "possibly related" to the study drug.

NOV 28 1986

Perusal of the records showed the appearance of tachycardia immediately following the administration of alfentanil and subsiding after a barbiturate induction dose. Two hours later the patient developed PAC's and PAT which responded to carotid massage. It apparently was considered drug related since the records show that alfentanil was discontinued and replaced by Forane.

Conclusion:

Judging from the submitted table and the ADR's reported, alfentanil use appears to be generally safe since only 4 serious ADR's have been reported during a 12 month period from the 1057 patients exposed to the drug during that time in the USA. On the other hand we have not yet received any other safety data from the 1057 patients already exposed to alfentanil in the open multicenter study which proposed to collect data on a total of 2000 patients. Since this study design was open, forthcoming results should be considered as a phase IV safety confirmation. Therefore, based on the information provided by the updated safety report from the Firm, alfentanil is considered safe as described in the proposed labeling.

2. A reprint from Acta Anaesth. Scand. 30:35-40 by Raeder and Hole from the Anesthesia Dep. Univ. Hosp. Trondheim, Norway has been submitted for a clinical study outside of the U.S.A.

Results from this study conducted in 25 patients undergoing major abdominal surgery, i.e. cholecystectomy, under general anesthesia with alfentanil administered as a bolus induction followed by continuous infusion of alfentanil for maintenance at 5 different dosage levels provided interesting data. There were 5 groups of 5 patients each. For groups I-IV the investigators followed the manufacturers recommendations of induction and maintenance dosage range, while for patients assigned to group V an attempt was made to dose according to the anticipated degree of surgical stress. The following observations have been reported:

- a. Even with slow administration of alfentanil chest rigidity was observed in a high proportion of patients following high dose alfentanil induction. This confirms known experience reported for 30 - 60% of cases in published studies.
- b. Although the majority of the patients were awake rapidly, usually within 10 minutes or less, delayed severe respiratory depression and/or respiratory arrest did occur after 20-45 minutes of recovery and spontaneous ventilation. The rapid awakening appeared to be independent of length of anesthesia, i.e. 72-236 minutes while the delayed respiratory depression appeared to be dose dependent. It is noted that the dosages listed for this study are higher than those recommended in the proposed labeling.

The occurrence of delayed respiratory depression has previously been reported in studies reviewed by the Agency and did not appear to be consistently dose dependent.

- c. The results from the study confirmed also that considerable variations between patients exist in dosage requirements independent of whether dosages were calculated on a per kg body weight basis, per kg/minutes basis or from clinical observations. The investigators refer to publications which reported that, although the alfentanil elimination half-time is 1/3 that of fentanyl, some patients have half-lives up to four times the usual 80-90 minutes. In addition, secondary serum concentration peaks 30-60 minutes after anesthesia reversal have been reported in some patients (Hull and CAMU). Gastric trapping may, in the opinion of the investigators, explain those cases with early awakening followed by delayed respiratory arrest.
- d. Alfentanil has been described as providing suppression of catecholamine mediated stress responses and thus cardiovascular stability. Two figures presented in the article depicting systolic blood pressure measurements and heart rate pre- and intra-operative show that some hemodynamic changes did appear following alfentanil administration independent of the dosages used. This observation confirms results of other studies reviewed previously.
- e. An interesting finding was the result from serum cortisol and serum glucose measurements to evaluate endocrine (metabolic) stress response. No significant rises in either one was found during anesthesia and surgery, however, all groups showed significant elevations 2 hours postoperatively in serum glucose and serum cortisol concentrations confirming an increased metabolic stress response reflecting the short-acting effect of alfentanil.

#### Conclusion

The dosages recommended by the investigators of a 50 ug/kg bolus dosage followed by an infusion rate of 1. - 1.5 ug/kg/minute supplemented with 0.5 mg increments p.r.n. confirm to the dosage schedule of the proposed labeling. In addition, the study results confirm that although generally, awakening even after high doses is rapid, delayed serious respiratory depression and/or respiratory arrest may follow alfentanil anesthesia. Similar confirmation has been provided for changes in hemodynamic parameters occurring during alfentanil anesthesia independent of the dosages used.

3. A list of those countries outside of the U.S.A. where Alfentanil is an approved drug is presented and updated from the previously submitted one. Two additional countries, Venezuela and Yugoslavia

approved the drug in 1986. No changes in marketing dates appears. The updated Adverse Experience Report of cases outside the U.S.A. between October 1985 and November 1986 is tabulated by countries (U.K. and Germany). Alfentanil has been marketed in both countries for over 3 years. Of 7 cases reported from the U.K. bradycardia has been reported most frequently (5 cases) and for 3 cases from Germany. Individual case report forms have been included for these 10 patients.

Perusal of these case report forms can be summarized as follows:

The occurrence of bradycardia followed the administration of alfentanil and was probably related to alfentanil. In case #1 from the U.K. which also reported asystole, the experience occurred immediately following moving the patient to the operating table which appears to have been contributory. When the patient was rechallenged after successful resuscitation with a lower dosage of alfentanil the drug was tolerated without further cardiovascular instability.

The 2 cases (#4 and 5) in whom the bradycardia and cardiac arrest were reported to have followed immediately the local spraying of the larynx with lidocaine occurred in the same Hospital on 2 successive days. Although both patients had received around 2 mg of alfentanil before the spray, it is difficult from the sketchy information provided to implicate solely the administration of alfentanil for the reaction. Fortunately both patients recovered without sequelae and the surgery was cancelled.

Case #3 who experienced muscle twitching and respiratory difficulty appears to have been caused by alfentanil. Both experiences are known to occur following the administration of alfentanil. Case #7 had a history of ischemic heart disease and although we do not know the total dose of alfentanil administered the experience of bradycardia and asystole was probably caused by alfentanil.

Case #6 who experienced severe bronchospasm and a blotchy red discrete urticarial rash was, in the opinion of the anesthesiologist, drug related. The patient had experienced urticaria before. The experience is considered a histamine release type reaction.

There is no question that the bradycardia observed in case #2 was related to alfentanil.

The 3 case reports from Germany of bradycardia and hypotension have been considered drug related. The occurrence of both of these cardiovascular changes are known to occur following the administration of alfentanil.

**Summary:**

The updated safety report of November 18, 1986 for NDA 19-353 Alfenta (Alfentanil HCl) did not disclose new, unexpected drug experiences. It confirmed that delayed respiratory depression and/or respiratory arrest appears to be a risk despite the generally observed rapid awakening independent of drug amount used. In addition it was also confirmed that bradycardia and/or hypotension may be a problem following pre-or induction with either bolus or infusion administration of alfentanil although hemodynamic parameter changes observed during maintenance have generally been within acceptable ranges and not different from comparative agents used. We do not have any information from the 1057 patients exposed to alfentanil who are a part of the expected 2000 patients participating in the multicenter open study which commenced since the previous safety update of October 1985. It should be of interest to know the incidence of chestwall rigidity following alfentanil induction, the occurrence of hypotension and or bradycardia following induction of anesthesia with alfentanil and the hemodynamic parameter changes, if any, observed during maintenance for each of the four parts of the study.

During the period between the two safety update: a progress report has been submitted (for details see review of 5-28-86) which provided the final results for two original NDA studies (#021-MOGELNICKI induction study and #016-BRICKNELL infusion study). Study #021 involved 20 surgical patients, 11 received alfentanil as an induction agent and 9 received thiopental sodium. Loss of consciousness was significantly faster with thiopental. During induction there were no significant differences in blood pressure changes, however, heart rate changes (increases) were significantly larger following thiopental, e.g. 29, 6% vs. 11.0%. During maintenance comparable increases or decreases of more than 20% of control values in vital signs were reported for the two treatment groups. Observed recovery times were comparable, while PARR scores of respiratory, blood pressure, consciousness and color were significantly superior in the thiopental group. There were two cases of delayed respiratory depression with pulmonary edema following alfentanil use.

Study #016 involved 55 adult surgical patients. Alfentanil by infusion was administered either before or after thiopental for induction of anesthesia. Cardiovascular stability was assessed by maintaining blood pressure, and heart rate during induction and maintenance of anesthesia. Changes were recorded for both groups during induction and maintenance. Therefore, alfentanil did not provide superior cardiovascular stability as originally claimed by the sponsor. Chestwall rigidity occurred only in the alfentanil 1st group. The most frequently observed side effects were hypotension, tachycardia and bradycardia for both groups. Rates of recovery were not different between the two groups. These two additional NDA study results confirm that the administration of alfentanil either by bolus or infusion administration provided effective anesthesia. However, the use of alfentanil does not provide superior safety aspects compared to other, marketed agents.

**Recommendation:**

To accept the updated safety report. Re-evaluation of the proposed labeling appears justified.

*Brigitta Dassler, M.D. 11/25/86*  
Brigitta Dassler, M.D.  
Medical Officer

**NDA 19-353**

HFN-160

HFN-340

R/D BDassler 11/21/86

R/D Init. by JCKeally 11/24/86, PGWalters 11/24/86

FT OLA 2483N 0017M 11/24/86

Doc. Room 160

NDA - 19-353

December 3, 1986

Medical Reviews of Amendment

Sponsor: Janssen Pharmaceutica  
40 Kingsbridge Rd.  
Piscataway, NJ 08854

Name of Drug: Alfenta (alfentanil hydrochloride)

Category of Drug: Synthetic narcotic analgesic

Dosage Form: Sterile, preservative free aqueous solution containing  
alfentanil HCl equivalent to 500 ug/ml alfentanil base.

Route of Administration: Intravenous

Date of Submission November 24, 1986

Received for Review: December 2, 1986

Review completed: December 3, 1986

Related NDA, -

Background:

The amendment provides for the requested additional information of two ADR's which have been listed under the NDA safety update of November 18, 1986. Therefore, the following evaluation should be made part of the NDA safety update of November 18, 1986.

Evaluation:

The additional information for Dr. Glass's patient M.F.L. (AL-4) who experienced a wandering atrial pacemaker while undergoing right wrist synovectomy at Duke University Medical Center, and who was enrolled in protocol IRD 39,209/500, discloses that this 33 year old black female patient experienced a wandering atrial pacemaker 27 minutes following anesthesia induction and maintenance with alfentanil, i.e. bolus of 4, 5 mg and infusion of 1-2 ug/kg/min. Simultaneously with the appearance of the wandering atrial pacemaker bradycardia had developed. The episode lasted for 20 minutes during which time alfentanil infusion was continued. The record indicates that the wandering pacemaker subsided without discontinuence of the alfentanil infusion. This is in contrast to the entry in Form 1639 which states that the reaction abated after stopping the drug. The investigator concluded that the non-disturbing intraoperative adverse effect was possibly related to alfentanil.

The second additional information provided by Dr's Gelman and Vinik from the University of Alabama School of Medicine concerns a 49 year old male patient who had undergone major abdominal surgery under alfentanil infusion at 2.1 ug/kg/min anesthesia for 345 minutes receiving a total of 57.5 mg of alfentanil. Judging from the submitted records, both, surgery and anesthesia appear to have been uneventful. During the anesthesia the patient received a total of 16 mg Valium in divided doses. The patient arrived in the PARR still intubated and was ventilated for 55 minutes at a rate of 8/min. At that time, which was 1 hr. 47 minutes after cessation of the alfentanil administration, he demonstrated adequate tidal volume and FVC and was extubated and considered alert. Six minutes later the patient experienced respiratory arrest and showed ventricular tachycardia. He was reintubated and ventilated and responded to command 30 minutes later. The patient developed fibrillation/flutter at a rate of 160 with a blood pressure of 184/96. Verampamil treatment was followed by hypotension and a neosynephrine infusion was given to maintain the blood pressure at 100 systolic. Ventricular tachycardia reappeared but responded to lidocaine, however the EKG confirmed the remaining flutter/fibrillation rhythm. A cardiac consult was obtained, cardioversion and digoxin administered. The atrial flutter fibrillation persisted for 3 days with the patient improving under digitalis therapy. There was no evidence of myocardial damage. The patient appeared fully recovered 5 days later. The investigator considered the ADR probably alfentanil related.

Conclusion:

The additional information provided for two of the four ADR's reported for the ongoing multicenter study in which 1057 patients have been exposed to alfentanil within one of the 4 different treatment schedules, provides no unexpected adverse drug experiences. However, it confirms that delayed severe respiratory depression and arrest may follow the alfentanil administration. In addition, cardiac arrhythmias may occur during alfentanil administration.

Recommendation:

To accept the additional information. No action appears indicated.

*Brigitte Dassler, M.D.* 12/16/86  
Brigitte Dassler, M.D.  
Medical Officer

IND 18,327  
HFN-160, HFN-340  
Doc Rm 160  
R/D BDassler 12/3/86  
R/D init by JCKenealy 12/3/86; PGWalters 12/3/86  
Ft/MPatterson (w2216k) 12/16/86

Date: June 3, 1986

Medical Review of NDA 19-353  
(New Correspondence)

Sponsor: Janssen Pharmaceutica  
Piscataway, NJ 08854

Name of Drug: Alfenta (alfentanil HCl) Injection

Category: Synthetic narcotic analgesic

Proposed Use: As an analgesic adjunct to general anesthesia.

Date of Correspondence: May 23, 1986

Received for Review: May 29, 1986

Review Completed: June 3, 1986.

Background: This submission was made in response to a request by Dr. Paula Botstein for summary tables of recovery times from the controlled clinical incremental, infusion and induction studies which had been submitted in the NDA.

Evaluation:

The coversheet for the individual studies for the three categories lists page numbers. However, these numbers refer to the respective coversheets for each study and not to the location of actual data necessary for verification of the submitted tables. In order to hasten the review, the firm was called on May 30th for listing of the necessary page numbers for the infusion and induction studies. See memo of telephone conversation which is attached. For the incremental studies, the correct data pages were located by this reviewer.

1. Table "Alfentanil Incremental Studies". Seven studies have been listed six of those provide comparative median recovery times in minutes for four observations. Eyelash reflex, respond to command, alert, and extubation when alfentanil was compared to fentanyl for a total of 165 alfentanil, 156 fentanyl, and 9 placebo patients. In the 7th study, alfentanil was compared to halothane in 16 points each. Comparison of the table with the raw data from which it has been composed, only minor discrepancies were found. The

patient numbers stated on the table are incorrect for fentanyl in the Giesecke and Rosow study and for alfentanil in the Kallar study. The same applies to the P values stated for White and Stanley. The table in the NDA lists the White P values as 0.05 and not 0.0002 and no p value for the Stanley study. Overall results of the median recovery time in minutes shows no significant superiority of alfentanil when compared to fentanyl with the exception of the Stanley study where recovery was faster with fentanyl compared to alfentanil after approximately equal duration of anesthesia. In addition, the ratio of 4:1 for the alfentanil loading dose (30 ug/kg) to fentanyl was found to be inadequate requiring a substantially higher overall mean ug/kg dose of alfentanil. Some, but not all of the NDA tables provide not only for median times but for ranges also, minimum and maximum times (Brown, Vattar, Stanley) which confirms that the presentation of median times only in the submitted summary tables is somehow misleading since it reduces the influence of prolonged recovery times. It is assumed that the Kruskal-Wallis H-test has been used for the analysis, since it appears on some tables of the NDA data, which, of course, would reduce the influence of these patients with prolonged recovery times; however, it should be kept in mind that prolonged recovery did occur. The same applies to p-values presented on the summary tables with no explanation of which analysis was used to produce them. The comparison of alfentanil to halothane in the small Youngberg study shows that recovery for all four observations was significantly faster following alfentanil at p 0.01.

The summary table labeled "Recovery times, incremental studies alfentanil vs. fentanyl" based on the data from Brown, Rosow, White, Giesecke and Kallar is of no value since the patient numbers are incorrect. It should read: Alfentanil 135 patients and fentanyl 126 patients.

2. Table "Alfentanil Infusion Studies". Two alfentanil-enflurane comparisons (Steen and Howie) and three alfentanil-fentanyl comparisons (McLeskey, Davies, and White) have been tabled. Note that the White study #030 is listed again for those data where infusions have been compared. In the NDA White study #025 was listed as an infusion study and #030 as an incremental study, however, study #030 includes both bolus and infusion administration comparison to fentanyl while study #025 compared different dose ranges of alfentanil for induction and maintenance infusions in superficial and intraabdominal surgical procedure anesthesia. Again there appear minor discrepancies for the patient numbers. The column representing the observation "Awake" for the two enflurane studies actually represents the "responses to verbal command" and is therefore somewhat misleading. A patient responding to verbal

commands often is not yet "awake". This has been emphasized by the fact that usually two separate observations have been recorded during recovery namely: "Respond to command" and "awake". However, there is clear evidence that those patients from the enflurane groups required significantly longer median recovery times than those from the alfentanil group. The p-values on the table for 'awake' and 'alert' from the Steen study are different from those stated in the NDA records namely  $p = 0.01$  instead of 0.006 for awake and 0.01 instead of 0.04 for alert. The data from the 3 studies comparing alfentanil to fentanyl show a faster recovery for the alfentanil patients in McLeskey and White, while results from the Davis study showed the opposite. As a side observation, the figures under extubation in the White study belong under the heading 'alert' since these patients have not been intubated. The summary table from the Howie and Steen studies with the heading "Recovery times Infusion Studies Alfentanil vs Enflurane requires an explanation of the analysis used to produce them since p-values stated on the prior table do not conform with NDA values.

3. Table "Alfentanil Induction Studies" lists five studies in which an alfentanil induction was compared to a barbiturate (thiopental) induction. A total of 73 patients received alfentanil and 66 patients thiopental. Two of the thiopental patients from the Smith study have been excluded from the recovery evaluations due to surgical problems. Seven (7) of the 19 Berman patients who received alfentanil for induction of anesthesia required naloxone prior to extubation as did two of the Murphy patients. For the observation "awake" the results show no significant difference between the two administration sequences for 3 studies (Stanley, Steen, Berman) while results from the studies by Murphy and Smith (thio-succinylcholine) showed a faster recovery after the barbiturate induction. The same results were observed for the observations "extubation" and "alert" for results from the Murphy and Smith studies. Results from the Stanley, Steen and Berman study for the observation "alert" show faster recovery for the alfentanil patient group and it could generally be confirmed by the ranges displayed in the NDA data. Median times for extubation were overall faster following the barbiturate induction especially when one remembers that 7 of the 19 patients from the Berman study had received naloxone before. The final table displaying summary results from four studies for recovery times from the induction studies comparing alfentanil to thiopental not only requires an explanation of the analysis used to produce the p-values but as important an explanation if the seven Berman patients who received naloxone have been included. It is not clear from the median recovery times in minutes listed on the table if they have been included or excluded. The latter only would represent correct comparisons.

Conclusion:

The three sets of summary tables of recovery time observations which had been requested by Dr. Paula Botstein, have been reviewed in detail on the foregoing pages.

Disregarding discrepancies between some figures of the tables and NDA data as well as the missing explanation of the analysis used to produce p-values for the medians, which were used rather than the means because the data were skewed, the results showed that there was clinically no significant difference in recovery time observations between alfentanil and fentanyl when either drug was used in incremental doses for balanced general anesthesia. In contrast, results from the comparison of alfentanil to halothane as an adjunct to general anesthesia in the small number of patients enrolled in that study, showed a clinically significant faster recovery for the alfentanil group. The same results were obtained in those two studies where alfentanil infusion administration has been compared to enflurane in a limited total number of patients (Al = 39; Enf = 40). When the administration by infusion was compared between alfentanil and fentanyl the results showed inconsistent faster recovery in two studies and slower recovery in one study for the alfentanil group. The results of the comparison between alfentanil and thiopental, when either one was used for induction of general anesthesia, showed clinically no significant faster recovery for the alfentanil group in 3 studies and faster recovery in two studies for the thiopental group for the observation "awake"; while the alfentanil groups in all of the studies showed faster median recovery times for the observation "alert".

Based on the results from the summary tables submitted the claim for faster recovery following the administration of alfentanil by infusion or in incremental doses should only be made where alfentanil has been compared to halogenated inhalation agents, e.g. enflurane and halothane, while there was inconsistent faster recovery following alfentanil administration by infusion compared to fentanyl and clinically no significant difference when either drug was used incrementally. Finally, clinically significant differences for "alertness" only were observed when alfentanil was compared to thiopental as an induction agent and inconclusive results for the observation "awake". It should be kept in mind, however, that prolonged recovery did occur as well as delayed recovery after an initial fast awakening following alfentanil, an observation known to follow the use of opioid analgesics.

*Brigitta Dassler, M.D. 6-5-86*  
Brigitta Dassler, M.D.  
Medical Officer

cc: NDA 19-353  
HFN 160, HFN 340  
Doc Room 160  
HFN 101/Botstein  
R/D BDassler, 6/3/86  
R/D init. JCK, 6/3/86  
FT/jb, W5069P, D3641P, 6/5/86

JUN 10 1986

Medical Officer's Labeling Review  
of NDA 19-353

Labeling Review

The sponsor, Janssen Pharmaceutica, has submitted labeling changes since the originally submitted proposed labeling of December 1984, on April 9 and October 2, 1985.

My original review of the NDA was based on the first labeling claims and changes considered necessary geared to the original submission. After having reviewed the most recent submission, I found several of my contemplated change requests already incorporated.

The October 2, 1985, draft labeling evaluation for ALFENTA (alfentanil hydrochloride) Injection is as follows:

Caution: Acceptable

Description

Acceptable, with the following changes requested by the Chemist:

1. The molecular weight of the drug substance should reflect that the drug is a monohydrochloride, monohydrate, i.e. MW = 471. This would agree with the USAN listing.

2. Both the chemical name and structural formula of the drug should indicate that it is both a monohydrochloride and a monohydrate.
3. It is recommended that the Description section indicate that the drug product is nonpyrogenic.

### Clinical Pharmacology

The sponsor should specify if potency, onset and duration of action are based on animal data since clinical evidence for values and times has not been substantiated. Any reference to ALFENTA's superior hemodynamic stability to reference agents should be deleted since substantial evidence for this claim has not been provided. In addition, reference to rapid recovery should read: slightly more rapid recovery. The evidence provided has not been consistent for significantly shorter recovery compared to the parent compound, fentanyl. In the reference to ALFENTA's provision of analgesic protection against hemodynamic responses to stress, the word "good" should be deleted since evidence is spurious. The reference to pharmacokinetics should be changed to read:

The pharmacokinetic of ALFENTA can be described as a three-compartment model with mean values of distribution half-life of approximately 1-3 minutes, redistribution half-life of approximately 9-17 minutes and a terminal elimination half-life of approximately 94 minutes (comparable terminal elimination half-life for fentanyl and sufentanil are 219 and 148 minutes respectively). The liver and small intestine are the major sites of biotransformation.

(Sponsor to provide reference for "small intestine" or delete)

Approximately 81% of the administered dose is excreted within 24 hours and only 0.2% of the dose is eliminated as unchanged drug with urinary excretion being the major route of elimination. Plasma protein binding of ALFENTA is approximately 92%.

ALFENTA has an apparent volume of distribution of 0.6-1.0 L/kg which is approximately 1/4 that of fentanyl with plasma clearance of 5-8 ml/min/kg as compared with 12.6 ml/min/kg for fentanyl. Lower lipid solubility limits penetration of the blood-brain barrier and alfentanil shows less cumulative effect than fentanyl; however, repeated administration will result in increasing plasma concentrations and some cumulative effect can be expected.

The following paragraph should read: ALFENTA plasma concentrations of 312-338 ng/ml provided adequate anesthesia for lower abdominal surgery. In one study involving 50 patients undergoing abdominal gynecologic procedures, mean plasma concentration at skin closure was 186.1 ng/ml. A plasma concentration range of 100-200 ng/ml provided adequate anesthesia for superficial surgical procedures.

The last paragraph on page 3 and 1st on page 4 have been changed to read:

Induction doses of 100-250 ug/kg were demonstrated to provide reliable loss of response to spoken command with 100% loss of eyelash reflex at 250 ug/kg in healthy unpremedicated patients. A consistent ED<sub>90</sub> of 182 ug/kg for loss of response to placement of nasopharyngeal airway was observed. Requirements for inhalation anesthetics were reduced by 30-50% during the first 60 minutes following 149-153 ug/kg induction doses of ALFENTA in a comparison study which used induction doses of 4.06-5.18 mg/kg of thiopental.

The sponsor should provide the reference for the statement of the last paragraph on page 4. The first three paragraphs on page 5 are acceptable.

The fourth paragraph should read:

Patients administered doses up to 200 ug/kg of ALFENTA have shown no increase in histamine levels and no clinical evidence of histamine release.

The fifth and sixth paragraph should be revised to read:

More rapid onset of action resulted in frequent observation of chest wall rigidity occurring within 90 seconds of induction doses of ALFENTA. Respiratory depression and increased airway resistance are dose related, but have also been observed with lower doses. Higher doses will produce apnea and longer duration of respiratory depression.

Indication and Usage - Acceptable

Contraindications - Acceptable

Warning - Boldtype first two paragraphs acceptable.

Follow with: As with other CNS depressants, patients who have received ALFENTA should have appropriate surveillance.

In the following paragraph which ends on page 8 the sponsor should clarify the 130 ug/kg ALFENTA dosage since muscular rigidity has followed lower dosages and pre-curarization.

The last paragraph under 'Warnings' acceptable.

Precautions

General: To be added in bold print. ALFENTA should be administered only by persons adequately trained in the administration and management of general anesthesia.

The last paragraph on page 8 is acceptable.

This should be added to the following text which has been reworded from the proposal.

In one clinical trial, the dose of ALFENTA required to produce EEG delta wave changes compatible with anesthesia was 40% lower in elderly patients than that required by healthy, young adults.

The second paragraph on page 9 is acceptable as is the next sentence.

The last sentence of the next paragraph should be reworded as follows: Consideration should be given to fluid replacement prior to induction in these patients.

Follow with: Bradycardia produced by ALFENTA may be treated with atropine. Diazepam administered immediately prior to or in conjunction with high doses of ALFENTA may produce vasodilation, hypotension and result in delayed recovery.

The last paragraph and the first two on page 10 are acceptable.

Replace the third paragraph with the following text:

Impaired Respiration

ALFENTA should be used with caution in patients with pulmonary disease, decreased ventilatory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled ventilation. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of the respiratory depression produced by ALFENTA persists longer than the action of the opioid antagonist action, appropriate surveillance should be maintained.

Interaction with Other Central Nervous System Depressants:

Change to Drug Interactions. See next page.

Head Injuries - Acceptable

The next paragraph "Impaired Respiration" has been moved and reworded and appeared in a prior location.

Impaired Hepatic or Renal Function - Acceptable

Drug Interactions

An additive effect may be observed when ALFENTA is combined with other central nervous system depressants such as barbiturates, tranquilizers, other opioids or inhalation general anesthetics. In such cases of combined treatment, the dose of one or both agents should be reduced. Requirements for general inhalation anesthetics may be reduced by 30-40% for the first hour following ALFENTA induction.

Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce clearance and result in delayed recovery.

Carcinogenesis, Mutagenesis and Impairment of Fertility - Acceptable

Pregnancy Category C - Acceptable

Labor and Delivery - Acceptable

Nursing Mothers - Acceptable

Pediatric Use

Change to: Adequate data to support the use of ALFENTA in children under 12 years of age are not available.

Animal Toxicology - Acceptable

### Adverse Reactions

Change to: The common adverse reactions are extensions of known pharmacological effects of opioids. Respiratory depression and skeletal muscle rigidity are frequently observed with synthetic opioids of the fentanyl group.

In clinical trials involving 1183 patients of whom 785 received ALFENTA (alfentanil hydrochloride) the reported incidences of adverse effects were: (Insert Table 1)

Other adverse reactions with a reported incidence of 2% or less were:

laryngospasm, postoperative confusion, headache, coughing, shivering, euphoria, skin allergic reaction and blurred vision.

Drug Abuse and Dependence: Acceptable

Overdosage: Change to the following:

Overdosage would be manifested by extension of the pharmacological actions of ALFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. No experience with overdosage of ALFENTA was reported during clinical trials. Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following ALFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not delay the immediate establishment of a patent airway, administration of oxygen and support of ventilation. If respiratory depression is accompanied by muscular rigidity, a neuromuscular blocking agent may be required to facilitate establishment of the airway and assisted or controlled ventilation. Intravenous fluids and other vasoactive drugs may be required to manage hemodynamic instability.

The intravenous LD<sub>50</sub> of ALFENTA in male rats is 43.0-50.9 mg/kg.

Dosage and Administration

Acceptable but change "case" to patient in second line.

Delete Usage in Children: The data available from a total of 37 children between 2 and 11 years have been considered too limited to recommend the use of ALFENTA in children under 12 years of age at the present time.

Premedication and Neuromuscular Blocking Agents - Both are acceptable

How Supplied: The following changes are requested by the Chemist:

This section remains confusing. For example, one copy doesn't indicate which firm manufactures the ampules, but does indicate Survivial Technology below the syringes. This implies that Survivial Technology manufactures the product in both ampules and syringes. In addition, it is recommended that the storage statement be separated from the identification of the manufacturer and distributor.

The Dosage Range Chart will have to be clarified by the sponsor and should include directions for preparing infusion.

Brigitta Dasser, M.D. 11-7-85  
Brigitta Dasser, M.D. 11-23-85

November 28, 1986

ADDENDUM TO MEDICAL OFFICER'S ORIGINAL REVIEW  
OF NDA 19-353

Because of persisting discrepancies between FDA's and the Firm's percentage figures for the major side effects presented in tabular form the NDA data from all 29 studies originally submitted were re-checked by me and Dr. Haggerty and the correct numbers and percentages can be seen in the two attached tables. One table represents side effects recorded from the 12 safety studies (original page 122) and the second table represents side effect incidence reported from all 29 studies, incremental, infusion and induction studies (original page 125).

These tables confirm that alfentanil does not provide superior hemodynamic stability compared to the comparative drugs used and listed.

*Brigitta Dausler, M.D. 12/2/86*  
Brigitta Dausler, M.D.  
Medical Officer

NDA 19,353

HFN-160

HFN-340

R/D BDassler 11/28/86

R/D Init. by JCKenealy 12/2/86, PGWalters 12/2/86

FT OLA 2491N 0017M 12/1/86

Doc. Room 160

DEC 11 1986

## SIDE EFFECTS RECORDED FROM 12 SAFETY STUDIES

	Alfentanil		Fentanyl		Thiopental		Enflurane		Placebo	
	#	%	#	%	#	%	#	%	#	%
Number of patients exposed	283		61		58		20		8	
Chest wall rigidity	41	14.5	0	0	1	1.7	0	0	0	0
Bradycardia	29	10.2	3	4.9	2	3.4	1	5	0	0
Tachycardia	20	7	2	3.3	19**	32.8	8	40	0	0
Hypotension	18	6.4	1	1.6	6*	10.3	2	10	0	0
Hypertension	44	15.5	3	4.9	17**	29.3	6	30	0	0
Skeletal Muscle movements	27	9.5	1	1.6	0	0	0	0	0	0
Laryngo/bronchospasm	3	1.1	0	0	2	3.4	0	0	0	0
Arrhythmia	2	.7	1	1.6	2	3.4	2	10	0	0
Apnea	39	13.8	0	0	0	0	0	0	0	0
Nausea	31	10.9	19	31.1	3	5.2	0	0	0	0
Vomiting	25	8.8	9	14.8	5	8.6	0	0	0	0
Skin irritation	4	1.4	0	0	0	0	0	0	0	0
Other (allergic, headache, urine retention, wheeze, coughing)	8	2.8	1	1.6	2	3.4	2	10	0	0

\*When administered with muscle relaxant.

\*\*11/17 When administered with muscle relaxant.

10/19 When administered with muscle relaxant.

SIDE EFFECTS<sup>1</sup> REPORTED FROM ALL 29 STUDIES  
Table 1

INCREMENTAL, INFUSION AND INDUCTION STUDIES  
INCIDENCE

	<u>ALFEN- TANIL</u>	<u>FEN- TANYL</u>	<u>THIOPENTAL SODIUM</u>	<u>ENFLUR- RANE</u>	<u>HALO- THANE</u>	<u>SALINE PLACEBO</u>	<u>TOTAL</u>
Total Number of Patients*	785	243	66	55	16	18	1183
<u>SIDE EFFECTS</u>							
Nausea	217 28%	107 44%	9 13.6%	3 5%	0	4	340
Vomiting	137 17.5%	74 30.5%	7 10.6%	5 9%	2	3	228
Chest Wall** Rigidity	101 12.9%	29 11.9	1 0.1%	0	0	0	123
Bradycardia	112 14.3	16 6.6	5 7.6	1	0	0	133
Hypertension	144 18.3%	31 12.8	20 30%	11 20	1	0	209
Hypotension	79 10.1	20 8.2	6 9.1	4 7%	0	0	108
Tachycardia	95 12.1	33 11.7	26 39.4	20 36.4	5	2	177
Apnea	55 7%	1 .4	0 0%	0	0	0	58
Skeletal Muscle Movements	36 4.6%	4 1.6%	4 6%	1	0	0	45

\*Patients evaluable for efficacy

\*\*Does not include patients from Bartkowski/024 (42 patients), where 34 patients, experienced chest wall rigidity.

ADDENDUM TO THE ORIGINAL MEDICAL LABELING REVIEW  
NDA 19-353 11/26/85 + 12/2/85

On November 26, 1985, Janssen submitted its final draft version of the proposed labeling for ALFENTA (alfentanil hydrochloride) Injection. Preceding the above submission the sponsor and the Division met on November 7, 1985, to discuss the proposed draft labeling of October 2, 1985. In addition, an informal revision of the labeling was received, reviewed, and comments relayed to the sponsor by telephone in conversations between the Division Director and the firms Manager for Regulatory Affairs on November 14 and 25, 1985.

The wording of the medical parts of the labeling as proposed in the November 26, 1985 amendment is generally acceptable. However, for consistency of comparative descriptions the last sentence of page 11 under the section "Drug Interactions" should read: Limited clinical experience indicates that requirements for volatile inhalation anesthetics are reduced by 30 to 50% for the first sixty (60) minutes following ALFENTA induction. The fourth paragraph on page 9 should read: Induction doses of ALFENTA should be administered slowly (over three minutes). Rapid administration may produce loss of vascular tone and hypotension. Consideration should be given to fluid replacement prior to induction. On page 15, which displays adverse reactions reported in form of a table, the percent incidence figures under the subsection "Cardiovascular" for tachycardia and hypertension are incorrect and should be changed accordingly (see original labeling review). The percent for tachycardia is 12% and for hypertension 18%. In addition, corrected figures for vomiting for the fentanyl group (25%) and for post-operative respiratory depression for the fentanyl (0%) and thiopental sodium groups (2%) have been submitted by the sponsor on 12/6/85.

5  
Finally, on page 4 appears a typographical error in the spelling of the word "laryngoscopy."

RECOMMENDATION: Provided that the above outlined corrections in the proposed labeling for ALFENTA are made, the labeling is approvable.

*Brigitta Dassler, M.D. 12/10/85*  
Brigitta Dassler, M.D.  
Medical Officer

NDA 19-353  
HFN-160  
HFN-340  
DocRm. 160  
R.D. BDassler 12/9/85  
R.D. init by:JCKenealy 12/9/85:PHRussell 12/9/85  
shg W2186K 12/10/85

DEC 21 1985

NDA-19-353

MEDICAL OFFICER'S REVIEW OF ORIGINAL NDA

SPONSOR: Janssen Pharmaceutica  
40 Kingsbridge Road  
Piscataway, N.J. 08854

DATE COMPLETED: 20 November 1985  
ORIGINAL APPROVAL DATE:

NAME OF DRUG: Trade: ALFENTA  
Generic: Alfentanil Hydrochloride  
PHARMACOLOGIC CATEGORY OF DRUG: Synthetic narcotic, short-acting opioid analgesic

CLASSIFICATION: 1 B  
DOSAGE FORM: Sterile, preservative free, aqueous solution containing Alfentanil hydrochloride equivalent to 500 mcg/ml Alfentanil base

ROUTE OF ADMINISTRATION: Intravenous administration

PROPOSED INDICATIONS:

1. As an analgesic adjunct in the maintenance of balanced general anesthesia in incremental doses of 8 - 60 mcg/kg.
2. As a maintenance analgesic/anesthetic with nitrous oxide - oxygen at a rate of 0.5 - 3.0 mcg/kg/min.
3. As a primary anesthetic for the induction of anesthesia for general surgical procedures with a minimum expected duration of 45 min. in which endotracheal intubation and mechanical ventilation are required.

DATE OF SUBMISSION: December 24, 1984

DATE ASSIGNED: March 11, 1985

TYPE OF SUBMISSION : NDA - 71 volumes

AMENDMENTS DATED: 4/9/85, 5/8/85, 7/24/85; 9/20/85, 10/2/85; 10/25/85

RELATED IND:

General Comment

The administration of a narcotic analgesic as an adjunct to balanced anesthesia has been well accepted. Approximately 10 years ago, the synthetic opioid fentanyl was introduced as an alternative narcotic. It demonstrated some advantages over morphine since it was found to be 100 times more potent with faster recovery, generally shorter duration of depressed respiration and an overall improved safety margin.

The sponsor, Janssen Pharmaceutica Inc., developed subsequently two chemically and pharmacologically related compounds Sufentanil and Alfentanil. The former has been approved for marketing 2 years ago and the latter is the subject of this NDA.

NDA - 19-353

December 3, 1986

Medical Reviews of Amendment

Sponsor: Janssen Pharmaceutica  
40 Kingsbridge Rd.  
Piscataway, NJ 08854

Name of Drug: Alfenta (alfentanil hydrochloride)

Category of Drug: Synthetic narcotic analgesic

Dosage Form: Sterile, preservative free aqueous solution containing  
alfentanil HCl equivalent to 500 ug/ml alfentanil base.

Route of Administration: Intravenous

Date of Submission November 24, 1986

Received for Review: December 2, 1986

Review completed: December 3, 1986

Related NDA, -

Background:

The amendment provides for the requested additional information of two ADR's which have been listed under the NDA safety update of November 18, 1986. Therefore, the following evaluation should be made part of the NDA safety update of November 18, 1986.

Evaluation:

The additional information for Dr. Glass's patient M.F.L. (AL-4) who experienced a wandering atrial pacemaker while undergoing right wrist synovectomy at Duke University Medical Center, and who was enrolled in protocol IRD 39,209/500, discloses that this 33 year old black female patient experienced a wandering atrial pacemaker 27 minutes following anesthesia induction and maintenance with alfentanil, i.e. bolus of 4, 5 mg and infusion of 1-2 ug/kg/min. Simultaneously with the appearance of the wandering atrial pacemaker bradycardia had developed. The episode lasted for 20 minutes during which time alfentanil infusion was continued. The record indicates that the wandering pacemaker subsided without discontinuance of the alfentanil infusion. This is in contrast to the entry in Form 1639 which states that the reaction abated after stopping the drug. The investigator concluded that the non-disturbing intraoperative adverse effect was possibly related to alfentanil.

NDA 19-353  
Page 2

B. Initial Submission: 9-26-84  
Amendments: 1-8-86, 1-15-86, 1-24-86  
Supporting Documents: IND  
DMF's

C. Remarks:

The three amendments were submitted in response to deficiencies noted in the chemistry aspect of the manufacturing and controls section.

D. Conclusions:

The supplemental amendments are acceptable from the standpoint of chemistry. The approval letter should include the "Draft of Chemist's Part, Letter to Applicant" attached to this review.

*Patricia M. Stewart*  
\_\_\_\_\_  
Patricia M. Stewart

cc: NDA 19-353  
HFN 160, Doc Room 160  
R/D PMStewart, 1/30/86  
R/D init. CPHoiberg, 1/31/86  
FT/jb, W4626P, D3623P, 2/3/86

Addendum to Medical Officer's Review  
of NDA 19-353

This review concerns the safety update report which has been submitted on October 25, 1985. The report covers three items.

1. U.S. Clinical Studies

Sixty eight (68) patients were entered into five ongoing studies at the time of the NDA submission dated December 26, 1984.

An adverse drug experience occurred in one patient in study #101 (T. Joyce). The patient F.E.D. was scheduled to undergo a postpartum tubal ligation. She received an induction dose of 125 ug/kg alfentanil which was immediately followed by 100 mg succinylcholine to facilitate endotracheal intubation. At that time the patient developed masseter spasm with generalized body muscle rigidity and a marked tachycardia. The patient was intubated with difficulty, ventilated and the anesthesia terminated and surgery was cancelled. Since the muscle rigidity and masseter spasm were clinically different from the chest wall rigidity known to follow high doses of alfentanil it was suspected to be an early sign for the development of malignant hyperthermia. The patient's temperature was normal at that time and she made an uneventful recovery. CPK's were measured repeatedly and were reported twice the normal value. The patient was informed that she is a high risk suspect for malignant hyperthermia, should carry a card identifying her as such, and encouraged her to have her family members screened also.

Conclusion:

I agree with the investigator that this adverse drug reaction was triggered by succinylcholine in a high risk suspect for malignant hyperthermia based on the repeated CPK values. I do not consider alfentanil the causative agent.

2. Non-U.S. Clinical Studies: In a report of a clinical alfentanil infusion study by Y. Lamarche et al from the Canadian Anaesthesia Soc. J. 31 (3): S 64-S 65, 1984, two patients who received an alfentanil infusion of 3 ug/kg/min developed bradycardia, a junctional rhythm of less than 50/min and hypotension necessitating treatment with atropine or ephedrine. This complication was not seen at lower dose infusion rates (0.75 and 1.5 ug/kg/min). One of the high dose (3 ug/kg/min) infusion patients received this dose for 3 hours and subsequently developed respiratory arrest in the recovery room 40 minutes later. One other patient required naloxone 30 minutes after termination of the anesthesia because of respiratory depression.

**Conclusion:** These two case reports confirm that respiratory depression is one of the clinically important pharmacological effects of alfentanil, the severity of it appeared to be dose dependant in these cases. In addition, the report stresses the fact that a rapid recovery from alfentanil infusion anesthesia should not be considered "sine qua non" because an initial rapid recovery may be followed by delayed respiratory depression including sudden respiratory arrest.

3. Non- U.S. Marketing History:

Listed are 12 countries in which ALFENTA (alfentanil hydrochloride) received approval during 1983 - 1985. In 5 of these countries the drug has not been marketed yet. In addition a table listing 12 Adverse Drug Experience reports from the U.K. has been provided, and the table is attached. Additional information for the first two case reports comes from a published report by P.S. Sebel et al Br. Med. J. Vol. 289:1581-1582, December 1984. The authors describe that although respiratory depression is a recognized complication after the administration of opioid analgesics alfentanil administration by infusion has been considered advantageous because of its "rapid, clear recovery". However, in two of their patients the initial rapid, clear recovery was followed by sudden respiratory arrest in the recovery room. For one of these patients plasma alfentanil concentration was below that which could be expected to cause respiratory arrest. Doses used were 1 ug/kg/min infusion for 2 hours for the 72 year old male patient for 2 hours, while 1.6 mg/kg/min infusion was administered for 110 minutes in the 54 year old female patient.

**Conclusion:** These two cases again demonstrate that delayed respiratory depression may occur despite an initial rapid postoperative recovery. Therefore, respiration should be monitored very closely in the postoperative period.

Case #3 reports of a 40 year old male patient who received 8 ug/kg/min of alfentanil for 10 minutes followed by an infusion of 0.8 ug/kg/min for 1 hour. After extubation 20 minutes later he was recorded to have been fully awake and breathing at a rate of more than 10 bpm, however, 15 minutes later he stopped breathing, was cyanotic and had pin-point pupils. Naloxone was required twice because ventilation with 100% O<sub>2</sub> for 5 minutes was unseccesful.

Conclusion: The patient presented signs of re-narcotization with respiratory arrest following relatively low alfentanil induction and maintenance infusion dosages.

The next 3 case reports come from the same investigator (J. Sear/Oxford) and cover 3 apparently healthy adults who experienced delayed respiratory depression leading to apnea after an initial short recovery. All of the patients received normal alfentanil induction and maintenance infusion dosages.

Conclusion: Delayed severe respiratory depression following an initial rapid awakening did not appear to be dose dependent since the dosages used are well within the dose recommendation from the proposed labeling. These three cases were part of a clinical study in the U.K. and a summary table for ADR's has also been submitted which is appended.

Information for the 7th patient is incomplete with only the age, sex, weight and total alfentanil dose of 205 ug/kg provided. The patient experienced bradycardia (47 bpm) after receiving the alfentanil infusion for 4 minutes.

Conclusion: The occurrence of decreased heart rate has been observed frequently and does not add additional safety information.

There are 3 cases of cardiac arrest reported from one investigator (Jeffries) without any necessary information to evaluate this ADE.

Finally, the 12th case describes the occurrence of asystole in a 21 year old female who received gallamine, suxamethonium, thiopental, halothane and a total dose of 20 ug/kg alfentanil. No meaningful evaluation is possible from the incomplete information provided.

Summary:

The safety update report for NDA 19-353 of October 25, 1985 highlights that severe and or delayed respiratory depression may occur following the administration of ALFENTA (alfentanil hydrochloride) infusion during general anesthesia with N<sub>2</sub>O/O<sub>2</sub> following an immediate rapid recovery. The information provided appears to confirm that this effect may occur in a non-dose-related form.

The sponsor explained to be unable to provide any necessary background data for the three cases of cardiac arrest.

*Brigitta Damb, M.D. 11-5-85*  
Brigitta Dassler, M.D.  
Medical Officer

DEC 10 1985

Pharm

NDA # 19-353

Review # 1

Applicant: Janssen Pharmaceutica Inc.  
Piscataway, NJ 08854

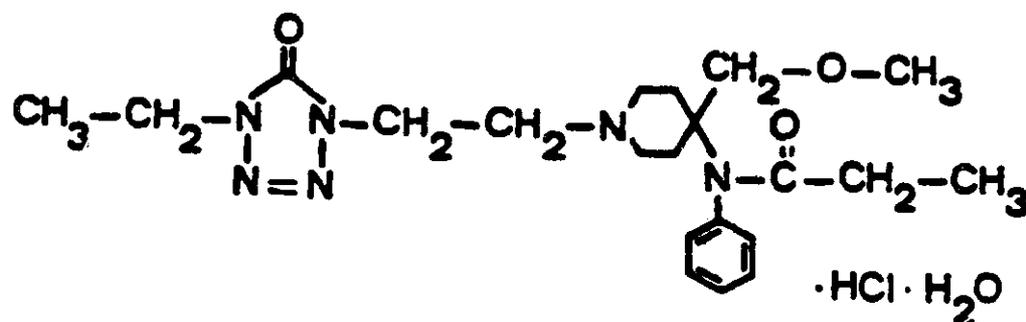
Date of Review: February 1, 1985

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA  
Original Summary

Date Received - December 26, 1984

Drug: Alfenta (alfentanil hydrochloride) Injection  
R 39,209

Structural formula:



Chemical name:

N-[1-[2-(4-ethyl-4,5-dihydro-5-oxo-1H-tetrazol-1-yl)ethyl]-4-(methoxymethyl)-4-piperidinyl]-N-phenyl-propanamide monohydrochloride monohydrate.

Empirical formula: C<sub>21</sub>H<sub>32</sub>N<sub>6</sub>O<sub>3</sub> · HCl · H<sub>2</sub>O

Formulation:

(Available as 500 ug/ml in 2, 5, 10 & 20 ml ampoules or prefilled syringes)

FEB 12 1985

Category: Intravenous Short-Acting Opioid Analgesic (analog of fentanyl) - Anesthetic Adjunct

Related INDs:

NDA's: 16-619 - Sublimaze (fentanyl citrate)  
19-050 - Sufenta Injection (sufentanil citrate)

Marketing Indications: Analgesic adjunct given in incremental doses in the maintenance of balanced general anesthesia at dosages of 8-60 ug/kg for surgical procedures with an expected duration of up to one hour.

Maintenance analgesic/anesthetic administered by continuous infusion with nitrous oxide/oxygen at a rate of 0.5 to 3.0 ug/kg/min in the maintenance of general anesthesia.

Primary anesthetic agent for the induction of anesthesia in patients for whom pronounced increases in heart rate or blood pressure during laryngoscopy, endotracheal intubation and incision could be detrimental. Alfenta may be used as anesthetic induction agent for general surgical procedures with a minimum expected duration of 45 minutes in which endotracheal intubation and mechanical ventilation are required.

DOSE RANGE CHART

Initial Dose	Approximate Duration of Anesthesia	Total Dose	Increments/Infusion	Effects
8-20 (spontaneously breathing)	≤ 30 mins	8-40	2-5 ug/kg .5-1 ug/kg/min	minimal hemodynamic change with some attenuation of sympathetic response to surgical stress. More rapid recovery than fentanyl.
20-50 (ventilated)	30-60 mins	up to 75 ug/kg	5-15 ug/kg	minimal hemodynamic changes with attenuation of response to laryngoscopy and intubation. Recovery times better than or equal to fentanyl.
50-75 (ventilated)	> 45 mins	dependent on duration of procedure	.5-3.0 ug/kg/min	Attenuation of cardiovascular response to intubation and incision, intra-operative stability and faster recovery than thiopental/inhalation techniques.
120-245 (ventilated)	> 45 mins	dependent on duration of procedure	.5 to 1.5 ug/kg/min general anesthesia	Induction of anesthesia with prevention of cardiovascular response to intubation and incision. Reduced requirements for concentrations of inhalation agents with early awakening.

## INFUSION DOSAGE

Continuous Infusion: .5-30 ug/kg/min administered with nitrous oxide/oxygen in patients undergoing general anesthesia. Following an anesthetic induction dose of alfentanil, the infusion rate should be reduced by fifty percent for the first hour of maintenance. The infusion rate may be increased to 4.0 ug/kg/min as determined by changes in vital signs that indicate surgical stress or lightening of analgesia. Infusion rates should be adjusted downward in the absence of these signs. Alfentanil infusion (@1.5 ug/kg/min) has been shown to maintain cardiovascular stability, dampen sympathetic responses to surgical stress and to provide rapid recovery with some postoperative analgesia. Administration of alfentanil infusion should be discontinued 10-15 minutes prior to the end of surgery.

Preclinical Studies: Nonclinical Laboratory: Janssen Pharmaceutica n.v.  
B-2340 Beerse, Belgium

GLP Statements:

Acute Intravenous Toxicity - Mice & Rats

Preclinical Research Report R 39,209/8 (N21302)  
Vol. 1.6 p. 10-00483

This study was conducted in the pharmacology laboratories of Janssen Pharmaceutica, n.v., Beerse, Belgium prior to the effective date of the GLP regulations. It has been reviewed for compliance with the Good Laboratory Practice regulations set forth in 21 CFR 58 and the following observations were noted:

1. The purpose of the study is not specifically stated, however, it is apparent from the study title.
2. The term investigator is used in place of study director and has the same meaning.
3. When this study was conducted (prior to June, 1979), individual protocols were not written for each acute toxicity study. Therefore no protocol is presented.
4. The dated signature of the study director (investigator) is not present. This testing facility is a very stable organization regarding personnel. Dr. Niemegeers has been directing such studies for the pharmacology laboratories of Janssen Pharmaceutica Belgium for more than 20 years.
5. The purity, stability and batch identity of the new drug substance were not addressed in the original report. It was determined from retained records that the sample testing was from batch V765-340 and the certificate of analysis has been added to the report. The stability of the new drug substance is addressed in Section 8p of this NDA.
6. The purity and stability of the test article was not addressed in the original report. However, the tested formulations were made immediately before injection by dilution with distilled water.

7. The source of the Wistar rats was not identified or their use justified. The rats were products of Janssen's permanent breeding colony (established 1956). Similar rats from this colony have been used in like experiments over the years and their responses are well known to this testing laboratory.
8. The assignment of animals to the dose groups was not described.
9. Quality assurance audits were not conducted.
10. Location of retained raw data and final report is not provided. These records are being stored in the archives of Janssen Pharmaceutica, n.v., Beerse, Belgium.
11. The starting and completion dates are not provided.

Acute Intravenous Toxicity - Rats (Injection Rate)  
Preclinical Research Report R 39,209/14 (N23592)  
Vol. 1.6 p. 10-00596

This study was conducted in the pharmacology laboratories of Janssen Pharmaceutica, n.v., Beerse, Belgium. It has been reviewed for compliance with the Good Laboratory Practice regulations set forth in 21 CFR 58 and the following observations were noted:

1. The purpose of the study is not specifically stated, however, it is apparent from the study title.
2. The protocol was not presented. However the conduct of the study is adequately described in the materials and methods.
3. The term investigator is used in place of study director and has the same meaning.
4. The dated signature of the study director (investigator) is not present. This testing facility is a very stable organization regarding personnel. Dr. Niemegeers has been directing such studies for the pharmacology laboratories of Janssen Pharmaceutica Belgium for more than 20 years.
5. The purity and stability of the new drug substance tested were not addressed in the original report. It was determined from retained records that the sample tested was from batch A01/1. The certificate of analysis has been added to the report. Stability is addressed in Section 8p of this NDA.
6. The purity and stability of the test article was not addressed in the original report. However, the tested formulation was made immediately before injection by dilution with distilled water.

7. The source of the Wistar rats was not identified or their use justified. The rats were products of Janssen's permanent breeding colony (established 1956). Similar rats from this colony have been used in like experiments over the years and their responses are well known to this testing laboratory.
8. The assignment of animals to the dose groups was not described.
9. Quality assurance audits were not conducted.
10. Location of retained raw data and final report is not provided. These records are being stored in the archives of Janssen Pharmaceutica, n.v., Beerse, Belgium.
11. The starting and completion dates are not provided.

6 Hour Infusion - Rats

Preclinical Research Report R 39,209/22 (N25861)  
Vol. 1.6 p. 10-00624

This study was conducted in the pharmacology laboratories of Janssen Pharmaceutica, n.v., Beerse, Belgium. It has been reviewed for compliance with the Good Laboratory Practice regulations set forth in 21 CFR 58 and the following observations were noted:

1. The purpose of the study is not specifically stated, however, it is apparent from the study title.
2. The protocol was not presented. However the conduct of the study is adequately described in the materials and methods.
3. The term investigator is used in place of study director and has the same meaning.
4. The dated signature of the study director (investigator) is not present. This testing facility is a very stable organization regarding personnel. Dr. Niemegeers has been directing such studies for the pharmacology laboratories of Janssen Pharmaceutica Belgium for more than 20 years.
5. The purity and stability of the new drug substance tested were not addressed in the original report. It was determined from retained records that the sample tested was from batch A1301. The certificate of analysis has been added to the report. Stability is addressed in Section 8p of this NDA.
6. The purity and stability of the test article was not addressed in the original report. However, the tested formulation was made immediately before injection by dilution with distilled water.

7. The source of the Wistar rats was not identified or their use justified. The rats were products of Janssen's permanent breeding colony (established 1956). Similar rats from this colony have been used in like experiments over the years and their responses are well known to this testing laboratory.
8. The assignment of animals to the dose groups was not described.
9. Quality assurance audits were not conducted.
10. Location of retained raw data and final report is not provided. These records are being stored in the archives of Janssen Pharmaceutica, n.v., Beerse, Belgium.
11. The starting and completion dates are not provided.

#### Acute Intravenous Toxicity Studies - Guinea Pigs & Dogs

Studies were conducted in the pharmacology laboratories of Janssen Pharmaceutica, n.v., Beerse, Belgium. It has been reviewed for compliance with the Good Laboratory Practice regulations set forth in 21 CFR 58 and the following observations were noted:

1. The purpose of the studies is not specifically stated, however, it is apparent from the study title.
2. The term investigator is used in place of study director and has the same meaning.
3. The dated signature of the study director (investigator) is not present. This testing facility is a very stable organization regarding personnel. Dr. Niemegeers has been directing such studies for the pharmacology laboratories of Janssen Pharmaceutica Belgium for more than 20 years.
4. The purity and stability of the new drug substance tested were not addressed in the original report. The certificate of analysis has been added to the report. Stability is addressed in Section 8p of this NDA.
5. The purity and stability of the test article was not addressed in the original report. However, the tested formulations were made immediately before injection by dilution with distilled water.
6. The test system used (inbred albino guinea pigs<sup>and dogs</sup>) was not justified. These animals were from Janssen's production colony, and were familiar to Janssen laboratory personnel.
7. The assignment of animals to the dose groups was not described.
8. Quality assurance audits were not conducted.
9. Location of retained raw data and final report is not provided. These records are being stored in the archives of Janssen Pharmaceutica, n.v., Beerse, Belgium.

10. The starting and completion dates are not provided.

7

Subacute Intravenous Toxicity - Rats  
Toxicological Research Report No. 921 (N22307)  
Vol. 1.6 p. 10-00636

This study was conducted in the laboratories of the Toxicology Department, Janssen Pharmaceutica, n.v., Beerse, Belgium. The final report has been reviewed for compliance with GLP regulations as set forth in 21 CFR 58 and the following observations were noted:

1. Although the report is signed by study director, the study pathologist and the vice president of toxicology and veterinary research, the signatures are not dated.
2. The stability of the new drug substance is addressed in section 8p of this NDA.
3. The stability of the test article was not addressed. However, the tested formulation was made immediately before use by dilution with a saline solution.
4. The animals were assigned to the dosage groups on the basis of their sex and body weight.
5. Individual rat clinical data and ophthalmologic data were not provided. These are available (untranslated) in the archives of Janssen Pharmaceutica n.v., Beerse, Belgium.

Subacute Intravenous Toxicity - Dogs  
Toxicological Research Report No. 922 (N22308)  
Vol. 1.7 p. 10-00958

This study was conducted in the laboratories of the Toxicology Department, Janssen Pharmaceutica, n.v., Beerse, Belgium. The final report has been reviewed for compliance with GLP regulations as set forth in 21 CFR 58 and the following observations were noted:

1. Although the report is signed by study director, the study pathologist and the vice president of toxicology and veterinary research, the signatures are not dated.
2. The stability of the new drug substance is addressed in section 8p of this NDA.
3. The stability of the test article was not addressed. However, the tested formulation was made immediately before use by dilution with a saline solution.
4. Method of animal randomization is not included. However, dogs were assigned to dose groups according to body weight, sex, and litter of origin (litter mates divided among dose groups).
5. Individual dog clinical data were not provided. These are available (untranslated) in the archives of Janssen Pharmaceutica n.v., Beerse, Belgium.

Mutagenicity Study  
In Vitro Research Report - N24817  
Vol. 1.8 p. 10-01743

This study was conducted in the laboratories of Toxicologie et Bromatologie, Brussels, Belgium under the supervision of Professor F. Poncelet. Following are the differences in practices used in this study and those of studies conducted under Good Laboratory Practice regulations set forth in 21 CFR 58:

1. The purpose of this study is not specifically stated, but it is evident from the study title.
2. The signature of the study director (indicated as the Principal Investigator) is present but undated.
3. The batch number of the new drug substance was not indicated. From retained records at Janssen Pharmaceutica, n.v., it was determined that batch A0301 was tested and the appropriate analytical certificate has been added.
4. The stability of the new drug substance is addressed in section 8p of this NDA.
5. The stability or formulation of the test article was not addressed. However, the tested formulation was made by dilution with doubly-distilled water immediately prior to use.
6. A protocol specific for this study is not provided. Standardized techniques were used throughout its conduct.
7. Quality Assurance audits were not conducted.
8. The locations of retained raw data and original report are not provided. However, these reports are retained by the testing facility (the University of Louvain).
9. The starting and finishing dates are not furnished and the report is not dated.

Dominant Lethal Tests - Mice  
Micronucleus Test - Rats

Studies were conducted in the laboratories of the Toxicology Department, Janssen Pharmaceutica, n.v., Beerse, Belgium. The final report has been reviewed for compliance with GLP regulations as set forth in 21 CFR 58 and the following observations were noted:

1. Although the report is signed by study director, the study pathologist and the vice president of toxicology and veterinary research, the signatures are not dated.
2. The stability of the new drug substance is addressed in section 8p of this NDA.
3. The stability of the test article was not addressed. However, the tested formulation was made immediately before use by dilution with a saline solution.
4. The animals were assigned to the dosage groups on the basis of their sex and age.

Intra-arterial Injection - Rabbits  
Preclinical Research Report - R 33,209/19 (N25829)  
Vol. 1.8 p. 10-01814

This study was not considered to be part of the animal safety studies, but rather as a special interest study. Therefore, Good Laboratory Practices regulations, as set forth in 21 CFR 58, were not considered applicable.

In this study, the test agent was alfentanil formula FO 2. Stability data for this formulations is provided herein.

Preclinical data from IND are summarized in the Evaluation section of this review. Reference is made to the following pharmacology reviews dated:

2-4-81  
8-12-81  
2-1-82  
1-11-83  
6-10-83  
10-28-83

## Evaluation

Alfenta (alfentanil hydrochloride) is a short-acting intravenous opioid analgesic (analog of fentanyl) indicated as an analgesic adjunct (8-60 ug/kg), as a maintenance analgesic/anesthetic administered with nitrous oxide/oxygen, and as a primary anesthetic agent at doses up to 500 ug/kg. Alfentanil is related to two additional morphine analogs of fentanyl: sufentanil (NDA 19-050), which has an analgesic potency 5 times that of fentanyl in the dog and a longer-acting experimental analgesic, lofentanil, which is approximately 50 times more potent than fentanyl.

Preclinical data from IND are summarized below. Deviations from GLP's are considered minor and do not prevent the acceptance of these studies.

Pharmacologic intravenous studies have shown that alfentanil is a potent narcotic which has a duration of action 1/3 that of fentanyl in the rat and an analgesic potency 1/4 that of fentanyl in the rat and dog. Alfentanil has an onset of action 3 times faster than fentanyl, reaches its peak effect within 2 minutes and has a duration of 11 minutes in the rat. In the rat, the intravenous ED<sub>50</sub> is calculated to be 0.044 mg/kg for alfentanil, 3.15 mg/kg for morphine and 0.011 mg/kg for fentanyl. The therapeutic index for alfentanil in the rat was calculated to be 1080 (LD<sub>50</sub>:47.5 mg/kg/ED<sub>50</sub>:0.044 mg/kg).

Pharmacologic intravenous studies in the mouse showed that alfentanil is about 50-60 times more potent than morphine and 1/4 as potent as fentanyl. The analgesic ED<sub>50</sub>=0.11 mg/kg (hot plate test) and the mydriatic ED<sub>50</sub>=0.17 mg/kg. Onset of action was very rapid with a very short duration of action of less than 5 minutes at two times the ED<sub>50</sub>. At more than ten times the ED<sub>50</sub> (1.25 mg/kg), the duration was only about 10 minutes. The therapeutic index for alfentanil in mice was 669 or 1.5 times higher than fentanyl and 19 times higher than morphine.

In the dog, the relative potency of alfentanil administered intravenously is approximately 30 times greater than morphine.

Cardiovascular studies in conscious dogs showed that the most pronounced effect was a decrease in heart rate (50-400 ug/kg, i.v.). High doses, greater than 1.25 mg/kg, were well tolerated especially when the animals were artificially ventilated. Short periods of convulsions were observed between 100-400 ug/kg, i.v. when relatively low PO<sub>2</sub> levels were reached. The most pronounced change in the anesthetized dogs was a significant fall in LVdP/dt max and LV dP/dt max/P, associated with a rise in left ventricular end-diastolic pressure at 5 mg/kg, i.v., suggesting negative inotropic properties at this high level. Sinus arrest and A-V dissociation associated with ventricular escape beats in unanesthetized dogs and AV block in anesthetized dogs at 0.16 mg/kg was probably due to vagal activity of the drug. At higher doses (greater than 1.25 mg/kg, i.v.), these disturbances disappeared and sinus rhythm was restored.

In conscious dogs, bolus administration of alfentanil (0.32 mg/kg, i.v. over 20 seconds) caused marked, prolonged hemodynamic effects (increases in left and right atrial pressures, increased systemic vascular resistance) but no significant differences in any hemodynamic measurements between spontaneous and controlled ventilatory states.

In anesthetized dogs, alfentanil (500 ug/kg, i.v.) and fentanyl (100 ug/kg, i.v.) caused similar decreases in the resting heart rate (43-44%) and MAP (28-31%) which returned to baseline within 180 minutes with alfentanil, but did not with fentanyl. Fentanyl decreased the somato-cardiovascular reflexes by 73% and 82% compared with a small reduction of 54% and 55% with alfentanil. Change in MAP recovered in 15 minutes and change in heart rate by 70 minutes with alfentanil as compared to 70 and 90 minutes, respectively, for fentanyl. This study demonstrated that alfentanil (500 ug/kg) had the same maximum effect on the resting circulation as fentanyl (100 ug/kg), but that it had a shorter duration of action. However, there was a dissociation between the effects of these drugs on the resting circulation and on somato-cardiovascular reflexes, as shown by the significantly smaller effect of alfentanil compared with fentanyl. There was also a dissociation between the effect of these drugs on the evoked cardiovascular responses which recovered relatively rapidly and the effects on the resting circulation which were more prolonged.

In dogs, alfentanil (0.2 mg/kg) produced a significant increase in the slope of the pressure-length relationship during the first 20 minutes after administration. Left ventricular peak pressure and  $dp/dt$  were also significantly increased while  $-dL/dt$  did not change. The inotropic stimulation seen after alfentanil administration shifted the end-systolic pressure-volume relationship to the left and upward so that a given pressure ejection occurred to a smaller chamber size. This study defined the increased inotropism caused by alfentanil and may support the use of this drug in the failing heart.

The respiratory depressant properties of alfentanil are responsible for the decrease in  $PO_2$  and the increase in  $PCO_2$  in conscious dogs, reaching significance at 200 ug/kg and 100 ug/kg, i.v., respectively. In rabbits, both alfentanil and fentanyl produced dose-dependent changes in the respiratory frequency and minute volume. The peak effect was 3 minutes and 5 minutes with alfentanil and fentanyl, respectively. Alfentanil (4-10 ug/kg, i.v.) caused decreases in respiratory rate and minute volume for 5 minutes. Therefore, in the rabbit, alfentanil had an earlier peak effect and shorter duration than fentanyl, but otherwise the respiratory effects of the two drugs were similar. Fentanyl was between 2 and 3.5 times more potent than alfentanil. Repeated doses of alfentanil produced reproducible peak effects even when only 10 minutes was allowed between administrations.

In dogs, alfentanil, at an anesthetic dose of 0.32 mg/kg, i.v., did not alter cerebral blood flow responses to hypoxia or hypercarbia. Results showed that while the lower limit of autoregulation is not altered by alfentanil the upper limit is increased significantly. Bolus injections of alfentanil (0.16-0.64 mg/kg, i.v.) had no effect on cerebral blood flow, mean arterial blood pressure or cerebral vascular resistance.

EEG studies of alfentanil (0.04 to 0.63 mg/kg, i.v.) in the dog revealed fast cortical activity with spindle-like bursts of high-amplitude and high amplitude theta waves in the subcortical structures; decreased EEG frequency, increased total power (between 0.5 and 40 Hz) correlated with the narcotic-hypnotic phase, increased power in the delta band (0.5 to 3.5 Hz), decreased power in the higher frequency bands (greater than 17.5 Hz), duration of increased power was co-incident with the period of loss of righting, rapid normalization of the EEG after single dose and after bolus followed by infusion. Effects in subcortical structures appeared long-lasting than in the cortex.

In dogs, alfentanil has a very rapid onset of activity on the EEG, as well as in cortical and subcortical structures; after an initial high peak in the EEG activity, there is a gradual decrease, except for the activity in the occipital-occipital derivation which appears to persist after infusion; spontaneous breathing occurs soon after infusion and there is rapid behavioral recovery.

Studies of alfentanil (0.04 to 0.63 mg/kg, i.v.) on somatosensory-evoked potentials in the dog suggest that ~~alfentanil does not block the afferent sensory pathway~~, that there is possibly ~~no direct cortical inhibition~~, but rather ~~a suppression~~ from remote structures modifying sensory input. Thus, sensory input reaches cortical sensory receiving structures, but is not perceived because of an inhibition of association regions.

In the dog, alfentanil (0.04, 0.16 & 0.63 mg/kg, i.v.) ~~increased~~ the ~~amplitude~~ of the ~~EEG~~, ~~decreased~~ the ~~frequency~~ of the EEG and produced spindle-like bursts of biphasic waves to a greater degree than morphine, fentanyl and sufentanil. Alfentanil did not produce significant post-drug effects.

Drug interaction studies in dogs showed that parasympatholytic compounds reinforced stimulation, parasympatholytics and central vasomotor depressors partially inhibited this excitation but did not totally block and sympathomimetics reinforce and prolong stimulation. Succinylcholine (1 mg/kg, i.v.) had no appreciable effect on cardiac and hemodynamic variables. Pancuronium bromide (0.10 mg/kg, i.v.) stimulated cardiovascular variables. Studies with propranolol (0.16 mg/kg, i.v.) showed negative chronotropic and inotropic properties and peripheral vasoconstriction.

The ~~effects of alfentanil~~, like those of fentanyl, in a variety of ~~in-vitro~~ tests were restricted to a potent inhibition of contractions of the guinea pig ileum induced by electrical stimulation of intramural nerve tissues or by ganglionic stimulation with nicotine, both indirect cholinergic stimuli. The ~~reduced release of acetylcholine~~ after stimulation of cholinergic nerves in the gut wall was the only activity of alfentanil over at least a thousandfold concentration range; alfentanil was more specific than fentanyl. ~~Complete reversibility by naloxone of the inhibitory effects on~~ transmurally-stimulated guinea pig ileum ~~indicates~~ an action via-specific opiate receptors.

In the rat, a single dose of 0.02 mg/kg i.v. naloxone completely and irreversibly antagonized the effects (muscular rigidity, loss of righting reflex, blocking of pinna, inhibition of tail withdrawal reaction) of alfentanil (0.16 mg/kg, i.v.). In the rabbit, naloxone (5 mcg/kg, i.v.) was a more effective antagonist of the respiratory depressant effects of alfentanil than those of fentanyl.

In the dog, the ~~convulsion threshold~~ for alfentanil is ~~5 mg/kg, i.v.~~ Comparing the intravenous dose producing severe convulsions with the dose necessary for deep surgical analgesia, a safety margin (62.5) for neurological toxicity was calculated. Morphine and fentanyl have safety margins of 72 and 160, respectively. Slow injection, administration in perfusion and concomitant use of this narcotic with benzodiazepines, neuroleptics or hypnotics increase the convulsion threshold.

In the dog, alfentanil is a potent anti-emetic (ED<sub>50</sub> = 0.032 mg/kg, i.v.).

Acute intravenous toxicity studies of alfentanil were carried out in 4 species:

	LD <sub>50</sub> mg/kg
mouse	72.2-73.6
rat	43.0-50.9
guinea pig	71.8-81.9
dog	59.5-87.5

The lowest LD<sub>50</sub> (43.0 mg/kg in the rat) corresponds to 86 times the maximum human dose. Morphine-like effects such as catatonia, loss of righting reflex and blockade of pinna and corneal reflexes occurred in rodents at doses as low as 2.5 mg/kg. Convulsions occurred in the dog at the lowest test dose of 10 mg/kg.

Intravenous toxicity studies of alfentanil in the rat showed that mortality was unaffected by the rate of injection but the LD<sub>50</sub> of an infusion (400 mg/kg) was more than 8 times the LD<sub>50</sub> of a bolus injection (56.3 mg/kg). Respiratory depression was the cause of death.

A ~~one month subacute intravenous toxicity~~ study of alfentanil (0.08, 0.31 & 1.25 mg/kg, corresponding to 0.16x, 0.62x and 2.5x the maximum human dose respectively) in the Wistar ~~rat~~ revealed temporary diarrhea, transient muscle rigidity, exophthalmos and loss of righting reflex in all treated groups, ~~mortality~~ at ~~0.31~~ and 1.25 mg/kg, especially in males, and significantly decreased total food consumption in both sexes at 1.25 mg/kg. There were no apparent adverse effects on body weight, hematology, clinical chemistry, urinalysis, ophthalmologic examination, organ weight or gross and histopathology.

A ~~one month subacute intravenous toxicity~~ study of alfentanil (0.08, 0.31 & 1.25 mg/kg, corresponding to 0.16x, 0.62x and 2.5x the maximum human dose respectively) in the beagle ~~dog~~ revealed transient dose-related ~~ataxia, catatonia,~~ apnea, convulsions and dyskinesia at ~~1.25~~ mg/kg, reduced appetite and food consumption in all treated animals throughout the study, significant body weight loss in all dosage groups, increased SGPT values at all dose levels, decreased total protein at 0.31 and 1.25 mg/kg, ~~increased relative organ weights of lungs,~~ spleen and ~~heart~~ at 1.25 mg/kg and decreased thymus weight at 0.31 and 1.25 mg/kg, involution of the thymus in both sexes at nearly all dose levels and altered vaginal epithelium in high dose females. (Investigators attributed these microscopic findings to body weight loss.) There were no apparent adverse effects on mortality, hematology, heart rate, ECG, indirect blood pressure, ophthalmologic examination or gross pathology.

A ~~Segment II intravenous~~ reproduction study of alfentanil (0.08, 0.31 & 1.25 mg/kg, corresponding to 0.16x, 0.62x & 2.5x the human dose, respectively) in the Wistar ~~rat~~ showed ~~no embryotoxic or teratogenic~~ effects. During the study, 4 pregnant dams (1 medium dose and 3 high dose) died; cause of death could not be determined. There appeared to be no other adverse effects on adults or litters.

A ~~Segment II intravenous~~ reproduction study of alfentanil (0.08, 0.31 & 1.25 mg/kg, corresponding to 0.16x, 0.62x & 2.5x the human dose, respectively) in the New Zealand White ~~rabbit~~ showed a dose-related ~~decrease~~ in the number of ~~live fetuses~~ per litter and mean ~~litter size~~ (-33% at ~~1.25~~ mg/kg) and a significantly ~~decreased~~ 24 hour pup survival rate at ~~1.25~~ mg/kg. One low dose (0.08 mg/kg) fetus with cranioschisis was not considered drug-related. Body weight gain of dams showed a dose-related decrease (significant at 1.25 mg/kg). Deaths of 1 control, 1 mid dose and 4 high dose pregnant females could not be determined.

Segment III intravenous reproduction study of alfentanil (0.08, 0.31 & 1.25 mg/kg, corresponding to 0.16x, 0.62x & 2.5x the human dose, respectively) in the Wistar rat revealed a significantly lower birth weight at 0.31 mg/kg and a significantly decreased pup survival rate at 0.31 mg/kg during the first two weeks after birth and at 1.25 mg/kg within the first 4 days after birth. Offspring revealed no gross abnormalities or adverse effects on litter size or body weight gain. One mid dose and one high dose dam died during the study; cause of death could not be determined. Pregnancy rate and duration of gestation were essentially unremarkable.

Pharmacokinetic intravenous studies of tritium-labelled alfentanil were conducted in the male Wistar rat and male beagle dog.

In the rat, 88.3% of the administered radioactivity was excreted after 24 hours, 95.1% after 48 hours, and 96.8% after four days: 72.8% in the urine and 24% in the feces. Unchanged alfentanil accounted for approximately 0.2% of the dose. Alfentanil was rapidly metabolized into a large number of metabolites. Oxidative N-dealkylation at the piperidine nitrogen was a major metabolic pathway.

In the dog plasma levels decreased very rapidly. The parent drug accounted for approximately 80% of the total plasma radioactivity 10 minutes after dosing; for 15 to 20% one hour after dosing and for 1.1 to 1.4% six hours after dosing. Approximately half of the administered radioactivity was excreted 24 hours after dosing; an additional 20% was excreted during the second day after dosing. Within four days, approximately 85% of the administered radioactivity had been excreted: 77% in the urine and 8% in the feces. Unchanged alfentanil accounted for approximately 4% of the dose. Alfentanil was rapidly metabolized into a large number of metabolites. Oxidative N-dealkylation at the piperidine nitrogen and oxidative O-demethylation were major metabolic pathways.

Pharmacokinetic studies showed that alfentanil can be measured in biological materials by radioimmunoassay and gas chromatography with either thermionic specific detection or nitrogen/phosphorus detector.

After intravenous administration of tritiated-labelled drug, alfentanil plasma levels decayed biphasically in rats ( $t_{1/2\beta} = 42$  minutes) and triphasicly in dogs ( $t_{1/2\beta} = 104$  minutes) and man ( $t_{1/2\beta} = 88$  minutes). In rats, alfentanil levels in most tissues were lower than in plasma. The drug was distributed mainly to well-perfused tissues, the highest levels being found in kidneys, liver and lungs. Brain levels were about 9 times lower than in the plasma. Drug levels in plasma and brain, corresponding to pharmacologic activity in the tail withdrawal test in rats, were 80 ng/ml and 9 ng/ml, respectively. Placental transfer of drug and metabolites was very limited since maximally 0.5% of the dose was present in the fetus.

In rats and dogs, less than 1% of the dose was excreted as unchanged drug. Alfentanil was metabolized rapidly into a large number of inactive metabolites, more than 70% of which were excreted in the urine within 4 days. The main metabolic pathways in the rat and dog were oxidative N- and N-dealkylation.

The pharmacokinetics of alfentanil were comparable in dogs and man. The short duration of the analgesic effect of alfentanil may be due to its rapid redistribution from the brain, its rapid metabolism and limited storage in the tissue compartment.

In mice, single intravenous doses of alfentanil (1.25, 5 & 20 mg/kg, corresponding to 2.5, 10 & 40 times the maximum human dose) did not show any dominant lethal mutations induced by alfentanil in male or female mice germ cells.

Alfentanil was not mutagenic in vitro in the Ames Salmonella/microsomal activation test (up to 2000 ug/plate) and in vivo in the micronucleus test (up to 20 mg/kg) in the rat.

Tissue extravasation studies showed that intra-arterial injection of alfentanil (0.15 mg/kg) induced no drug-related changes in the femoral or intramuscular arteries or in the extensor digitorum longus and anterior tibialis muscles of the rabbit hind leg.

In vitro hemolysis-protein flocculation tests (alfentanil 50 ug/ml) indicated that at effective pharmacological doses alfentanil does not induce significant hemolysis or plasma precipitation.

Alfentanil did not inhibit formation of phagocytes when studied on mouse marrow colony growth suggesting no effect on cell proliferation.

In dogs, plasma levels of histamine did not seem to be significantly affected after intravenous administration of alfentanil (0.63 mg/kg) or sufentanil (0.15 mg/kg).

Labeling is considered satisfactory by pharmacology.

#### Conclusion

This NDA is approvable from the standpoint of pharmacology.

  
Clyde G. Oberlander  
Pharmacologist

cc: NDA 19-353  
HFN 160, HFN 340  
Doc Room 160  
HFN 102 Glocklin  
R/D CGOberlander, 2/1/85  
R/D init. JKinscoe, 2/5/85

MA 19-353

Applicant: Janssen Pharmaceutica Inc.  
Piscataway, NJ 08854

Review #3

Date of Review: September 12, 1985

11/3  
9-16-85

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA  
C - July 24, 1985  
A-BP - August 30, 1985

Drug: Alfenta (alfentanil hydrochloride) Injection (R 39,209)

Category: Intravenous Short-Acting Opioid Analgesic (analog of fentanyl)  
Anesthetic Adjunct

C - July 24, 1985

A draft SBA for Alfenta Injection is submitted. Our comments and recommendations for the Pharmacology portion are made in the Recommendations section below.

A-BP - August 30, 1985

This amendment contains a response to our questions concerning alfentanil repeat dose and reproduction studies which were raised in our review of August 5, 1985, during phone conversations with the sponsor on August 21, 1985 and our meeting with the sponsor on August 23, 1985. Sponsor's comments follow:

- 1) The cause of death for the rats that died in these studies was suffocation. Rapid intravenous injection of alfentanil at relatively high doses produced the expected narcotic effects of rigidity and loss of righting reflex; the rats subsequently assumed relatively unnatural positions, with heads twisted or facing downward in the corners of the cages. [NOTE: The cages used in these studies had wire-mesh bottoms with full stainless-steel walls.]

In the acute toxicity studies, the cause of death was respiratory depression, a direct effect of the drug. However, in the repeat dose toxicity and reproduction studies, mortality was due to suffocation. Death occurred as an indirect consequence of the expected pharmacologic effects of rigidity and loss of righting reflex produced by intravenous administration of a potent narcotic at high doses. Mortality was not caused by a direct drug-induced toxicity. Consequently, there was no clear relationship between dose and mortality in the repeat dose studies.

SEP 18 1985

- 2) The mortality rates observed in repeat dose toxicity and reproduction studies for alfentanil were comparable to the mortality rates observed in the sufentanil studies, as shown in the attached table. In the studies for both sufentanil and alfentanil, death was caused by suffocation and not by any direct drug effect, with no consistent dose relationship in the rate of mortality.
- 3) The toxic effects of morphine, primarily cardiovascular effects associated with histamine release, would require repeat dose studies for morphine to be conducted at doses much lower than those used in alfentanil or sufentanil studies. The relative safety of alfentanil and sufentanil allowed for toxicity and reproduction studies for both drugs to be conducted using very high doses that would produce profound narcotic effects.
- 4) The clinical relevance of the experimental conditions and dosage schedules under which these studies were conducted is extremely limited. First, alfentanil was administered on a daily basis in very high doses over a period of ten days to eight weeks. Secondly, during clinical use of alfentanil in anesthesia, patients would be closely monitored, with ventilatory and other supportive measures provided as clinically indicated in the presence of qualified personnel and adequate facilities for the management of anesthesia. No equivalent supportive measures were used during the repeat dose animal studies.
- 5) At the high dose in the Segment I reproduction study, there was apparent parental toxicity as shown by a relatively high mortality rate in the high-dose male group mated with non-dosed females, which precludes any meaningful interpretation of the results. Furthermore, the interval between coupling and mating was increased as a consequence of sedation in males, following daily administration of alfentanil over an eight week period. The pregnancy rate for the high dosed males mated with non-dosed females was 5 out of 8 as compared to 17 out of 20 in the control group. This difference was not statistically significant.
- 6) In the four week rat subacute toxicity study, the animals experienced rigidity and loss of righting reflex during the entire study period. Some qualitative indications of tolerance apparently developed in the last week of the study, with less severe rigidity and loss of righting reflex. The mortality rate during week four was 2 out of 120 dosed rats as compared to 6 out of 120 dosed rats during each of the first three weeks of the study.

Mortality Rates - Alfentanil/Sufentanil Toxicology and Reproduction Studies  
(Number of Deaths/Number of Animals per Dosage Group)

	<u>Dosage Groups</u>	<u>Sufentanil</u>	<u>Dosage Groups</u>	<u>Alfentanil</u>
<u>Toxicology</u>				
4 week subacute (rats)				
Week 1	Control	0/20	Control	0/40
	0.31 mg/kg	2/20	0.08 mg/kg	0/40
	1.25 mg/kg	2/20	0.31 mg/kg	4/40
	5 mg/kg	5/20	1.25 mg/kg	2/40
Subtotal		9/80		6/160
Week 2	Control	0/20	Control	0/40
	0.31 mg/kg	1/20	0.08 mg/kg	0/40
	1.25 mg/kg	1/20	0.31 mg/kg	3/40
	5 mg/kg	1/20	1.25 mg/kg	3/40
Subtotal		3/80		6/160
Week 3	Control	0/20	Control	0/40
	0.31 mg/kg	0/20	0.08 mg/kg	0/40
	1.25 mg/kg	0/20	0.31 mg/kg	4/40
	5 mg/kg	0/20	1.25 mg/kg	2/40
Subtotal		0/80		6/160
Week 4	Control	0/20	Control	0/40
	0.31 mg/kg	1/20	0.08 mg/kg	1/40
	1.25 mg/kg	0/20	0.31 mg/kg	1/40
	5 mg/kg	1/20	1.25 mg/kg	0/40
Subtotal		2/80		2/160
TOTAL		14/80		20/160
<u>Reproduction</u>				
Segment I (rats)				
	Control	0/20 F 0/20 M	Control	1/20 F 0/20 M
	0.005 mg/kg	3/20 F 6/20 M	0.08 mg/kg	1/20 F 1/20 M
	0.02 mg/kg	13/20 F 15/20 M	0.31 mg/kg	7/20 F 9/20 M
	0.08 mg/kg	8/20 F 16/20 M	1.25 mg/kg	10/20 F 12/20 M
TOTAL		24/80 F 37/80 M		19/80 F 22/80 M
Segment II (rats)				
	Control	0/20	Control	0/20
	0.005 mg/kg	0/20	0.08 mg/kg	0/20
	0.02 mg/kg	2/20	0.31 mg/kg	1/20
	0.08 mg/kg	4/20	1.25 mg/kg	3/20
TOTAL		6/80		4/80
Segment II (rabbits)				
	Control	0/15	Control	1/15
	0.005 mg/kg	0/15	0.08 mg/kg	0/15
	0.02 mg/kg	7/15	0.31 mg/kg	1/15
	0.08 mg/kg	9/15	1.25 mg/kg	4/15
TOTAL		16/60		6/60
Segment III (rats)				
	Control	0/20	Control	0/20
	0.005 mg/kg	2/20	0.08 mg/kg	0/20
	0.02 mg/kg	3/20	0.31 mg/kg	1/20
	0.08 mg/kg	5/20	1.25 mg/kg	1/20
TOTAL		10/80		2/80

Evaluation/Conclusion

The draft SBA should be modified as recommended below.

The response to our questions regarding repeat dose toxicity and reproduction studies satisfies our request for additional animal data.

Recommendations

With regard to the draft SBA, please clarify whether the reference to clinical potency and duration of action of alfentanil, in the first paragraph under Pharmacology, is based upon extrapolation from animal data or clinical data.

Inasmuch as the sixth paragraph under B (page 8) discusses human pharmacokinetic data only, we recommend that this section be placed in the medical portion of the SBA.

Additional clarification in the section on reproduction studies should be made as follows:

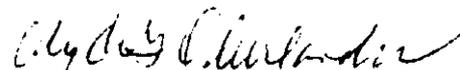
The last sentence in paragraph 7 under B (page 8) should be modified to read "Mortality rate increased significantly in both male and female rats (Segment I) at 0.31 and 1.25 mg/kg."

The third sentence in paragraph 8 under B (page 9) should be modified to read "Increased dead fetuses/decreased live fetuses, decreased pup weight at birth, and decreased pup survival rates at day 4 and week 2 were observed in rats (Segment III) at 0.31 mg/kg or 0.62X proposed human high dose."

DRAFT OF PHARMACOLOGY PORTION OF LETTER TO APPLICANT

Copy recommendations.

NDA 19-353  
HFN-160  
HFN-340  
DocRm. 160  
R.D. CGOberlander 9/12/85  
R.D. Init by:JKInscoc 9/16/85  
Xeroxed by shg 9/16/85

  
Clyde G. Oberlander  
Pharmacologist

NDA 19-353

Review #2

Date of Review: August 5, 1985

Applicant: Janssen Pharmaceutica Inc.  
Piscataway, NJ 08854

IK J  
8-5-85

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA  
Addendum to Review of February 1, 1985

Drug: Alfenta (alfentanil hydrochloride) Injection (R 39,209)

Category: Intravenous Short-Acting Opioid Analgesic (analog of fentanyl)  
Anesthetic Adjunct

NEW PRECLINICAL STUDIES

Reproduction - Segment I

Rat - Intravenous

Nonclinical Lab: Janssen Pharmaceutica  
2340 Beerse, Belgium

GLP Statement: Adequate

Study Dates: Initiation: 1-14-80; Completion: 6-6-80

Test Article: Alfentanil, batch A0301  
Control: saline

Test System: Wistar rats (20/sex/group)

Dosage Levels: 0, 0.08, 0.31 & 1.25 mg/kg, i.v.

Methodology: Males were dosed 56 days prior to mating with non-dosed females, and females were dosed for 14 days prior to mating with non-dosed males and throughout gestation.

AUG - 7 1985

## Results:

Body weight:

Body weight of the females, which were sacrificed on day 22 of their respective pregnancies, was individually recorded on day 1, 7, 14 and 21 of their presumed pregnancy.

Individual results indicate that at this time, there was an increase in weight among all pregnant females, controls as well as pregnant females dosed at 0.08, 0.31 and 1.25 mg/kg.

In dosed pregnant females treated for 14 days before being exposed to control males and further till mating occurred and during the complete gestation period, the average body weight gain during the third week of pregnancy was:

- + 82.3 g (0.08 mg/kg dosed females)
- + 91.6 g (0.31 mg/kg dosed females)
- + 73.0 g (1.25 mg/kg dosed females)

as compared to

- + 86.6 g for the control group

No differences in body weight gain were noted between the groups of the dosed pregnant females.

In non-dosed pregnant females mated with dosed males, treated for 56 days and further till copulation, the average body weight gain during the third week of pregnancy was:

- + 78.1 g (0.08 mg/kg dosed males)
- + 87.0 g (0.31 mg/kg dosed males)
- + 89.8 g (1.25 mg/kg dosed males)

as compared to

- + 84.1 g for the control group

No differences in body weight gain were noted between the groups of the non-dosed pregnant females.

Food consumption

During pregnancy the food consumption was recorded individually (Tables 2 to 9) and averaged per group of pregnant females (Table 1). Food consumption in males was not controlled.

Food consumption in dosed pregnant females was 736.8 g (controls), 705.9 g (0.08 mg/kg), 731.2 g (0.31 mg/kg) and 649.0 g (1.25 mg/kg).

Food consumption in non-dosed pregnant females was 711.6 g (controls), 661.6 g (0.08 mg/kg), 641.7 g (0.31 mg/kg) and 721.6 g (1.25 mg/kg).

No differences between groups were noted.

Mortality

Among the 80 females, dosed for 14 days before being exposed to control males, and further throughout gestation, the following mortalities occurred: control: 1/20 - 0.08 mg/kg: 1/20 - 0.31 mg/kg: 7/20 and 1.25 mg/kg: 10/20.

Among the 80 males, dosed for 56 days prior to mating with non-dosed females, the following mortalities occurred: control: 0/20 - 0.08 mg/kg: 1/20 - 0.31 mg/kg: 9/20 and 1.25 mg/kg: 12/20. No mortalities occurred in the non-dosed females coupled with these dosed-males.

Mortality rate increased significantly in both males and females dosed at 0.31 and 1.25 mg/kg.

Pregnancies

The females of each group were sacrificed on the 22nd day post mating and they were examined for pregnancies. The percentage of pregnancies in the various groups of dosed females coupled with non-dosed males was:

20/20 (control females)  
 18/19 (0.08 mg/kg dosed females)  
 16/17 (0.31 mg/kg dosed females)  
 12/14 (1.25 mg/kg dosed females)

The percentage of pregnancies in the various groups of non-dosed females coupled with dosed males was:

17/20 (control males)  
 17/19 (0.08 mg/kg dosed males)  
 11/11 (0.31 mg/kg dosed males)  
 5/8 (1.25 mg/kg dosed males)

Two control males and respectively two, zero and one male at the 0.08, 0.31 and 1.25 mg/kg dose-level failed to copulate.

Pregnancy rate was comparable between groups, except in high dose male group.

Cohabitation - mating time interval (median values)

Mating of the females of the various groups occurred at various times after exposure to males. Dosed females coupled with non-dosed males became pregnant after:

3 days (control females)  
 3 days (0.08 mg/kg dosed females)  
 3 days (0.31 mg/kg dosed females)  
 3 days (1.25 mg/kg dosed females)

Non-dosed females coupled with dosed males became pregnant after:

3 days (control males)  
 3 days (0.08 mg/kg dosed males)  
 2 days (0.31 mg/kg dosed males)  
 15 days (1.25 mg/kg dosed males)

No dose-related differences were noted between the various groups except for the 1.25 mg/kg dosed male group with increased cohabitation mating time interval.

B. Litter dataOffspring

In the groups with dosed females, litter size was:

12.0 (control)  
 11.0 (0.08 mg/kg)  
 13.4 (0.31 mg/kg)  
 11.3 (1.25 mg/kg)

The average number of live, dead and resorbed fetuses per litter were respectively:

11.9	0.1	0.2	(control)
11.0	0.0	0.4	(0.08 mg/kg)
13.4	0.0	0.2	(0.31 mg/kg)
11.1	0.2	0.3	(1.25 mg/kg)

At resection the average body weight of live pups was:

5.4 g (control)  
 5.5 g (0.08 mg/kg)  
 5.3 g (0.31 mg/kg)  
 5.1 g (1.25 mg/kg)

No differences were noted between the various groups of the dosed females.

In the groups with the non-dosed females litter size was:

11.2 (control)  
 11.4 (0.08 mg/kg)  
 11.6 (0.31 mg/kg)  
 9.2 (1.25 mg/kg)

The average number of live, dead and resorbed fetuses per litter were respectively:

11.2	0.0	0.4	(control)
11.4	0.0	0.3	(0.08 mg/kg)
11.6	0.0	0.0	(0.31 mg/kg)
9.2	0.0	0.0	(1.25 mg/kg)

At resection, the average body weight of the live pups was:

5.5 g (control)  
 5.5 g (0.08 mg/kg)  
 5.4 g (0.31 mg/kg)  
 5.6 g (1.25 mg/kg)

No differences were noted between the various groups of the non-dosed females.

Abnormalities

The following abnormalities were observed after gross observation, fetal skeletal examination and fetal sectioning.

Groups of dosed females

- control group  
none
- low dosage group: 0.08 mg/kg  
none
- medium dosage group: 0.31 mg/kg  
1 fetus removed from female No. 189 had waved ribs
- high dosage group: 1.25 mg/kg  
none

Groups of non-dosed females

- control group  
2 fetuses removed from female No. 309 had waved ribs and another fetus had short ribs.
- low dosage group: 0.08 mg/kg  
none
- medium dosage group: 0.31 mg/kg  
2 fetuses removed from female No. 267 had waved ribs and another had short ribs.
- high dosage group: 1.25 mg/kg  
1 fetus removed from female No. 257 had waved ribs

Waved ribs were regularly encountered in control fetuses of previous experiments and are therefore considered of no importance.

Table 1: Pregnancy and litter data in rats and their offspring after daily i.p. dosing of R 39209 to males (minimum 35 days prior to mating) or to females (14 days prior to mating and further during pregnancy).

Experiment No. 923	Dose group R 39209 mg/kg							
	non dosed males + dosed females				dosed males + non dosed females			
	0	0.08	0.31	1.25	0	0.08	0.31	1.25
Adult rat data								
No. of treated males	0	0	0	0	20	20	20	20
No. of treated females	20	20	20	20	0	0	0	0
No. of pregnant females (1)	20/20	19/19	16/17	12/14	17/20	17/19	11/11	5/8
No. of dead females (1)	1/20	1/20	7/20	10/20**	0/20	0/19	0/11	0/8
No. of dead males (1)	0/20	0/20	0/20	0/20	0/20	1/20	3/20**	12/20***
Avg. weight change of dams d21-d14 (2)	95.5	92.3	91.5	73.0	84.1	78.1	87.0	99.8
Avg. food intake of dams (3w) (2)	735.8	705.9	731.2	649.0	711.5	651.6	641.7	721.5
Cohab. - Mating interval (median) (2)	3.0	3.0	3.0	3.0	3.0	3.0	2.0	13.0
Litter data								
Avg. No. of resorption sites (2)	0.2	0.4	0.2	0.3	0.4	0.3	0.0	0.0
Avg. No. of dead pups (2)	0.1	0.0	0.0	0.1	0.0	0.0	0.0	0.0
Avg. No. of alive pups (2)	11.3	11.0	13.4	11.1	11.2	11.4	11.5	9.2
Mean litter size (2)	12.0	11.0	13.4	11.0	11.2	11.4	11.6	9.2
Avg. weight of pups at cand. sect. (2)	5.4	5.5	5.3	5.1	5.5	5.5	5.4	5.5
Losses (2)	0/223	0/199	1/174	2/102	3/120	0/123	3/129	1/46

(1) Chi-Square Test  $p < 0.05$

(2) Mann-Whitney U Test  $** p < 0.01$

\*\*\*  $p < 0.001$

Evaluation

A Segment I intravenous study of alfentanil (0.08, 0.31 & 1.25 mg/kg, corresponding to 0.16, 0.62 & 2.5 times the proposed clinical dose, respectively) in Wistar rats showed no apparent adverse effects on the fertility of the male or female animals, except for a lower pregnancy rate (62.5%) in non-dosed females mated with high dose males. Mortality rates increased significantly in both males and females at 0.31 and 1.25 mg/kg and the cohabitation mating time interval increased (15 days) in the 1.25 mg/kg dosed males compared to 3 days in controls. No adverse effects were observed in the offspring of the various groups. The effect on male fertility was equivocal due to the high mortality rates in the mid and high dose groups.

Conclusion

Additional animal data are requested prior to the approval of this NDA.

Recommendations

Day of death and cause of death in the Segment I intravenous reproduction study of alfentanil in the rat should be submitted.

It is noted that a pattern of unexplained deaths occurred in repeated dosing studies (e.g. one month i.v. study in the rat and other reproduction studies) at doses considerably lower than one would expect based upon the acute toxicity studies. It was noted in the 4 week i.v. rat study, that deaths appeared during all 4 weeks. Since the development of tolerance would be expected during repeat dosing with this class of drug, these deaths are surprising. Please provide an explanation for these observations.

In the Segment I i.v. reproduction study of alfentanil in the rat, an explanation should be given for the lower pregnancy rate observed in non-dosed females mated with high dose males.

DRAFT OF PHARMACOLOGY PORTION OF LETTER TO APPLICANT

Copy recommendations.

  
Clyde G. Oberlander  
Pharmacologist

cc: NDA 19-373  
HFN 160, HFN 340  
Doc Room 160  
R/D CGOberlander, 8/5/85  
R/D init. JKInscoc, 8/6/85

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Chem

REV 3

DSDOP  
Chemist's Review #1

A. 1. NDA #19-353

Date Completed: Jan. 8, 1985

APPLICANT: Janssen Pharmaceutica

ADDRESS: 40 Knightsbridge Road  
Piscataway, New Jersey 08854

2. PRODUCT NAMES:

Proprietary: ALFENTA Injection  
Nonproprietary: Alfentanil hydrochloride

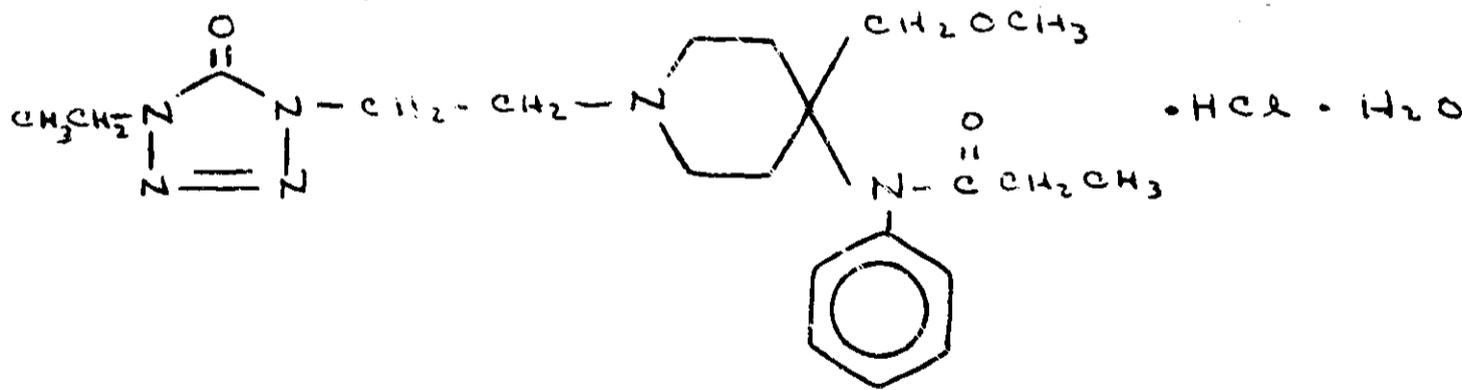
3. DOSAGE FORM & ROUTE OF ADMINISTRATION:

Rx. Aqueous solution for intravenous administration.

4. PHARMACOLOGICAL CATEGORY & PRINCIPAL INDICATION:

Narcotic analgesic for the maintenance and/or induction of anesthesia.

5. STRUCTURAL FORMULA & CHEMICAL NAME:



N-[1-[2-(4-ethyl-4,5-dihydro-5-oxo-1H-tetrazol-1-yl)ethyl]-4-(methoxymethyl)-4-piperidinyl]-N-phenyl propanamide monohydrochloride, monohydrate.

JAN 23 1985

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Page 2

B. 1. INITIAL SUBMISSION

1B Presubmission Cover Letter: September 26, 1984  
Received HFN-160: October 18, 1984  
Received by Chemist: October 22, 1984

2. AMENDMENTS: None

3. SUPPORTING DOCUMENTS

DMFs: All held by Janssen Pharmaceutica,  
n.v. A letter of authorization  
dated Dec. 16, 1982 is included

DMF

DMF

DMF

C. COMMENT:

This NDA pre-submission contains numerous chemistry deficiencies. These deficiencies are found in virtually every section of Part 8 of the application. The deficiencies are discussed in the Review Notes and cited in the draft letter to the applicant.

D. CONCLUSION/RECOMMENDATION

This application is not approvable from the standpoint of chemistry.

The applicant should be informed of the chemistry deficiencies promptly so that corrective action can be initiated.



John J. Gibbs, Ph.D.

cc: NDA 19-353  
HFN 160, Doc Room 160  
HFN 102 Kunkumian  
R/D JJGibbs, 1/8/85  
R/D init. CPHoiberg, 1/9/85  
FT-jb, W3376P, D0074P, 1/10/85

DSDDP  
Chemist's Review #2

A. 1. NDA #19-353

Date Completed: 11/27/85

Applicant: Janssen Pharmaceutica

Address: 40 Knightsbridge Road  
Piscataway, New Jersey 08854

Principal Manufacturing Sites:

- a)
- b)
- c)

2. Product Names:

Proprietary: ALFENTA Injection

Nonproprietary: Alfentanil hydrochloride

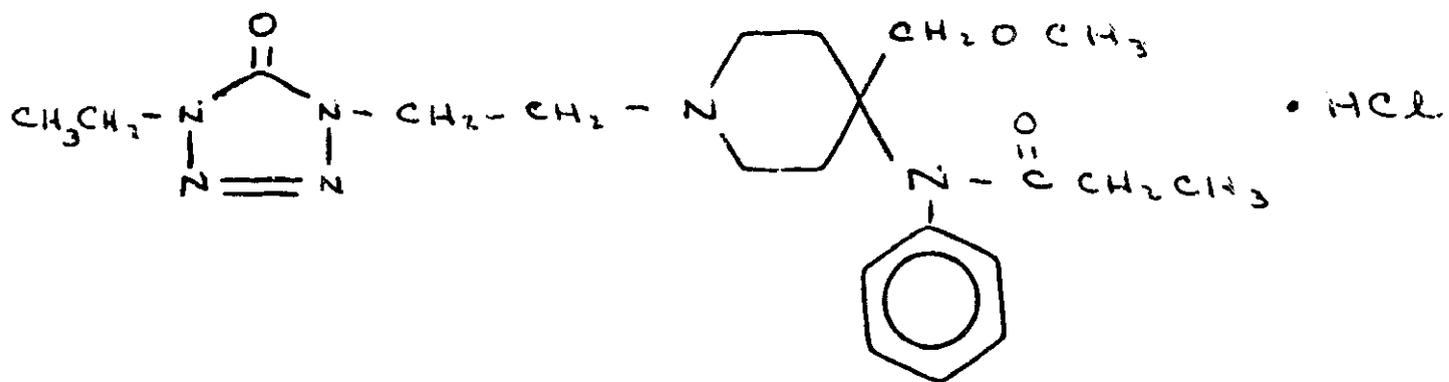
3. Dosage Form & Route of Administration:

Rx. Aqueous solution for intravenous administration.

4. Pharmacological Category & Principal Indication

Narcotic analgesic for the maintenance and/or induction of anesthesia.

5. Structural Formula & Chemical name



N-[1-[2-(4-ethyl-4,5-dihydro-5-oxo-1H-tetrazol-1-yl)ethyl]-4-(methoxymethyl)-4-piperidyl]-N-phenyl propanamide monohydrochloride, monohydrochloride.

DEC 19 1985

8. 1. Initial Submission:

I B Chemistry Presubmission: September 26, 1984  
Received HFN-160: ; October 18, 1984  
Received by chemist: October 22, 1984  
Chemistry deficiencies issued: January 15, 1985  
Initial Submission: December 24, 1984 (subject of this review).

2. Amendments:

April 2, 1985: Answers to 1/15/85 chemistry deficiencies (subject of this review)  
May 23, 1985 " (stability data)  
May 24, 1985 " (added RM specification)  
June 19, 1985 " (NDS assay revision)  
Sept. 6, 1985 " (draft labels)  
Oct. 2, 1985 " (draft labeling)  
Oct. 2, 1985 " (stability data)  
Oct. 18, 1985 " (manufacturing directions)  
Oct. 25, 1985 " (labeling)  
Nov. 5, 1985 " (labeling)

3. Supporting Documents

IND  
DMFs listed in Chemist's Review #1 except DMF and DMF which have been deleted.

C. Comments:

This application, as amended, still contains numerous chemistry deficiencies. These deficiencies are discussed in the review notes and specified in the draft letter to the applicant.

D. Conclusion/Recommendation

This application, as amended, remains not approvable in the area of chemistry.

The deficiencies should be forwarded to the sponsor for correction.

  
John J. Gibbs, Ph.D.

cc: NDA 19-353  
HFN 160, Doc Room 160  
R/D JJGibbs, 11/27/85  
R/D init. CPHoiberg, 11/29/85  
FT/jb, W4437P, D3619P, 12/4/85

Division of Surgical-Dental Drug Products  
Chemist's Review #J

Date Completed: 1/2/86

A. 1. NDA 19-353

Applicant: Janssen Pharmaceutica  
40 Knightsbridge Road  
Piscataway, New Jersey 08854

Principal Manufacturing Sites:

- a)
- b)
- c)

2. Product Names:

Proprietary: Alfenta injection  
Non-proprietary: Alfentanil hydrochloride

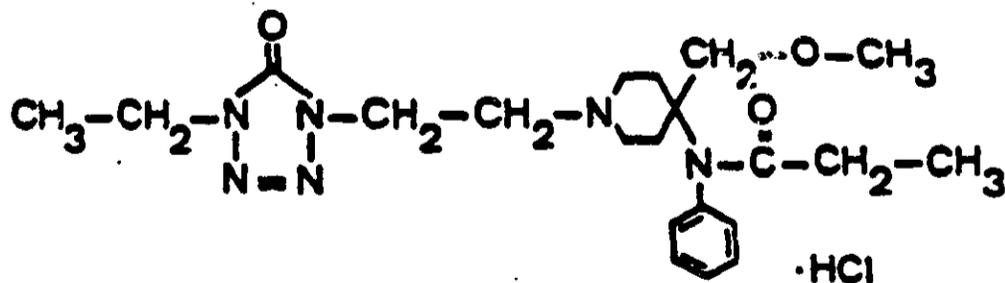
3. Dosage Form & RDA:

Ampoule or syringe. Intravenous

4. Pharmacological Category:

Narcotic analgesic

5. Structural Formula and Chemical Name:



N-[1-[2-(1-ethyl-4,5-dihydro-5-oxo-1H-tetrazol-1-yl)ethyl]-4-(methoxymethyl)-4-piperidinyl]-N-phenylpropanamide monohydrochloride

NDA 19-353  
Page 2

B. Initial Submission: 9/26/84

Amendments: 11/26/85; 12/5/85

Supporting Documents: IND  
DMF's

C. Remarks:

This application, as amended, still contains numerous chemistry deficiencies. These deficiencies are specified in the draft letter to the applicant.

D. Conclusions:

This application, as amended, remains not approvable in the area of chemistry.

cc: NDA 19-353  
HFN 160, Doc Room 160  
R/D PMStewart, 1/2/86  
R/D init. CPHoiberg, 1/2/86 &  
PHR, 1/2/86  
FT/jb, W4541P, D3621P, 1/8/86

Patricia M. Stewart  
Patricia M. Stewart

Division of Surgical-Dental Drug Products  
Chemist's Review #4

Date Completed: 1/30/86

A.1. NDA 19-353

Applicant: Janssen Pharmaceutica  
40 Knightsbridge Road  
Piscataway, New Jersey 08854

Principal Manufacturing Sites:

- (a)
- (b)
- (c)

2. Product Names:

Proprietary: Alfenta Injection  
Non-proprietary: Alfentanil hydrochloride

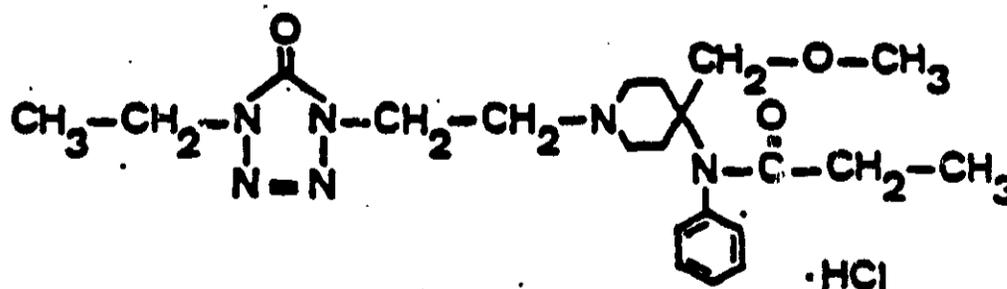
3. Dosage Form & ROA:

Ampoule or syringe, Intravenous.

4. Pharmacological Category:

Narcotic analgesic.

5. Structural Formula and Chemical Name:



N-[1-[2-(4-ethyl-4,5-dihydro-5-oxo-1H-tetrazol-1-yl)ethyl]-4-(methoxymethyl)-4-piperidinyl]-N-phenylpropanamide monohydrochloride

FEB 12 1986

NDA 19-353  
Page 2

B. Initial Submission: 9-26-84  
Amendments: 1-8-86, 1-15-86, 1-24-86  
Supporting Documents: IND  
DMF's

C. Remarks:

The three amendments were submitted in response to deficiencies noted in the chemistry aspect of the manufacturing and controls section.

D. Conclusions:

The supplemental amendments are acceptable from the standpoint of chemistry. The approval letter should include the "Draft of Chemist's Part, Letter to Applicant" attached to this review.

*Patricia M. Stewart*  
\_\_\_\_\_  
Patricia M. Stewart

cc: NDA 19-353  
HFN 160, Doc Room 160  
R/D PMStewart, 1/30/86  
R/D init. CPHoiberg, 1/31/86  
FT/jb, W4626P, D3623P, 2/3/86

NDA

19-353

Microbiology  
Revs

Division of Surgical-Dental Drug Products

Microbiologist's Review No. 2

January 15, 1986

- A. 1. NDA 19-353 Original New Drug Application

Applicant: Janssen Pharmaceutica  
40 Kingsbridge Road  
Piscataway, NJ 08854

2. Product Name: Alfenta(R) (alfentanil hydrochloride)  
Injection
3. Dosage Forms: Sterile solution in ampoules and pre-filled  
syringes.
4. Pharmacological Category and/or Principal Indication:  
Adjunct to anesthesia

- B. 1. Initial Submission: December 24, 1984

2. Amendments:

April 2, 1985  
May 23, 1985  
May 24, 1985  
June 19, 1985  
September 6, 1985  
October 2, 1985  
October 2, 1985  
October 18, 1985  
October 25, 1985  
November 5, 1985  
December 5, 1985  
January 8, 1986 (subject of this review)  
received for review January 10, 1986

3. Supporting Documents:

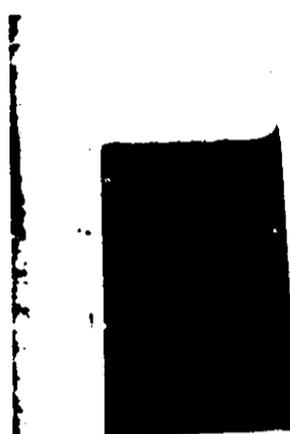
4. Related Documents: NDA 16-619/S-015

- C. Remarks:

The current Amendment (January 8, 1986) responds to microbiology deficiencies cited in Microbiologist's Review No. 1 dated December 27, 1985. These deficiencies were communicated by telephone to the Applicant on January 2, 1986. Reference is made to the two telephone memos dated January 2, 1986 filed with this application.

JAN 23 1986

The applicant has stated the conditions used for media fill validations of the prefilled syringes manufactured by Survival Technology. A commitment has been made to supply the results of the validation studies after their completion. The conditions are as follows:



Media fill validation will be conducted upon initiation of commercial-scale manufacturing, prior to product release of ALFENTA prefilled syringes. The validation results will be submitted for your information.

It is understood by this reviewer that manufacture of the drug product will not occur unless validation results are successful. This should be covered under CGMP Regulations.

The applicant has provided a copy of the procedure used in the LAL endotoxin validation studies. The procedure allows interpretation of the validation tests and is adequate. Pyrogen retesting in rabbits has been withdrawn due to the potent pharmacologic effects of the drug product on the test animals. The response is correct and adequate.

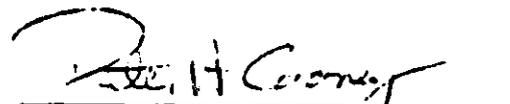
Concerning the question of whether the aseptically filled drug product in syringes can support microbial growth, reference is made to the telecon dated January 14, 1986. The applicant has made a commitment to perform USP Preservative Effectiveness tests upon commercial scale manufacturing. As stated in the telecon, the USP test as such is not appropriate. The direct question to be addressed is as follows: Does the drug product in question support microbial growth? The high level inoculum used in the USP test is better suited to demonstrate reductions in number of organisms.

Policy concerning terminally sterilized versus aseptically filled dosage forms is at this time under discussion. It therefore seems inappropriate at this time to withhold approval of this drug product solely on the outcome of this testing. A commitment to do this testing is therefore considered appropriate in this case. The methods used in the testing will be discussed with the applicant.

D. Conclusions:

The application is considered approvable on the basis of microbiology. The commitments discussed under "Remarks" above should be enforced and are summarized as follows:

- (1) Media fill validation results for the pre-filled syringes are to be provided.
- (2) A testing program to determine if the drug product supports microbial growth will be carried out and results supplied to the Agency prior to marketing the prefilled syringe dosage form.

  
Peter H. Cooney, Ph.D.

NDA 19-353  
HFN-150, HFN-160/Doc Rm  
HFN-160/PHCooney:1/15/86  
R/D init. by CPHoiberg:1/15/86/PHRussell:1/15/86  
f/t deg: 1/15/86 w2270X/D0029

BIO/DIS

REV

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drugs and Biologics  
Office of Drug Standards

DATE : NOV 22 1985

TO : Patricia H. Russell, M.D.  
Acting Director,  
Division of Surgical-Dental Products

FROM : Jerome P. Skelly, Ph.D.  
Acting Director,  
Division of Biopharmaceutics

SUBJECT: Biopharmaceutics Recommendation of Approval of NDA 19-353  
Alfentanil Hydrochloride for Injection, 500 ug/ml  
ALFENTAR<sup>R</sup>, Janssen Pharmaceutica Inc.  
Submission Date: December 24, 1984 & August 23, 1985

Background:

Alfentanil is an opioid analgesic that is chemically and pharmacologically related to fentanyl. The proposed uses of alfentanil in surgery are (1) as an analgesic adjunct given in incremental doses, (2) as a baseline analgesic administered by continuous infusion, and (3) as a primary anesthetic agent for the induction of anesthesia.

Results:

1. The disposition of alfentanil after intravenous administration can be described by a three-compartment open model. The alpha, beta and gamma half-lives are approximately 2, 15 and 94 minutes, respectively. It should be noted that these values are only approximations, as they are quite variable.
2. Alfentanil is extensively metabolized. Less than 1% of the administered dose is excreted in the urine unchanged in 48 hours. It is reported that the metabolites of alfentanil are inactive.
3. It appears that the disposition of alfentanil is linear at concentrations up to 1000 ng/ml.
4. Alfentanil is 92% bound to plasma proteins. Alpha-1-acid glycoprotein is believed to be the main binding plasma component for alfentanil.

5. In patients with cirrhosis of the liver the free clearance of alfentanil was shown to be decreased, therefore the alfentanil dose should be carefully adjusted in these patients. In addition, the dose should be carefully adjusted in patients with renal disease (because of a possible increase in free fraction and decrease in free clearance), obese patients, the elderly and children.

Overall Conclusion:

The Division of Biopharmaceutics has determined that the data is acceptable. It is concluded that this submission fulfills the requirements for demonstrating the bioavailability and pharmacokinetic disposition of alfentanil hydrochloride, the subject of NDA 19-353.



Jerome P. Skelly  
Acting Director,  
Division of Biopharmaceutics

Prepared by Gene D. Mason, Pharm.D.  
RD Initialed by Mei-Ying Huang, Ph.D.  
FT Initialed by C.T. Viswanathan, Ph.D. *CTV*

*11/19/85*

cc: HFN-220(Skelly, Shulman), HFN-226(Mason), Drug, Chron and FOI Files.

GDM:smj:kek: 10-10-85

Alfentanil hydrochloride  
NDA 19-353  
ALFENTANIL<sup>R</sup>  
Injection-500 ug/ml  
2, 5, 10 and 20 ml ampules  
2, 5, 10 and 20 ml prefilled syringes  
Reviewer: Gene D. Mason, Pharm.D.  
Wang # [REDACTED]  
12 S, 20

Janssen Pharmaceutica Inc.  
Piscataway, New Jersey 08854  
Submission Dated.  
December 24, 1984  
August 23, 1985

NOV 2 1985

Review of NDA

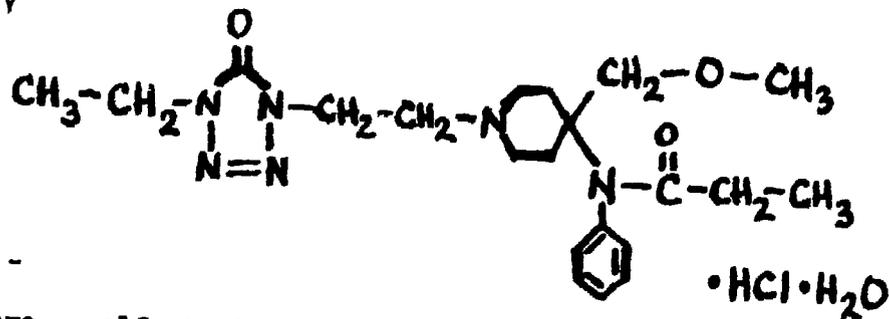
I BASIC INFORMATION

A. BACKGROUND

Alfentanil, is a rapid acting, opioid analgesic with a short duration of action. It is chemically and pharmacologically related to fentanyl, however, alfentanil is reported to be only approximately 1/4 as potent. In brief, the intended uses of alfentanil in surgery are (1) as an analgesic adjunct given in incremental doses, (2) as a baseline analgesic administered by continuous infusion, and (3) as a primary anesthetic agent for the induction of anesthesia.

The Division of Biopharmaceutics has no record of previous submissions to this division concerning alfentanil-[REDACTED] NDA 19353, the subject of this review.

B. CHEMISTRY



Structure -

Generic Name - alfentanil hydrochloride

Chemical Name - N-[1-[2-(4-ethyl-4,5-dihydro-5-oxo-1H-tetrazol-1-yl)ethyl]-4-(methoxymethyl)-4-piperidinyl]-N-phenyl-propanamide monohydrochloride monohydrate

C. FORMULATION

Dosage Form - a sterile aqueous solution for intravenous injection

How Supplied - 500 ug/ml : 2, 5, 10, and 20 ml ampules

Composition - 500 ug/ml : 2, 5, 10, and 20 ml prefilled syringes  
alfentanil hydrochloride  
sodium chloride, U.S.P.  
water for injection, U.S.P.

#### D. ADMINISTRATION/DOSAGE - PROPOSED

1. as an analgesic adjuvant in incremental doses -  
8 to 60 ug/kg for surgical procedures with and expected duration of up to one hour
2. as a baseline analgesic administered by continuous infusion -  
0.5 to 3.0 ug/kg/min for the maintenance of balanced general anesthesia
3. as a primary anesthetic agent for the induction of anesthesia for whom pronounced increases in heart rate and blood pressure during laryngoscopy, intubation or incision could be detrimental -  
140 to 245 ug/kg

#### II STUDIES/REFERENCES

##### PHARMACOKINETICS

1. Comparative Pharmacokinetics of Fentanyl and Alfentanil, S Bower, C Hull, Br J Anaesth, 1982;54:871, Vol 1.9-pg 12-25007
2. The Pharmacokinetics of Alfentanil (R39209): A New Opioid Analgesic, J Bovill, et al, Anesthesiology, 1982;57:439, Vol 1.9-pg 12-25022
3. Pharmacokinetics of Alfentanil in Man, F Camu, et al, Anesth Analg, 1982;61:657, Vol 1.9-pg 12-25027
4. Pharmacokinetics of the Infusion of Alfentanil in Man, R Fragen et al, Br J Anaesth, 1983;55:1077, Vol 1.9-pg 12-25073

##### DOSE PROPORTIONALITY

5. Pharmacokinetics of Alfentanil Following Long-Term Intravenous Infusion(English Abstract), Firm's Clinical Research Report, February 1983, Vol 1.9-pg 12-25078

##### METABOLISM

6. Plasma Levels, Urinary Excretion and Metabolism of Alfentanil in Man, Firm's Clinical Research Report, September 1984, Vol 1.9-pg 12-25093

##### PROTEIN BINDING

7. Plasma Protein Binding and Distribution of Fentanyl, Sufentanil, Alfentanil and Lofentanil in Blood, Firm's Clinical Report, Vol 1.8/1.10, pg 10-00305

## SPECIAL POPULATIONS

### Liver Disease

8. Alfentanil Pharmacokinetics in Patients with Cirrhosis, Firm's Clinical Research Report, Vol 1.9-pg 12-25147

### Renal Disease

9. Pharmacokinetics of Alfentanil in Patients with Chronic Renal Insufficiency, Firm's Clinical Research Report, February 1984, Vol 1.9-pg 12-25193

### Obesity

10. Clinical Evaluation of Alfentanil, Firm's Clinical Report, Vol 1.14-pg 12-00893

### Elderly

13. Alfentanil Kinetics in the Elderly, H Helmers, A Van Peer, et al, Clin Pharmacol Ther, 1984;36(2):239-243.(reviewer obtained from literature)

### Children

14. Pharmacokinetics of alfentanil in children with an age of 5 to 8 years., Firm's Clinical Report, Vol 1.9 - pg 12-25164.

## ANALYTICAL METHODS

11. Rapid and sensitive gas chromatographic method for the determination of alfentanil and sufentanil in biological samples(literature reference: Journal of Chromatography, 1981;224:122-127) Volume 1.8/1.10, pg 10-00250

12. Radioimmunoassay of the New Opiate Analgesics Alfentanil and Sufentanil--Preliminary Pharmacokinetic Profile in Man. J Pharm Pharmacol, 1983, 35(2):86-93.

15. Determination of alfentanil in human plasma samples by gas chromatography or radioimmunoassay: an interlaboratory study. From submission dated August 23, 1985. Attachment III.

## III SUMMARY OF BIOAVAILABILITY/PHARMACOKINETICS

### Bioavailability

Alfentanil is a solution intended solely for intravenous administration. Therefore, the in vivo bioavailability of alfentanil is not necessary for the product to achieve any of its intended purposes.

### Pharmacokinetics (references #1,2,3,4)

The disposition of alfentanil after intravenous administration can be described by a three-compartment model. Pharmacokinetic parameters measured in adults are listed below.

#### 3-compartment open model

#### Adult Parameters

Ref	C1 (ml/min/kg)	Vc l/kg	Vd(ss) l/kg	Vd(beta) l/kg	pi	half-life(mins)*	
						alpha	beta
#3-Camu (patients, N=5); drug administered by IV bolus							
	8.3	0.22	-	1.03	3.5	16.8	94
(SD)	(3.3)	(0.05)		(0.5)	(1.3)	(6.4)	(38)
#2-Bovill (11 patients; 6 low dose, 5 high dose); drug given by IV bolus							
lo dose	7.6	0.11	-	1.0	1.3	9.4	94
(SEM)	(2.4)	(0.04)		(0.32)	(0.48)	(2.6)	(8.3)
(S.D.)**	(5.9)	(0.1)		(0.8)	(1.2)	(6.4)	(20.3)
hi dose	5.1	0.08	-	0.71	1.1	+	94
(SEM)	(1.1)	(0.01)		(0.17)	(0.14)	+	(9.3)
(S.D.)**	(2.4)	(0.02)		(0.44)	(0.31)	(1.1)	(20.7)

\* Usually the initial disposition phase is termed alpha and subsequent phases are named sequentially, however, the above convention was used by the investigators and therefore used here.

\*\* calculated by reviewer from SEM and N

#### 2-compartment open model

Ref	C1 (ml/min/kg)	V1 l/kg	V2 l/kg	Vd(ss) l/kg	alpha (mins)	beta (mins)
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#### #1-Bower (volunteers, N=7); drug administered by short infusion(2.5 mins)

lo dose	3.4	0.15	0.23	0.39	--	97.7
(SD)	(1.1)	(0.03)	(0.06)	(0.07)		(25.4)
hi dose	5.2	0.18	0.35	0.53	--	95.3
(SD)	(3.8)	(0.07)	(0.22)	(0.29)	--	(16.7)

#### #4-Fragen (patients, N=5); drug administered by infusion(1 hr) and IV bolus

	3.3	0.13	0.22	--	7.4	86.7
(SD)	(0.75)	(0.05)	(0.07)	--	(3.1)	(15.8)

SD = standard deviation; SEM = Standard error of the mean

The variability in the above pharmacokinetic parameters is evident. Some possible explanations are the small number of subjects in each study, concomitant administration of routine anesthetic medications, the physiologic changes produced by anesthetic conditions and differences in subjects(e.g. ages, medical conditions), and variability in assay methodology.

In an abstract by J Reitz, et al (Anesthesia and Analgesia, 63(2):175, 1984), the total plasma clearance of alfentanil was shown to decrease in 2 patients undergoing major intraabdominal surgery. No conclusions can be drawn from this data because of the small number of subjects, the possibility that a change in protein binding may account for the observations and the failure to measure free clearance.

#### Metabolism(reference #6)

Alfentanil is extensively metabolized. Unchanged alfentanil excreted in the urine over 48 hours accounted for 0.2-0.5% of the dose administered(#6). Noralfentanil was reported to be the main urinary metabolite and accounted for 30.9% of the dose excreted in the urine over 24 hours. It was not reported as to whether or not noralfentanil has any activity. The second major metabolite reported was HAM2(a glucuronide of HAM5) which accounted for 14.4% of the dose excreted in the urine in 24 hours(refer to Figure 6-4 of this review). A large number of metabolites of lesser importance were also reported. In reference #3(Camu, pg 12-25031, vol 1.9) it states that the metabolites of alfentanil have no pharmacologic activity. However, this was not substantiated in the reference cited(Niemegheers C, Janssen P, Drug Dev Res 1981;1:83-88).

#### Dose Proportionality(reference #2)

A formal dose proportionality study over the recommended dosing range was not investigated and may not be needed. Nevertheless, limited information on the subject can be gleaned from studies that administered incremental doses or a continuous infusion of alfentanil.

Bovill(ref#2) administered 50 ug/kg and 125 ug/kg as an IV bolus to patients. The half lives and the dose/intercept ratios were not significantly different between the high and low dose groups. Plasma concentrations for the high dose group were less than 1000 ng/ml.

Levron(ref#5) administered 1-2.5 ug/kg/min as a continuous infusion of duration 3.5 to 8 hours to 4 patients. The pharmacokinetic parameters, half-life(beta), Vd(beta), and clearance were measured and are smaller (clearance, volume) but comparable to those obtained after an IV bolus. Generally, plasma concentrations observed with the continuous infusions measured up to 500 to 800 ng/ml.

In summary, it appears that the disposition of alfentanil is linear at concentrations up to 1000 ng/ml.

#### Protein Binding(reference #7)

Alfentanil is 92 % bound to human plasma proteins. Plasma protein binding of alfentanil is independent of drug concentration over the range 10-1000 ng/ml. Alpha-1-acid glycoprotein is believed to be the main binding plasma component for alfentanil.

### Liver Disease(reference #8)

The clearance of alfentanil is decreased in patients with cirrhosis of the liver. Ferrier, et al(8), reported a mean( $\pm$  S.D.) clearance of 3.1 ( $\pm$  1.6) and 1.6 ( $\pm$  1.3) ml/min/kg (P less than 0.01) in normals and cirrhotic patients, respectively. The unbound clearance in patients with cirrhosis was 8.3 ( $\pm$  4.6) vs 26.3 ( $\pm$  8.9) ml/min/kg in normal controls (P less than 0.01). The mean terminal elimination half-life in cirrhotic patients was reported to be 219 minutes as compared to 90 minutes in normal subjects. Patients with cirrhosis had a higher (P less than 0.01) alfentanil free fraction (18.6  $\pm$  9.4 %) compared with the control patients (11.5  $\pm$  3.9 %).

This data suggests that the dose should be carefully adjusted in patients with liver disease.

### Renal Disease(reference #9)

The elimination of alfentanil in patients with chronic renal insufficiency appears not to be substantially different from that in normal patients. However, Levron et al(9), noted a greater free fraction(approx 0.2) in renal failure patients than that observed in normals(approx 0.1). The patients studied by Levron also had a lower unbound clearance but no change in total clearance when compared to normals. A free clearance of 18.5 ( $\pm$  11.1) ml/min/kg was measured by Levron. Ferrier(8) measured a free clearance of 26.3 ( $\pm$  8.9) in normals. Although a cross study comparison of the above results is limited, an increase in free fraction may increase the pharmacologic effect if a real difference in free clearance exists between patients with renal failure and normals.

### Obesity(reference #10)

Preliminary data suggests that the disposition of alfentanil in patients with obesity differs from that of normals. The clearance of alfentanil in obese subjects was significantly less (P less than 0.01) than that in nonobese subjects(179 ml/min vs 321 ml/min, respectively; or 1.45 vs 5.0 ml/min/kg (using TBW), respectively). The beta half-life in obese subjects(172 mins) was also significantly longer (P less than 0.005) than that in nonobese subjects(92 mins). The volume of distribution at steady state (Vdss) was similar in both the obese (35L) and nonobese (30L) patients.

Although unexplained, preliminary evidence indicates that obese patients have a lower clearance of alfentanil than nonobese patients. If clinical data in obese patients supports the above findings, then dosing should be carefully adjusted in obesity. Until a more predictable framework is available, it seems prudent that empiric dosing in obese patients be based on ideal body weight.

### Elderly (reference #13)

		Vc ml/kg	Vdss ml/kg	Vd(beta) ml/kg	Cl ml/min/kg	alpha t1/2 min	beta t1/2 min
Young (N=9)	Mean	201	460	746	6.47	11.4	83
	(S.D.)	61	141	224	2.06	2.4	23
Elderly (N=15)	Mean	211	543	772	4.37*	13.1	137**
	(S.D.)	56	132	237	2.61	6.6	33

\*P less than 0.05; \*\*P less than 0.001

These results indicate that elderly patients (greater than 65 YO) have a lower clearance of alfentanil than younger adults. Similar volumes of distribution in elderly subjects and younger adults suggest that the lower clearance in elderly subjects may be due to a reduction in hepatic clearance. If clinical findings support these observations, then maintenance doses (vs. loading doses) of alfentanil may need to be lower in elderly patients.

### Children - ages 5 to 8 years old (reference #14)

		Vc ml/kg	Vdss ml/kg	Vd(beta) ml/kg	Cl ml/min/kg	alpha t1/2 min	beta t1/2 min
Children (N = 8)	Mean	69.8	163.5	289.8	4.73	5.13	40.32
	(S.D.)	56.3	110.4	180.2	1.75	2.11	8.95
	(% C.V.)	80.6	67.5	62.2	37.0	41.1	22.2

The differences in parameters between children and adults can not be explained by protein binding, as the value in children (85.5 - 89.5) was similar to that observed in adults. This investigation indicates that children have a lower clearance and a smaller distribution volume than adults. Thus, dosing in children vs adults should reflect these differences.

### IV Analytical Methods by Study

<u>Reference</u>	<u>Method</u>
#1-Bower	Radioimmunoassay; H(3)-alfentanil and rabbit antibody obtained from Janssen Pharmaceutica, Beerse, Belgium
#2-Bovill	Radioimmunoassay (Michiels, et al, Radioimmunoassay of the opioid analgesics alfentanil and sufentanil- Preliminary pharmacokinetic profile in man, <u>J Pharm Pharmacol</u> , 1983;35(2):86)
#3-Camu	Gas-liquid chromatography (Woestenborghs <u>J Chromatogr</u> 1981;224:122)

- #4-Fragen Radioimmunoassay, performed at Janssen Pharmaceutica (Michiels, et al, Radioimmunoassay of the opioid analgesics alfentanil and sufentanil-Preliminary pharmacokinetic profile in man, J Pharm Pharmacol, 1983;35(2):86)
- #5-Levron (Abstract) - Radioimmunoassay (Michiels, et al, Radioimmunoassay of the opioid analgesics alfentanil and sufentanil-Preliminary pharmacokinetic profile in man, J Pharm Pharmacol, 1983;35(2):86)
- #6-Meuldermans Scintillation counting, gas-liquid chromatography (Woestenborghs J Chromatogr 1981;224:122), & HPLC
- #8-Ferrier Radioimmunoassay (Michiels, et al, Radioimmunoassay of the opioid analgesics alfentanil and sufentanil-Preliminary pharmacokinetic profile in man, J Pharm Pharmacol, 1983;35(2):86)
- #9-Levron Radioimmunoassay (Michiels, et al, Radioimmunoassay of the opioid analgesics alfentanil and sufentanil-Preliminary pharmacokinetic profile in man, J Pharm Pharmacol, 1983;35(2):86)
- #10-Brown Gas chromatography
- #13-Helmerts Radioimmunoassay (Michiels, et al, Radioimmunoassay of the opioid analgesics alfentanil and sufentanil-Preliminary pharmacokinetic profile in man, J Pharm Pharmacol, 1983;35(2):86)
- #14-Levron Radioimmunoassay (Michiels, et al, Radioimmunoassay of the opioid analgesics alfentanil and sufentanil-Preliminary pharmacokinetic profile in man, J Pharm Pharmacol, 1983;35(2):86)

Reference #15 is an interlaboratory study on the accuracy and reproducibility of the RIA and GC methods. This information was requested by the reviewer for reasons outlined in the Comments section of the review. Generally, the data shows that both assays are acceptable for measuring alfentanil concentrations. However, too little raw data was provided to make specific conclusions about the relative merits of the GC and RIA assays. The RIA method appears to be sensitive to alfentanil concentrations greater than 1 ng/ml, whereas the GC method is sensitive at concentrations greater than 3 ng/ml.

## V COMMENTS

1. A study entitled "Optimization of the Radioimmunoassays for Measuring Fentanyl and Alfentanil in Human Serum" by J Schuttler and P White published in Anesthesiology 61:315-320, 1984, demonstrated that measurement of serum alfentanil concentrations by radioimmunoassay(RIA) may result in significant errors and high variability when the technique described in the available alfentanil RIA kit is used. The authors found a 49-94% overestimation of measured alfentanil serum levels when radio-labeled alfentanil was added lastly to the mixture of antiserum and samples(as recommended by Janssen). It is stated that the alfentanil-RIA kits were supplied by Janssen Pharmaceutica, Beerse, Belgium. The sequence of adding the various reagents was as described in the Manual for Radioimmunoassay: Alfentanil. To optimize the RIA for alfentanil, the authors recommended adding the antiserum lastly to the mixture of sample and labeled drug.

On May 31, 1985, in a 3-way telephone connection with representatives of the firm(Jos Heykants in Beerse, Belgium & Carol Karp in Piscataway, N.J.) it was learned that the information in the above article is incorrect. The firm stated that Janseen has always added the antiserum lastly to the mixture of sample and labeled drug and never used or recommended the method described by the Schuttler/White paper. After a request by the reviewer for supportive analytical data, the firm offered to provide documentation of inter-laboratory assay reproducibility that includes laboratory work for the Camu(ref #3) and Bovill(ref #2) studies contained in the NDA. The firm also stated that it would send a copy of their manual for radioimmunoassay of alfentanil. The reviewer requested that the firm document in writing all of the above comments and responses and forward them to the Agency. P. White defended the data in his paper(Anesthesiology 61:315-320, 1984) in a telephone conversation(415-497-6787) with the reviewer on September 27, 1985.

The firm complied with the above request and provided the following data(submission dated 8/23/85) to support analytical methodology.

1. Interlaboratory study of RIA and GC methods.
2. Laboratory manual for the radioimmunoassay of alfentanil(1984)

Review of the analytical data submitted indicates that the GC and RIA methods used for quantitating alfentanil may be acceptable. Too little raw data was provided by the firm to make specific conclusions about the relative merits of the GC and RIA methods. The recommendation given in the laboratory manual(Alfentanil-Radioimmunoassay Kit, catalog A1, June 1983) is identical to that recommended by Drs. Schuttler and White for mixing reagents used in the radioimmunoassay of alfentanil.

It is concluded that intra-assay variability and inter-laboratory differences may account for some of the variability in the observed pharmacokinetic parameters.

2. The issue of activity, if any, of major metabolites has not been adequately addressed by the firm.

3. The following comments pertain to labeling and the proposed package insert dated April 1, 1985.

a. pg. 2; "distribution time of 0.97-1.4 minutes... of 83-92 minutes." "Distribution time" and "distribution half-life" are not equivalent terms. The firm should substitute the word "half-life" for "time" to convey the appropriate meaning. The firm should also avoid using the terms "distribution, redistribution, and elimination" to describe the polyexponential decline in plasma concentrations of alfentanil. The statement should read "The pharmacokinetics of ALFENTA can be described as a three-compartment model, with an mean alpha half-life of approximately 1-3 minutes, a mean beta half-life of approximately 9-17 minutes and a mean gamma half-life of approximately 94 minutes." It should be noted that the values for the pharmacokinetic parameters reported are quite variable. The values given by the firm seem to convey a high degree of accuracy and were adjusted to reflect the data reported in studies by Camu(Ref #3) and Bovill(Ref #2).

b. pg. 2; "The liver and small intestine are the major sites of biotransformation."  
The firm did not provide data that substantiates metabolism by the small intestines.

c. pg. 3; "Approximately 88% of the administered...unchanged drug."

The value 88% was obtained in rat studies. The firm demonstrated that approximately 81% of total radioactivity administered was collected in the urine of 3 human subjects in 24 hours and 88% in 48 hours(ref 6). Unchanged alfentanil excreted in the urine accounted for 0.2-0.5% of the dose administered.

d. pg. 3; "Alfentanil has an immediate onset of action with limited accumulation".

It is unclear how "onset of action" and "accumulation" are related as used in this sentence.

e. pg. 10; section "Impaired hepatic or renal function"

It was demonstrated in study #6 that less than 1% of alfentanil is excreted unchanged by the kidney. The kidney is not an important organ of elimination for the parent drug alfentanil. It is stated that the metabolites of alfentanil are inactive.

It should be noted in the package insert that the free fraction may be greater in patients with renal dysfunction(C<sub>1</sub>cr less than 10 ml/min) than normals, 0.19 vs. 0.06-0.1, respectively.

f. It may be useful to include in the labeling that alpha-1-acid glycoprotein is believed to be the main binding plasma component.

4. The following comments pertain to individual references as cited below.

Reference 2

1. Subjects(patients) received routine anesthetic medications(e.g. diazepam, lorazepam) and alfentanil concomitantly. This situation creates a potential source of variability in the data. Coadministration of other drugs should be considered when evaluating the data from this study.
2. The age of patients varied from approximately 20 to 65 for both treatment groups.

Reference 3

1. Subjects(patients) received routine anesthetic medications(e.g. diazepam, halothane, atropine, etomidate, N<sub>2</sub>O) and alfentanil concomitantly. This situation creates a potential source of variability in the data. Coadministration of other drugs should be considered when evaluating the data from this study.

Reference 4

1. Subjects(patients) received routine anesthetic medications(e.g. diazepam, thiopentone, nitrous oxide) and alfentanil concomitantly. This situation creates a potential source of variability in the data. Coadministration of other drugs should be considered when evaluating the data from this study.
2. The clearance measured in this study is lower than that measured in studies by Camu(ref #3) and Bovill(ref #2). The reason for the difference is not apparent.

Reference 5

1. It is likely that subjects(patients) received routine anesthetic medications and alfentanil concomitantly. This situation creates a potential source of variability in the data. Coadministration of other drugs should be considered when evaluating the data from this study.
2. The data was taken from the English abstract because this study was submitted in French. At best, the results are preliminary.

Reference 6

1. It should be noted that only 3 subjects were utilized in this study and may account for the variability in the data.
2. The activity, if any, of metabolites should be stated or investigated if unknown.

Reference 8

1. Subjects(patients) received routine anesthetic medications(e.g. diazepam, thiopentone, nitrous oxide) and alfentanil concomitantly. This situation creates a potential source of variability in the data. Coadministration of other drugs should be considered when evaluating the data from this study.

Reference 9

1. Subjects(patients) received routine anesthetic medications(e.g. diazepam, thiopentone, nitrous oxide) and alfentanil concomitantly. This situation creates a potential source of variability in the data. Coadministration of other drugs should be considered when evaluating the data from this study.

#### Reference 10

1. There is a discrepancy in the number of subjects enrolled in the study observed when the "clinical" report is compared with the "statistical" report. The clinical report states that 1 patient in group III received alfentanil by infusion. In contrast, the final evaluation in the statistical report has patients receiving the infusion all in Group IV. The data from the statistical report was utilized for review.
2. The values reported in this study are identical to those reported in the abstract "Obesity and Alfentanil Pharmacokinetics", J Bently, et al, Anesth Analg 1983;62:245-92, contained on page 12-00986, vol 1.14 of this submission. It was concluded that the raw data for the abstract was obtained from the study under review(protocol #JRD 39,209/008; vol 1.14).
3. Raw data to support the analytical methodology utilized was not provided. A published article entitled "Rapid and sensitive gas chromatographic method for the determination of alfentanil and sufentanil in biological samples"(in vol 1.8 & 1.10 excerpts) was included in the submission and reviewed. If this was the methodology used to analyze samples from this study it should also be stated in the submission.
4. Values for pharmacokinetic parameters(clearance, volume, half-life) in individual patients and a measure of variability(e.g. standard deviation) were excluded. The firm should have included the pharmacokinetic methods used to generate the parameters.
5. The firm used "body mass index" to define obesity. For completeness of review, formulas to determine body mass index and lean body weight should have been included in the submission.
6. A source of plasma level variability comes from failure to obtain plasma samples at the same times. It is stated on pg 12-00963 of vol 1.14 that plasma levels were collected within five minutes of the stated time point through 30 minutes post administration and thereafter within 15 minutes. Differences in sample collection times are also documented on pg 12-00976, vol 1.14, table 3A. It must be pointed out that the shorter the drug half-life the greater the impact these sampling errors may have on true levels.
7. It must be noted that the doses administered differed from that stated in the protocol and varied from patient to patient.
8. Subjects(patients) recieved routine anesthetic medications(e.g. diazepam, thiopentone, nitrous oxide) and alfentanil concomitantly. This situation creates a potential source of variability in the data. Coadministration of other drugs should be considered when evaluating the data from this study.

#### Reference 13

1. A nonlinear least squares regression program was used to obtain pharmacokinetic parameters. However, an indicator of goodness of fit was not provided.
2. Subjects(patients) recieved routine anesthetic medications(e.g. diazepam, atropine, etomidate, nitrous oxide) and alfentanil concomitantly. This situation creates a potential source of variability in the data. Coadministration of other drugs should be considered when evaluating the data from this study.

#### Reference 14

1. A nonlinear least squares regression program was used to obtain pharmacokinetic parameters. However, an indicator of goodness of fit was not provided.
2. Subjects (patients) received routine anesthetic medications (e.g. enflurane, alcuronium chloride) and alfentanil concomitantly. This situation creates a potential source of variability in the data. Coadministration of other drugs should be considered when evaluating the data from this study.

#### VI Discussion

According to CFR 320.25,d(1), for previously unmarketed active drug ingredients or therapeutic moieties, the purpose of an in vivo bioavailability study involving a drug product containing an active drug ingredient that has not been approved for marketing is to determine:

- (i) The bioavailability of the formulation proposed for marketing; and
- (ii) The essential pharmacokinetic characteristics of the active drug ingredient, such as the rate of absorption, the extent of absorption, the half-life of the therapeutic moiety in-vivo, and the rate of excretion and/or metabolism. Dose proportionality of the active drug ingredient needs to be established after single dose administration and in certain instances after multiple-dose administration. This characterization is a necessary part of the investigation of the drug to support drug labeling.

We agree that the bioavailability of an intravenously administered product is self evident and that a "bioavailability" study per se need not be undertaken. The requirement that essential pharmacokinetic parameters be described still holds for this drug. The data submitted and reviewed adequately characterizes the essential pharmacokinetics of alfentanil.

The analytical issues have been adequately addressed by the firm. However, a request for laboratory inspection (Biomonitoring) has been generated as a result of the analytical uncertainties. It is concluded that assay variability may contribute to the observed variability in the data. Predictions (based on pharmacokinetic parameters) regarding clinical effects can only be general, at best, given the variability in the data.

## VII CONCLUSION

1. The disposition of alfentanil after intravenous administration can be described by a three-compartment open model. The alpha, beta and gamma half-lives are approximately 2, 15, and 94 minutes, respectively. It should be noted that these values are only approximations, as they are quite variable. Factors contributing to this variability must be identified and studied sufficiently to permit use of pharmacokinetic information in a prospective manner.
2. Alfentanil is extensively metabolized. Less than 1% of the administered dose is excreted in the urine unchanged in 48 hours.
3. It appears that the disposition of alfentanil is linear at concentrations up to 1000 ng/ml.
4. Alfentanil is approximately 92% bound to plasma proteins. Alpha-1-acid glycoprotein is believed to be the main binding plasma component for alfentanil.
5. The dose should be carefully adjusted in patients with liver disease, renal disease (because of a possible increase in free fraction and decrease in free clearance), obesity, the elderly and children.
6. It is reported that metabolites of alfentanil are inactive.

## VIII Recommendation

The Division of Biopharmaceutics recommends that the biopharmaceutics/pharmacokinetics portion of the submission (NDA 19-353) be accepted.

Comment number 3 pertaining to labeling should be forwarded to the firm.

*Gene D. Mason Pharm.D. 11/13/85*  
Gene D. Mason, Pharm.D.  
Pharmacokinetic Evaluation Branch

RD Initialed by Mei-Ying Huang, Ph.D.

FT Initialed by C.T. Viswanathan, Ph.D. *CVV*

*11/15/85*

cc: NDA 19-353 orig., HFN-160(2), HFN-226(Mason), Chron, Drug, & FOI Files

GDM:gdm/dea/kek/██████ (6/18/85)

**Appendix I**

**Individual Studies**

Study : Reference #1 (literature reference)

Title: Comparative Pharmacokinetics of Fentanyl and Alfentanil

Investigator/Site: S Bower & J Hull  
Department of Anaesthesia  
University of Newcastle upon Tyne

Dosing: Single dose

Part I - Low dose; simultaneous administration of both drugs by short infusion

- A. fentanyl - approximately 165 ug(see table 1-1) over 2.5 minutes
- B. alfentanil - approximately 164 ug(see table 1-1) over 2.5 minutes

Part II - High dose

- A. alfentanil - 1 mg administered alone by I.V. infusion over 2.5 minutes

Subjects:

Seven healthy volunteers age 24-60 year old and weighing 55-84 kg(see Table 1-1). Subjects also received routine anesthetic medications.

Samples:

Venous blood samples were taken at 2 mins intervals from 0 to 12 mins, and then at increasing intervals until half-hourly sampling was adopted between 90 and 360 mins. The investigation was terminated at 360 mins.

Analytical Methods:

A radioimmunoassay sensitive to approximately 2 pg/ml was used to measure alfentanil. It is reported that cross-reactivity of each drug in assay for the other was negligible. No additional data was provided.

Pharmacokinetic Analysis:

A two-compartment open model was fitted to each set of data. Values of apparent volume of distribution, terminal half-life and total clearance were calculated from the model parameters.

Results:

It is reported that biexponential curves fitted the declining plasma concentrations of both drugs with a percentage fit of 97%. Figure 1-1 shows log-concentration time data for a subject and Figure 1-2 shows data for all subjects.

Pharmacokinetic variables calculated for subjects given simultaneous infusions of alfentanil and fentanyl are in Table 1-2.

Pharmacokinetic variables calculated for subjects given 1 mg of alfentanil are in Table 1-3.

Study: Reference #2 (literature reference)

Title: The Pharmacokinetics of Alfentanil(R39209): A New Opioid Analgesic

Investigator/Site: J Bovill, et al  
Department of Anaesthesia, Academic Hospital  
University of Amsterdam, Netherlands

Dosing: single intravenous bolus

Either alfentanil 50 ug/kg(six patients), or  
alfentanil 125 ug/kg(five patients)

Subjects:

Eleven patients undergoing a variety of surgical procedures were studied. Patients characteristics are in Table 2-1. Subjects also received routine anesthetic medications.

Samples:

Blood - control, 1, 2, 3, 5, 10, 15, 30, 45 and 60 minutes and thereafter every hour until 6 hr(50 ug/kg group) or 8-10 hrs(125 ug/kg group) after injection.

Analytical Methods:

Determined by radioimmunoassay technique. It was reported that no significant cross-reactivity between alfentanil and any of its likely metabolites. The average intra- and inter-assay coefficients of variation were 3.7% and 3.3%, respectively, over a range of 0.18 to 4.4 ng/ml. For comparison with RIA methodology, plasma samples from two patients were assayed separately using liquid-liquid extraction which is specific for unchanged drug.

Pharmacokinetic Analysis:

Alfentanil plasma concentration time data was fitted by computer to bi- and tri-exponential equations using weighted nonlinear least square regression analysis. Volumes of distribution, total body clearance, and the apparent first-order intercompartmental transfer rate constants were calculated using equations described by Gibaldi and Perrier. Comparison between groups was by unpaired student's t-test, and P values less than 0.05 were considered significant.

Results:

Figure 2-1 shows mean plasma concentration vs time displayed graphically.

Kinetic parameters are shown in tables 2-2 and 2-3. The plasma concentration time curves were best described by triexponential equations in all patients. Neither the half-lives nor the dose/intercept were significantly different between the groups, thus the data from the two groups was discussed collectively.

Author's Conclusion:

1. The disposition of alfentanil can be described by a three compartment open model.

Study: Reference #3 (Literature reference)

Title: Pharmacokinetic of Alfentanil in Man

Investigator/Site: F Camu, et al, Department of Anesthesia,  
Flemish University of Brussels, School of Medicine  
University Medical Center, Brussels

Dosing: single bolus dosing

alfentanil - 120 ug/kg, administered as a bolus over 30 seconds

Subjects: Five healthy female patients scheduled for routine surgery and free of clinical or biochemical evidence of hepatic or renal disease were included in the study. Patient data are shown in Table 3-1. Subjects also received routine anesthetic medications.

Samples:

blood - control (just before injection), 2, 5, 10, 15, 30, 45, 60, 90, and 120 minutes after injection, then hourly for an additional 4 hours.

Analytical Methods:

Plasma alfentanil levels were determined by gas-liquid chromatography with specific thermionic detection (R Woestenborghs, et al, J Chromatogr, 1981;224:122-7).

Pharmacokinetic Analysis:

Plasma levels of alfentanil from each patient were fitted to a three-compartment open-mamillary model using nonlinear least-squares regression analysis. Apparent volume of distribution, volume of the central compartment, half-lives of the distribution and elimination phases, total plasma clearance, first-order rate constants for drug transfer between compartments, and the elimination rate constant were calculated using methods published by Gibaldi and Perrier (Pharmacokinetics, New York, Marcel Dekker, 1975:4-96). In this model, drug elimination was assumed to occur via the central compartment with first-order kinetics.

Results:

- Plasma concentration of alfentanil at each sampling time for individual patients is shown in Table 3-2.
- Mean plasma concentration in five subjects is displayed graphically in Figure 3-1.
- In Table 3-3 are summarized the nonlinear least-squares estimates for the three-compartment model parameters listed, together with the model-derived pharmacokinetic parameters calculated for each patient. It is reported that the goodness of fit, as indicated by the sum of weighted squares of deviation between observed and predicted concentration values, was significantly better for the three-exponential model than the two-exponential model.
- The time course of the apparent concentrations expressed as fractions of the alfentanil dose appearing in the three compartments of the model is described in Figure 3-2.

Author's Conclusions:

1. The plasma concentration decay of alfentanil can be adequately described by a three-compartment open-mamillary model.

Study: Reference #4 (literature reference)

Title: Pharmacokinetics of the Infusion of Alfentanil in Man

Investigator/Site: R Fragen, et al  
Department of Anaesthesia  
Northwestern University Medical School  
Chicago, Illinois, U.S.A.

Dosing: simultaneous administration of bolus and short infusion

Bolus - alfentanil 80 ug/kg over 30 seconds  
Infusion - alfentanil 3 ug/kg/min; It is reported that the infusion was given for 1 hour so that each patient received a total alfentanil dose, bolus plus infusion, of 260 ug/kg.

Subjects: 5 healthy patients (two male), scheduled for elective surgery participated in the study. Patient characteristics are given in Table 4-1. Subjects also received routine anesthetic medications.

Samples:  
Blood - 2, 5, 10, 15, 30, 45 and 60 mins after start of bolus injection, and 2, 5, 10, 15, 30, 60, 120, 240 and 360 mins after termination of the infusion

Analytical Methods:

It is reported that plasma alfentanil concentrations were measured with a sensitive and specific radioimmunoassay by Janssen Pharmaceutica.

Pharmacokinetic Analysis:

Kinetic parameters were determined by NONLIN analysis. It is reported that the time course of the mean plasma concentrations of alfentanil indicated that the disposition could be described by a two-compartment model. The plasma concentration-time curve was analyzed by the NON-LIN program and was divided into three parts: part one was the input of the bolus injection plus the infusion; part two was the infusion minus the elimination of the bolus, and part three was the elimination period.

Results:

- Measured plasma concentrations for each patient are in table 4-2.
- Mean plasma concentration-time curve is displayed graphically in Figure 4-1.
- Pharmacokinetic parameters calculated for each patient are in Table 4-3.

Author's Conclusions:

1. Pharmacokinetic parameters reported are similar to those previously reported in the literature for alfentanil.

Study: Reference #5 (firm's clinical report, English abstract)

Title: Pharmacokinetics of Alfentanil Following Long-term Intravenous Infusion

Investigator/Site: J Levron, et al  
Laboratoire de pharmacocinetique et Service Medical,  
Janssen-Le Brun, Aubervilliers, Paris(France)

J Callar, J Kielen  
Hospital St. Eloi - Montpellier (France)

Dosing: The following infusion schemes were used:

Loading Dose (ug/kg)	Infusion Rate (ug/kg/min)	Duration of Infusion(hrs)	Number of Patients
25	1	3.5	1
100	2.5	4	1
280	1.5	8	2

Subjects: Four patients undergoing surgery.

Samples: Serial plasma samples were obtained during and after termination of the infusion.

Analytical Methods: Methods not stated in abstract.

Pharmacokinetic Analysis: Methods not stated in abstract.

Results:

The following pharmacokinetic parameters were obtained:

	Mean +/- S.D. (n = 4)
half-life(beta)	101 +/- 16.7 min
Vd(beta)	0.52 +/- 0.22 l/kg
clearance	3.7 +/- 1.7 ml/min/kg

Tables: (It is acknowledged that the following tables listed are in French)

Table 5-1: Individual doses and patient characteristics

Table 5-2: Individual pharmacokinetic parameters

Figure 5-1 thru 4: plasma concentration-time profiles for individual subjects

Study: Reference #6 (firm's clinical report)

Title: Plasma levels, urinary excretion and metabolism of alfentanil in man

Investigator/Site: W Meuldemaans, et al  
Departments of Drug Metabolism and Pharmacokinetics,  
Analytical Research and Clinical Research  
Janssen Pharmaceutica, B-2340 Beerse  
Belgium

Dosing: single dose, short infusion

alfentanil-3H base : 2.5 mg in 50 ml solution, over 60 minutes

Subjects: Three healthy male volunteers, weighing 72-76 kg, age 28-43, height 175-183 cm, participated in the study. No medication was allowed from one week prior to and during the study.

Samples:

Blood - before start of infusion, and at 0 (end of infusion), 3, 8, 15, 30 mins, and 1, 2, 3, 4, 6, 8, 12 and 24 hours after the end of the infusion.

Urine - control sample, infusion sample(-1 to 0 hr) voided just after the end of infusion, and 0-1, 1-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-36 and 36-48 hours after the end of infusion.

Analytical Methods:

plasma - scintillation cocktails from duplicate samples were prepared for determination of total radioactivity. Other aliquots were prepared for determination of non-volatile radioactivity levels. Plasma levels of unchanged alfentanil were determined by a gas chromatographic method (Woestenborghs, et al. Rapid and sensitive gas chromatographic method for the determination of alfentanil and sufentanil in biological samples. J. Chrom., 1981; 224: 122-127;)

urine - urine levels of the total radioactivity, of non-volatile radioactivity and of the parent drug were determined as described for plasma

Methods of investigating the nature, mass balance, and characterization of urinary metabolites and study of plasma metabolites were described in detail. Analytical instrumentation included HPLC, mass spectrometry, and liquid scintillation spectrometry.

Pharmacokinetic Analysis:

Pharmacokinetic parameters were estimated by either the nonlinear extended least squares curve fitting program ELS-PLUS or were calculated by standard methods described in 'Pharmacokinetics', Gibaldi & Perrier, Marcel Dekker, Inc., 1982.

## Results:

### Pharmacokinetics

- Table 6-1 presents the individual and mean plasma levels of the total radioactivity and of the parent drug.
- Figure 6-1 displays mean plasma levels of total radioactivity, non-volatile radioactivity and of the parent drug.
- Figure 6-2 displays individual plasma levels of total radioactivity, non-volatile radioactivity and of the parent drug.
- Table 6-2 presents pharmacokinetic parameters for individual patients for alfentanil as calculated from the plasma level-time data.

### Excretion/Metabolism

- Table 6-3 presents data on urinary excretion of total radioactivity and Figure 6-3 shows the cumulative excretion of total radioactivity graphically.
- Table 6-4 gives urinary output, urine levels of unchanged alfentanil and of its main metabolite noralfentanil.
- Table 6-5 gives mass balance of alfentanil and its major metabolites in the urine over a 24 hour period.
- Figure 6-4 shows the proposed metabolic pathways for alfentanil.

### Firm's Conclusion:

1. Pharmacokinetic parameters for the parent drug were similar to those previously reported in the literature.
2. Alfentanil is rapidly metabolized into many metabolites. Unchanged alfentanil excreted with the urine accounted for only 0.2-0.5 % of the dose.
3. Noralfentanil was the main urinary metabolite and accounted for 30.9% of the dose excreted in the urine in 24 hours. The second major urinary metabolite of alfentanil was HAM2 (a glucuronide of HAM5) which accounted for 14.4% of the dose excreted in the urine in 24 hours. A large number of minor metabolites were present in the urine.

Study: reference #7 (literature reference) Vol. 1.8/1.10, pg 10-00305

Title: Plasma Protein Binding and distribution of Fentanyl, Sufentanil, Alfentanil and Lofentanil in Blood

Investigator/Site:

W.Meuldermans, R. Hurkmans, J. Heykants  
Department of Drug Metabolism and Pharmacokinetics  
Janssen Pharmaceutica, B-2340 Beerse, Belgium

Methods:

Drugs - Tritium-labelled fentanyl, sufentanil, alfentanil and lofentanil are presented in figure 2-1.

Proteins - Pentex<sup>R</sup> human plasma proteins, albumin fatty acid free, alpha-globulins, alpha-1-globulins, Beta-globulins, gamma-globulins, and glycoproteins

Blood and Plasma - Male Wistar rats, male Beagle dogs, male healthy human volunteers (who had not taken any medications for at least 2 weeks)

Binding to plasma proteins - Equilibrium dialysis was performed using a Dianorm system. A dialysis time, of 4 hours was used because equilibrium was obtained within 2-3 hours for mixtures of plasma with the various drugs.

Radioactivity measurements - Drug concentrations were determined by radioactivity measurement, using a Packard Tri-Carb<sup>R</sup> 460 CD microprocessor controlled multi-user liquid scintillation system with automatic external standardization.

Results:

Protein Binding and distribution in plasma of rats, dogs and man is shown in Table 7-1.

The effect of plasma dilution on free drug fraction is represented in figure 7-2. A reduction of the plasma protein concentration to 2/3 of the value resulted in a relative increase in the percent of free drug of about 50, 35, 25, and 55% for fentanyl, sufentanil, alfentanil and lofentanil respectively.

The influence of drug concentration on plasma protein binding was studied and showed that the degree of binding was  $92.0 \pm 0.8\%$  in the range 10-1000 ng/ml for alfentanil.

Comparison of the free fraction of alfentanil in human albumin solutions (figure 7-3) with that in plasma (figure 7-2) suggests that albumin is not the only binding protein. Therefore, binding to varying concentrations of other plasma proteins was also measured. Alfentanil was not or only very slightly bound to alpha-1, beta, and gamma-globulin fractions. Alfentanil was bound to a small extent to the alpha-globulin fraction (figure 7-4). In contrast, binding to glycoprotein (6% alpha-1-acid glycoprotein) was high (figure 7-5). Figure 7-6 shows the relation between the free drug fraction and the alpha-1-acid glycoprotein concentration in healthy volunteers. A significant linear relation between the alpha-1-acid glycoprotein concentration and the free drug fraction in plasma samples was observed.

In contrast to fentanyl, the free fraction of alfentanil in human plasma was independent of pH (figure 7-7). The actual changes in free fraction were nil or very small (over pH 7.4 to 7.0: + 6% ; over pH 7.4 to 7.8: unchanged).

The distribution of alfentanil in blood is given in Table 1.

Conclusions:

1. Alfentanil binding to plasma of humans is 92%.
2. Plasma protein binding of alfentanil is independent of drug concentration over the range 10-1000 ng/ml.
3. Plasma protein binding of alfentanil is not altered by small variations around physiologic pH.
4. Alpha-1-acid glycoprotein could be the main binding plasma component for alfentanil.

GDM:kek: [REDACTED] : 4-17-85

Study: Reference # 8 (unpublished report)

Title: Alfentanil Pharmacokinetics in Patients with Cirrhosis

Investigator/Site: C. Ferrier, et al  
Department of Anesthesia, Saint Jacques Hospital

Dosing: single dose, IV bolus

alfentanil - 50 ug/kg

Subjects:

Eleven patients with biopsy proven cirrhosis (secondary to alcoholism) were enrolled in the study. It was reported that none of the patients were ingesting alcohol for at least one week and none had ascites. Ten control patients with normal hepatic and renal function were enrolled in the study. The controls underwent abdominal surgery. Patient characteristics are given in Table 8-1. All subjects also received routine anesthetic medications.

Samples:

Blood - 5, 10, 15, 30, 60, 90, 120, 180, 240, 300, 360, 480 and 600 minutes after drug administration.

Analytical Methods:

Alfentanil plasma concentration was determined by radioimmunoassay sensitivity to 0.5 ng/ml. It is reported that the antibody used for alfentanil radioimmunoassay did not cross react with fentanyl.

Pharmacokinetic Analysis:

Clearance was determined by dividing the dose by the area under the curve as determined by the linear trapezoidal rule. The volume of distribution at steady state was determined as described by Benet and Galeazzi (JPS, 1979; 68(8):1071). The terminal elimination half-life was determined by linear regression of the log-plasma concentration versus time data after the distribution phase. Pharmacokinetic parameters based upon free alfentanil levels were also determined. Plasma protein binding of alfentanil was measured by equilibrium dialysis.

Results:

Figure 8-1 shows mean plasma concentration-time curve for control and cirrhosis groups.

Table 8-2 gives pharmacokinetic parameters for individual patients in control and cirrhosis groups.

Table 8-3 gives protein binding study results and pharmacokinetic parameters based on unbound concentrations.

Figure 8-2 shows relationship between free alfentanil concentrations and alpha-1-acid glycoprotein concentrations.

Author's Conclusions:

1. The pharmacokinetics of alfentanil are altered by cirrhosis: plasma clearance is decreased and unbound fraction is increased.
2. The consequences of these changes are a greater effect due to the increase free fraction and a prolonged effect due to the increased elimination half-life.

Study: Reference # 9 (Firm's Clinical Report)

Title: Pharmacokinetics of alfentanil in patients with chronic renal insufficiency

Investigator/Site: J Levron, et al  
Janssen Le Brun, Aubervilliers, Paris, France  
Janssen Pharmaceutica, Beerse, Belgium  
Ambroise Pare Hospital, Boulogne, France

Dosing: single bolus dose

alfentanil - 50 ug/kg intravenously, over 1 minute

Subjects:

Nine surgical patients suffering from renal insufficiency with a creatinine clearance less than 10 ml/min were enrolled in the study. Individual patient demographic data is given in Table 9-1. Subjects also received routine anesthetic medications.

Samples:

Blood - 5 mins prior to dose, then 5, 10, 15, 30, 45, 60, 90 minutes, 2, 3, 4, 5, 6 and 7 hours after the injection.

Analytical Methods:

Alfentanil plasma concentrations were determined by radioimmunoassay (method of Michiels, et al, Janssen Pharmaceuticals). It is reported that the sensitivity of the method is  $0.05$  ng/ml in plasma, and the intra- and inter-test variation coefficients amount to 3.7 and 3.3% respectively for spiked quantities of 0.09 to 2.2 ng. Plasma protein binding was measured by equilibrium dialysis.

Pharmacokinetic Analysis:

The fitting of plasma concentration curves as a function of time was performed by non-linear weighted regression (NONLIN). A bicompartamental model was used for 7 patients. The kinetic parameters of 2 patients could only be solved according to a monocompartmental model because of the absence of samples within short times.

## Results:

Tables 9-2a,b,c gives alfentanil plasma concentration-time values for individual patients.

Table 9-3 gives rate constants and half-lives for individual patients.

Table 9-4 provides pharmacokinetic parameters for individual patients.

Table 9-5 provides mean pharmacokinetic parameters in patients suffering from renal insufficiency.

Table 9-7 displays plasma protein binding data in patients with renal insufficiency. A statistically significant correlation (P less than 0.05) between the serum concentration of albumin or that of alpha-1-acid glycoprotein and the free fraction of alfentanil could not be found.

## Firm's Conclusion:

1. The pharmacokinetics of alfentanil in patients with chronic renal insufficiency appear not to be substantially modified as compared with normal patients.
2. An increase in free fraction due to a decrease in plasma protein binding not explained by a modification in serum protein concentration does not modify distribution and elimination parameters of alfentanil but may increase its effect.

Study: reference #10 (firm's clinical study)

Title: Clinical Evaluation of Alfentanil

Investigator/Site: Burnell Brown, Jr. M.D., Ph.D.  
John Bentley, M.D.  
Department of Anesthesiology  
The University of Arizona  
Health Sciences Center  
Tucson, Arizona 85724

Objective: (1) To evaluate renal and hepatic function in patients receiving alfentanil in general surgical procedures, and (2) compare pharmacokinetics in various patient types

Design: open, no crossover, no randomization, clinical investigation

Patients:

Forty-four(44) ASA class I or II patients participated in the study, however 6 patients were excluded from all analysis due to their receiving doses of alfentanil much higher than required by the protocol. All patients were male or female surgical patients(with normal renal and hepatic function) at The University of Arizona, Health Sciences Center, in Tucson. The study group was divided as follows:

- a. Group I consisted of 8 patients (1 was excluded) at least 18 and less than 40 years old
- b. Group II consisted of 6 patients (1 was excluded) between the ages of 40 and 60 years old
- c. Group III consisted of 12 patients (3 were excluded) over the age of 60
- d. Group IV consisted of 18 (1 was excluded) morbidly obese patients (defined as having a body mass index greater than 30) and at least 18 and less than 60 years old

Note: The protocol designated that each of the 4 groups would be further subdivided into Subgroups A and B (approximately 5 patients each group). The patients in Subgroup A received alfentanil by bolus. Patients in Subgroup B received alfentanil by infusion.

No patients included in groups I,II or III were morbidly obese.

Criteria for inclusion of patients is in table 10-3a and criteria for exclusion of patients is in Table 10-3b.

Patients underwent routine physical examination, history and preoperative laboratory analysis(hematology, urinalysis, chemistry).

Table 10-1 contains characteristics of patients for all groups. (this table also contains data for an unidentified patient excluded from analysis but not from the table)

Table 10-2a contains characteristics of patients who received bolus dosing.

Table 10-2b contains characteristics of morbidly obese patients listed by bolus vs infusion.

Dosing: Patients will be fasted for at least 8 hours.

I. Pre-op Medications: see appendix 2 for this report

II. Induction Medications: see appendix 2 for this report

III. Maintenance PROTOCOL (alfentanil dosing only; other medications are listed in appendix 1) - Patients were divided into groups as described in the section patients.

Subgroup A (Groups I, II, III and IV)

IV BOLUS -- Alfentanil, 75 ug/kg, as an IV bolus

Subgroup B (Groups I, II, III and IV)

SHORT LOADING INFUSION FOLLOWED BY MAINTENANCE INFUSION

a. Groups I, II and III:

1. 10 mg alfentanil administered over a 5 minute period (this may be started prior to thiopental and intubation)
2. maintenance infusion: 80 ug/minute until 10-15 minutes prior to end of operation

b. Group IV patients will receive:

1. 4 mg alfentanil administered over a 5 minute period (this may be started prior to thiopental and intubation)
2. maintenance infusion: 45 ug/minute until 10-15 minutes prior to end of operation

Note: Obese patients with a body mass index over 25 were dosed on estimated lean body weight. Those with a body mass index under 25 were dosed by their true body weight.

#### IV. Maintenance-ACTUAL DOSES RECEIVED

In contrast to the design of the protocol as listed above, 9 patients received alfentanil infusion (all in group IV). The remaining 29 patients received a single bolus dose of alfentanil. In addition, the doses administered differed from that stated in the protocol and varied slightly from patient to patient. The reason for the deviation from protocol was not stated in the submission.

Actual doses administered by IV bolus are given in table 10-4.  
Actual doses administered by infusion are given in table 10-5.

Patients 1, 2, 3, 4, and 5 received bolus alfentanil doses ranging from 201 to 1,000 ug/kg, while the other bolus alfentanil doses ranged from 76 to 120 ug/kg. For this reason these patients (1, 2, 3, 4, and 5) were excluded from all analyses. Patient 32 received a total infusion alfentanil dose of 298 ug/kg while the other total infusion alfentanil doses ranged from 50 to 79 ug/kg. For this reason this patient was excluded from all analyses.

#### Concurrent Medications (all groups):

All concurrent medications were continued in the perioperative period as clinically indicated. All such medications were entered on the case record form.

#### Specimens:

Blood: Obtained intraoperatively - 1, 3, 5, 10 and every 15 minutes post-alfentanil administration; obtained postoperatively 15 and every 30 minutes for 4 hours, then at 8 and 12 hours for select patients.

Note: Plasma samples were not always collected at the same times. All plasma level data analyzed was collected within 5 minutes of the time point through 30 minutes post-administration, and within 15 minutes after that time point.

#### Analytical Procedures:

A gas chromatographic derivitization assay was used. Data to support sensitivity, linearity, reproducibility and specificity of the assay was not provided. The identity of the method was omitted.

#### Results:

A. Median alfentanil plasma levels at each time point were compared by treatment group. A lognormal distribution was assumed and median values were subjected to statistical evaluation.

In patients who received bolus dosing, no statistically significant treatment differences were found through 150 minutes (2.5 hours) post administration. Statistically significant treatment group differences were found at 180 minutes (3 hrs), 240 minutes (4 hrs), 300 minutes (5 hrs), 480 minutes (8 hrs) and 720 minutes (12 hrs) post administration. At these time points the median plasma level for group IV is higher than that of groups I, II and III. Statistically significant differences by group are given in table 10-6.

The median plasma levels for group III was higher than those of groups I and II with many of the differences between groups I and III being statistically significant. No statistically significant differences were found between groups I and II.

Comparison of Alfentanil plasma levels were performed with one-way analysis of variance.

## B. Pharmacokinetic Parameters (means)\*

<u>yrs.</u> <u>Parameter</u>	<u>Treatment Group</u>		
	<u>Elderly</u>	<u>Obese</u>	<u>Nonobese, less than 60 YO</u>
Beta Half-life(min)	127	172	92
Clearance(ml/min)	225	179	321
Vd steady-state(L)	30.4	35.0	30.0

\*Brown B and Bentley J: Personal Communication, date?;(see note below); standard deviations not provided

### Significant differences:

1. Beta half-life  
(P less than 0.05) - Elderly vs. nonobese (less than 60 YO)  
(P less than 0.005) - obese (less than 60 YO) vs nonobese (less than 60 YO)
2. Clearance  
(P less than 0.01) - obese (less than 60 YO) vs nonobese (less than 60 YO)

Note: The values reported in this study are identical to those reported in the abstract "Obesity and Alfentanil Pharmacokinetics", J. Bentley, et al, Anesth Analg 1983;62:245-92, contained on page 12-00986, vol 1.14 of this submission. Although not specifically stated in the study, it was concluded that the raw data for the abstract was obtained from the study under review (protocol #JRD 39,209/008; vol. 1.14). Information contained in the abstract was reviewed in conjunction with information contained in the study.

### Tables:

- Table 10-6: Mean alfentanil plasma levels for infusion patients
- Table 10-7: Mean alfentanil plasma levels for bolus patients
- Table 10-8: Median alfentanil plasma levels for bolus patients
- Figure 10-1: Median alfentanil plasma levels from 0 to 30 minutes displayed graphically for bolus patients
- Figure 10-2: Median alfentanil plasma levels from 30 to 300 minutes displayed graphically for bolus patients
- Figure 10-3: Median alfentanil plasma levels from 0 to 30 minutes for infusion patients Study: reference #12
- Figure 10-4: Median alfentanil plasma levels from 30 to 300 minutes for infusion patients
- Table 10-9: Mean Pharmacokinetic Parameters for alfentanil
- Appendix 10-1
- Appendix 10-2

### Firm's Conclusions:

1. Plasma levels of alfentanil peak within one minute, with the bolus technique providing higher initial levels than the infusion technique and equally sustained levels.
2. The initial dose of alfentanil should probably be reduced in elderly patients
3. Obese patients should be dosed on lean body weight.

Study: Reference #11(literature reference) Vol. 1.8/1.10 b., pg 10-00250

Title: Rapid and sensitive gas chromatographic method for the determination of alfentanil and sufentanil in biological samples(Journal of Chromatography, 224(1981) 122-127)

Investigator/Site:

R. Woestenborghs, L. Michielsen, J. Heykants  
Department of Drug Metabolism and Pharmacokinetics  
Janssen Pharmaceutica Research Labs., B-2340 Beerse (Belgium)

Objective: To describe a rapid, sensitive and specific gas chromatographic procedure for the determination of alfentanil(AF) and sufentanil(SF) in plasma and other biological samples.

Apparatus: All the analyses were performed on a [REDACTED] gas chromatograph equipped with a thermionic specific detector, containing an electrically heated ceramic-alkali bead. Nitrogen was used as a carrier gas at a flow-rate of 35 ml/min. A [REDACTED] data system was used for the integrations, the calculations and the plotting of the chromatograms.

Procedure: Plasma and Urine samples - using an internal standard, the sample aliquot was subjected to a series of centrifugations, separations and extractions. The sample was evaporated to dryness under nitrogen in a water bath, reconstituted with methanol, and injected into the gas chromatograph.

Alfentanil standard curves were prepared by spiking blank human plasma with AF at concentrations ranging from 0.001 to 1 ug/ml, and with IS at a fixed concentration of 0.1 ug/ml. In the same way, sufentanil standard curves were prepared using 0.1 ug AF per ml as the internal standard. These samples were extracted and chromatographed as described above and the peak area ratios of AF and SF, relative to their corresponding internal standard, were plotted against the concentrations of AF and SF, respectively.

Tissue Samples - Animal tissues were ground by means of a Waring commercial blender and homogenized in distilled water before subjection to a series of extractions followed by evaporation and reconstitution. An aliquot of the sample was injected into the gas chromatograph .

**Results:**

The chemical structures of alfentanil, sufentanil and the internal standard are given in figure 11-1.

Gas chromatograms of extracts from rat plasma and rat heart tissue are shown in figure 11-2.

The calibration curves for AF and SF, extracted from plasma and tissue, are given in table 11-1.

The minimum detectable amount of AF and SF was reported to be 1 ng/ml of plasma and 2 ng/g of tissue.

It is reported that reproducibility was checked by analyzing samples of different animal tissues (liver, kidney, pancreas, fat) spiked with several concentrations of alfentanil. The results are given in table 11-2. The recovery over the concentration range studied was  $89 \pm 4\%$  (mean  $\pm$  S.D., n=6) and the precision was 3.0%.

Figure 11-3 shows a plasma concentration versus time curve generated using the analytical methodology described herein. The patient received 0.125 mg/kg intravenously.

**Study:** reference #12

**Title:** Radioimmunoassay of the new opiate analgesics alfentanil and sufentanil--Preliminary pharmacokinetic profile in man.  
J Pharm Pharmacol, 1983;35(2):86-93

**Investigator/Site:** M Michiels, et al  
Department of Drug Metabolism and Pharmacokinetics  
Janssen Pharmaceutica, B-2340 Beerse, Belgium

**Note:** only data pertaining to alfentanil will be discussed

**Materials/Methods:**

All drugs and test compounds were synthesized in the Janssen Research Laboratories, Beerse, Belgium. Preparation of the hapten-derivatives, of the immunogens and immunization procedures were described in detail.

Standard curves of alfentanil were obtained by incubating increasing amounts of unlabelled drug together with fixed amount of the radioligand in the presence of 0.2 ml of a dilution of antisera which bound nearly 30-35% of the tracer, as found by previous titration.

The inter- and intra-assay variability and the accuracy of the procedure were tested over 3 weeks by repetitive analysis of alfentanil standards, added to control human plasma and by assaying increasing volumes of a same plasma sample. All samples were assayed in duplicate.

Procedure in man - Alfentanil was injected IV as a bolus in patients at 50 and 125 ug/kg. Blood samples were collected before, and from 1 min to 6 hour after the bolus injection. Plasma samples were determined by RIA, either directly or after selective extraction, using antibodies directed to alfentanil. Drug concentrations in man were calculated from simultaneously run standard curves processed in the same way as the unknown samples.

Comparison with Gas Chromatography - Results of plasma samples obtained from patients and analyzed by RIA without prior extraction were compared to analysis of plasma extracts by gas chromatography according to Woestenborghs, et al (reference #11 of this review).

## Results:

### Assay Characteristics

**Specificity** - It was reported that non-specific binding to control rabbit serum was less than 1.5% at dilutions studied. Following logit transformation a standard curve for unlabelled alfentanil added to control plasma was reported to give a linear response from 0.05 to 5 ng if the limit of significance was restrained to 10% inhibition of (<sup>3</sup>H-alfentanil binding). The specificity of the antiserum towards various structural congeners and possible metabolites of alfentanil is shown in Table 12-1. Fentanyl, sufentanil, carfentanil and lofentanil did not bind to any measurable degree to alfentanil antibodies(see Table 12-2).

**Reproducibility** - The intra- and inter-assay coefficients of variation were reported to be 3.7 and 3.3% respectively in a range of 0.09 to 2.2 ng per test tube. To insure that the RIA gave a quantitative measure of alfentanil, known amounts added to control human plasma were measured at various occasions. The correlation found between calculated and measured alfentanil concentrations was reported to be excellent (slope = 0.941; r = 0.999) and C.V. values were less than 9%(22 determinations of each pool).

**Validation** - The validity of the assay for alfentanil in human plasma samples was demonstrated by the assay, either directly or after selective extraction, of samples obtained from patients who received 50 ug/kg IV. It is reported that the regression line calculated for the plasma concentration of alfentanil determined after extraction versus alfentanil levels measured directly in pooled plasma samples, showed a slope of 1.27 and an intercept of nearly 1.0. The correlation coefficient was 0.998 over a concentration range of 2 to 540 ng/ml(n = 12). The results obtained by RIA(without extraction), were compared to those obtained by gas chromatographic analysis of samples. The correlation coefficient(r) found was 0.998(log y = 0.96 log x + 0.07, range 5-1670 ng/ml, n = 22).

Plasma concentrations in two subjects after an intravenous bolus of 50 ug/kg are shown in figure 12-1.

**Sensitivity** - The limit of detection was reported to be 50 pg for alfentanil.

Study: Reference #13 (literature reference)

Title: Alfentanil Kinetics in the Elderly

Investigator/Site: H Helmers, A Van Peer, et al  
Department of Anaesthesia, Hospital De Lichtenberg,  
Amersfoort, The Netherlands  
Departments of Pharmacokinetics and Clinical Research  
Janssen Pharmaceutica, Beerse, Belgium

Dosing: Single dose

bolus - 50 ug/kg alfentanil over 2 minutes

Subjects: Fifteen elderly patients (68 to 91 YO) and 9 younger adult patients (27 to 44 YO) scheduled for intra-abdominal surgery were included in the study. It is reported that no patient had significant impairment of hepatic or renal functions. Subjects also received routine anaesthetic medications (e.g. diazepam, atropine, etomidate, nitrous oxide)

Samples:

Blood - 3, 5, 10, 30, 60, 120, 180, 240, 360 and 480 minutes after dosing.

Analytical Methodology:

Radioimmunoassay (method of Michiels, et al, J Pharm Pharmacol 35:86-93, 1983). The detection limit of the assay was reported as 0.1 ng/ml.

Pharmacokinetic Analysis:

Plasma concentration-time data were fitted to a two compartment open model. Initial estimates of parameters were obtained by the method of residuals. Final estimates were calculated by the nonlinear least-squares regression program of SAS. Some parameters were calculated by standard methods published by Gibaldi and Perrier (Pharmacokinetics, New York, Marcel Dekker, Inc., 1975).

Results:

Time course of mean plasma concentrations in young adults and in elderly subjects are shown in Fig 13-1.

Kinetic parameters for both groups are listed in Table 13-1.

Author's Conclusion:

1. Alfentanil seems to be equally distributed over the same initial distribution space in elderly and younger adult subjects.
2. As reflected in  $V_{dss}$  and  $V_{darea}$ , distribution of alfentanil to slower equilibrating tissues was not influenced by age.
3. The prolonged half-life ( $\beta$ ) in elderly subjects and the unchanged volumes of distribution can be explained by a reduction in hepatic clearance.

Study: Reference #14

Title: Pharmacokinetics of alfentanil in children with an age of 5 to 8 years.

Investigator/Site: J Levron, B Flaisler & P Stephan  
Laboratoire de pharmacocinetique et Service Medical,  
Janssen-Le Brun, Aubervilliers, Paris (France)  
C Saint Maurice  
Hospital St. Vincent de Paul, Paris (France)

Dosing: Single IV dose of alfentanil - 20 ug/kg over 1 minute

Subjects: Eight children between 5 and 8 years of age hospitalized for short surgical interventions were included in the study. It is reported that all patients had normal hepatic and renal functions and did not have metabolic or cardiovascular disorders. Patient characteristics are given in table 14-1.

Samples:

blood - before (control), 1, 3, 5, 7, 10, 15, 30, 45, 60, 90 minutes and 2, 3, 4, 5, and 6 hours after dosing.

Analytical Methods:

Determined by the RIA method of Michiels, et al [J Pharm Pharmacol, 1983;35(2):86]. Plasma protein binding was determined by equilibrium dialysis.

Pharmacokinetic Analysis:

It is reported that smoothing of the plasma concentration-time curves was done by computer exponential regression with the FARMSTRIP program in APL language developed by Janssen Pharmaceutica (J Heykants).

Results:

Plasma concentration-time points for each patient are given in Table 14-2. Individual and mean pharmacokinetic parameters are given in Table 14.3. Plasma protein binding is given in Table 14-4.

It is reported that the disposition of alfentanil was described by a 2 compartment model. A third compartment may have been present but was not perceived because of too few early sampling times.

Author's Conclusions:

1. The distribution and elimination half-lives in children ( $\alpha = 5$  min,  $\beta = 40$  min) are shorter than that in adults.
2. The value of the average clearance (4.7 ml/min/kg) is similar to that observed in adults.
3.  $V_d(\beta)$  in children (0.29 l/kg) is smaller than that in adults.
4. Plasma protein binding in children (85-90%) is similar to that observed in adults.

Study: Reference #15

Title: Determination of alfentanil in human plasma samples by gas chromatography or radioimmunoassay: an interlaboratory study.

Investigator/Site: R Woestenborghs, F Van Rompaey, J Heykants  
Department of Drug Metabolism and Pharmacokinetics  
Janssen Pharmaceutics, B-2340 Beerse, Belgium

Objective: To evaluate and compare in spiked and clinical plasma samples the existing assay methods (RIA & GC) for the determination of alfentanil. The accuracy and reproducibility of the RIA and GC methods will be assessed for 8 different laboratories.

Methods: Ten blank plasma samples, spiked with known amounts of alfentanil and twenty samples from treated patients were analyzed with gas chromatograph (GC) and/or radioimmunoassay (RIA) by 8 different laboratories.

Radioimmunoassay - performed by laboratories 1, 2, 3, 5, 6, 7 and 8. Each laboratory used its own version of the procedure, described by Michiels, et al (J Pharm Pharmacol, 35:66-93, 1983). Laboratory 1 applied the RIA method with and without extraction.

Gas Chromatography - performed by laboratories 1, 4 and 8. The procedures were based on the method described by Woestenborghs, et al (J Chromatogr, 224:122-127, 1981).

The laboratories that participated in the study are listed in table 1.

### Results:

Table 3 shows alfentanil concentrations in the spiked control samples as found by the different laboratories.

Table 4 gives accuracy and precision based on differences between estimated concentrations and the known, "true" values for the spiked control samples.

Tables 5 & 6 gives linear regression equations for spiked plasma samples.

Tables 7 & 8 gives linear regression equations for clinical samples.

Figure 1 is the correlation between alfentanil plasma concentrations determined by the tested methods and the concentrations from the spiked test samples.

Figure 2 is the correlation between alfentanil plasma concentrations determined by the tested methods and the reference method in a series of clinical samples.

### Firm's Conclusion:

Both the RIA and GC are equivalent and valid methods for the determination of alfentanil plasma concentrations.

GDM:gdm/dea [redacted]: 7/2/85

(14 pages in part I, 38 pages total)

Appendix II

Tables and Graphs

Table 4-1

TABLE I. Patient characteristics

Patient	Age (yr)	Weight (kg)	Sex
1	34	84	M
2	39	67	F
3	48	64	F
4	44	66	F
5	29	80	M

Table 4-2

TABLE II. Measured plasma concentrations of alfentanil ( $\text{ng ml}^{-1}$ )

Treatment scheme	Time (min)	1	2	3	4	5	Mean	SD	SEM
30- $\mu\text{g kg}^{-1}$ bolus	0	<1	<1	<1	<1	<1	<1	—	—
	2	898	582	350	630	174	667	227	102
+ 3- $\mu\text{g kg}^{-1} \text{ min}^{-1}$ infusion	5	592	533	382	500	661	534	125	47
	10	592	336	382	390	612	452	129	58
	15	672	398	442	426	622	512	125	56
	45	684	458	420	453	628	529	119	53
	60	728	544	512	500	750	607	122	55
Infusion stopped	60	740	560	536	532	777	650	119	53
After infusion	2	620	484	420	409	686	524	124	56
	5	620	384	366	374	652	479	144	64
	10	520	374	307	330	560	417	116	52
	15	460	274	292	292	428	349	88	39
	30	394	238	210	208	428	296	107	48
	60	314	164	162	190	310	228	78	35
	120	172	92	118	132	192	141	40	18
	240	58	34	65	56	40	49	15	7
360	17	11	22	20	21	14	4	2	

Figure 4-1

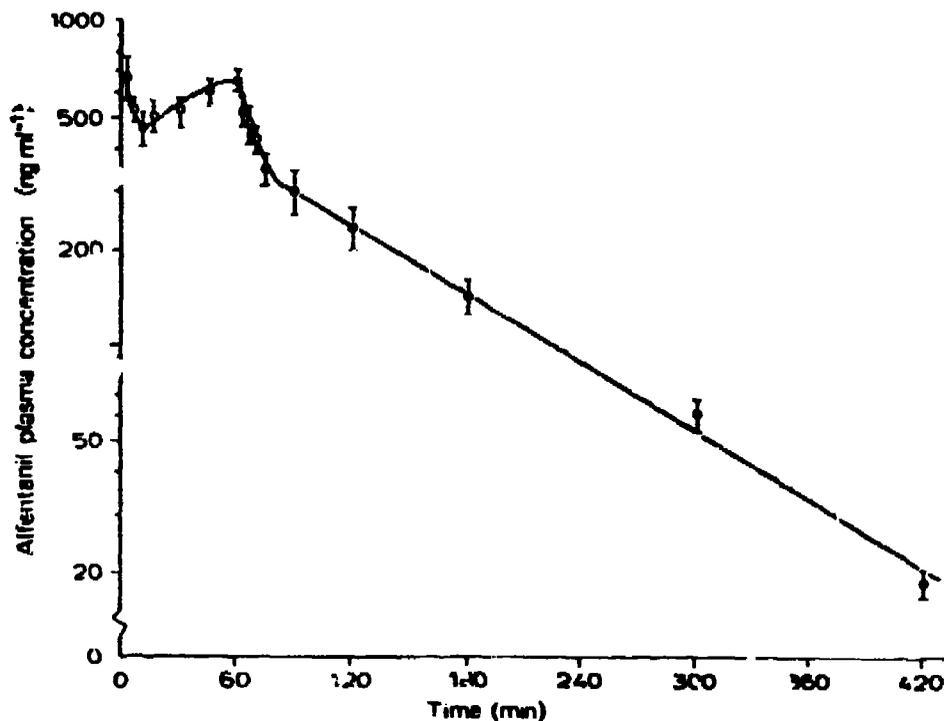


FIG. 1. Plasma concentrations of alfentanil after a 30-s bolus injection of 30  $\mu\text{g kg}^{-1}$  and a 1-h continuous infusion at a rate of 3  $\mu\text{g kg}^{-1} \text{ min}^{-1}$  starts simultaneously. Each data point represents the mean  $\pm$  standard deviation from five patients.

TABLE III. Calculated pharmacokinetic indices

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Mean $\pm$ SD
$\alpha$ ( $\text{min}^{-1}$ )	0.119	0.102	0.053	0.112	0.124	$0.102 \pm 0.028$
$\beta$ ( $\text{min}^{-1}$ )	0.009	0.009	0.005	0.007	0.008	$0.008 \pm 0.002$
$T_{1/2}$ (min)	5.62	6.83	13.0	6.20	5.58	$7.44 \pm 3.14$
$T_{1/2}^{\beta}$ (min)	73.0	74.6	110.1	95.4	80.4	$86.7 \pm 15.8$
$k_{12}$ ( $\text{h}^{-1}$ )	3.61	2.96	1.37	3.71	4.01	$3.13 \pm 1.06$
$k_{21}$ ( $\text{h}^{-1}$ )	2.38	1.85	1.02	1.57	2.27	$1.82 \pm 0.55$
$k_{10}$ ( $\text{h}^{-1}$ )	1.70	1.84	1.19	1.86	1.70	$1.66 \pm 0.27$
$\bar{V}_1$ (litre $\text{kg}^{-1}$ )	0.09	0.14	0.20	0.12	0.09	$0.13 \pm 0.05$
$V_2$ (litre $\text{kg}^{-1}$ )	0.14	0.22	0.27	0.29	0.16	$0.22 \pm 0.07$
$C$ ( $\mu\text{g ml}^{-1}$ )	701	484	454	478	671	$558 \pm 118$
$Cl_R$ ( $\text{ml kg}^{-1} \text{min}^{-1}$ )	2.00	4.09	3.82	3.68	2.46	$3.33 \pm 0.75$
$Cl_B$ ( $\text{ml min}^{-1}$ )	218	274	245	243	197	$235 \pm 29.2$
$V^{\text{app}}$ (litre $\text{kg}^{-1}$ )	0.28	0.45	0.63	0.52	0.29	$0.44 \pm 0.15$
$V^{\text{app}}$ (litre)	23.7	30.4	40.5	34.4	23.3	$30.5 \pm 7.30$

TABLE IV. Calculation of proposed alfentanil bolus and infusion regimen (Mitsuhachi and Ogilvie, 1972)

Apparent vol. of distribution (area) ( $V^{\text{app}}$ )	0.44 litre $\text{kg}^{-1}$
Plasma clearance rate ( $Cl_R$ )	3.33 $\text{ml kg}^{-1} \text{min}^{-1}$
Desired alfentanil concentration ( $C^{\text{d}}$ )	400 $\mu\text{g ml}^{-1}$
Calculated bolus dose ( $C^{\text{d}} \cdot V^{\text{app}}$ )	176 $\mu\text{g kg}^{-1}$
Calculated infusion rate ( $C^{\text{d}} \cdot Cl_R$ )	1.3 $\mu\text{g kg}^{-1} \text{min}^{-1}$

Table 5-1

TABLERU 1

PARAMETRES INDIVIDUELS

SUJETS	BOLUS μg.kg <sup>-1</sup>	DOSE D'ENTREE- TIEN μg.kg <sup>-1</sup> mic <sup>-1</sup>	DUREE DE LA PERFUSION EN H.	POIDS	AGE
1 ALL. H	25	1	3,5	60	21
2 MAR. H	100	2,5	4	50	71
3 PRI. H	280	1,5	8	65	32
4 TER. F	280	1,5	8	45	57

Table 5-2

TABLERU 2

PARAMETRES PHARMACOCINETIQUES INDIVIDUELS  
DE L'ALFENTANIL APRES ADMINISTRATION  
PAR PERFUSION : V

N° Sujet	Clairance ml.min <sup>-1</sup>	Volume ml	Clairance ml.min <sup>-1</sup>	Clairance ml.min <sup>-1</sup>
1	141 ± 26	100	100	100
2	141 ± 26	100	100	100
3	141 ± 26	100	100	100
4	168 ± 123	100	100	100

\* Calculé d'après les moyennes des deux plans: liquidé et dilués le 1<sup>er</sup> du placet jusqu'à la fin de la perfusion.

Fig 5-1

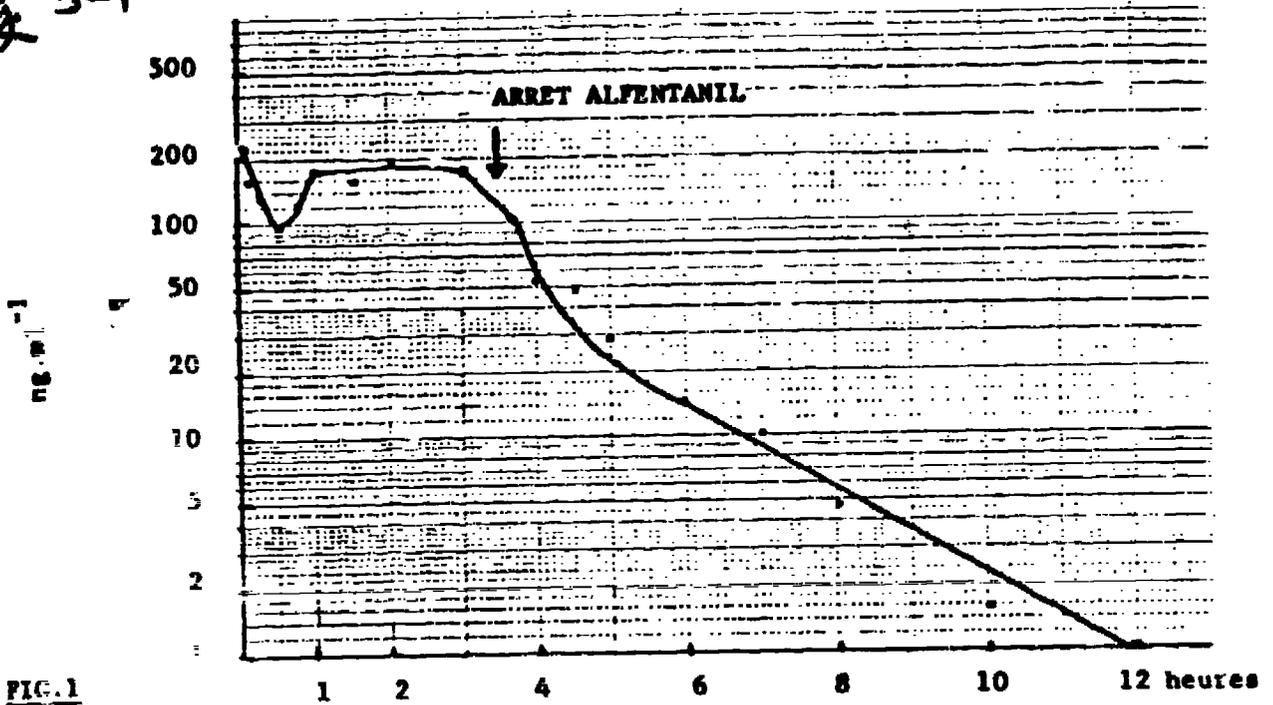


FIG.1

Cinétique plasmatique d'alfentanil chez le sujet n°1  
Dose charge =  $25 \mu\text{g.Kg}^{-1}$ , Entretien:  $1 \mu\text{g.Kg}^{-1}.\text{min}^{-1}$

Fig 5-2

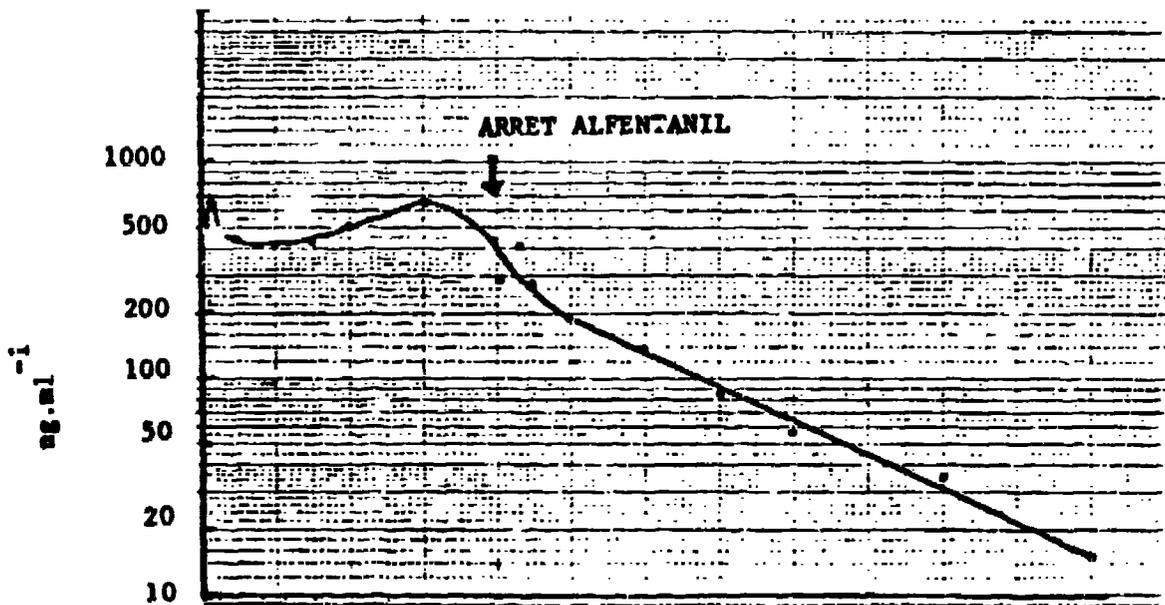
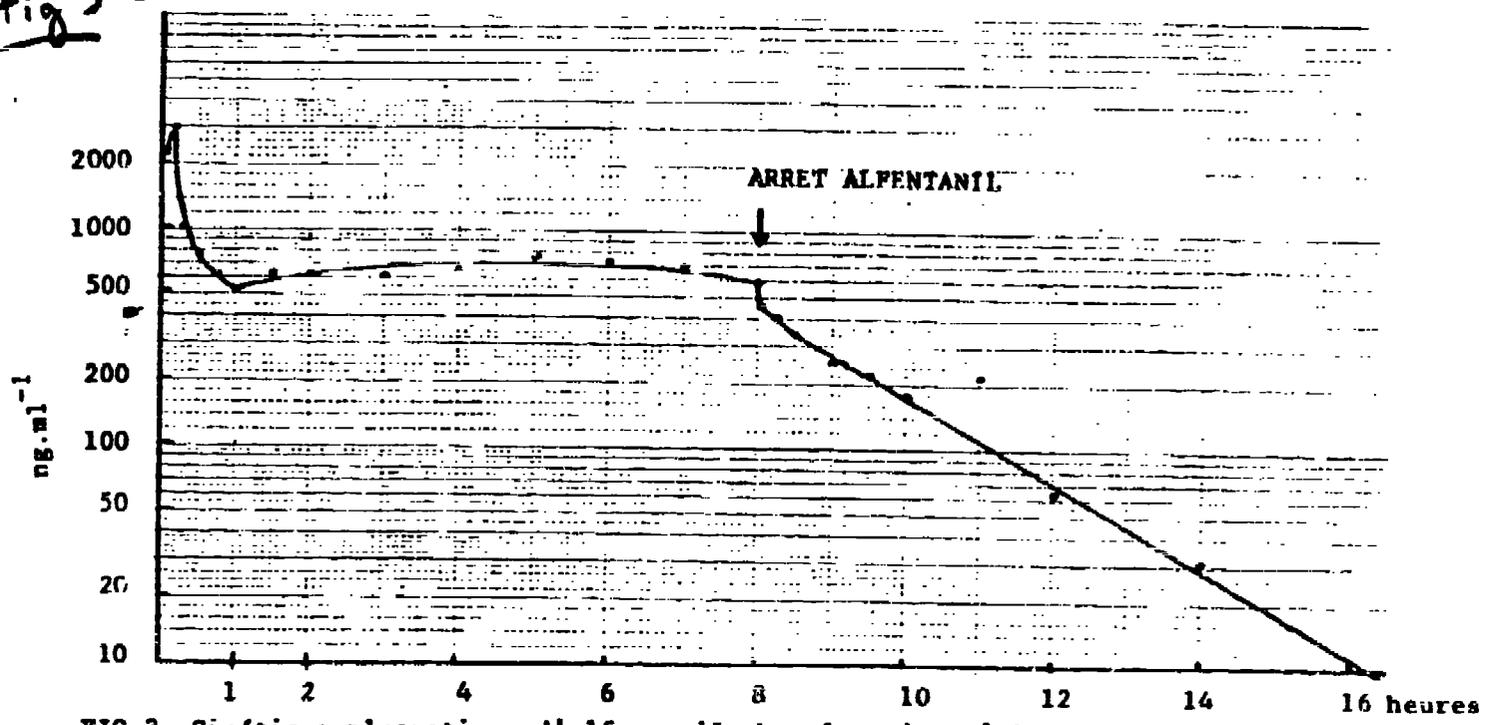


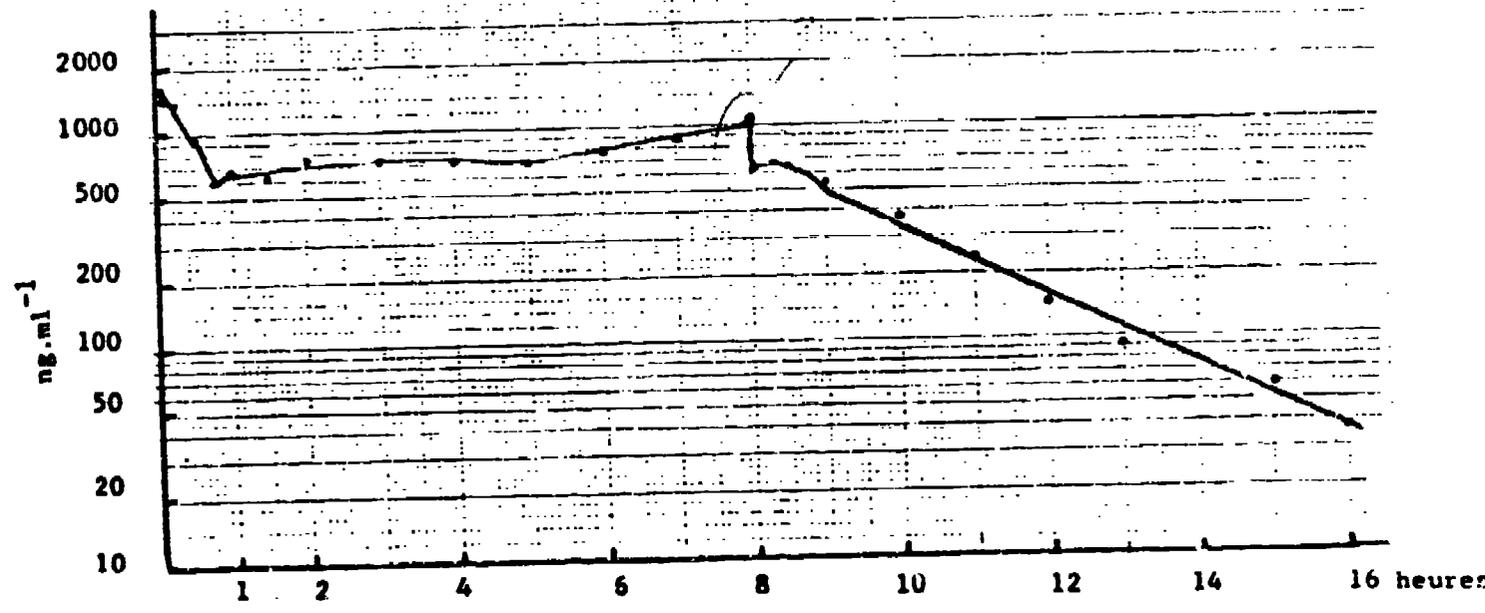
FIG.2

Cinétique plasmatique d'alfentanil chez le sujet n°2  
Dose charge =  $100 \mu\text{g.Kg}^{-1}$ , Entretien =  $2,5 \mu\text{g.Kg}^{-1}.\text{min}^{-1}$



**FIG.3** Cinétique plasmatique d'alfentanil chez le sujet n° 3  
 Dose charge :  $280 \mu\text{g.Kg}^{-1}$ , Entretien :  $1,5 \mu\text{g.Kg}^{-1}.\text{min}^{-1}$

Fig 5-4



**FIG.4** Cinétique plasmatique d'alfentanil chez le sujet n°4.  
 Dose charge =  $280 \mu\text{g.Kg}^{-1}$ , Entretien =  $1,5 \mu\text{g.Kg}^{-1}.\text{min}^{-1}$

# Table 6-1

**Table 1:** Plasma levels of the total radioactivity (T.R.), non-volatile radioactivity (N.V.R.) and unchanged (U.D.) in three male volunteers after a 1-hour infusion of 2.5 mg of alfentanil-3. Figures between brackets represent the per cent of the sample radioactivity (T.R.) accounted for by the non-volatile radioactivity or the parent drug.

Time after end of infusion	T.R. (ng equiv./ml)			N.V.R. (ng equiv./ml)	U.D. (ng/ml)
	JH	HW	BY		
0				Mean ± S.D. (% of T.R.)	Mean ± S.D.
3 min	132 ± 20			131 ± 23 (99.2)	1121 ± 217
8 min	127 ± 18			127 ± 17 (100.0)	1227 ± 330
15 min	123 ± 29			125 ± 26 (101.6)	1179 ± 336
30 min	103 ± 20			101 ± 20 (98.1)	899 ± 116
1 h	83.6 ± 16.7			84.5 ± 15.5 (101.1)	592 ± 117
2 h	65.6 ± 7.8			66.3 ± 11.3 (101.1)	464 ± 110
3 h	48.8 ± 7.2			48.2 ± 8.6 (103.0)	291 ± 117
4 h	32.7 ± 5.5			34.3 ± 6.5 (106.6)	196 ± 110
6 h	26.7 ± 4.4			26.1 ± 5.9 (97.8)	143 ± 111
8 h	17.8 ± 3.6			17.1 ± 4.9 (96.1)	111 ± 115
12 h	12.5 ± 2.1			11.4 ± 2.2 (91.2)	81 ± 110
24 h	8.0 ± 2.1			6.9 ± 2.1 (86.2)	52 ± 110
	3.3 ± 0.6			3.2 ± 0.7 (66.7)	27 ± 11

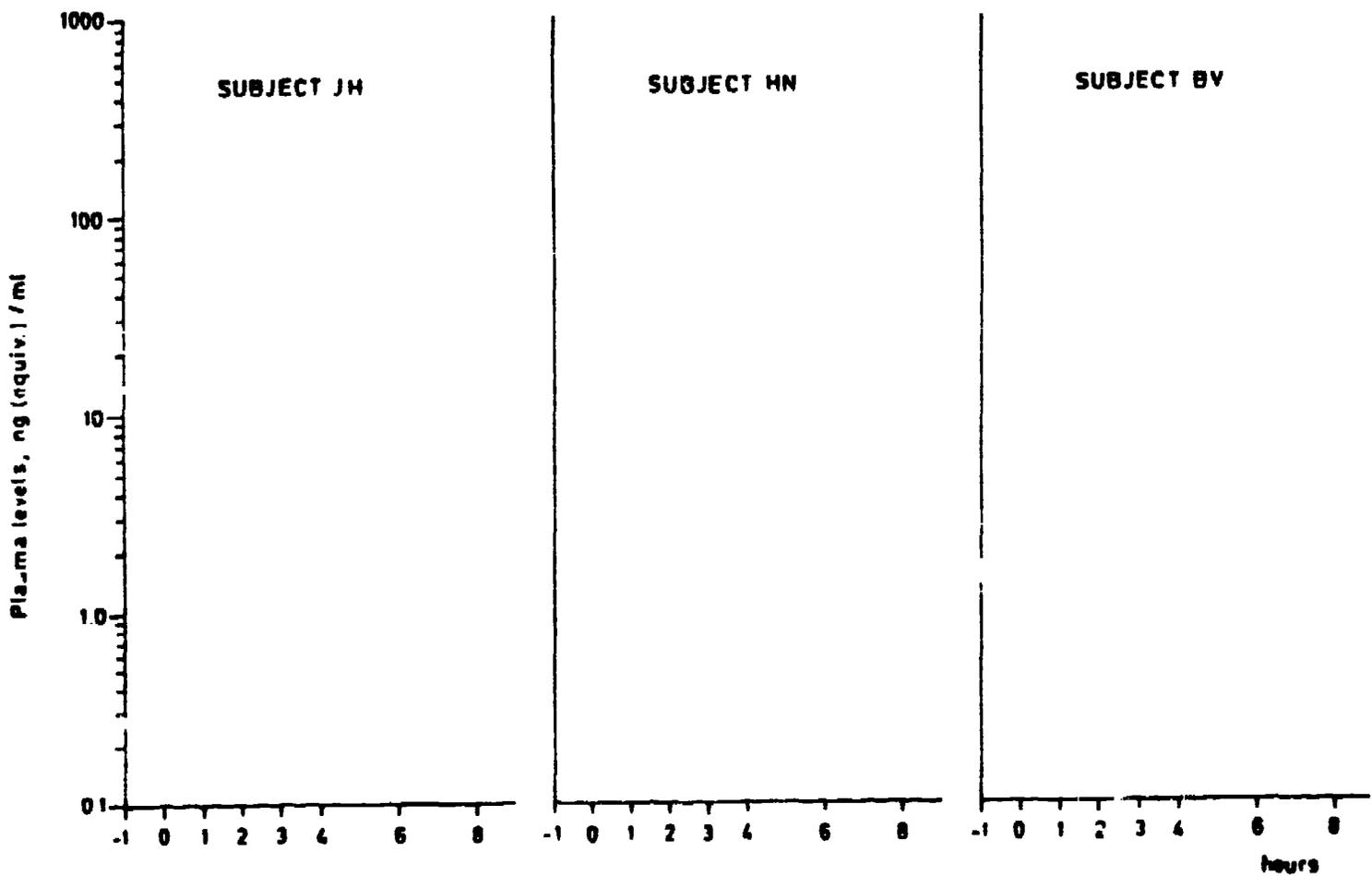
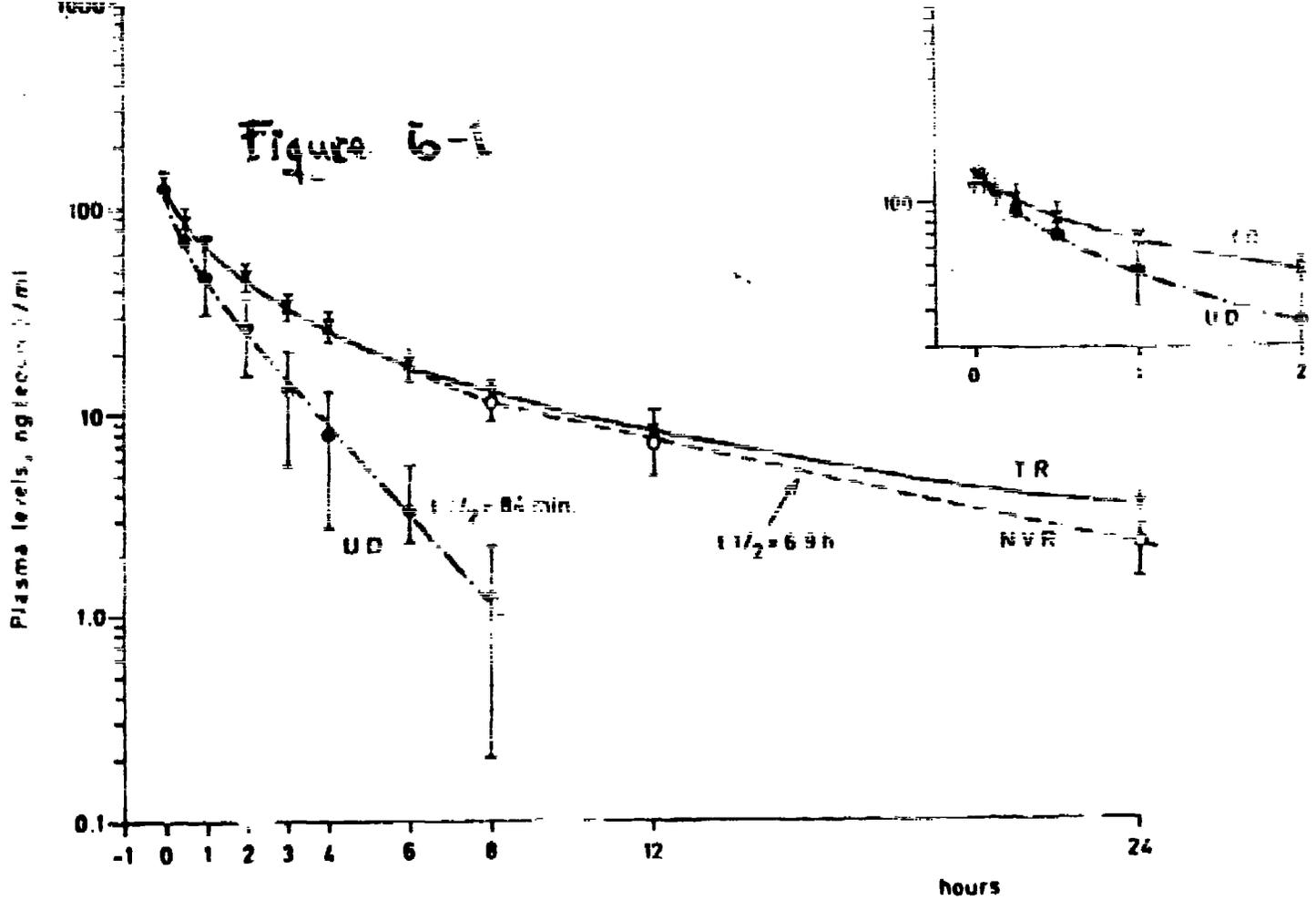


Figure 2

Figure 6-2

Table 6-2

volunteers after 61-hour infusion of 2.5 mg of alfentanil  $^{3}H$ . Calculations were performed as described in P. 5.

Parameters	JH	NN	BV	Mean $\pm$ S.D.
Age, years	43	39	28	37 $\pm$ 8
Body weight, kg	72	75	76	74 $\pm$ 2
Height, cm	175	176	183	178 $\pm$ 4
$V_c$ , ml				12485 $\pm$ 3323
$V_c$ , ml.kg $^{-1}$				168 $\pm$ 43
$\lambda$ , min $^{-1}$				0.0278 $\pm$ 0.0046
$\beta$ , min $^{-1}$				0.00839 $\pm$ 0.00124
$k_{21}$ , min $^{-1}$				0.0149 $\pm$ 0.0025
$t_{1/2\alpha}$ , min				25 $\pm$ 4
$t_{1/2\beta}$ , min				84 $\pm$ 13
$k_{10}$ , min $^{-1}$				0.0159 $\pm$ 0.0034
$k_{12}$ , min $^{-1}$				0.0055 $\pm$ 0.0019
$Cl$ , ml.min $^{-1}$				198 $\pm$ 72
$Cl$ , ml.min $^{-1}$ .kg $^{-1}$				2.65 $\pm$ 0.90
$V_{dss}$ , ml				16839 $\pm$ 3691
$V_{dss}$ , ml.kg $^{-1}$				226 $\pm$ 48
$V_{d\beta}$ , ml				23572 $\pm$ 7436
$V_{d\beta}$ , ml.kg $^{-1}$				316 $\pm$ 94

Table 6-3

Table 3: Excretion of the total radioactivity as a per cent of the administered radioactivity with the urine of three male volunteers after a 1-hour infusion of 2.5 mg of alfentanil  $^{3}H$ .

Time interval (hours)	% of dose per sample				cumulative % of dose
	JH	NN	BV	Mean $\pm$ S.D.	Mean $\pm$ S.D.
-1-0 <sup>a</sup>				1.83 $\pm$ 1.91	1.83 $\pm$ 1.91
0-1				5.43 $\pm$ 3.18	7.26 $\pm$ 5.07
1-2				9.81 $\pm$ 3.43	17.0 $\pm$ 5.22
2-4				15.23 $\pm$ 0.96	32.30 $\pm$ 6.07
4-6				13.52 $\pm$ 1.50	45.82 $\pm$ 6.21
6-8				8.82 $\pm$ 1.01	54.64 $\pm$ 7.01
8-12				10.68 $\pm$ 2.09	65.32 $\pm$ 5.09
12-24				15.79 $\pm$ 1.99	81.10 $\pm$ 3.43
24-36				9.97 $\pm$ 1.46	86.08 $\pm$ 2.00
36-48				1.83 $\pm$ 0.55	87.90 $\pm$ 1.47
0-48				87.90 $\pm$ 1.47	

<sup>a</sup> the 1-hour infusion period

<sup>b</sup> no sample could be voided at the end of the infusion period

Table 6-4

**Table 4:** Urinary output, and urine levels of unchanged alfentanil and of its main metabolite noralfentanil (R 49 469) in three male volunteers after a 1-hour infusion of 2.5 mg of alfentanil-3H. Levels of the parent drug were determined by a GLC-assay (2.5.2), levels of noralfentanil by radio-HPLC (2.5.3.3). Figures between brackets represent the per cent of the radioactivity accounted for by alfentanil or noralfentanil.

Sample	Urinary output (ml)		Alfentanil (ng/ml)				R 46 469 (ng/ml)
	JH	BV	JH	NR	BV	JH	
-1-0 h							
0-1 h							
1-2 h							
2-4 h							
4-6 h							
6-8 h							
8-12 h							
12-24 h							
24-36 h							
36-48 h							

1 Calculated from levels in ng equivalent to alfentanil/ml by multiplication with 0.6635, the ratio between the molecular weights of noralfentanil and alfentanil.

2 No sample.

7  
D  
U

# Table 1-1

TABLE I. Subject data and doses of fentanyl and alfentanil given in the simultaneous infusion study

Subject	Sex	Age (yr)	Wt. (kg)	Fentanyl dose (µg)	Alfentanil dose (µg)
1	F	35	54.9	164.41	161.74
2	M	42	82.0	170.85	170.24
3	F	46	61.2	167.03	163.70
4	M	55	76.0	164.40	163.19
5	M	60	65.1	164.16	167.46
6	M	24	60.2	164.57	159.84
7	M	37	83.8	163.70	163.01

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## Figure 1-1

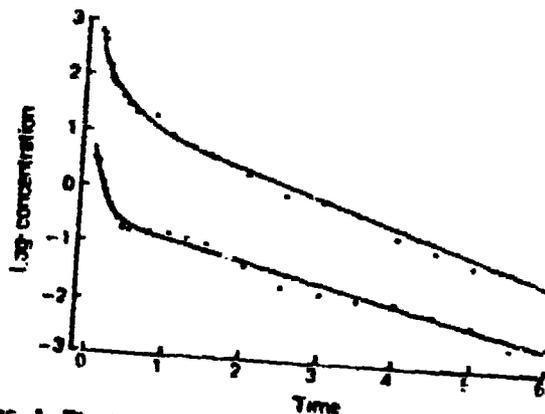


FIG. 1. The  $\log$ -concentration (in  $\text{ng ml}^{-1}$ )-time (h) data for subject 1, and the  $\log$ -concentration-time characteristics of best-fitting two-compartment open models for both drugs, after simultaneous i.v. administration. Upper trace: alfentanil; lower trace: fentanyl.

## Figure 1-2

### FENTANYL AND ALFENTANIL

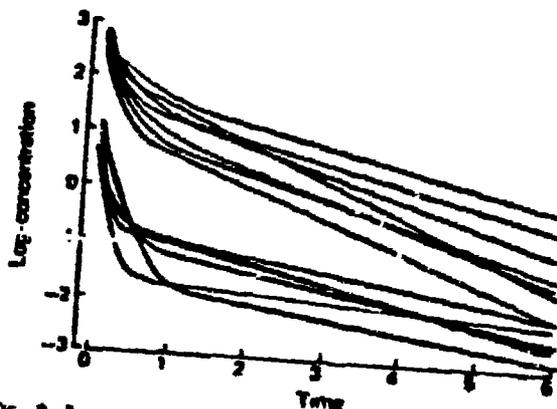


FIG. 2. Log-concentration (in  $\text{ng ml}^{-1}$ )-time (h) data for the two-compartment open models fitted to the data of all subjects given simultaneous doses of fentanyl and alfentanil. Upper group: alfentanil; lower group: fentanyl.

# Table 6-5

**Table 6:** Mass balance of alfentanil and its major metabolites in the urine of three male volunteers after a 1-hour infusion of 2.5 mg of alfentanil-<sup>3</sup>H. Mass balances were obtained by radio-HPLC analysis of individual urine pools (2.5.3.3), whether or not after enzymatic hydrolysis with  $\beta$ -glucuronidase/arylsulphatase, and were expressed as the per cent of the sample or dose (figures between brackets) radioactivity accounted for by the various metabolites or metabolite fractions (mean values  $\pm$  S.D., n = 3)

HAM 9 = unchanged alfentanil

Metabolite or metabolite fraction <sup>1</sup>	without previous enzymatic hydrolysis			% of dose 0-24 h sum
	-1-4 h (32.30 $\pm$ 5.07 %)	4-8 h (22.34 $\pm$ 3.41 %)	8-24 h (26.47 $\pm$ 3.71 %)	
HAM1	<1.0-1.3 (-0.3)	3.6 $\pm$ 0.6 (0.8 $\pm$ 0.2)	4.9 $\pm$ 0.4 (1.3 $\pm$ 0.1)	2.4
HAM2	16.2 $\pm$ 1.0 (5.2 $\pm$ 0.7)	19.2 $\pm$ 2.2 (4.3 $\pm$ 0.8)	19.1 $\pm$ 2.6 (5.0 $\pm$ 0.6)	14.5
HAM3	4.2 $\pm$ 1.2 (1.4 $\pm$ 0.6)	4.8 $\pm$ 0.2 (1.1 $\pm$ 0.1)	4.2 $\pm$ 0.6 (1.2 $\pm$ 0.3)	3.7
HAM4	<1.0-4.3 (<0.3-1.2)	2.8 $\pm$ 0.4 (0.6 $\pm$ 0.1)	2.4 $\pm$ 1.1 (0.6 $\pm$ 0.3)	1.35
HAM5	2.3 $\pm$ 1.6 (0.8 $\pm$ 0.7)	3.0 $\pm$ 1.0 (0.7 $\pm$ 0.3)	2.6 $\pm$ 0.5 (0.7 $\pm$ 0.1)	2.2
HAM6	6.0 $\pm$ 0.4 (1.9 $\pm$ 0.5)	5.3 $\pm$ 0.5 (1.2 $\pm$ 0.1)	6.2 $\pm$ 0.9 (1.7 $\pm$ 0.5)	4.8
HAM7	4.7 $\pm$ 0.9 (1.5 $\pm$ 0.4)	4.8 $\pm$ 0.4 (1.1 $\pm$ 0.1)	4.0 $\pm$ 1.4 (1.0 $\pm$ 0.4)	3.6
HAM8	42.2 $\pm$ 3.2 (13.5 $\pm$ 1.9)	35.4 $\pm$ 5.4 (7.8 $\pm$ 0.5)	35.6 $\pm$ 3.7 (9.5 $\pm$ 2.3)	30.8
HAM9	1.2 $\pm$ 0.2 (0.4 $\pm$ 0.1)	<1.0	<1.0	0.4
sum	79.0 $\pm$ 4.4 (25.4 $\pm$ 4.0)	78.9 $\pm$ 4.1 (17.6 $\pm$ 1.0)	79.1 $\pm$ 2.3 (20.9 $\pm$ 3.2)	~ 64.35
	after enzymatic hydrolysis			
	-1-4 h	4-8 h	8-24 h	% of dose 0-24 h sum
HAM1	<1.0	<1.0	<1.0	
HAM2	1.5 $\pm$ 0.3 (0.4 $\pm$ 0.1)	1.5 $\pm$ 0.3 (0.3 $\pm$ 0.1)	2.2 $\pm$ 0.2 (0.6 $\pm$ 0.1)	1.3
HAM3	4.3 $\pm$ 1.9 (1.4 $\pm$ 0.7)	7.8 $\pm$ 0.7 (1.7 $\pm$ 0.3)	9.7 $\pm$ 0.5 (2.6 $\pm$ 0.4)	5.7
HAM4	<1.0	<1.0	<1.0	
HAM5	16.6 $\pm$ 1.8 (5.4 $\pm$ 1.3)	19.8 $\pm$ 3.2 (4.5 $\pm$ 1.2)	20.0 $\pm$ 4.8 (5.2 $\pm$ 0.7)	15.1
HAM6	9.1 $\pm$ 0.8 (3.0 $\pm$ 0.7)	8.7 $\pm$ 1.5 (2.0 $\pm$ 0.6)	6.9 $\pm$ 0.7 (1.8 $\pm$ 0.4)	6.8
HAM7	5.6 $\pm$ 0.2 (1.8 $\pm$ 0.3)	6.3 $\pm$ 0.2 (1.4 $\pm$ 0.2)	4.6 $\pm$ 0.9 (1.2 $\pm$ 0.3)	4.4
HAM8	43.0 $\pm$ 3.5 (13.8 $\pm$ 2.1)	39.1 $\pm$ 5.1 (8.6 $\pm$ 0.3)	37.3 $\pm$ 4.6 (10.0 $\pm$ 2.6)	32.4
HAM9	<1.0-1.5 (<0.3-0.6)	<1.0	<1.0	0.45
sum	80.5 $\pm$ 3.7 (26.0 $\pm$ 4.9)	83.2 $\pm$ 0.3 (18.5 $\pm$ 2.1)	80.7 $\pm$ 1.6 (21.4 $\pm$ 3.4)	66.15

<sup>1</sup> for the retention times on the C-18 column, see Table 7.

Subject	% Fit	V <sub>1</sub> (litre)	V <sub>2</sub> (litre)	V <sub>m</sub> (litre)	k <sub>12</sub> (h <sup>-1</sup> )	k <sub>21</sub> (h <sup>-1</sup> )	k <sub>10</sub> (h <sup>-1</sup> )	C <sub>l</sub> (litre h <sup>-1</sup> )	T <sub>1/2</sub> (h)
<b>Fentanyl</b>									
1	99.81	67.64	168.16	295.80	5.11	2.06	1.31	88.25	2.10
2	99.52	34.03	223.03	257.06	11.61	1.77	2.72	92.49	2.27
3	99.91	57.15	249.22	306.40	3.67	0.84	1.54	93.67	2.97
4	99.87	54.70	286.55	341.25	3.34	0.64	2.22	121.32	2.92
5	99.29	91.10	196.22	287.32	3.96	1.84	0.79	72.25	3.02
6	99.92	47.90	221.80	249.70	4.73	1.02	1.81	86.67	2.74
7	97.71	65.36	584.91	630.27	10.59	1.23	1.35	88.7	3.62
Mean		59.70	275.70	335.40	6.20	1.54	1.69	91.65	3.09
SD		17.85	141.42	143.00	3.54	0.55	0.64	14.77	1.17
<b>Alfentanil</b>									
1	99.96	8.94	16.22	25.16	3.24	1.79	1.71	19.26	1.42
2	99.98	11.10	24.18	35.28	5.39	2.47	2.11	23.38	1.25
3	99.97	11.00	12.25	23.25	2.21	1.98	1.11	12.29	1.52
4	99.87	8.26	18.26	26.52	5.12	2.31	1.27	10.49	1.97
5	99.68	13.04	10.17	23.21	0.91	1.17	0.61	7.91	2.84
6	99.98	9.15	9.34	18.49	3.76	3.68	1.36	12.41	1.14
7	99.91	15.17	23.52	38.69	2.47	1.59	1.20	18.24	1.76
Mean		10.95	16.28	27.23	3.30	2.14	1.34	14.28	1.63
SD		2.47	6.06	7.18	1.61	0.81	0.47	5.19	0.42
P		<0.001*	<0.01*	<0.01*	0.06	0.12	0.08	<0.001*	0.02*

V<sub>2</sub> 4/kg  
 0.29  
 0.29  
 0.20  
 0.24  
 0.156  
 0.135  
 0.28  
 0.227 ± 0.04  
 C<sub>l</sub> ml/min  
 4.63  
 4.75  
 3.35  
 2.3  
 2.0  
 2.99  
 3.63  
 3.38  
 + 1.06  
 + 0.069  
 + 0.386

V<sub>1</sub> (4/kg)  
 .1625  
 .135  
 .18  
 .109  
 .2  
 .132  
 .181  
 .153  
 ± .034

Table 1-3

TABLE III. Pharmacokinetic variables calculated for five subjects given alfentanil 1 mg

Subject	% Fit	V <sub>1</sub> (litre)	V <sub>2</sub> (litre)	V <sub>m</sub> (litre)	k <sub>12</sub> (h <sup>-1</sup> )	k <sub>21</sub> (h <sup>-1</sup> )	k <sub>10</sub> (h <sup>-1</sup> )	C <sub>l</sub> (litre h <sup>-1</sup> )	T <sub>1/2</sub> (h)
1	99.91	16.87	39.90	56.77	2.80	1.18	2.33	39.35(?)	1.47
2	99.96	10.84	14.71	26.75	5.69	3.42	1.36	13.65	1.49
3	99.91	8.57	18.56	27.23	8.09	3.78	1.54	13.32	1.55
4	99.98	13.81	13.32	27.33	1.56	1.59	1.25	17.23	1.36
7	99.95	12.26	37.05	39.31	1.75	0.79	1.61	19.75	2.07
Mean		12.33	23.15	35.48	3.98	2.15	1.62	20.66	1.59
SD		3.22	10.62	13.03	2.83	1.36	0.42	10.78	0.28

V<sub>2</sub> 4/kg  
 1.03  
 0.326  
 0.445  
 0.36  
 0.47  
 5.2  
 ± 3.77  
 ± 0.288  
 3.93

V<sub>1</sub> 4/kg  
 0.307  
 0.122  
 0.142  
 .1817  
 .1463  
 0.1398 ± 0.074

Figure 1-3

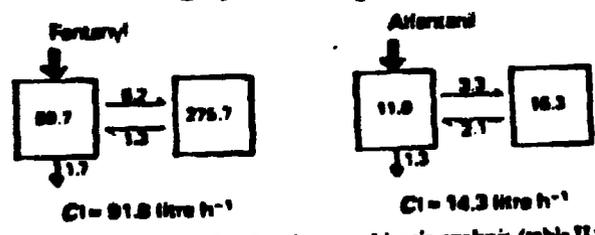


FIG. 3. Mean values for the pharmacokinetic analysis (table II) presented as compartmental diagrams. Rate constants = h<sup>-1</sup>, volumes = litre.

V<sub>2</sub> 4/kg  
 .73  
 .20  
 .30  
 .18  
 .32  
 .346  
 ± 0.223

Figure 6-3

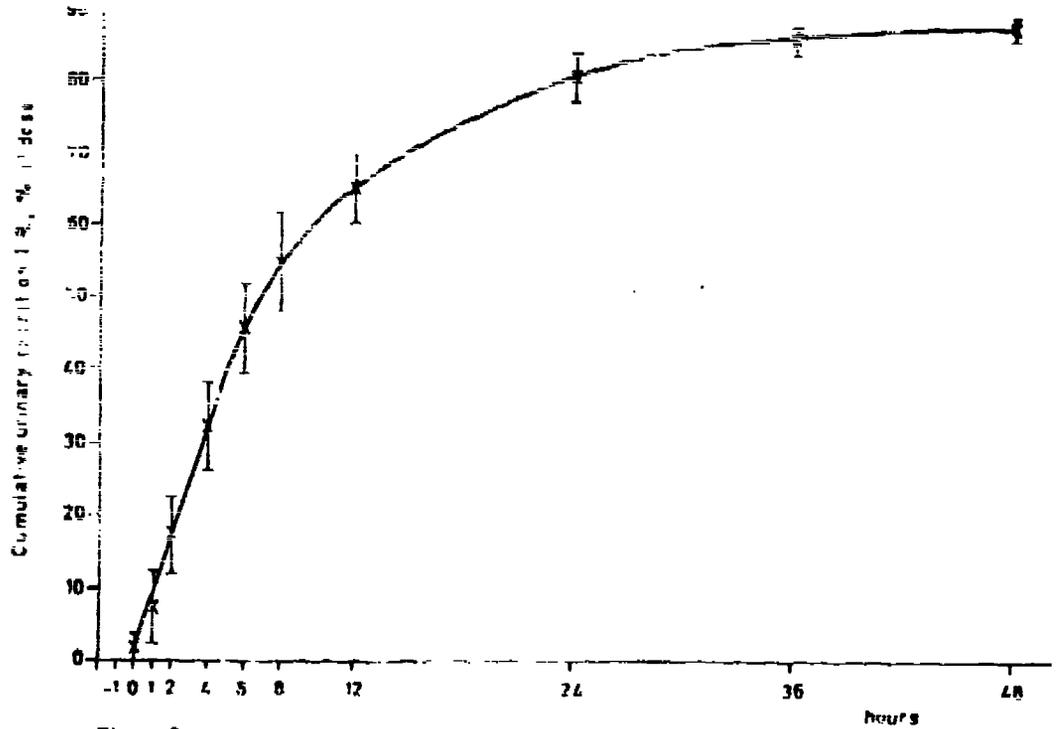
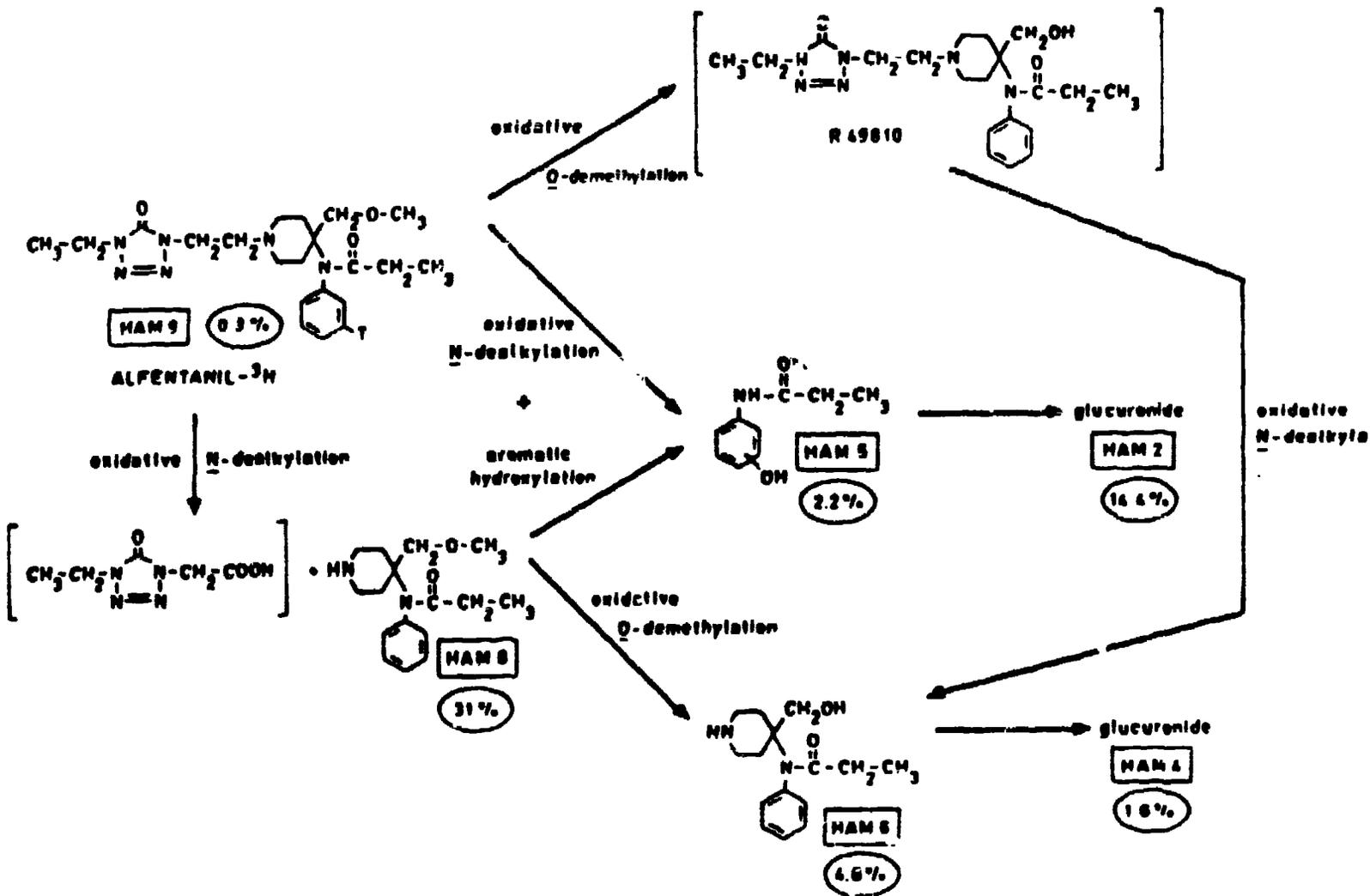


Figure 3

Figure 6-4



# Table 2-1

TABLE 1. Patient Details

Patient Number	Sex	Age (yr)	Weight (kg)	ASA Class	Operation
<b>50 µg/kg</b>					
1	Male	50	78	II	Medianinoscopy
2	Male	54	79	II	Craniotomy
3	Female	40	67	I	Laminectomy
4	Female	22	75	I	Strabismus correction
5	Male	64	70	I	Laminectomy
6	Female	45	70	I	Laminectomy
Mean		42	75		
± SEM		5.8	2.0		
<b>125 µg/kg</b>					
7	Male	65	80	II	Pneumonectomy
8	Male	65	69	II	Lobectomy
9	Female	19	52	I	Laminectomy
10	Female	55	64	II	Craniotomy
11	Male	23	80	I	Laminectomy
Mean		45	69		
± SEM		9.8	5.3		

# Figure 2-1

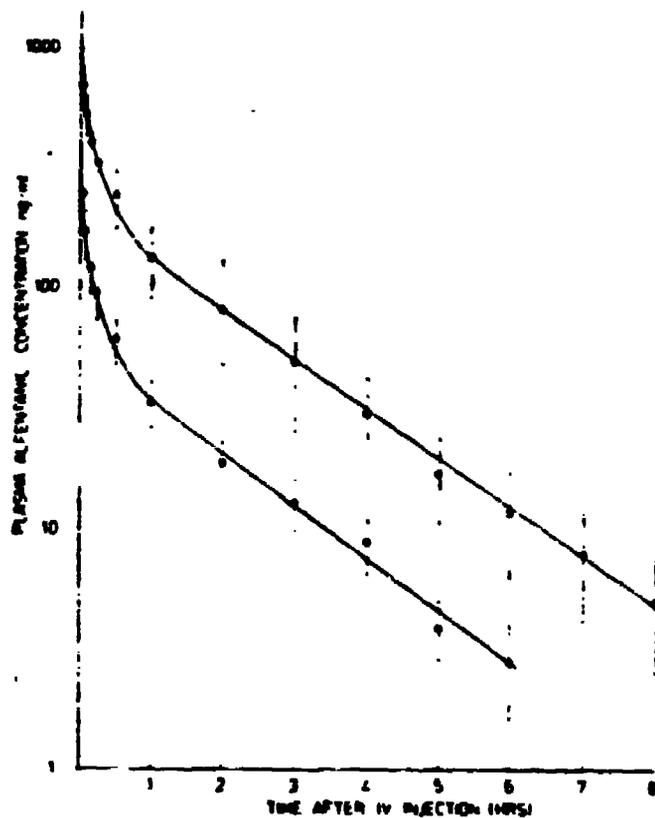


FIG. 2 Plasma concentrations of alfentanil (R59209) after 50 µg/kg (lower curve) and 125 µg/kg (upper curve). Each data point represents the mean ± SEM for each dose.

# Table 2-2

TABLE 2 Alfentanil Pharmacokinetics after Bolus Injection

Patient Number	P (ng/ml)	$\alpha$ (min <sup>-1</sup> )	$t_{1/2\alpha}$ (min)	A (ng/ml)	$\alpha$ (min <sup>-1</sup> )	$t_{1/2\alpha}$ (min)	B (ng/ml)	$\beta$ (min <sup>-1</sup> )	$t_{1/2\beta}$ (min)	$r^2$
<b>50 µg/kg</b>										
1	981	0.280	2.47	285	0.059	11.6	59.9	0.0058	118.7	0.9884
2	472	0.225	3.11	115	0.032	21.6	24.2	0.0072	96.3	0.9998
3	494	1.975	0.50	266	0.109	6.4	78.6	0.0065	109.5	0.9998
4	151	1.595	0.45	57	0.152	4.6	17.0	0.0072	97.1	0.9997
5	190	1.105	0.65	62	0.108	6.4	51.9	0.0091	76.5	0.9996
6	1402	0.979	0.71	150	0.124	5.6	98.9	0.0108	64.1	0.9999
Mean	512	0.926	1.51	152	0.097	9.4	51.7	0.0077	93.7	
± SEM	187.9	0.2504	0.477	40.8	0.0179	2.65	19.39	0.00076	8.29	
<b>125 µg/kg</b>										
7	655	0.759	0.94	469	0.051	15.5	481	0.0074	95.5	0.9990
8	1997	0.519	1.34	551	0.046	15.0	182	0.0090	76.9	0.9993
9	996	0.477	1.45	320	0.057	12.1	105	0.0085	81.4	0.9996
10	898	0.876	0.79	314	0.048	14.4	51	0.0054	129.5	0.9982
11	980	0.907	0.76	284	0.040	17.0	88	0.0079	87.9	0.9991
Mean	1105	0.709	1.06	388	0.048	14.4	181	0.0076	95.8	
± SEM	321.1	0.0888	0.142	51.9	0.0027	2.82	78.0	0.00065	9.51	

P, A, B = the ordinal intercepts computed from the least-square analysis of the data;  $\alpha$ ,  $\beta$  = the first-order rate constants; and  $t_{1/2\alpha}$ ,  $t_{1/2\beta}$  = the half-lives for the rapid ( $\alpha$ ) and slow ( $\beta$ ) distribution phase

and the elimination phase ( $\beta$ ).  

$$r^2 = \frac{\sum(\text{observed})^2 - \sum(\text{deviation})^2}{\sum(\text{observed})^2}$$

# Table 2-3

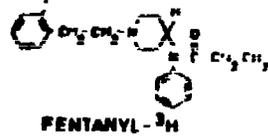
TABLE 3 Calculated Kinetic Variables after Bolus Injection of Alfentanil

Patient Number	Vc (l/kg)	Vd (l)	Cl (ml·min <sup>-1</sup> ·kg <sup>-1</sup> )	K <sub>10</sub> (h <sup>-1</sup> )	K <sub>12</sub> (h <sup>-1</sup> )	K <sub>21</sub> (h <sup>-1</sup> )	K <sub>31</sub> (h <sup>-1</sup> )	K <sub>32</sub> (h <sup>-1</sup> )
<b>50 µg/kg</b>								
1	0.0669	0.522	3.05	2.65	4.75	2.86	9.66	0.82
2	0.0818	0.766	5.51	4.04	5.92	1.36	4.41	0.62
3	0.0596	0.519	3.29	3.31	38.73	0.57	37.01	1.67
4	0.2442	2.472	17.64	4.35	45.42	14.14	39.17	2.21
5	0.1765	1.295	11.72	3.99	32.91	8.92	25.02	2.33
6	0.0307	0.998	4.30	8.42	23.35	19.39	15.17	2.57
Mean	0.1151	0.996	7.58	4.38	22.75	8.95	20.68	1.69
± SEM	0.03756	0.3256	2.59	0.856	5.951	2.685	5.565	0.332
<b>125 µg/kg</b>								
7	0.0778	0.225	1.67	1.38	16.18	1.68	27.01	1.76
8	0.0458	0.386	3.48	4.56	16.07	2.75	10.07	1.02
9	0.0881	0.745	6.52	4.31	12.95	3.65	10.56	1.10
10	0.0989	1.362	7.31	4.43	30.06	3.99	17.04	0.65
11	0.0924	0.824	6.49	4.227	33.20	2.54	16.45	0.91
Mean	0.0806	0.708	5.06	3.76	21.69	2.84	16.23	1.03
± SEM	0.00935	0.1974	1.065	0.622	4.127	0.565	3.058	0.185

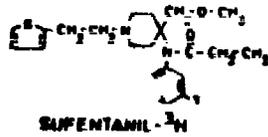
Vc = apparent volume of the central compartment; Vd = apparent volume of distribution; Cl = total body clearance; K<sub>10</sub> = elimination

rate constant, and K<sub>12</sub> to K<sub>31</sub> = transfer rate constants between compartments.

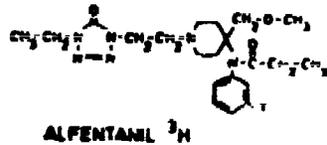
Figure 7-1



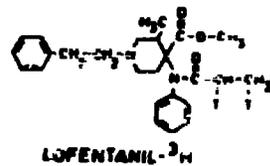
pK	$\log P_u$ (pH)	$\log P_n$ (pH)
8.43	-0.28 (pH 7.2)	2.98 (pH 9.8)



pK	$\log P_u$ (pH)	$\log P_n$ (pH)
8.01	0.00 (pH 7.3)	2.95 (pH 9.8)



pK	$\log P_u$ (pH)	$\log P_n$ (pH)
8.50	-1.17 (pH 7.2)	1.16 (pH 9.8)



pK	$\log P_u$ (pH)	$\log P_n$ (pH)
7.82	-0.54 (pH 7.2)	2.72 (pH 9.8)

Chemical structures of fentanyl, sufentanil, alfentanil and lofentanil, and position of the tritium labels (T), ionization constants (pK) and partition coefficients of the ionized ( $\log P_u$ ) and non-ionized drugs ( $\log P_n$ ).

Figure 7-2

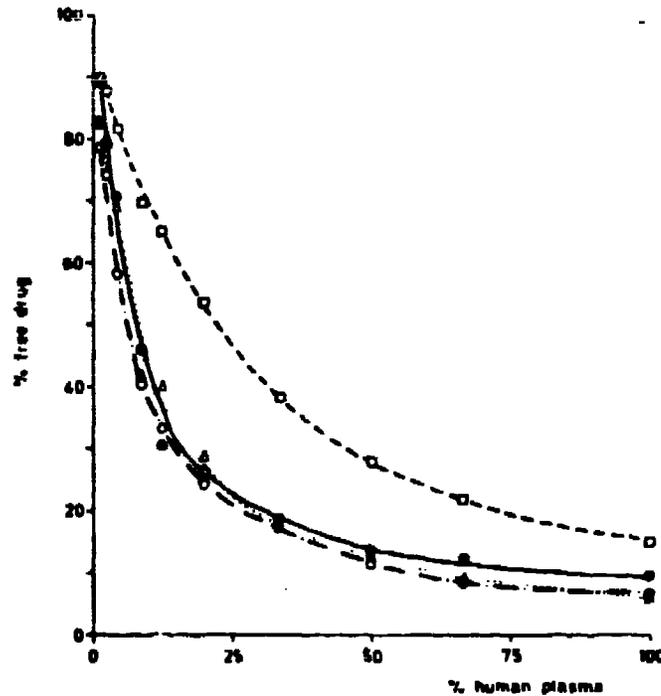


FIG. 2

Free fraction of fentanyl (□ --- □), sufentanil (○ --- ○), alfentanil (● — ●) and lofentanil (Δ ···· Δ) in human plasma diluted with isotonic phosphate buffer pH 7.35.

TABLE I

*In vitro* plasma protein binding and distribution of fentanyl, sufentanil, alfentanil and lofentanil in blood of rats, dogs and humans. Drugs were added at therapeutic levels: 0.01 µg/ml for fentanyl, 0.1 µg/ml for sufentanil, 0.1 µg/ml for alfentanil and 0.1 µg/ml for lofentanil

Drug	Species	H <sup>1</sup>	f <sub>b</sub> <sup>2</sup>	f <sub>b</sub> (1-H) <sup>3</sup>	f <sub>pr</sub> (1-H) <sup>4</sup>	f <sub>bc</sub> (H) <sup>5</sup>	C <sub>p</sub> /C <sup>6</sup>	f <sub>bc, H</sub> <sup>7</sup>
Fentanyl	rat <sup>8</sup>	0.58 ± 0	0.834 ± 0.026	0.175 ± 0.006	0.514 ± 0.024	0.322 ± 0.029	0.891 ± 0.042	0.681 ± 0.025
	dog <sup>9</sup>	0.49 ± 0.05	0.782 ± 0.031	0.165 ± 0.017	0.388 ± 0.102	0.448 ± 0.100	0.939 ± 0.085	0.732 ± 0.037
	man <sup>10</sup>	0.42 ± 0.01	0.844 ± 0.019	0.177 ± 0.012	0.434 ± 0.051	0.195 ± 0.051	0.985 ± 0.055	0.888 ± 0.017
Sufentanil	rat <sup>8</sup>	0.39 ± 0	0.931 ± 0.007	0.069 ± 0.002	0.749 ± 0.015	0.180 ± 0.017	0.744 ± 0.016	0.721 ± 0.013
	dog <sup>9</sup>	0.47 ± 0.04	0.928 ± 0.015	0.067 ± 0.007	0.754 ± 0.085	0.199 ± 0.070	0.658 ± 0.013	0.764 ± 0.044
	man <sup>10</sup>	0.42 ± 0.02	0.924 ± 0.007	0.066 ± 0.007	0.699 ± 0.049	0.220 ± 0.044	0.741 ± 0.049	0.742 ± 0.013
Alfentanil	rat <sup>8</sup>	0.39 ± 0	0.836 ± 0.006	0.158 ± 0.014	0.724 ± 0.034	0.118 ± 0.019	0.692 ± 0.015	0.429 ± 0.012
	dog <sup>9</sup>	0.48 ± 0.01	0.729 ± 0.062	0.196 ± 0.037	0.619 ± 0.102	0.170 ± 0.070	0.623 ± 0.011	0.518 ± 0.046
	man <sup>10</sup>	0.42 ± 0.01	0.921 ± 0.015	0.075 ± 0.015	0.653 ± 0.030	0.075 ± 0.027	0.630 ± 0.021	0.480 ± 0.035
Lofentanil	rat <sup>8</sup>	0.39 ± 0	0.888 ± 0.001	0.056 ± 0.005	0.802 ± 0.019	0.141 ± 0.013	0.711 ± 0.011	0.725 ± 0.011
	dog <sup>9</sup>	0.51 ± 0.02	0.855 ± 0.019	0.071 ± 0.016	0.678 ± 0.055	0.250 ± 0.039	0.659 ± 0.055	0.776 ± 0.027
	man <sup>10</sup>	0.42 ± 0.01	0.936 ± 0.006	0.077 ± 0.007	0.738 ± 0.023	0.185 ± 0.022	0.712 ± 0.025	0.692 ± 0.041

<sup>1</sup> H = haematocrit value

<sup>2</sup> f<sub>b</sub> = fraction of bound drug in plasma (= 1-f<sub>u</sub>)

<sup>3</sup> f<sub>b</sub>(1-H) = fraction of drug distributed in blood to plasma water

<sup>4</sup> f<sub>pr</sub>(1-H) = fraction of drug distributed in blood to plasma proteins

<sup>5</sup> f<sub>bc</sub>(H) = fraction of drug distributed in blood to blood cells

<sup>6</sup> C<sub>p</sub>/C = ratio of total drug concentration in blood to that in plasma

<sup>7</sup> f<sub>bc, H</sub> = fraction of drug distributed in a blood cell suspension to blood cells

<sup>8</sup> pools of plasma and blood from 4 rats were investigated in duplo (mean ± S.D.)

<sup>9</sup> individual plasma and blood samples from 4 dogs were investigated (mean ± S.D.)

<sup>10</sup> individual plasma and blood samples from 6 volunteers were investigated (mean ± S.D.)

Table 3-1

ALFENTANIL PHARMACOKINETICS

TABLE 1  
Data for Five Female Patients\*

Patient	Age	Weight	Height	BSA*	Alfentanil dose	Operation
	yr	kg	cm	m <sup>2</sup>	mg	
1 (D.T.)	36	62	164	1.51	6.24	Thyroidectomy
2 (V.V.)	55	72	172	1.84	8.64	Hysterectomy
3 (D.R.)	48	58	161	1.64	7.08	Thyroidectomy
4 (V.A.)	33	59	159	1.64	7.08	Thyroidectomy
5 (T.M.)	43	48	150	1.40	5.52	Splenectomy
Av ± SD	43 ± 9	67.4 ± 9.7	157 ± 5	1.61 ± 0.16	6.91 ± 1.17	

\* Abbreviation used is: BSA, body surface area.

Table 3-2

TABLE 2  
Plasma Levels of Alfentanil following Intravenous Bolus Injection of 0.120 mg·kg<sup>-1</sup>

Time min	Patients receiving alfentanil (ng)/milliliter of plasma					Mean ± SD
	D.T.	V.V.	D.R.	V.A.	T.M.	
2	533.0	931.0	599.0	449.0	612.0	565 ± 74.5
5	398.0	476.0	339.0	360.0	423.0	399 ± 53.0
10	263.0	396.0	243.0	261.0	329.0	302 ± 61.3
15	216.0	303.0	161.0	225.0	241.0	229 ± 51.1
30	127.0	201.0	124.0	119.0	166.0	145 ± 34.3
45	81.8	171.0	74.7	82.8	118.0	108 ± 40.3
60	55.2	130.0	59.7	62.8	109.0	81.3 ± 35.7
90	32.5	85.1	37.0	21.7	56.6	48.7 ± 28.1
120	21.1	105.0	26.2	29.3	36.6	43.8 ± 34.6
180	10.2	77.7	14.0	19.8	12.1	28.8 ± 28.7
240	7.55	56.5	10.9	7.87	5.66	17.7 ± 21.8
300	5.10	43.8	6.85	4.03	2.00	12.4 ± 17.7
360	3.08	—	3.84	—	1.0	—

Figure 3-1

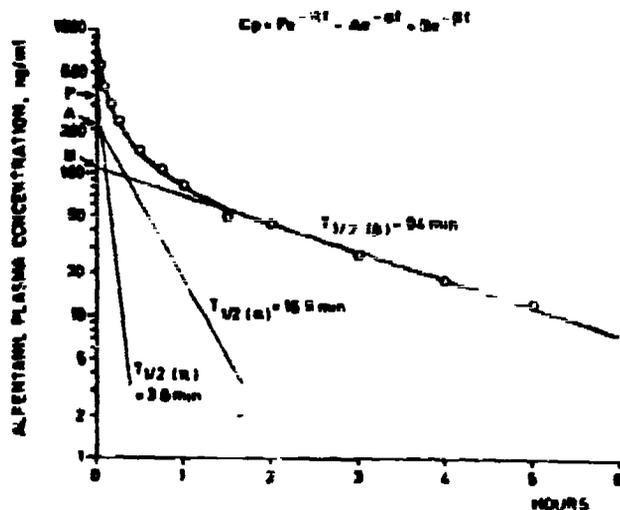


Fig 1. Mean plasma alfentanil concentrations in five subjects following 0.120 mg·kg<sup>-1</sup> intravenous injection.

TABLE 3

Pharmacokinetic Parameters for Alfentanil in Individual Patients\*

Parameter (units)	D.T (52 kg)	V.V (72 kg)	D.R (58 kg)	V.A (59 kg)	T.M (46 kg)	Mean ± SD
P (ng/ml)	415	267	642	120	230	363 ± 181
A (ng/ml)	289	141	181	370	188	222 ± 97
B (ng/ml)	35	188	44	109	205	116 ± 79
$\alpha$ ( $\text{min}^{-1}$ )	0.237	0.127	0.243	0.309	0.183	0.220 ± 0.068
$\alpha'$ ( $\text{min}^{-1}$ )	0.034	0.043	0.027	0.072	0.058	0.047 ± 0.018
$\beta$ ( $\text{min}^{-1}$ )	0.007	0.006	0.006	0.011	0.015	0.009 ± 0.004
$t_{1/2\alpha}$ (min)	2.9	5.5	2.9	2.2	3.8	3.5 ± 1.3
$t_{1/2\alpha'}$ (min)	20.6	16.2	25.5	9.7	11.9	18.8 ± 6.4
$t_{1/2\beta}$ (min)	104	141	114	84	46	84 ± 38
$V_c$ (L)	11.7	11.7	9.9	16.2	11.9	12.3 ± 2.3
$V_{d\beta}$ (L)	83.9	38.4	87.7	50.4	30.3	65.1 ± 26.3
$V_c$ (L/kg)	0.23	0.16	0.17	0.27	0.26	0.22 ± 0.05
$V_{d\beta}$ (L/kg)	1.61	0.53	1.51	0.85	0.66	1.03 ± 0.50
Plasma clearance (ml/min)	657	188	634	544	458	456 ± 155
Body clearance (ml/min·kg)	10.7	2.6	9.2	9.2	10.0	8.3 ± 3.3
$k_{10}$ ( $\text{min}^{-1}$ )	0.048	0.016	0.054	0.034	0.038	0.036 ± 0.015
$k_{12}$ ( $\text{min}^{-1}$ )	0.087	0.030	0.113	0.015	0.042	0.057 ± 0.041
$k_{21}$ ( $\text{min}^{-1}$ )	0.118	0.074	0.077	0.290	0.116	0.135 ± 0.089
$k_{13}$ ( $\text{min}^{-1}$ )	0.015	0.032	0.023	0.028	0.024	0.024 ± 0.007
$k_{31}$ ( $\text{min}^{-1}$ )	0.009	0.023	0.010	0.024	0.036	0.020 ± 0.011

\* Abbreviations used are: P,  $\alpha$ , A,  $\alpha'$ , B,  $\beta$ , three-compartment model parameters;  $t_{1/2\alpha}$ ,  $t_{1/2\alpha'}$ ,  $t_{1/2\beta}$ , half-lives of distribution and elimination phases;  $V_c$ , volume of central compartment;  $V_{d\beta}$ , volume of distribution;  $k_{12}$ ,  $k_{21}$ ,  $k_{13}$ ,  $k_{31}$ , first order rate constants for drug transfer between compartments;  $k_{10}$ , elimination rate constant.

Figure 3-2

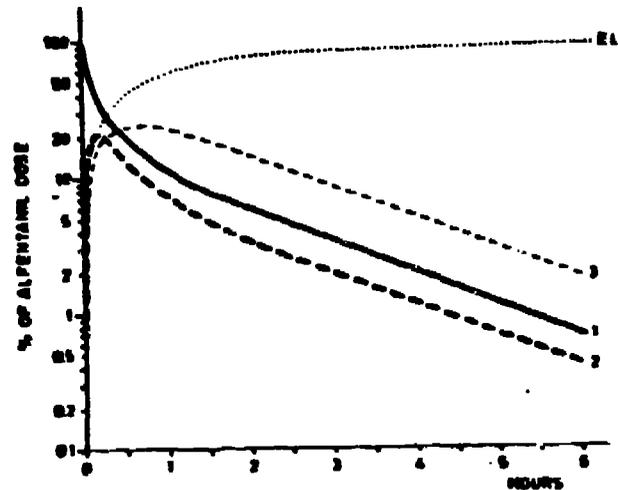


FIG 3. Fractions of alfentanil dose in various compartments 1, Central compartment, 2, shallow compartment; 3, deep compartment, EL, fraction of dose eliminated.

Figure 3-4

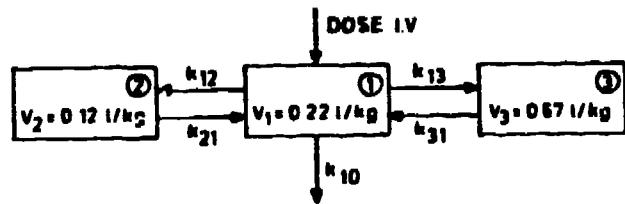


FIG 2. Three-compartment open model for alfentanil pharmacokinetics.

Figure 7-3

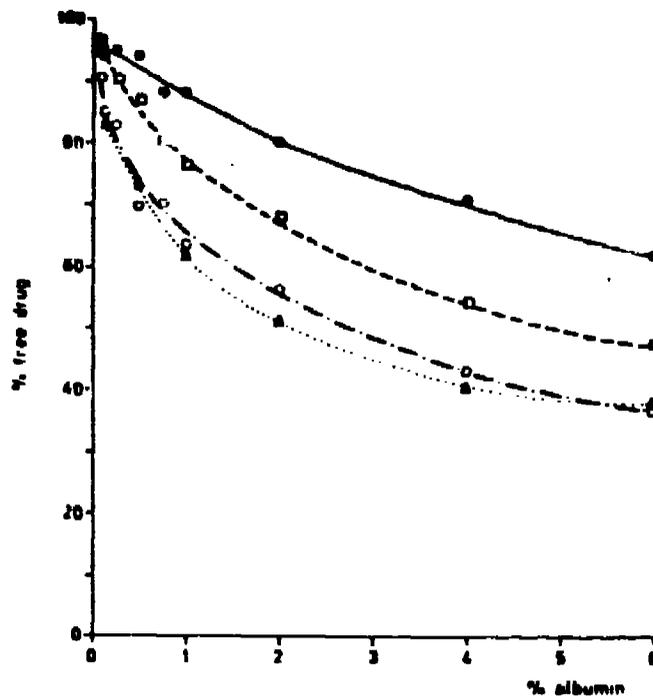


FIG. 3

Free fraction of fentanyl (□---□), sufentanil (○---○), alfentanil (●---●) and lofentanil (Δ.....Δ) in human serum albumin solutions.

Figure 7-4

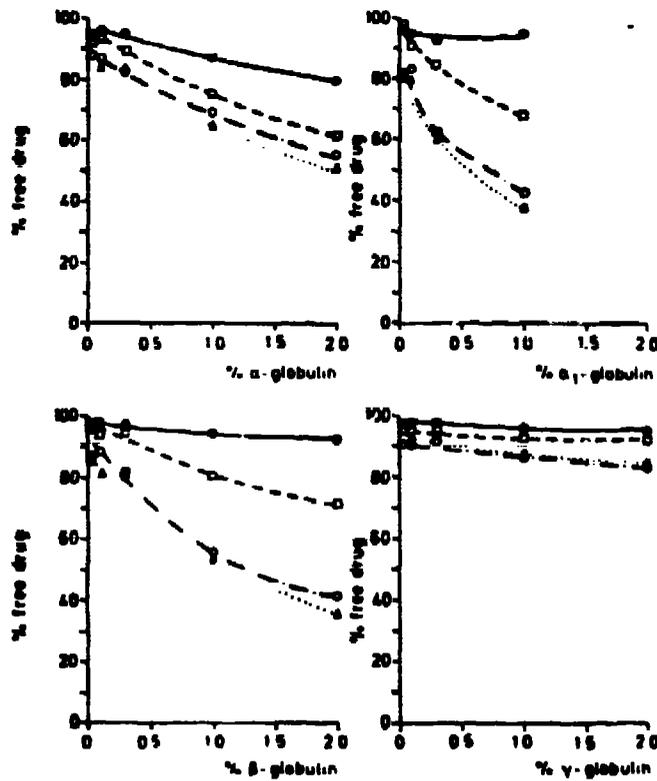


FIG. 4

Free fraction of fentanyl (□---□), sufentanil (○---○), alfentanil (●---●) and lofentanil (Δ.....Δ) in solutions of human α-globulins, α<sub>1</sub>-globulins, β-globulins, and γ-globulins.

Figure 7-5

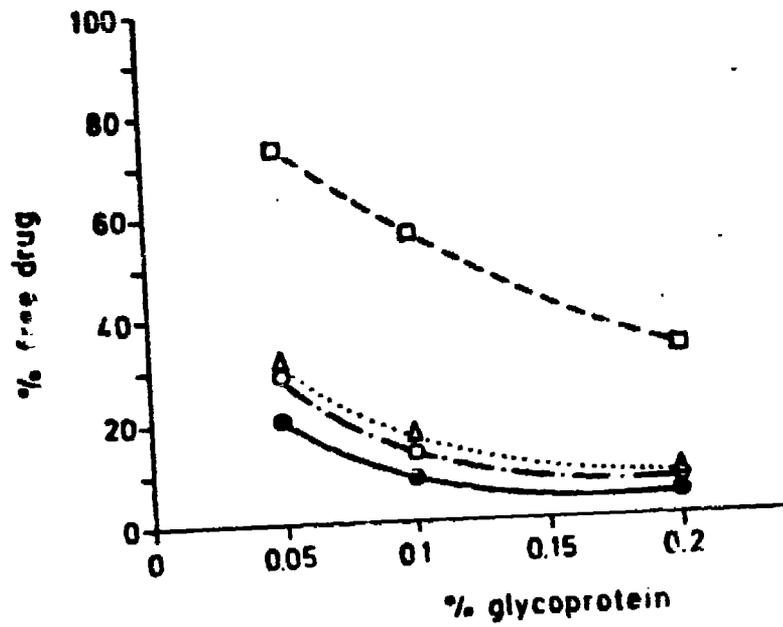


FIG. 5

Free fraction of fentanyl (□---□), sufentanil (○---○), alfentanil (●---●) and lofentanil (Δ---Δ) in solutions of human glycoproteins.

Figure 7-6

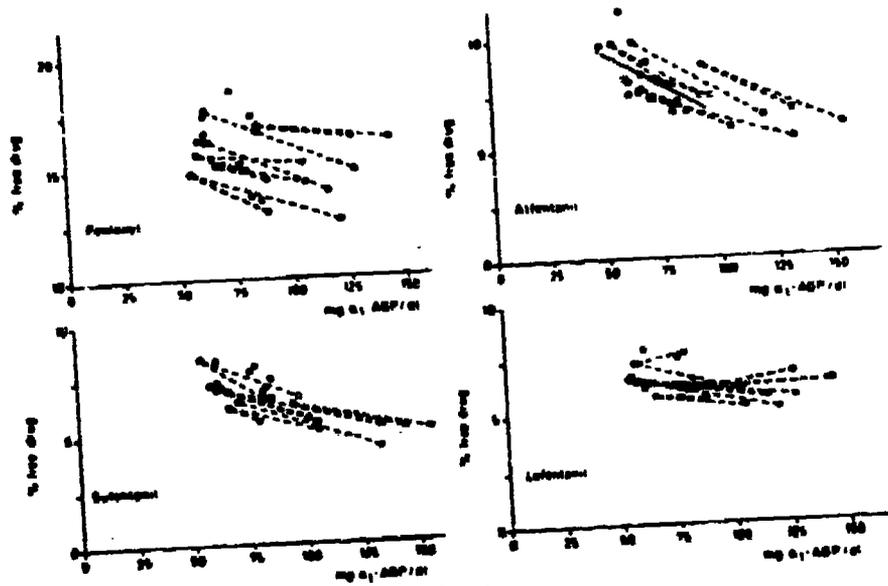


FIG. 6

Relation between the free drug fraction and the concentration of  $\alpha_1$ -acid glycoprotein ( $\alpha_1$ -AGP) in the plasma of 16 healthy volunteers (●). To various plasma samples, different amounts of glycoprotein (Cohn fraction VI) were added, and the free drug fraction as well as the resulting  $\alpha_1$ -AGP concentration were determined (○).

Figure 7-7

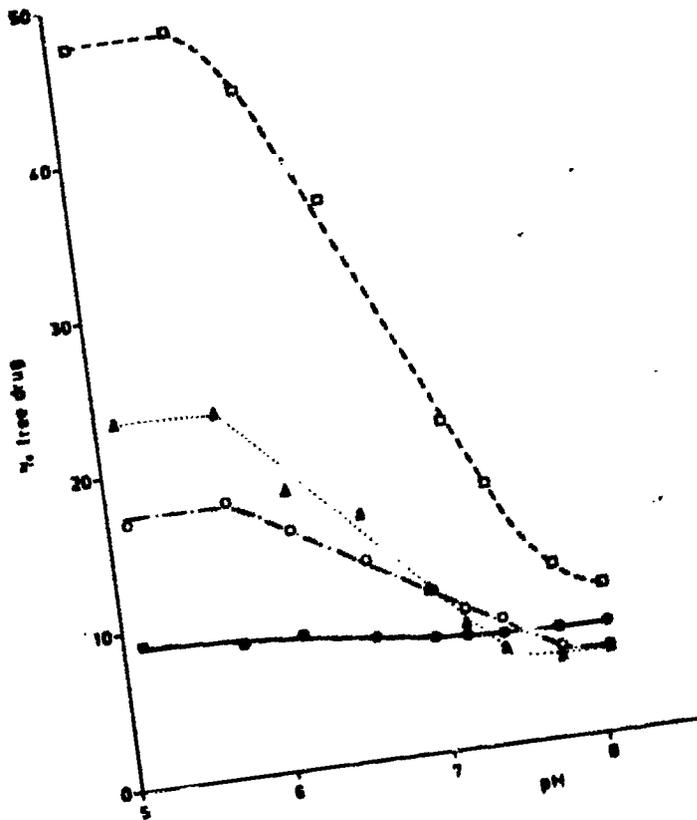


FIG. 7  
pH dependence of the free fraction of fentanyl (□---□), sufentanil (○---○), alfentanil (●---●) and lofentanil (Δ.....Δ) in human plasma.

Figure 7-8

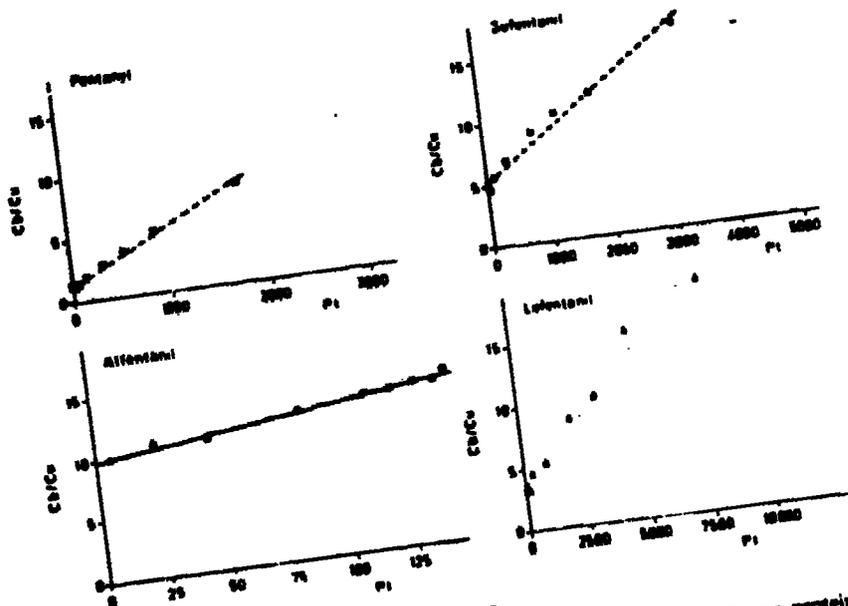


FIG. 8  
Relation between the partition of fentanyl and its analogues between plasma proteins and plasma water ( $C_p/C_u$ ) and their partition between a lipid phase—*n*-octanol—and an aqueous phase ( $P_1$ ).

Table 8-1

Characteristics and liver function tests of cirrhotic patients

Patient Number	Sex	Age (yr)	Surgical Procedure	SCPT (IU/ml)	Serum alkaline phosphatase* (IU/ml)	Serum bilirubin $\mu$ mol/l	Prothrombin (% of normal)
LAR 1	F	39	Porto caval shunt	15	228	27	62
FRA 2	F	55	Spleno renal shunt	19	159	24	79
TAR 3	F	68	Hysterectomy	21	161	41	90
LER 4	M	60	Abdominal herniae	19	109	24	64
GUI 5	M	70	Cholecystectomy	27	77	30	78
PRA 6	F	52	Spleno renal shunt	27	177	17	81
BAT 7	M	40	Sclerosis of oesophageal varices	85	176	57	65
KLE 8	M	72	" "	19	92	30	63
CHA 9	F	48	" "	63	130	17	100
DAU 10	M	40	" "	23	77	39	87
PON 11	M	69	" "	44	66	43	73

Figure 8-1

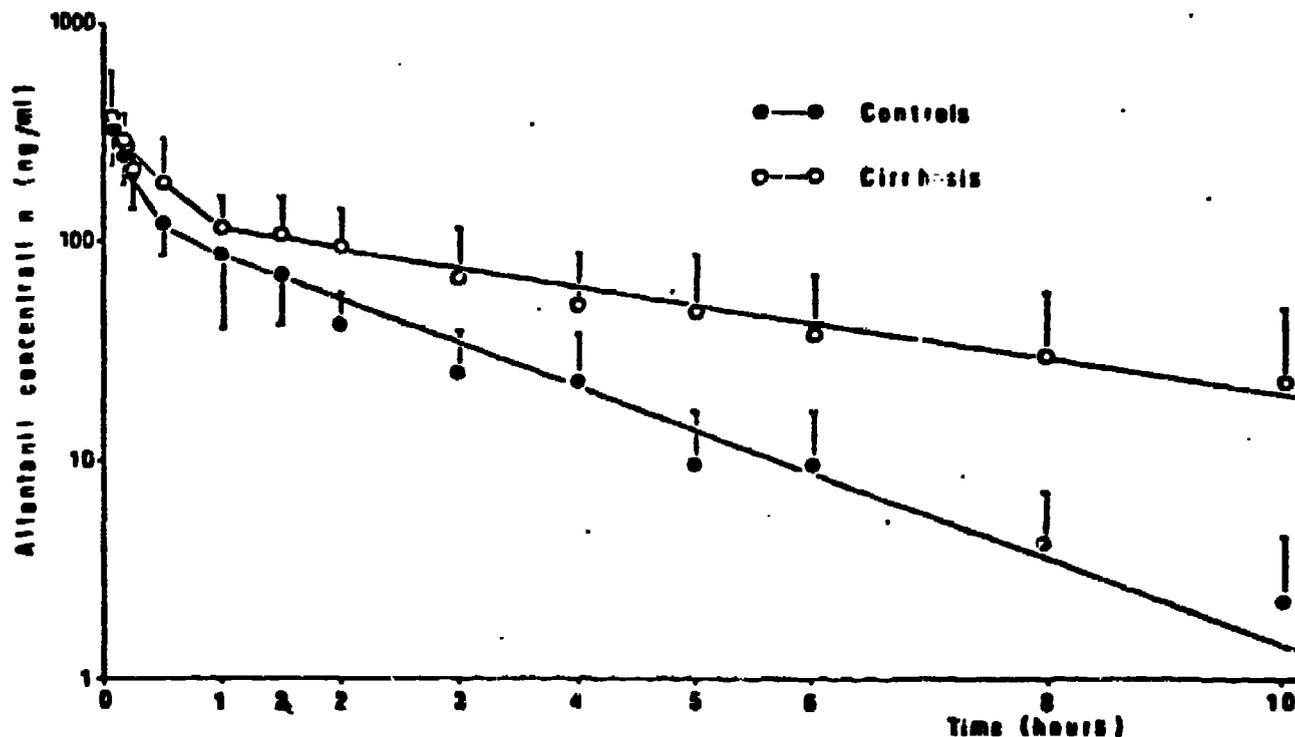
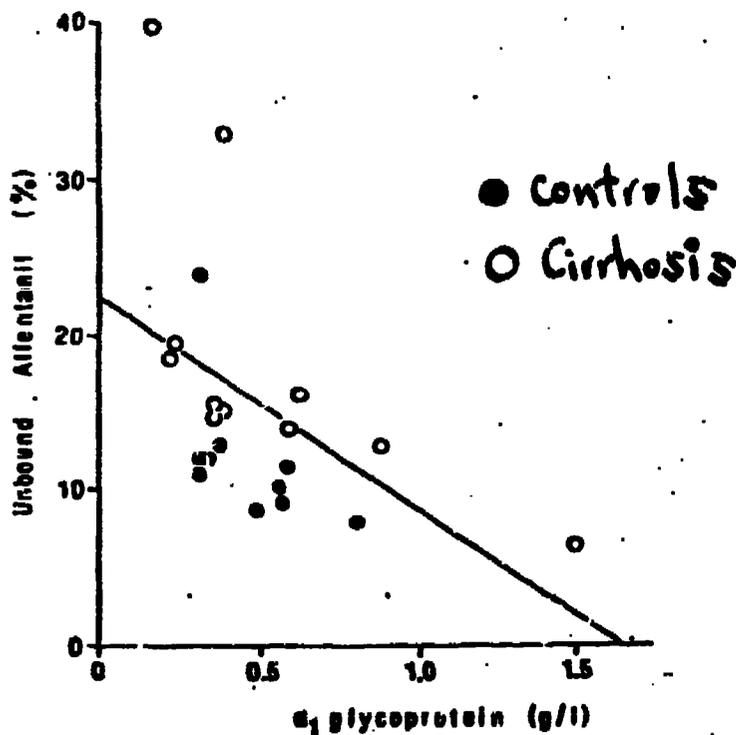


Table 8-2

Subject	Body weight (kg)	Volume of distribution at steady state (ml.kg <sup>-1</sup> )	Clearance (ml.min <sup>-1</sup> .kg <sup>-1</sup> )	Elimination half-life (min)
<b>Patient with cirrhosis</b>				
1	43			
2	58			
3	63			
4	70			
5	60			
6	56			
7	54			
8	73			
9	56			
10	59			
11	72			
Mean ± SD	60 ± 9	351 ± 206	1.6 ± 1.3**	219 ± 128**
<b>Control</b>				
1	34			
2	73			
3	68			
4	84			
5	35			
6	40			
7	60			
8	63			
9	61			
10	50			
Mean ± SD	59 ± 14	281 ± 97	3.1 ± 1.6	90 ± 18

\* p < 0.05    \*\* P < 0.01    vs. control

Figure 8-2



POOR ORIGINAL

Table 8-3

Table 3		Plasma protein concentration and alfentanil pharmacokinetic parameters in cirrhotic and normal patients				
Subject	Albumin plasma (g.l-1)	$\alpha_1$ glycoprotein plasma (g.l-1)	Free fraction alfentanil concentration (50 ng.ml-1)	Free fraction alfentanil concentration (500 ng.ml-1)	Unbound volume of distribution (l.kg-1)	Unbound clearance (ml.min-1.kg-1)
<b>Patient with cirrhosis</b>						
-F- 1						
-RA 2						
-AR 3						
-ER 4						
-UI 5						
-TA 6						
-AT 7						
-LE 8						
-MA 9						
-MU 10						
-DA 11						
Mean $\pm$ SD	29 $\pm$ 5	0.52 $\pm$ 0.35	18.6 $\pm$ 9.4 <sup>ns</sup>	19.5 $\pm$ 10.0 <sup>ns</sup>	1.71 $\pm$ 0.76 <sup>ns</sup>	0.33 $\pm$ 0.61 <sup>ns</sup>
<b>Control</b>						
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
Mean $\pm$ SD	36 $\pm$ 2	0.47 $\pm$ 0.16	11.5 $\pm$ 3.9	11.0 $\pm$ 4.1	2.58 $\pm$ 0.57	26.31 $\pm$ 8.93

\* P < 0.05 \*\* P < 0.01 vs. control

# Table 9-1

## Individual characteristics of the patients

Patients	Age (years)	Body weight (kg)	Sex	Surgical procedure
1. GAR.	40	62	M	* AVF
2. LEC.	48	65	F	AVF
3. LOP.	31	47	M	Canalis carpi
4. BEN.	38	60	M	AVF
5. YAM.	53	62	M	AVF
6. VAL.	67	60	F	AVF
7. DES.	23	51	F	AVF
8. JOU.	53	79	M	Carotid
9. TRI.	36	65	M	AVF
Mean standard deviation =	43.2 + 13.3	61.2 + 9.0		

\* AVF = arteriovenous fistula

# Table-9-2a

## Table-9-2a

### Plasma concentrations of alfentanil in patients suffering from renal insufficiency

1. GAR.		2. LEC.		3. LOP.	
	ng/ml	5 min.	ng/ml	5 min.	ng/ml
8 min.		10		10	
15		15		15	
30		30		30	
65		45		45	
90		60		60	
120		90		90	
180		120		120	
240		180		180	
300		300		245	
360		360		365	
430		435			

Table 9-2b

Plasma concentrations of alfentanil in patients suffering from renal insufficiency					
4. <u>BEN.</u>		5. <u>YAM.</u>		6. <u>VAL.</u>	
5 min.	ng/ml	5 min.	ng/ml	5 min.	ng/ml
		10		10	
		15		15	
		20		34	
		30		45	
		45		60	
		60		90	
		90		120	
		120		174	
		170		240	
				295	
				360	
				420	

Table 2c

Table 9-2c

Plasma concentrations of alfentanil in patients suffering from renal insufficiency					
7. <u>DES.</u>		8. <u>JOU.</u>		9. <u>TRI.</u>	
5 min.	ng/ml	5 min.	ng/ml	5 min.	ng/ml
10		11		10	
19		15		15	
30		30		30	
45		45		60	
60		75		90	
90		90		150	
120		120		180	
180		150		210	
240		180		240	
300		240		355	
360		300		420	
430		360			
		420			





Table 10-1

CHARACTERISTICS OF PATIENTS

All Treatment Groups

	Treatment Group			
	<u>I</u>	<u>II</u>	<u>III</u>	<u>IV</u>
Number of Patients	7	5	109	17
Sex				
Male	0	1	1	3
Female	7	4	8	16
Race				
White	3	6	108	17
Black	0	0	0	0
Hispanic	3	1	0	1
Age (yrs.)				
Mean	29	45	66	37
(range)	(24-37)	(41-52)	(63-71)	(18-53)
Weight (kg.)				
Male Patients				
Mean	-	95	76	179
(range)		-	--	(133-205)
Female Patients				
Mean	64	62	69	117
(range)	(50-80)	(53-74)	(55-85)	(92-167)
ASA Class				
I	5	4	4	3
II	2	1	5	14

Treatment groups: I - under 40 years; II - 40-60 yrs; III = over 60 yrs; IV = morbidly obese

Significant difference for ASA Class, Groups I and II vs. Group IV.  
p<0.05.

No comparisons made for age and weight.

Table 10-2a

PATIENT CHARACTERISTIC PROFILE  
BOLUS PATIENTS

	Treatment Group			
	I	II	III	IV
Number of Patients	7	5	9	8
Sex				
Male	0	1	1	1
Female	7	4	8	7
Race				
White	4	4	8	7
Black	0	0	1	0
Hispanic	3	1	0	1
Age (yrs.)				
Mean	29	45	67	36
Std. Dev.	6	4	3	11
Min.	24	41	63	18
Max.	37	52	71	48
Weight (kg.)				
Male Patients	--	95	76	133
Mean	--	--	--	--
Std. Dev.	--	95	76	133
Min.	--	95	76	133
Max.	--	95	76	133
Weight (kg.)				
Female Patients	64	62	71	116
Mean	12	10	10	17
Std. Dev.	50	53	57	99
Min.	80	74	85	151
ASA Class				
I	5	4	4	0
II	2	1	5	8

Statistically significant overall treatment differences:  
ASA Class - Chi-square = 11.00, with 3 d.f., p = 0.01.  
Significant pairwise comparisons - Group II vs. Group IV, and Group I vs. Group IV, Fisher's exact test, p = 0.007. A p-value of 0.05/6 = 0.0083 is required for statistical significance when making pairwise comparisons.

Treatment groups were not compared for age and weight.

I = Alfentanil (under 40 years); II = Alfentanil (40 to 60 years);  
III = Alfentanil (over 60 years); IV = Alfentanil (Morbidly Obese).

Table 10-2b

PATIENT CHARACTERISTIC PROFILE

BOLUS VS. INFUSION  
MORBIDLY OBESE PATIENTS

	Method	
	Bolus	Infusion
Number of Patients	8	9
Sex		
Male	1	2
Female	7	7
Race		
White	7	9
Black	0	0
Hispanic	1	0
Age (yrs.)		
Mean	36	35
Std. Dev.	11	10
Min.	18	24
Max.	48	53
Weight (kg.)		
Male patients	133	202
Mean	--	4
Std. Dev.	133	199
Min.	133	205
Max.	133	205
Weight (kg.)		
Female patients	116	117
Mean	17	25
Std. Dev.	99	92
Min.	151	167
Max.	151	167
ASA Class		
I	1	3
II	11	6

# Table 10 - 3a

## Criteria for Inclusion of Patients

### a. Group I

- 1) at least 21 years of age
- 2) less than 40 years of age
- 3) ASA Class I or II
- 4) having surgery of such a nature that anesthesia is expected to last approximately 0.5-2.0 hours.

### b. Group II

- 1) at least 40 years of age
- 2) less than 60 years of age
- 3) ASA Class I or II

- 4) having surgery of such a nature that anesthesia is not expected to last longer than 2 hours.

### c. Group III

- 1) geriatric patients over the age of 60
- 2) ASA Class I or II
- 3) having surgery of such a nature that anesthesia is not expected to last longer than 2 hours.

### c. Group I

- 1) morbidly obese patients at least 21 years of age
- 2) less than 60 years of age
- 3) ASA Clas. I or II
- 4) having surgery of such a nature that anesthesia is expected to last approximately 1-2 hours.

# Table 10 - 3b

## Criteria for Exclusion of Patients

### a. Group I

- 1) under 21 years of age
- 2) above 39 years of age
- 3) pregnancy, unless surgery will result in termination of pregnancy
- 4) ASA Class III, IV, V and emergency surgery
- 5) anesthesia expected to exceed 2 hours
- 6) known renal or hepatic dysfunction

### b. Group II

- 1) under 40 years of age
- 2) above 59 years of age
- 3) ASA Class III, IV, V and emergency surgery
- 4) anesthesia lasting longer than 2 hours
- 5) known renal or hepatic dysfunction

### c. Group III

- 1) under the age of 61
- 2) ASA Class III, IV, V and emergency surgery
- 3) anesthesia lasting longer than 2 hours
- 4) known renal or hepatic dysfunction

### d. Group IV

- 1) not morbidly obese
- 2) under 21 years of age
- 3) above age 59
- 4) ASA Class III, IV, V and emergency surgery
- 5) anesthesia expected to exceed 2 hours
- 6) known renal or hepatic dysfunction

BOLUS PATIENTS

GROUP I - ALFENTANIL (Under 40 Years)

Patient	Total Dose	
	mg	ug/kg
13	6.52	87
18	6.40	86
19	6.36	100
20	5.60	100
22	5.00	100
41	5.80	112
44	7.05	95
Mean	6.10	96
Std. Dev.	0.68	10

BOLUS PATIENTS

GROUP II - ALFENTANIL (40 to 60 Years)

Patient	Total Dose	
	mg	ug/kg
10	5.40	100
11	5.35	101
15	6.50	99
22	5.00	100
23	7.30	99
42	8.35	88
Mean	6.58	97
Std. Dev.	1.28	5

BOLUS PATIENTS

GROUP III - ALFENTANIL (Over 60 Years)

Patient	Total Dose	
	mg	ug/kg
9	6.15	100
24	6.60	105
27	6.90	82
28	7.00	97
	6.15	80
29	6.80	120
30	6.65	100
36	7.60	100
43	6.40	76
Mean	6.69	96
Std. Dev.	0.46	14

BOLUS PATIENTS

GROUP IV - ALFENTANIL (Morbidly Obese)

Patient	Total Dose	
	mg	ug/kg
6	6.10	54
8	5.10	52
12	7.65	51
14	8.12	68
16	6.00	50
17	8.00	60
21	6.80	62
39	2.50	24
Mean	6.28	53
Std. Dev.	1.86	13

Table 10-5

STUDY DRUG DOSES  
BOLUS VS. INFUSION

MORBIDLY OBESE PATIENTS

BOLUS

Patient	Total Dose		Loading Dose		Infusion Dose	
	mg	ug/kg	mg	ug/kg	mg	ug/kg
6	6.10	54	6.10	54	--	--
8	5.10	52	5.10	52	--	--
12	7.65	51	7.65	51	--	--
14	8.12	68	8.12	68	--	--
16	6.00	50	6.00	50	--	--
17	8.00	60	8.00	60	--	--
21	6.80	62	6.80	62	--	--
39	2.50	24	2.50	24	--	--
Mean	6.28	53	6.28	53	--	--
Std. Dev.	1.86	13	1.86	13	--	--

INFUSION

Patient	Total Dose		Loading Dose		Infusion Dose	
	mg	ug/kg	mg	ug/kg	mg	ug/kg
25	7.24	68	4.80	57	3.24	31
26	10.74	53	4.00	22	5.94	30
31	8.05	77	4.00	38	4.05	39
33	9.67	83	4.00	34	5.67	49
34	10.08	79	4.00	31	6.08	48
35	8.41	50	4.00	24	4.41	26
37	6.93	75	4.00	43	2.93	32
38	9.85	50	4.00	20	5.85	29
40	7.60	72	4.00	38	3.60	34
Mean	8.72	67	4.09	32	4.64	35
Std. Dev.	1.39	13	0.27	8	1.25	8

Table 10-6

~~TABLE~~

ALFENTANIL PLASMA LEVELS  
 DESCRIPTIVE STATISTICS FOR INFUSION PATIENTS  
 MORBIDLY OBESE PATIENTS

<u>Time (Minutes Post- Administration)</u>	<u>N</u>	<u>Actual Time</u>	<u>Mean (ng/ml)</u>	<u>Std. Dev. (ng/ml)</u>	<u>Median (ng/ml)</u>
1	9	1.0	286.70	239.08	233.44
3	9	2.9	396.81	199.66	364.15
5	9	5.0	508.63	181.93	486.90
10	9	10.0	242.82	136.02	218.91
15	9	15.2	197.25	103.74	180.10
30	9	30.7	149.07	61.81	140.15
60	9	64.7	137.61	62.74	127.37
90	9	89.9	134.66	62.86	120.55
120	9	120.8	103.57	59.61	86.52
150	9	154.0	82.12	45.59	68.90

**Table 10-7**

ALFENTANIL PLASMA LEVELS  
DESCRIPTIVE STATISTICS FOR BOLUS PATIENTS

Time (Minutes Post Adminis- tration)	Treatment Group											
	I		II		III		IV					
	N	Mean (ng/ml)	Std. Dev. (ng/ml)	N	Mean (ng/ml)	Std. Dev. (ng/ml)	N	Mean (ng/ml)	Std. Dev. (ng/ml)	N	Mean (ng/ml)	Std. Dev. (ng/ml)
1	6	751.33	355.08	5	497.00	202.63	7	1045.00	476.54	6	932.50	414.42
2	7	611.43	215.32	5	496.40	136.38	8	689.50	312.19	6	739.00	315.09
5	7	437.00	76.49	3	325.33	91.45	9	486.72	156.07	5	435.80	77.96
10	7	309.57	53.03	5	274.80	91.70	9	326.79	89.46	6	313.83	118.38
15	5	221.20	55.79	5	222.40	69.02	7	262.29	68.29	6	284.17	129.67
30	7	166.71	35.47	5	194.40	101.50	9	186.34	68.02	5	140.40	65.58
60	7	87.67	33.32	5	125.40	62.69	9	118.27	36.63	6	107.67	47.28
90	6	55.77	22.48	4	71.25	41.65	8	82.59	29.06	6	96.33	22.34
120	6	53.37	22.92	4	73.50	44.96	8	71.25	30.32	6	84.00	27.79
150	7	44.11	19.97	3	56.93	49.33	6	62.43	23.96	6	69.67	16.46
180	5	31.94	12.60	3	55.33	28.92	6	62.10	22.18	5	63.80	18.25
210	5	22.52	12.58	3	38.10	32.29	2	56.40	32.67	5	58.20	15.25
240	5	17.42	8.68	4	22.72	11.30	7	42.47	20.28	5	48.86	19.80
300	6	11.40	6.20	1	13.60	--	6	29.55	17.06	6	39.82	17.61
360	6	7.24	4.44	1	22.40	--	2	23.35	21.85	5	30.52	17.61
420	3	6.10	2.93	4	7.95	6.66	2	17.29	17.70	4	27.75	16.66
480	2	4.05	1.91	1	0.83	--	1	4.80	--	4	23.95	14.79
600	4	1.31	1.08	2	0.77	0.47	1	2.20	--	3	6.73	1.46
720	3	0.90	0.52	2	0.26	0.01	2	1.70	0.85	2	3.65	1.06
1440	0	--	--	0	--	--	0	--	--	2	0.23	0.11

1 I = Alfentanil (under 40 years), II = Alfentanil (40 to 60 years),  
III = Alfentanil (over 60 years), IV = Alfentanil (Morbidly Obese).

**Table 10-8**

ALFENTANIL PLASMA LEVELS  
TREATMENT COMPARISONS FOR BOLUS PATIENTS

Time (Minutes Post Adminis- tration)	Treatment Group								F-value	P-value
	I		II		III		IV			
	N	Median <sup>2</sup> (ng/ml)	N	Median <sup>2</sup> (ng/ml)	N	Median <sup>2</sup> (ng/ml)	N	Median <sup>2</sup> (ng/ml)		
1	6	690.04	5	460.41	7	953.67	6	859.55	2.85	0.06
2	7	577.06	5	477.83	8	635.07	6	689.40	0.90	0.46
5	7	431.06	3	315.96	9	465.22	5	430.64	1.73	0.19
10	7	305.40	5	261.70	9	315.38	6	297.83	0.46	0.72
15	5	215.17	5	213.09	7	257.95	6	261.05	0.59	0.63
30	7	163.61	5	172.45	9	176.55	5	129.89	0.76	0.53
60	7	82.64	5	110.78	9	112.95	6	100.74	0.88	0.47
90	6	52.10	4	68.28	8	77.19	6	94.30	2.21	0.12
120	6	48.41	4	61.18	8	65.01	6	81.67	1.09	0.38
150	7	40.06	3	42.91	6	58.35	6	68.08	1.52	0.24
180 <sup>3</sup>	5	29.98	3	50.75	6	58.10	5	61.87	3.55	0.04
210	5	20.33	3	27.90	2	51.45	5	56.62	3.02	0.08
240 <sup>4</sup>	5	15.69	4	20.05	7	38.36	5	46.04	5.35	0.009
300 <sup>5</sup>	6	9.39	1	13.60	6	25.19	6	36.93	5.13	0.01
360	6	5.45	1	22.40	2	17.51	5	27.37	3.58	0.054
420	3	5.67	4	6.16	2	11.92	4	24.64	3.11	0.08
480 <sup>4</sup>	2	3.82	1	0.83	1	4.80	4	21.34	13.00	0.02
600	4	0.82	2	0.70	1	2.20	3	6.62	3.22	0.10
720 <sup>4</sup>	3	0.76	2	0.26	2	1.59	2	3.57	7.65	0.03
1440	0	--	0	--	0	--	2	.22	--	--

1 I = Alfentanil (under 40 years), II = Alfentanil (40 to 60 years),  
III = Alfentanil (over 60 years), IV = Alfentanil (Morbidly Obese).

2 Assuming a lognormal distribution.

3 Results of pairwise comparisons: Group I lower than groups III and IV.

4 Results of pairwise comparisons: Group IV greater than groups I and II.

5 Results of pairwise comparisons: Group III greater than group II.

6 Results of pairwise comparisons: Group I lower than group IV.

17-011020

17-011020

Table 10-9

PHARMACOKINETIC VALUES\*  
(Means)

<u>Parameter</u>	<u>Treatment Group</u>		
	<u>Elderly</u>	<u>Obese</u>	<u>Nonobese &lt;60 yrs.</u>
Beta Half-life (min)	127	172	92
Clearance (ml/min)	225	179	321
Volume Distribution (L/min)	30.4	35.0	30.0

Significant difference for beta half-life, elderly group vs. nonobese group <60 yrs,  $p < 0.05$ .

\*Brown B. and Bentley J.: Personal Communication, date?

GG- need info on  
no. pts, p-value (I guessed)  
+ stat test.  
Ray

Figure 10-1

### MEDIAN ALFENTANIL PLASMA LEVEL BOLUS PATIENTS

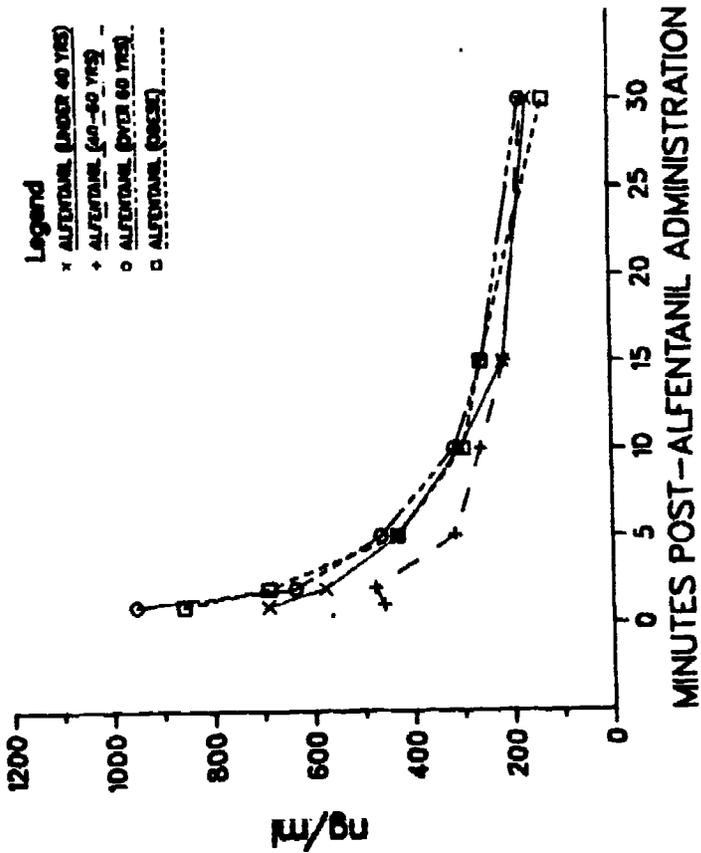


Figure 10-2

### MEDIAN ALFENTANIL PLASMA LEVEL BOLUS PATIENTS

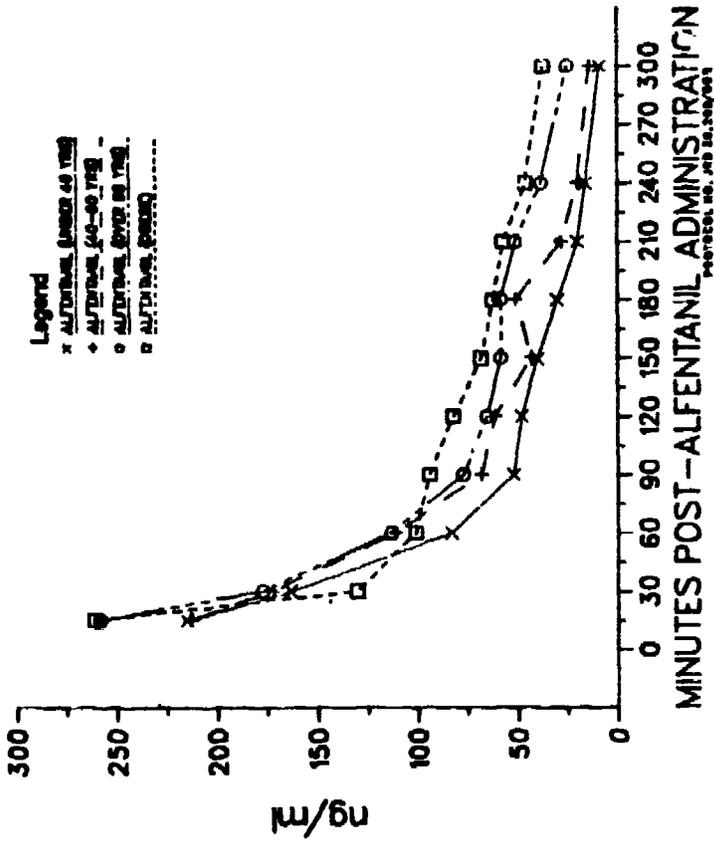
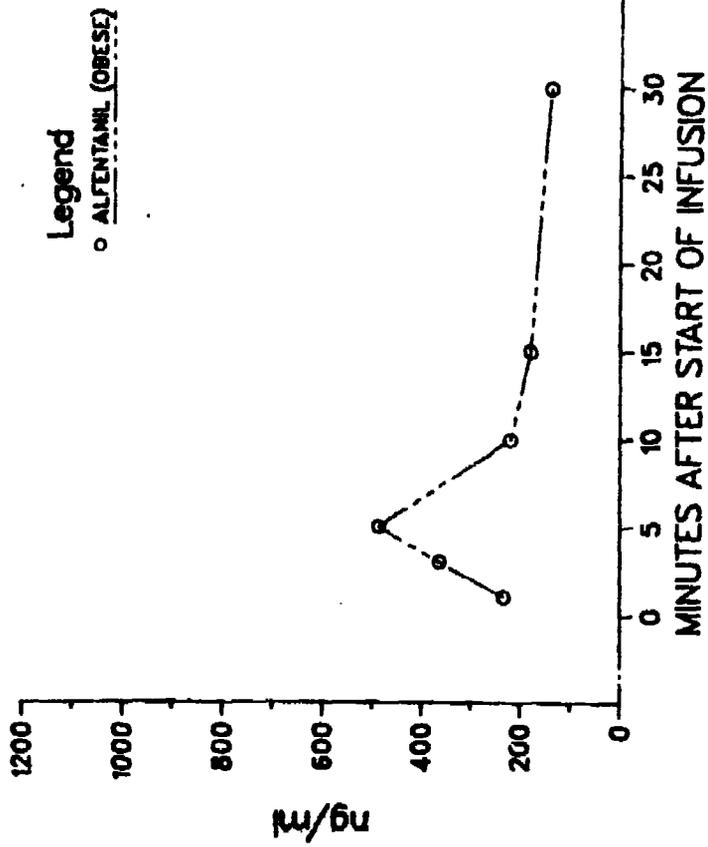


Figure 10-3

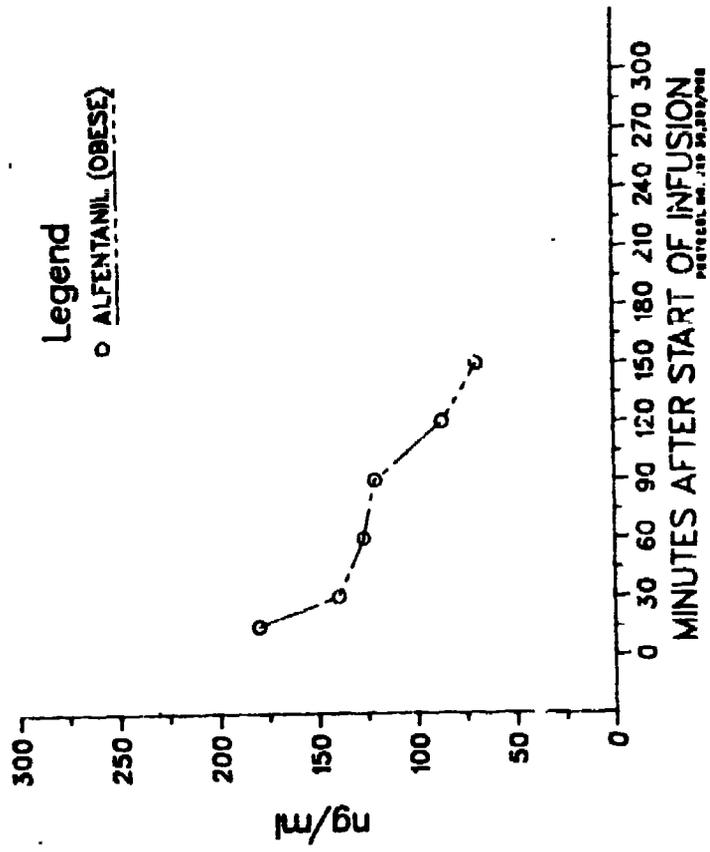
FIGURE 3  
MEDIAN ALFENTANIL PLASMA LEVEL  
INFUSION PATIENTS



PROTOCOL NO. JRB 35, 255/088

Figure 10-4

FIGURE 4  
MEDIAN ALFENTANIL PLASMA LEVEL  
INFUSION PATIENTS



Complete Maintenance Regimen Proposed:

NOTE: Obese patients with a body mass index over 25 will be dosed on estimated lean body weight. Those with a body mass index under 25 will be dosed by their true body weight.

SUBGROUP A (Groups I, II, III and IV)

- 1) Alfentanil, 75 ug/kg, as a bolus i.v.
- 2) N<sub>2</sub>O (60%) in O<sub>2</sub> with controlled ventilation
- 3) Pancuronium bromide, 0.1 mg/kg i.v.
- 4) If systolic arterial blood pressure exceeds 15% of control value, the patient may be given morphine (1-5 mg incrementally) or meperidine (25-75 mg incrementally), an intravenous vasodilator such as nitroprusside or nitroglycerin, or a potent inhalational agent such as halothane or enflurane. In any case, a notation will be made in the case record form with appropriate comments (under vasoactive agents).

SUBGROUP B (Groups I, II, III and IV)

- 1) Steady-state alfentanil plasma levels will be attained by the following infusion technique:
  - a. Groups I, II and III loading infusion:
    1. 10 mg alfentanil administered over a 5-minute period (this may be started prior to thiopental and intubation)
    2. maintenance infusion: 80 ug/minute until 10-15 minutes prior to end of operation
  - b. Group IV patients will receive:
    1. 4 mg alfentanil administered over a 5-minute period (this may be started prior to thiopental and intubation)
    2. maintenance infusion: 45 ug/minute until 10-15 minutes prior to end of operation
- 2) N<sub>2</sub>O/O<sub>2</sub> - 60%/40% - with controlled ventilation
- 3) Pancuronium bromide, 0.1 mg/kg i.v.
- 4) If systolic arterial blood pressure exceeds 15% of control value, the patient may be given an intravenous vasodilator such as nitroprusside, nitroglycerin, or a potent inhalational agent such as halothane or enflurane. In either case, a notation will be made in the case record form with appropriate comments (under vasoactive agents).

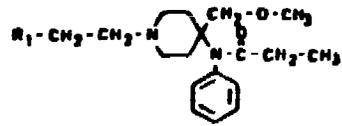
Appendix 2

Dosing:

Pre-op Medications: diazepam 10 mg, PO will be given 60-90 minutes pre-operatively; Group IV (morbidly obese) will receive glycopyrrolate, 0.2 - 0.3 mg IM and magnesium plus aluminum hydroxide, 30cc PO, 30 minutes preoperatively.

Induction Medications: thiopental sodium, 3-4 mg/kg IV, succinylcholine chloride, 1.5 mg/kg IV.

Figure 11-1



Compound	R <sub>1</sub>
AF	
SF	
IS	

Chemical structures of alfentanil (AF), sufentanil (SF) and the internal standard (IS).

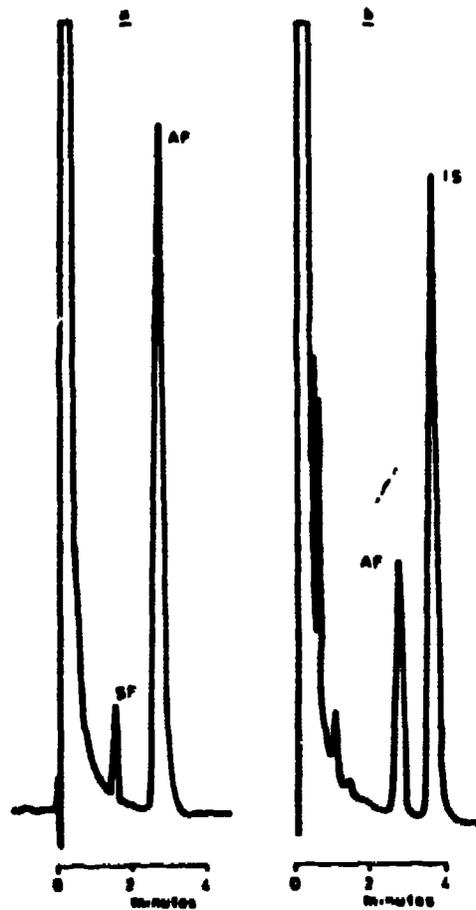


Figure 11-2

Gas chromatograms of extracts from (a) rat plasma, 2 min after an intravenous dose of sufentanil (SF), spiked with AF as the internal standard, and (b) rat heart tissue, 8 min after an intravenous dose of alfentanil (AF), spiked with IS as the internal standard. GC conditions were as indicated in the text.

**TABLE 1-1**

**STANDARD CURVES FOR ALFENTANIL (AF) AND SUFENTANIL (SF) IN BIOLOGICAL SAMPLES**

Compound	Sample	Internal standard (ng/sample)	Range (ng/sample)	Regression equation $y = ax + b^*$		Correlation coefficient	
				a	b	r	n
AF	Plasma (1 ml)	100	1 - 1000	1.040	-0.012	0.9998	11
	Tissue (1 g)	250	2.5 - 500	1.071	-0.008	0.9998	9
SF	Plasma (1 ml)	100	1 - 100	0.628	+0.005	0.9994	8
	Tissue (1 g)	250	2.5 - 250	0.550	-0.003	0.9996	8

\*y = peak area ratios (AF/IS and SF/AF, respectively); x = concentration ratios (AF/IS and SF/AF, respectively).

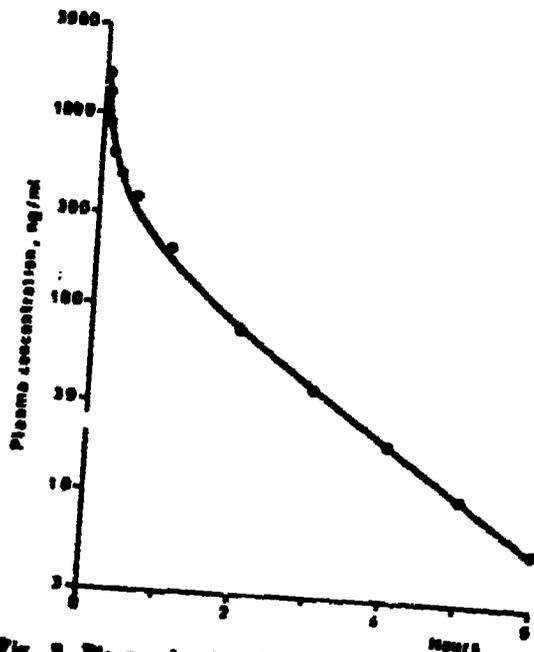
**TABLE 1-2**

**REPRODUCIBILITY DATA FOR THE DETERMINATION OF ALFENTANIL (AF) IN ANIMAL TISSUES**

Added (ng/g)	Found, mean ± S.E.M.* (ng/g)	S.E.M. (%)
12.5	14.6 ± 1.4	9.6
25	25.5 ± 1.7	6.7
50	48.2 ± 1.4	2.9
125	118 ± 2.2	1.9
250	248 ± 10	4.0
500	503 ± 24	4.8

\*S.E.M. = standard error of the mean (n = 4).

**Figure 1-3**



**Fig. 3. Plasma levels of alfentanil (AF) in a patient after an intravenous dose of 0.125 mg/kg body weight.**

# Table 12-1

Table 1. Antibody specificity: competition between various possible metabolites and [<sup>3</sup>H]alfentanil or [<sup>3</sup>H]sufentanil for binding to the respective antibodies. Cross-reaction is expressed as the molar ratio of alfentanil or sufentanil and the test compound required to inhibit by 50% complex formation between the tracer and the antiserum (ID<sub>50</sub>).

Structure	R <sub>1</sub>	R <sub>2</sub>	alfentanil	sufentanil
			<chem>CC1CN(C1)C(=O)CC</chem>	<chem>CC1CN(C1)C(=O)CC</chem>
			ID <sub>50</sub>	ID <sub>50</sub>
-CH <sub>2</sub> -O-CH <sub>3</sub>			1.0	1.0
-H-O-CH <sub>3</sub>			1.2	1.1
-CH <sub>2</sub> -O-CH <sub>3</sub>	-H		50	33
-CH <sub>2</sub> -OH			12	29
-CH <sub>2</sub> -OH	-H		—	73
-COOH			—	417
-H			288	51
			>1000	>1000

# Table 12-2

Table 2. Antibody specificity: competition between chemically related analgesics and [<sup>3</sup>H]alfentanil or [<sup>3</sup>H]sufentanil for binding to antibodies directed to alfentanil or sufentanil. Cross-reaction is expressed as the molar ratio of alfentanil or sufentanil and the test compound required to inhibit by 50% complex formation between the tracer and the antiserum (ID<sub>50</sub>).

Reference No. (generic name)	Structure	ID <sub>50</sub>	
		alfentanil	sufentanil
R33800 sufentanil		>1000	1
R39209 alfentanil		>1000	1
R4263 fentanyl		>1000	133
R33799 carfentanil		>1000	3.7
R34995 lofentanil		>1000	418

# Figure 12-1

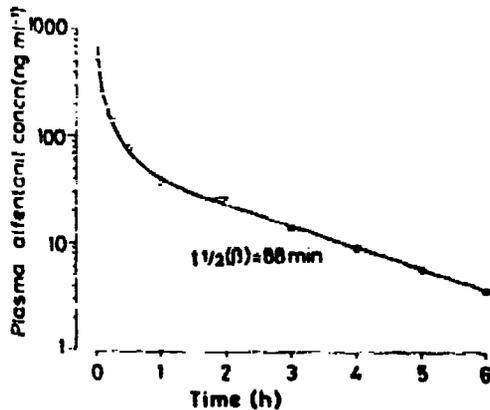


Fig. 2. Mean plasma alfentanil concentrations in surgical patients (n = 2) after intravenous administration of alfentanil at 50 μg kg<sup>-1</sup>. Concentrations were determined by RIA applied directly to plasma samples.

# Table 13-1

Alfentanil kinetics after an intravenous injection of 50 µg/kg in nine young adults

Subject No.	Sex	Age (yr)	Weight (kg)	Height (cm)	A (ng/ml)	B (ng/ml)	$\alpha$ (min <sup>-1</sup> )	$\beta$ (min <sup>-1</sup> )	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (min)	$k_{12}$ (min <sup>-1</sup> )	$k_{21}$ (min <sup>-1</sup> )	$V_c$ (ml/kg)	$V_d$ (ml/kg)	$V_{d_{ss}}$ (ml/kg)	Cl (ml/min/kg)
1	M	42	63	166	215	45.8	0.042	0.0102	16.6	68	0.009	0.016	192	304	508	5.18
2	F	27	57	159	187	31.2	0.061	0.0078	11.5	89	0.022	0.015	259	546	903	7.06
3	M	44	75	174	179	52.8	0.068	0.0113	10.1	62	0.024	0.024	216	424	608	6.84
4	F	27	65	173	320	39.1	0.073	0.0083	9.5	83	0.026	0.015	139	379	661	5.50
5	F	39	56	163	145	21.7	0.062	0.0087	11.1	80	0.034	0.016	304	703	1201	10.44
6	F	41	66	174	149	31.2	0.058	0.0078	12.6	89	0.027	0.016	278	624	956	7.49
7	M	43	89	174	283	43.1	0.058	0.0079	11.9	88	0.020	0.015	154	363	615	4.85
8	F	33	102	161	332	59.4	0.089	0.0051	7.8	135	0.056	0.018	128	492	836	3.26
9	F	27	54	156	259	29.2	0.062	0.0122	11.1	57	0.044	0.017	174	305	626	7.62
Σ		36	70	166	230	39.3	0.063	0.0068	11.4	83	0.032	0.017	201	460	746	6.47
SD		7	16	7	72	12.2	0.013	0.0021	2.4	23	0.006	0.003	61	141	224	2.06

M = male, F = female.

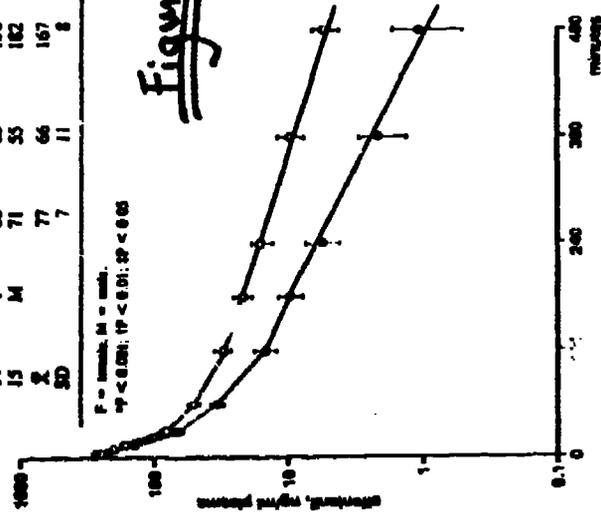
Alfentanil kinetics after an intravenous injection of 50 µg/kg in 15 elderly subjects

Subject No.	Sex	Age (yr)	Weight (kg)	Height (cm)	A (ng/ml)	B (ng/ml)	$\alpha$ (min <sup>-1</sup> )	$\beta$ (min <sup>-1</sup> )	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (min)	$k_{12}$ (min <sup>-1</sup> )	$k_{21}$ (min <sup>-1</sup> )	$V_c$ (ml/kg)	$V_d$ (ml/kg)	$V_{d_{ss}}$ (ml/kg)	Cl (ml/min/kg)
1	F	72	81	164	160	90.0	0.066	0.0041	10.6	170	0.010	0.033	200	454	500	2.04
2	M	77	62	158	108	100.8	0.170	0.0038	4.1	183	0.008	0.082	239	473	484	1.84
3	M	69	75	162	119	22.1	0.071	0.0095	9.7	73	0.035	0.026	334	338	1115	12.53
4	F	82	56	172	336	28.2	0.074	0.0050	9.4	140	0.036	0.010	177	377	586	4.84
5	F	72	46	164	266	46.3	0.065	0.0065	10.6	106	0.028	0.029	160	461	687	4.48
6	F	91	55	160	236	54.1	0.062	0.0047	11.2	148	0.019	0.032	172	336	696	3.25
7	M	70	70	178	249	20.7	0.051	0.0066	13.7	105	0.033	0.014	185	439	937	6.20
8	F	77	74	164	232	28.4	0.070	0.0046	9.9	151	0.027	0.035	192	773	1147	5.25
9	F	68	72	162	214	53.9	0.108	0.0047	6.4	148	0.020	0.067	187	679	790	3.70
10	F	83	78	168	163	40.1	0.036	0.0045	19.3	156	0.015	0.015	246	306	829	3.99
11	F	82	58	180	145	38.8	0.034	0.0065	20.4	273	0.020	0.008	167	424	667	5.67
12	M	69	79	170	271	73.1	0.055	0.0045	12.6	155	0.016	0.028	145	414	526	2.35
13	F	78	71	163	183	47.2	0.037	0.0058	18.5	119	0.018	0.012	217	361	561	3.84
14	F	88	63	156	186	60.8	0.068	0.0040	10.2	172	0.014	0.039	202	373	696	2.80
15	M	71	55	182	153	44.9	0.023	0.0047	30.4	148	0.012	0.007	252	440	655	3.06
Σ		77	66	167	201	50.0	0.066	0.0054*	13.1	137*	0.021	0.031	211	343	772	4.37*
SD		7	11	8	64	23.5	0.035	0.0017	6.6	33	0.009	0.021	56	132	237	2.61

F = female, M = male.

\*p < 0.05; †p < 0.01; ‡p < 0.005

Figure 13-1



Time course of plasma concentrations (X = SE) of alfentanil after an intravenous injection of 50 µg/kg in 15 elderly (○) and nine young (●) subjects.



**Table 14-3**

PHARMACOKINETIC PARAMETERS  
OF ALFENTANIL IN THE CHILD (I.V. 20  $\mu\text{g}\cdot\text{kg}^{-1}$ )

Sampling times in minutes	SEC.	COR.	NEV.	ARM.	GOT.	AFO.	TRA.	PER.	Average $\pm$ ET
$t_{1/2}$ (min)									5.13 $\pm$ 2. 40.23 $\pm$ 8.5
$V_d$ ml.kg <sup>-1</sup>									69.8 $\pm$ 56.3 93.7 $\pm$ 55.9 163.5 $\pm$ 110.4 289.8 $\pm$ 180.2
Clearance ml.min <sup>-1</sup> kg <sup>-1</sup>									4.73 $\pm$ 1.75
$K_1$ min <sup>-1</sup>	SEC.	COR.	NEV.	ARM.	GOT.	AFO.	TRA.	PER.	Average $\pm$ ET
$K_{12}$									0.051 $\pm$ 0.024
$K_{21}$									0.032 $\pm$ 0.006
$K_{e1}$									0.088 $\pm$ 0.034

**Table 14-4**

ALFENTANIL BINDING TO PLASMA PROTEINS  
IN THE 4 TO 8-YEAR-OLD CHILD

Concentration of alfentanil ng/ml of plasma	SEC.	COR.	NEV.	ARM.	GOT.	AFO.	TRA.	PER.	Average $\pm$ ET
500									85.5 $\pm$ 3.9
30									89.5 $\pm$ 2.4

**Table 15-1**

Laboratories participating in the interlaboratory study.

Ref # 6  
Meuldermans

Ref # 5  
Lawron

Ref # 2  
Bovill

No.	Laboratory
1	Department of Drug Metabolism and Pharmacokinetics Janssen Pharmaceutica, Beerse, Belgium
2	Laboratoire de Pharmacocinétique, Laboratoires Janssen, Aubervilliers, France
3	Anesthesiology Service, Stanford University School of Medicine, Palo Alto, CA, U.S.A.
4	Anaesthetics Unit, The London Hospital, London, U.K.
5	Department of Anesthesiology, University Hospital of Leiden, Leiden, The Netherlands
6	Department of Anesthesia, University of Bonn, Bonn, G.F.R.
7	Department of Anesthesiology, RWTH, Aachen, G.F.R.
8	Department of Anesthesiology, Emory University Medical School, Atlanta, GA, U.S.A.

Table 15-2: Alfentanil plasma levels in clinical samples.

**Table 15-2**

Sample No.	Alfentanil, ng/ml reported									
	Lab 1		Lab 2	Lab 3	Lab 4	Lab 5	Lab 6	Lab 7	Lab 8	
	GC (= reference method)	RIA RIA (R)	RIA	RIA	GC	RIA	RIA	RIA	RIA	GC
C11										
C12										
C13										
C14										
C15										
C16										
C17										
C18										
C19										
C20										
C21										
C22										
C23										
C24										
C25										
C26										
C27										
C28										
C29										
C30										

1 Not detectable by the method in question.  
2 Not enough plasma available to perform the assay.

**Table: 15-3**

**Table 7:** Alfentanil plasma levels in spiked control samples. (also see table 15-9)

Sample Alfentanil		Alfentanil, ng/ml reported											
		Lab 1			Lab 2	Lab 3	Lab 4	Lab 5	Lab 6	Lab 7	Lab 8		
		No.	ng/ml added	GC	RIA	RIA (E)	NIA	RIA	GC	RIA	RIA	RIA	NIA
C1	0.00												
C2	0.30												
C3	0.99												
C4	2.96												
C5	9.86												
C6	29.6												
C7	98.6												
C8	98.6												
C9	296												
C10	986												

- 1 Not detectable by the method in question.
  - 2 Values between brackets were not taken into account for the statistical analysis.
  - 3 Not measurable because of incomplete mixing of serum with RIA reagents.
  - 4 Not enough plasma available to perform the assay.
- GC: Gas chromatography (with nitrogen-phosphorous detection).  
 NIA: Direct radioimmunoassay.  
 RIA (E): Radioimmunoassay, preceded by extraction of the samples.

**Table: 15-4**

**Table 8:** Accuracy and precision of the RIA and GC procedures.

Sample No.		R.E., % <sup>a</sup>										
		Lab 1			Lab 2	Lab 3	Lab 4	Lab 5	Lab 6	Lab 7	Lab 8	
		GC	RIA	RIA (E)	RIA	NIA	GC	RIA	RIA	RIA	RIA	GC
C1												
C2												
C3												
C4												
C5												
C6												
C7												
C8												
C9												
C10												
M.R.E. % <sup>b</sup>	4.5	14.1	19.8	14.3	26.4	5.8	9.8	19.5	6.0	9.3	16.2	
Precision <sup>c</sup>	1.4	20.9	4.7	3.2	-	3.8	1.9	6.3	3.8	3.0	9.8	
% C.V.												

<sup>a</sup> R.E. : relative error (% deviation from the true value)  
<sup>b</sup> M.R.E.: mean relative error, calculated for the absolute values of the distinct relative errors for alfentanil concentrations above 1 ng/ml  
<sup>c</sup> % C.V.: coefficient of variation as measured from the results of the duplicate samples (C7 and C8) (C.V. does not take into account the "true" value)

**Table 15-5**

**Table 1:** Linear regression parameters (single linear regression for concentrations found in the spiked plasma samples).

Lab No.	Method	Regression equation: $y \pm s_y = (a \pm s_a) x + (b \pm s_b)$	n	r
1	GC	$y \pm 7.04 = (0.908 \pm 0.0081) x + (4.50 \pm 3.20)$	7	0.9998
	RIA	$y \pm 10.7 = (1.093 \pm 0.012) x + (2.42 \pm 4.08)$	9	0.9996
	RIA(R)	$y \pm 8.71 = (1.079 \pm 0.0074) x + (4.62 \pm 2.56)$	9	0.9998
2	RIA	$y \pm 19.7 = (0.931 \pm 0.017) x - (6.86 \pm 6.01)$	9	0.999
3	RIA	$y \pm 2.42 = (1.069 \pm 0.0030) x + (2.29 \pm 1.72)$	3	1.0000
4	GC	$y \pm 8.97 = (0.995 \pm 0.010) x - (5.96 \pm 4.31)$	6	0.9998
5	RIA	$y \pm 12.1 = (1.061 \pm 0.014) x - (2.20 \pm 5.30)$	7	0.9996
6	RIA	$y \pm 25.0 = (0.646 \pm 0.028) x + (11.2 \pm 9.37)$	9	0.994
7	RIA	$y \pm 9.81 = (0.896 \pm 0.0064) x + (2.94 \pm 2.22)$	9	0.9996
8	RIA	$y \pm 2.51 = (0.927 \pm 0.0027) x - (1.21 \pm 0.960)$	9	1.0000
	GC	$y \pm 3.79 = (0.934 \pm 0.0043) x + (4.15 \pm 1.91)$	6	1.0000

$s_y$  = standard error of estimate  
 $s_a$  = standard error of the slope  
 $s_b$  = standard error of the intercept  
 n = number of observations  
 r = correlation coefficient

x = alfentanil, ng/ml added  
 y = alfentanil, ng/ml found by tested method

**Table 15-6**

**Table 2:** Linear regression parameters (log-transformed concentrations found in the spiked plasma samples).

Lab No.	Method	Regression equation: $\log y \pm s_y = (a \pm s_a) \log x + (b \pm s_b)$	n	r
1	GC	$\log y \pm 0.016 = (0.992 \pm 0.074) \log x + (0.831 \pm 0.014)$	7	0.9999
	RIA	$\log y \pm 0.039 = (0.956 \pm 0.018) \log x + (0.141 \pm 0.030)$	9	0.999
	RIA(R)	$\log y \pm 0.046 = (0.966 \pm 0.014) \log x + (0.130 \pm 0.024)$	9	0.9993
2	RIA	$\log y \pm 0.062 = (0.956 \pm 0.019) \log x + (0.022 \pm 0.032)$	9	0.999
3	RIA	$\log y \pm 0.065 = (0.962 \pm 0.035) \log x + (0.155 \pm 0.064)$	3	0.9993
4	GC	$\log y \pm 0.013 = (1.013 \pm 0.008) \log x - (0.051 \pm 0.017)$	6	0.9999
5	RIA	$\log y \pm 0.019 = (0.987 \pm 0.009) \log x + (0.063 \pm 0.017)$	7	0.9996
6	RIA	$\log y \pm 0.051 = (0.938 \pm 0.015) \log x + (0.018 \pm 0.026)$	9	0.999
7	RIA	$\log y \pm 0.028 = (0.974 \pm 0.009) \log x + (0.021 \pm 0.015)$	9	0.9997
8	RIA	$\log y \pm 0.143 = (0.941 \pm 0.043) \log x + (0.073 \pm 0.074)$	9	0.993
	GC	$\log y \pm 0.052 = (0.912 \pm 0.025) \log x + (0.196 \pm 0.050)$	6	0.999

$s_y$  = standard error of estimate  
 $s_a$  = standard error of the slope  
 $s_b$  = standard error of the intercept  
 n = number of observations  
 r = correlation coefficient

x = alfentanil, ng/ml added  
 y = alfentanil, ng/ml found by tested method

**Table 15-7:**

Table 15-7: Linear regression parameters (log-transformed concentrations found in clinical samples).

Lab. No.	Method	Regression equation: $\log Y \pm S_y = (a \pm S_a) \log X + (b \pm S_b)$	n	r
1	BIA	$\log Y \pm 0.028 = (0.008 \pm 0.012) \log X + (1.042 \pm 0.023)$	19	0.999
	BIA(B)	$\log Y \pm 0.030 = (1.016 \pm 0.013) \log X + (0.043 \pm 0.027)$	19	0.999
2	BIA	$\log Y \pm 0.051 = (0.997 \pm 0.021) \log X - (0.051 \pm 0.040)$	19	0.996
3	BIA	$\log Y \pm 0.038 = (0.692 \pm 0.016) \log X + (0.131 \pm 0.035)$	19	0.998
4	GC	$\log Y \pm 0.090 = (1.118 \pm 0.037) \log X - (0.296 \pm 0.081)$	19	0.993
5	BIA	$\log Y \pm 0.032 = (0.969 \pm 0.013) \log X + (0.109 \pm 0.029)$	19	0.998
6	BIA	$\log Y \pm 0.037 = (0.928 \pm 0.024) \log X + (0.091 \pm 0.032)$	19	0.994
7	BIA	$\log Y \pm 0.051 = (0.976 \pm 0.021) \log X - (0.003 \pm 0.044)$	19	0.996
8	BIA	$\log Y \pm 0.025 = (0.970 \pm 0.010) \log X + (0.061 \pm 0.023)$	19	0.999
	GC	$\log Y \pm 0.042 = (1.070 \pm 0.039) \log X - (0.136 \pm 0.075)$	8	0.996

S<sub>y</sub> = standard error of estimate  
 S<sub>a</sub> = standard error of the slope  
 S<sub>b</sub> = standard error of the intercept  
 n = number of observations  
 r = correlation coefficient

X = concentrations as found by reference method  
 Y = concentrations as found by tested method

**Table 15-8**

Table 15-8: Linear regression parameters (simple linear regression of concentrations found in clinical samples).

Lab. No.	Method	Regression equation: $Y \pm S_y = (a \pm S_a) X + (b \pm S_b)$	n	r
1	BIA	$Y \pm 25.7 = (1.054 \pm 0.021) X + (4.24 \pm 7.06)$	19	0.997
	BIA(B)	$Y \pm 30.9 = (1.198 \pm 0.026) X + (1.94 \pm 9.56)$	19	0.996
2	BIA	$Y \pm 48.2 = (0.819 \pm 0.040) X + (13.1 \pm 14.9)$	19	0.980
3	BIA	$Y \pm 41.1 = (1.195 \pm 0.034) X + (19.1 \pm 12.7)$	19	0.993
4	GC	$Y \pm 33.7 = (1.003 \pm 0.030) X - (5.80 \pm 10.41)$	19	0.993
5	BIA	$Y \pm 21.4 = (1.070 \pm 0.018) X + (2.15 \pm 6.63)$	19	0.996
6	BIA	$Y \pm 44.2 = (0.549 \pm 0.037) X + (32.0 \pm 13.7)$	19	0.974
7	BIA	$Y \pm 45.4 = (0.899 \pm 0.038) X - (0.99 \pm 14.02)$	19	0.985
8	BIA	$Y \pm 18.7 = (0.972 \pm 0.016) X + (8.29 \pm 5.73)$	19	0.998
	GC	$Y \pm 12.0 = (1.080 \pm 0.058) X - (4.67 \pm 7.39)$	8	0.991

S<sub>y</sub> = standard error of estimate  
 S<sub>a</sub> = standard error of the slope  
 S<sub>b</sub> = standard error of the intercept  
 n = number of observations  
 r = correlation coefficient

X = concentrations as found with GC by reference method  
 Y = concentrations as found by tested method

**Table 15-9**

**Table 15-9**  
**Table 15-9**  
 Alfentanil plasma levels in spiked control samples.

Sample Alfentanil		Alfentanil, ng/ml reported										Mean	S.D.	CV(%)	n
		Lab 1	Lab 2	Lab 3	Lab 4	Lab 5	Lab 6	Lab 7	Lab 8						
No.	ng/ml added	RIA	RIA (B)	OC	RIA	OC	RIA	RIA	RIA	RIA	RIA	RIA	RIA	OC	
C1	0.00														
C2	0.30														
C3	0.99														
C4	2.96														
C5	9.26														
C6	29.6														
C7	99.6														
C8	99.6														
C9	296														
C10	996														

- 1 Not detectable by the method in question.
  - 2 Values between brackets were not taken into account for the statistical analysis.
  - 3 Not measurable because of incomplete mixing of serum with RIA reagents.(?)
  - 4 Not enough plasma available to perform the assay.
- OC: Gas chromatography (with nitrogen-phosphorous detection).  
 RIA: Direct radioimmunoassay.  
 RIA (B): Radioimmunoassay, preceded by extraction of the samples.

RIA (Labs 1(excluding extraction), 2, 3, 5, 6, 7, 8)

Mean	SD	CV(%)	Accur(%)	n	% conv.	
0.0	-1.2	-	-	1	-	
0.3	0.49	0.15	30.6	63.3	5	163.3%
0.99	1.03	0.28	27.2	4.04	5	104.0%
2.96	3.01	0.51	16.8	1.69	7	101.7%
9.86	10.46	2.25	21.5	6.1	7	106.1%
29.6	28.2	2.78	10.6	-4.7	6	95.3%
98.6	91.2	12.7	13.9	-7.5	6	92.5%
98.6	93.8	21.6	22.1	-0.8	6	99.2%
296	276.7	30.3	10.9	-6.52	6	93.5%
986	936.4	158.3	16.9	-5.0	7	95.0%

GC (Labs 1, 4, 8)

Mean	SD	CV(%)	Accur(%)	n	
0.0	-	-	-	-	
0.3	-	-	-	-	
0.99	-	-	-	-	
2.96	3.15	1.34	33.9	33.4	2
9.86	10.3	1.13	11.0	4.5	3
29.6	29.8	2.34	8.5	0.7	2
98.6	95.3	5.51	5.78	-3.35	3
98.6	100.3	7.62	4.6	+1.7	3
296	288.3	19.9	6.9	-2.6	3
986	959.7	30.1	3.14	-2.7	3

Table 15-9

Figure 15-1

INTERLABORATORY STUDY : ALFENTANIL  
PLASMA LEVELS IN SPIKED CONTROL  
SAMPLES (NG/ML)

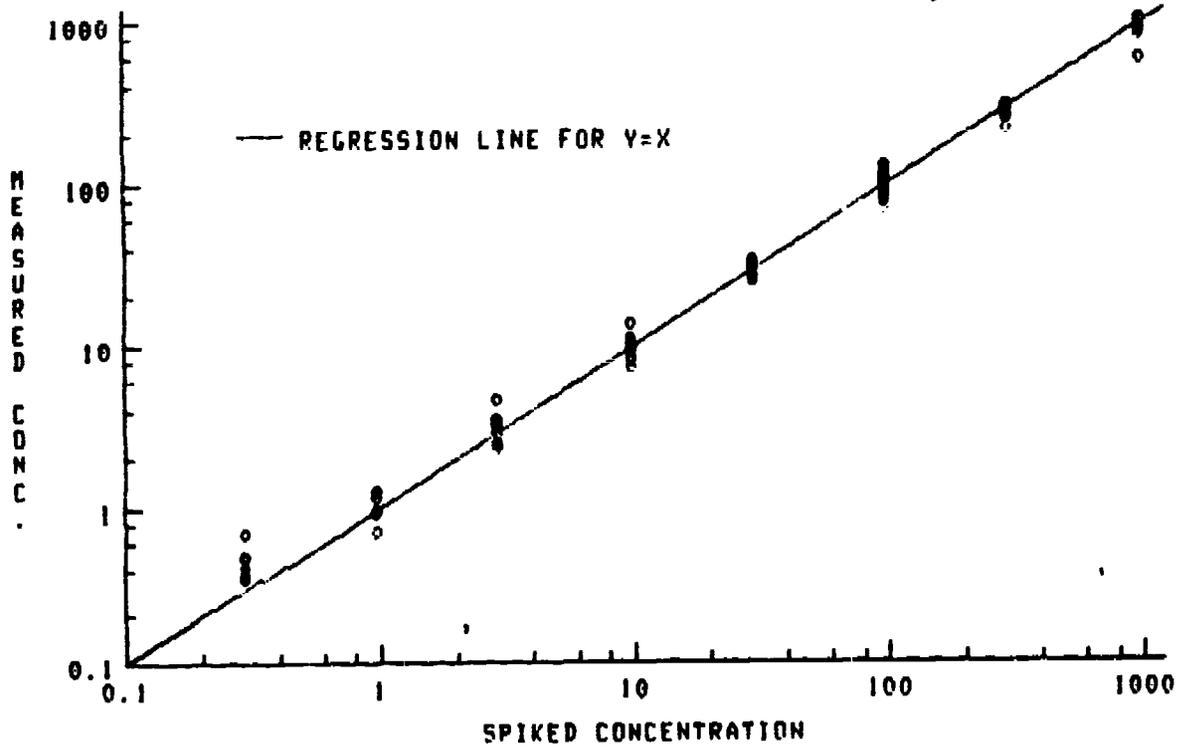


Figure 15-2

INTERLABORATORY STUDY : ALFENTANIL  
PLASMA LEVELS IN CLINICAL SAMPLES  
(NG/ML)

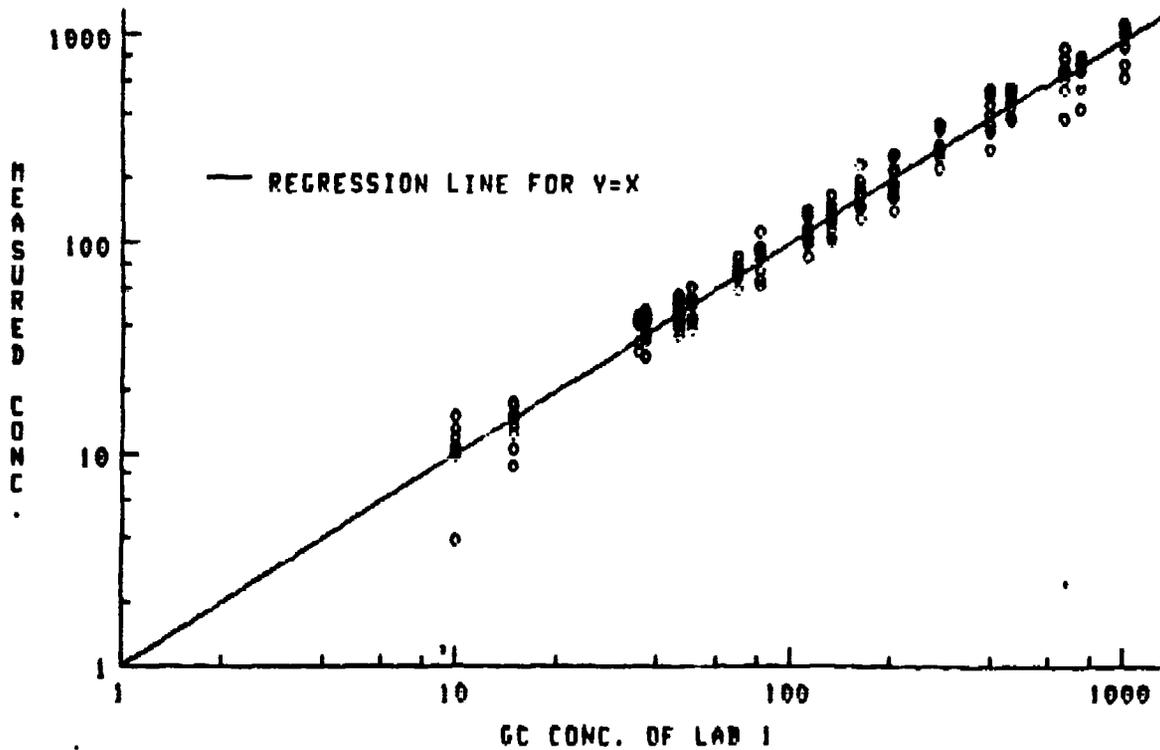


Figure 2