CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21134

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

FEB 23 2000

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA: 21-134 **SUBMISSION DATES**: June 2, 1999
Nitrostat® (Nitroglycerin sublingual tablets) August 23, 1999
0.3, 0.4, and 0.6 mg December 7, 1999
January 10, 2000

IND[ ] October 9, 1998

PARKE-DAVIS **REVIEWER**: Emmanuel O. Fadiran, Ph.D.

TYPE OF SUBMISSION: ORIGINAL NDA

BACKGROUND

Nitrostat® (Nitroglycerin sublingual tablets) has been manufactured and marketed by Parke-Davis for more than 5 decades. Nitrostat is currently manufactured by molding an alcohol wet granulation into tablets. The molded tablets show high friability due to low compression forces, high weight variability, loss of potency on storage and the equipment used for their manufacture is obsolete. These problems have caused disruptions in the supply of the product to patients and recalls due to failure to meet product specifications through expiration. The sponsor has developed a direct compression nitroglycerin tablet with the improved weight control, content uniformity, and physical stability (prevention of potency loss). In addition, [ ] has notified Warner-Lambert of the possibility of a labeling change for the current raw material (diluted nitroglycerin 10%) from "flammable solid" to an "explosive" status by the US Department of Transportation. Due to the transportation concerns for % nitroglycerin triturate and the quality of molded tablets, the sponsor decided to develop a direct-compression tablet formulation using diluted nitroglycerin with less that % active drug.

SYNOPSIS

Pharmacokinetic and Pharmacokinetic-Pharmacodynamic Studies: The sponsor conducted an open-label, single-dose, randomized, 3-period, repeated measures study to evaluate peripheral arterial vasodilatation associated with sublingual administration of marketed Nitrostat tablet, using real-time systolic:diastolic ratio (SDR) and to determine the inter- and intra-subject variability in the PD response in 20 healthy subjects (Study 782-13). The data obtained from this study showed that SDR increased to a mean maximal value (E_{100}) of 3.6. Similar variability in SDR (E_{25}, E_{50}, E_{75}, and E_{100}) was obtained at baseline (CV=10% for inter- and intra-subject variability) but higher variability in time to any PD effect (CV=40.2-43.6% for intra- and 23.6-45.5 for inter-subject variability). Comparison of mean SDR response between doses and at 1-minute intervals from 1 to 15 minutes showed that the 90% CI (using non-log transformed data) fell between 80-120%.

The sponsor also conducted open-label, single-dose, randomized, 3-way crossover study to compare the pharmacokinetics of nitroglycerin and its metabolites (1,2-GDN and 1,3-GDN)

following sublingual administration of new Nitrostat tablet formulation and marketed Nitrostat tablet, and to compare the pharmacodynamic effects of new Nitrostat tablet formulation with those of marketed Nitrostat tablet on the digital blood pressure waveform during the period of expected maximal antianginal effect in 36 healthy subjects (Study 782-16). The data obtained from this study showed that the new Nitrostat tablet formulations (2x0.3 mg, 1x0.6 mg) are bioequivalent to the marketed Nitrostat tablet (1x0.6 mg) with respect to 1,2-GDN and 1,3-GDN but bioinequivalent with respect to nitroglycerin. Similar SDR responses were obtained from the two formulations with 90%CI for all levels of PD effect (E_{25}, E_{50}, E_{75}, and E_{100}) for comparison of test to reference (using non-log transformed data) falling between 80-120%. Time required to attain the dynamic effect for the 0.6 mg new Nitrostat tablet formulation was delayed (about 30 seconds) relative to the marketed Nitrostat tablet (this might be due to the fact that the new formulations are compressed and the disintegration is slower than that of the marketed formulation which is molded). The bioinequivalence between the new and the marketed formulations with respect to nitroglycerin has been observed with other nitroglycerin formulations (patches in particular) and is possibly due to the high intersubject variability and the short half-life of nitroglycerin in plasma.

The summaries of Study 782-13 and Study 782-16 are attached (see appendix, page 5).

Pharmacokinetic-Pharmacodynamics Analysis: The population pharmacokinetic-pharmacodynamic analysis (see Attached report by Dr. Mishina, page 34) showed that pharmacodynamic effect for nitroglycerin obtained for the two formulations administered as three treatments in Protocol 782-16 were similar. Therefore, the new compressed nitrostat formulations and the currently marketed Nitrostat tablets produce similar pharmacodynamic effects on peripheral vasodilatation measured by digital plethysmography.

Composition of the formulation : See appendix (page 15).

Dissolution: The sponsor had earlier proposed that a disintegration test be used for product according to the current USP monograph but at the pre-NDA meeting with the sponsor the Agency requested the sponsor to develop a dissolution method for the product unless a correlation could be demonstrated between dissolution test and the current disintegration test. The sponsor agreed to include a dissolution test and specification in the NDA (see page 16). The sponsor has developed a satisfactory dissolution method using pH 6.5 phosphate buffer at 37° ± 0.5°C, USP Apparatus II (paddle) at 50 rpm with a specification of Q % in minutes.

Proposed Labeling: See appendix (page 22).

WAIVER OF BIOEQUIVALECE STUDY FOR THE 0.4 MG NEW NITROSTAT FORMULATION:

The sponsor did not include the 0.4 mg new nitrostat formulation in the bioequivalence Study 782-16 but has provided in-vitro dissolution data on several lots of the 0.4 mg new nitrostat formulation. Comparison of the *in vitro* dissolution data from the 0.3 mg and 0.6 mg new nitrostat formulations used for the bioequivalence study with those from the 0.4 mg tablet

showed that all the three tablet strengths have similar *in vitro* release profiles in three media (water, pH 4.5 buffer and pH 6.5 buffer) and therefore expected to have similar *in vivo* release profiles. A waiver of the bioequivalence study requirement for the 0.4 mg strength of the new nitrostat tablet formulation is therefore recommended.

COMMENT TO THE MEDICAL OFFICER

The observed bioinequivalence between the new and the marketed formulations with respect to plasma levels of nitroglycerin may be due the highly variable pharmacokinetics of nitroglycerin. This has been observed with other nitroglycerin formulations (patches and pump-spray). The pharmacokinetic-pharmacodynamic analysis (see Attached report by Dr. Mishina, page 34) showed that there was no significant difference in the pharmacodynamic effect obtained for the three treatments in Protocol 782-16. Therefore, the new compressed nitrostat formulations and the currently marketed Nitrostat tablets produce similar pharmacodynamic effects on peripheral vasodilatation measured by digital plethysmography.

RECOMMENDATION:

The Division of Pharmaceutical Evaluation I has reviewed the clinical pharmacology/biopharmaceutics data submitted by the sponsor and found that the Nitrostat® tablet formulations are bioinequivalent to the reference Nitrostat® tablet formulations based on pharmacokinetic data. However, supportive population pharmacokinetic-pharmacodynamic analysis showed that the pharmacodynamic effect for nitroglycerin obtained for the two formulations were similar.

QUESTION-BASED REVIEW APPROACH TO THE BIOEQUIVALENCE STUDY

Question: What is the clinical impact of the bioinequivalence with respect to nitroglycerin between the new nitrostat formulation and the marketed Nitrostat tablet?

Response: A small efficacy trial was done on the two formulations using the 0.6 mg tablets. The data obtained from the study showed that the two formulations beat placebo and have comparable efficacy (see Medical Officer's review). The data obtained from Study 782-16 showed that the new Nitrostat tablet formulations (2x0.3 mg, 1x0.6 mg) are bioequivalent to the marketed Nitrostat tablet (1x0.6 mg) with respect to 1,2-GDN and 1,3-GDN but bioinequivalent with respect to nitroglycerin. The population pharmacokinetic-pharmacodynamic analysis (see Attached report by Dr. Mishina, page 34) showed that pharmacodynamic effects for nitroglycerin obtained from the two formulations administered as three treatments in Protocol 782-16 were similar. Therefore, the new compressed nitrostat formulations and the currently marketed Nitrostat tablets produce similar pharmacodynamic effects on peripheral vasodilatation measured by digital plethysmography.

/S/ 2/23/2000

Emmanuel O. Fadiran, Ph.D.
Division of Pharmaceutical Evaluation I

FT Initialed by P. Marroum, Ph.D. /S/ 2/23/2000

CPB on 02/10/2000: Mehta, Huangs, Chen, Marroum, Gobburu, Robbie, Hu, Wang, Sahajwalla

cc: NDA 21-134, HFD-110, Williams (HFD-110), Chen (HFD-110), HFD-860 (Fadiran, Mehta, Mishina), BIOPHARM - CDR

BIOEQUIVALENCE STUDY
PROTOCOL NUMBER: 782-16 VOLUMES: 2-4

INVESTIGATOR AND LOCATION:

[ ]

STUDY DATE: October 13 to November 6 1997.

OBJECTIVES: 1. To compare the pharmacokinetics of nitroglycerin (GTN) and its metabolites, 1,2-dinitroglycerin (1,2-GDN) and 1,3-dinitroglycerin (1,3-GDN), following administration of compressed nitroglycerin tablets and Nitrostat tablets, 2. To compare the pharmacodynamic effects of compressed nitroglycerin tablets with those of Nitrostat tablets on the digital blood pressure waveform during the period of expected maximal antianginal effect.

FORMULATIONS AND TREATMENTS:

1. Treatment 1 (Reference, R) – 0.6 mg marketed Nitrostat tablets (Lot CJ0900997); one tablet administered sublingually and allowed to dissolve.
2. Treatment 2 (Test, T1) – 0.3 mg nitroglycerin compressed tablets (W1273-95, Lot CV0720897, Lot size [ ] two tablets administered sublingually and allowed to dissolve.
3. Treatment 3 (Test, T2) – 0.6 mg nitroglycerin compressed tablets (W1273-96, Lot CV0730897, Lot size [ ] one tablet administered sublingually and allowed to dissolve.

STUDY DESIGN: This was an open-label, single-dose, randomized three-way crossover study with 36 subjects (33 male and 3 female) with a wash period of seven days. Each subject received (sublingually) treatments 1 to 3 above after an overnight fast in randomized fashion. Blood samples (10 ml) were collected predose, 1, 2, 4, 6, 8, 10, 12.5, 15, 20, 25, 30, 45, 60, 75, 180, and 240 minutes post dose. Blood pressure (BP) was continuously monitored non-invasively (real time) and recorded on a computer for 15 minutes before and 30 minutes following each dose, using digital plethysmography (DGP). Beat-by-beat analysis of all BP waveforms provided key measurements of systolic BP amplitude (pulse pressure) and diastolic BP amplitude which permitted calculation of the systolic BP:diastolic BP ratio or SDR. The plots of SDR-time profiles were smoothed (5% degree of smoothing) and the following characteristics were obtained: SDR(E_{100}) and the time at which it occurred (t_{100}); SDRs at 25%, 50%, and 75% of maximum value of SDR (E_{25}, E_{50}, and E_{75}, respectively) and the times to these effects (t_{25}, t_{50}, and t_{75}, respectively)

ASSAYS:

[ ]

DATA ANALYSIS: AUC, C_{max}, t1/2, and T_{max} were calculated for GTN, 1,2- GDN and 1,3-GDN. ANOVA was done on the log-transformed Cmax and AUC. E_{25}, E_{50}, E_{75}, E_{100}, and the times to these effects, t_{25}, t_{50}, $_{75}$, t_{100} were calculated for the three treatments. ANOVA was done on these pharmacodynamic parameters.

RESULTS: Tables 1 and 2 and Figures 1–4 summarize the PK and PD data obtained from the study.

Table 1: Summary of the pharmacokinetic parameters

Parameter	TRT 1 (R)*	TRT 2 (T1)*	TRT 3 (T2)*	T1/R 90% CI	T2/R 90% CI	T1/T2 90% CI
Nitroglycerin						
AUC_{0-inf} (ng.min/ml)	12.17 (7.3)	14.89 (8.2)	14.9 (11.4)	109 - 140	102- 130	95 - 122
C_{max} (ng/ml)	1.73 (1.1)	2.34 (1.7)	2.13 (1.5)	113 - 157	103 - 142	94 - 130
T_{max} (min)	6.2 (4.6)	6.4 (2.5)	7.2 (3.2)	-	-	-
$t_{1/2}$ (min)	3.2 (1.4)	2.8 (1.1)	2.6 (0.6)	-	-	-
tlag (min)	2.9	3.0	3.2	-	-	-
1,2-GDN						
AUC_{0-inf} (ng.min/ml)	190.07 (45.3)	198.69 (45.3)	196.5 (47.5)	100 - 107	100 - 107	97 - 103
C_{max} (ng/ml)	3.83 (1.2)	4.31 (1.5)	4.4 (1.5)	105 - 121	105 - 122	93 - 107
T_{max} (min)	13.4 (7.7)	12.9 (6.3)	12.6 (4.9)	-	-	-
$t_{1/2}$ (min)	35.5 (3.6)	36.3 (4.2)	35.9 (4.3)	-	-	-
tlag (min)	3.3	3.6	3.4	-	-	-
1,3-GDN						
AUC_{0-inf} (ng.min/ml)	44.72 (11.0)	43.13 (10.1)	43.4 (10.5)	93 - 100	93 - 100	96 - 104
C_{max} (ng/ml)	0.86 (0.3)	0.88 (0.4)	0.90 (0.32)	93 - 110	97 - 115	88 - 104
T_{max} (min)	17.2 (8.1)	15.6 (7.2)	15.5 (6.6)	-	-	-
$t_{1/2}$ (min)	34.2 (10.4)	32.5 (7.3)	32.3 (8.2)	-	-	-
tlag (min)	4.5	4.9	5.0	-	-	-

TRT=Treatment; *Mean (Standard Deviation), R= Nitrostat (0.6 mg); T1 =0.3 new nitrostat formulation, T2 =0.6 new nitrostat formulation

Table 2: Summary of the pharmacodynamic parameters

Effect of Nitrostat (Reference) and 2 Nitroglycerin Formulations (test) on Mean SDR Values, Mean Times to Effect, 90% Confidence Intervals for Comparisons Between Reference and Test Formulations, and Variability of the Pharmacodynamic Responses Within and Among 36 Healthy Volunteers

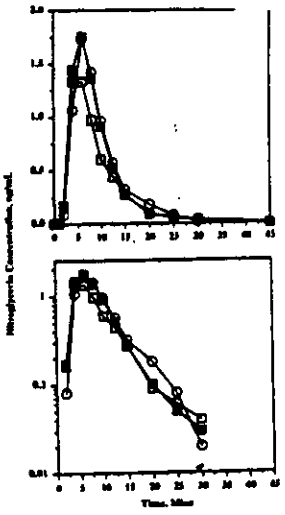
Percent of Maximal Effect	Mean SDR			SDR - 90% Confidence Intervals		Overall Mean SDR	Variability - CV (%)	
	TRT 1	TRT 2	TRT 3	TRT 2 vs TRT 1	TRT 3 vs TRT 1		Within Subject	Among Subject
E_0	2.4	2.4	2.5	95 - 102	98 - 105	2.4	8.6	8.7
E_{25}	2.9	2.8	2.9	94 - 102	97 - 106	2.9	11.2	10.1
E_{50}	3.3	3.2	3.3	92 - 103	94 - 106	3.3	14.5	13.8
E_{75}	3.8	3.6	3.7	90 - 104	93 - 107	3.7	17.6	17.2
E_{100}	4.2	4.1	4.2	89 - 104	91 - 107	4.2	20.0	20.2

Percent of Maximal Effect	Time to Effect (min)			Times - 90% Confidence Intervals		Overall Mean Time (min)	Variability - CV (%)	
	TRT 1	TRT 2	TRT 3	TRT 2 vs TRT 1	TRT 3 vs TRT 1		Within Subject	Among Subject
t_{25}	1.8	2.0	2.3	94 - 121	112 - 140	2.1	33.9	11.1
t_{50}	2.5	2.8	3.1	99 - 123	111 - 135	2.8	30.5	17.4
t_{75}	3.2	3.8	4.3	103 - 130	118 - 145	3.8	30.1	18.9
t_{100}	4.9	5.4	5.9	96 - 121	108 - 133	5.4	30.8	9.2

SDR = Systolic:Diastolic Ratio; TRT = Treatment; TRT 1 = 1x0.6 mg Nitrostat; TRT 2 = 2x0.3 mg nitroglycerin; TRT 3 = 1x0.6 mg nitroglycerin; CV = coefficient of variation

Event	Definition
E_{75}	Largest SDR $\leq$ 0.25.Baseline + 0.75.E_{100} that occurred between 0 minutes postdose and t_{100}
T_{75}	Time at which E_{75} occurred
E_{50}	Largest SDR $\leq$ 0.50.Baseline + 0.50.E_{100} that occurred between 0 minutes postdose and t_{75}
T_{50}	Time at which E_{50} occurred
E_{25}	Largest SDR $\leq$ 0.75.Baseline + 0.25.E_{100} that occurred between 0 minutes postdose and t_{50}
T_{75}	Time at which E_{25} occurred

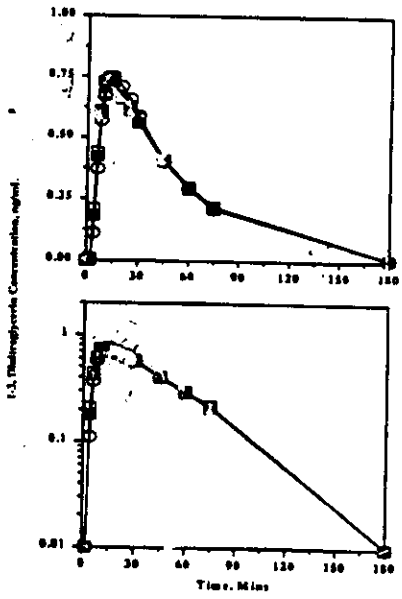
Figure 1:



Mean Plasma Nitroglycerin Concentrations Following Administration of 0.6-mg Nitrostat Tablets (□), 0.3-mg Nitroglycerin Tablets (■), and 0.6-mg Nitroglycerin Tablets(○). Protocol 782-16

Upper and lower panels are linear and semi-logarithmic scales, respectively.

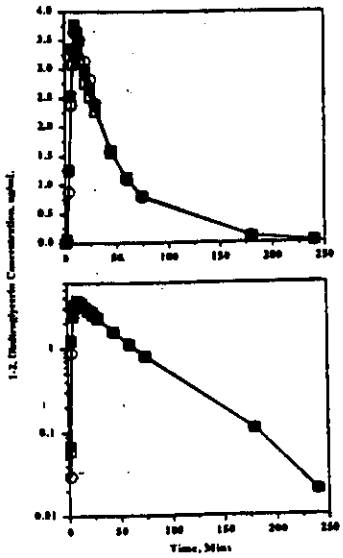
Figure 2:



Mean Plasma 1,3-GDN Concentrations Following Administration of 0.6-mg Nitrostat Tablets (□), 0.3-mg Nitroglycerin Tablets (■), and 0.6-mg Nitroglycerin Tablets (○): Protocol 782-16

Upper and lower panels are linear and semi-logarithmic scales, respectively.

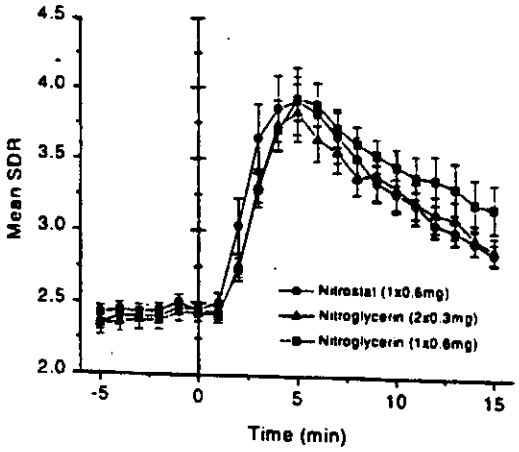
Figure 3:



Mean Plasma 1,2-GDN Concentrations Following Administration of 0.6-mg Nitrostat Tablets (□), 0.3-mg Nitroglycerin Tablets (■), and 0.6-mg Nitroglycerin Tablets (○): Protocol 782-16

Upper and lower panels are linear and semi-logarithmic scales, respectively.

Figure 4:



Mean (±SE) SDR Values, Plotted at 1-Minute Intervals, Obtained 5 Minutes Before and 15 Minutes After Sublingual Doses of 1x0.6 mg Nitrostat, 2x0.3 mg Nitroglycerin, and 1x0.6 mg Nitroglycerin, Each Administered 1 Week Apart to 36 Healthy Volunteers

Abscissa = Time Expressed in Minutes; Ordinate = SDR; Axis at Time 0 = Dose Administration.

CONCLUSIONS: The data obtained from the study shows that:

1. The three formulations are are bioinequivalent with respect to nitroglycerin but are bioequivalent with respect to two metabolites of nitroglycerin (1,2-GDN and 1,3-GDN).
2. Similar SDR (real-time systolic:diastolic ratio) responses were obtained from the three treatments with 90%CI for all levels of PD effect (E_{25}, E_{50}, E_{75}, and E_{100}) for comparison of test to reference (using non-log transformed data) falling between 80-120%.
3. Time required to attain the dynamic effect for the 0.6 mg new Nitrostat tablet formulation was delayed (about 30 seconds) relative to the marketed Nitrostat tablet. This might be due to the fact that the new formulations are compressed and the disintegration is slower than that of the marketed formulation which is molded.

PHARMACODYNAMIC STUDY

PROTOCOL NUMBER: 782-13 VOLUME: 1 **PAGES**: 143-473

INVESTIGATOR AND LOCATION:

[ ]

STUDY DATE: March 6 to March 31, 1995.

OBJECTIVES: 1. To evaluate blood pressure (BP) waveform as a pharmacodynamic endpoint to describe the vasodilatation associated with sublingual administration of Nitrostat, and to determine inter- and intrasubject variability in the pharmacodynamic response to sublingual administration of Nitrostat.

FORMULATION AND TREATMENT:
0.6 mg marketed Nitrostat tablets (Lot 10704F); each dose was administered sublingually and allowed to dissolve.

STUDY DESIGN:
Open-label, single-dose, 3-period, repeated measures study to evaluate peripheral arterial vasodilatation associated with sublingual administration of marketed Nitrostat tablet, using real-time systolic:diastolic ratio (SDR) and to determine the inter- and intra-subject variability in the PD response in 20 male healthy subjects. Each subject received (sublingually) the treatment above on 3 one week apart. Blood pressure (BP) was continuously monitored non-invasively (real time) and recorded on a computer for 5 minutes before and 15 minutes following each dose, using digital plethysmography (DGP). Beat-by-beat analysis of all BP waveforms provided key measurements of systolic BP amplitude (pulse pressure) and diastolic BP amplitude which permitted calculation of the systolic BP:diastolic BP ratio or SDR. The plots of SDR-time profiles were smoothed (5% degree of smoothing) and the following characteristics were obtained: SDR(E_{100}) and the time at which it occurred (t_{100}); SDRs at 25%, 50%, and 75% of maximum value of SDR (E_{25}, E_{50}, and E_{75}, respectively) and the times to these effects (t_{25}, t_{50}, and t_{75}, respectively)

DATA ANALYSIS: E_{25}, E_{50}, E_{75}, E_{100}, and the times to these effects, t_{25}, $t_{50, 75}$, t_{100} were calculated for the three treatments. ANOVA was done on these pharmacodynamic parameters.

RESULTS: Tables 1 and 2 and Figures 1 summarize the pharmacodynamic data obtained from the study.

Table 1.

Effect of Three 0.6-mg Nitrostat Doses Administered at Weekly Intervals on SDR Responses in 20 Healthy Subjects: Within and Among Subject Variability

Effect (SDR) as % of Maximal Response[a]	Overall Mean (SDR)	Within Subject Variability CV (%)[c]	Among Subject Variability CV (%)[c]
E_0	2.4	7.8	8.2
E_{25}	2.7	7.3	8.4
E_{50}	3.0	9.1	9.0
E_{75}	3.3	10.5	10.3
E_{100}	3.6	11.8	11.7
Time to Effect (minutes)[b]	**Overall Mean (minutes)**	**Within Subject Variability CV (%)[c]**	**Among Subject Variability CV (%)[c]**
t25	1.3	43.6	45.5
t50	2.1	41.8	25.1
t75	3.2	42.1	30.0
t100	4.9	40.2	23.6

[a] Subscript indicates % of maximal response.
[b] Subscript indicates time at corresponding % response.
[c] CVs obtained from repeated measures ANOVA

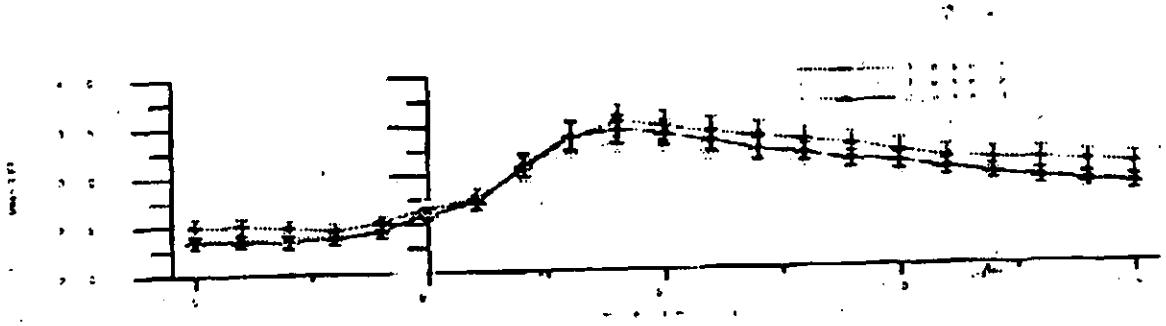
Table 2:

Comparisons of Effects (SDR) Between Doses on the 90% Confidence Intervals in 20 Healthy Subjects

% of Maximum Effect	Time to Effect (minutes)	Mean SDR			90% CI	
		Dose 1	Dose 2	Dose 3	Dose 2 vs 1	Dose 3 vs 1
0	N/A	2.5	2.4	2.4	92-100	91-100
25	1.3	2.7	2.6	2.7	91-101	94-103
50	2.1	3.1	2.9	3.0	89-99	93-102
75	3.2	3.4	3.2	3.3	88-99	92-103
100	4.9	3.7	3.5	3.6	87-99	92-104

Event	Definition
E_{75}	Largest SDR ≤ 0.25.Baseline + 0.75.E_{100} that occurred between 0 minutes postdose and t_{100}
T_{75}	Time at which E_{75} occurred
E_{50}	Largest SDR ≤ 0.50.Baseline + 0.50.E_{100} that occurred between 0 minutes postdose and t_{75}
T_{50}	Time at which E_{50} occurred
E_{25}	Largest SDR ≤ 0.75.Baseline + 0.25.E_{100} that occurred between 0 minutes postdose and t_{50}
T_{75}	Time at which E_{25} occurred

Figure 1:



Mean (±SE) SDR Values, Plotted at 1-Minute Intervals, Obtained 5 Minutes Before and 15 Minutes After a Sublingual Dose of 0.6 mg Nitrostat Administered on 3 Occasions to 20 Healthy Subjects

CONCLUSIONS: The data obtained from the study shows that:

1. Similar SDR (real-time systolic:diastolic ratio) responses were obtained from the three treatments and comparison of the three treatments showed that the 90%CI for all levels of PD effect (E_{25}, E_{50}, E_{75}, and E_{100}) were between 80-120% (using non-log transformed data).
2. Both within and among subject variability in E_{25}, E_{50}, E_{75}, and E_{100} were similar to the baseline values, with CVs on the order of 10%. The time to any specific level of effect demonstrated greater variability, both within (CV = 40.2-43.6%) and among (CV = 23.6 - 45.5).

FORMULATION: The quantitative composition of the tablet formulation to be marketed (25 mg) is shown on Table

	Label Claim mg/tablet		
	0.3 mg	0.4 mg	0.6 mg
Nitroglycerin			
Lactose Monohydrate, NF/EP			
Silicon Dioxide, Colloidal NF/EP			
Glyceryl Monostearate, NF (Myvaplex 600P®)			
Calcium Stearate, NF/EP			
Starch, Pregelatinized NF			
Total Tablet Weight			

[a] No overage

APPEARS THIS WAY
ON ORIGINAL

DRUG PRODUCT DISSOLUTION TESTING

The dissolution data submitted by the sponsor are shown on Tables 1-7

Table 1:

Dissolution of Nitrostat 0.3 mg Compressed Tablets, Recent Lot # 80287V, As Per Amendment 2

Tablet #	Percent Drug Dissolved							
	2 minutes		5 minutes		8 minutes		11 minutes	
	Analyst 1	Analyst 2	Analyst 1	Analyst 2	Analyst 1	Analyst 2	Analyst 1	Analyst 2
1								
2								
3								
4								
5								
6								
Mean	82	74	98	94	100	97	101	98
Absolute % Diff.	8		4		3		3	

Table 2:

Dissolution of Nitrostat 0.4 mg Compressed Tablets, Recent Lot # 80807V, As Per Amendment 2

Tablet #	Percent Drug Dissolved							
	2 minutes		5 minutes		8 minutes		11 minutes	
	Analyst 1	Analyst 2	Analyst 1	Analyst 2	Analyst 1	Analyst 2	Analyst 1	Analyst 2
1								
2								
3								
4								
5								
6								
Mean	88	92	97	97	97	97	97	99
Absolute % Diff.	4		0		0		2	

Table 3:

Dissolution of Nitrostat 0.4 mg Compressed Tablets, Aged Lot # 808O7V, As Per Amendment 2								
Tablet #	Percent Drug Dissolved							
	2 minutes		5 minutes		8 minutes		11 minutes	
	Analyst 1	Analyst 2	Analyst 1	Analyst 2	Analyst 1	Analyst 2	Analyst 1	Analyst 2
1								
2								
3								
4								
5								
6								
Mean	82	73	98	95	98	97	98	98
Absolute % Diff.	-9		-3		-1		0	

Table 4:

Dissolution of Nitrostat 0.3 mg Compressed Tablets, Aged Lot # 805O7V, As Per Amendment 2								
Tablet #	Percent Drug Dissolved							
	2 minutes		5 minutes		8 minutes		11 minutes	
	Analyst 2	Analyst 3	Analyst 2	Analyst 3	Analyst 2	Analyst 3	Analyst 2	Analyst 3
1								
2								
3								
4								
5								
6								
Mean	64	61	92	96	98	98	100	99
Absolute % Diff.	-3		4		0		-1	

Table 5

Dissolution of Nitrostat 0.6 mg Compressed Tablets, Aged Lot # 80387V, As Per Amendment 2								
Tablet #	Percent Drug Dissolved							
	2 minutes		5 minutes		8 minutes		11 minutes	
	Analyst 1	Analyst 2	Analyst 1	Analyst 2	Analyst 1	Analyst 2	Analyst 1	Analyst 2
1								
2								
3								
4								
5								
6								
Mean	83	80	99	94	100	97	101	98
Absolute % Diff.	-3		-5		-3		-3	

Table 6:

Dissolution of Nitrostat 0.6 mg Compressed Tablets, Recent Lot # 80387V, As Per Amendment 2								
Tablet #	Percent Drug Dissolved							
	2 minutes		5 minutes		8 minutes		11 minutes	
	Analyst 1	Analyst 2	Analyst 1	Analyst 2	Analyst 1	Analyst 2	Analyst 1	Analyst 2
1								
2								
3								
4								
5								
6								
Mean	89	73	97	91	99	96	99	98
Absolute % Diff.	-16		-6		-3		-1	

Table 7:

Summary of Dissolution Data for Nitrostat 0.3, 0.4, and 0.6 mg Compressed Tablets at Intermittent Stability Interval (~15 months)

ATA#	LOT#	Strength, mg	Quantity	% Nitroglycerin Dissolved							
				2 minutes		5 minutes		8 minutes		11 minutes	
				Mean	Range	Mean	Range	Mean	Range	Mean	Range
ATA990459	80407V	0.3	100's	72		97		97		98	
ATA990460	80407VA		25's	81		96		96		96	
ATA990461	80507V		100's	62		97		99		101	
ATA990462	80507VA		25's	66		99		101		101	
ATA990453	80507VFA		100's	60		96		97		98	
ATA990454	80507VFB		25's	72		98		99		99	
ATA990478	80287VA		100's	60		93		97		98	
ATA990479	80287VB		25's	72		96		100		99	
ATA990463	80707V	0.4	100's	75		95		96		97	
ATA990464	80707VA		25's	82		97		99		98	
ATA990465	80807V		100's	91		97		97		97	
ATA990466	80807VA		25's	100		98		99		100	
ATA990467	803N7V		100's	87		97		97		98	
ATA990468	803N7VA		25's	89		98		99		100	
ATA990451	80307VFA	0.6	100's	92		98		98		98	
ATA990452	80307VFB		25's	92		98		98		99	
ATA990455	80787V		100's	95		99		99		99	
ATA990456	80787VA		25's	93		97		97		96	
ATA990457	80307V		100's	78		96		97		98	
ATA990458	80307VA		25's	91		97		97		99	
ATA990480	80387VA		100's	88		96		98		99	
ATA990481	80387VB		25's	86		97		99		100	

Table 8: Comparison of Dissolution Results Between Water, pH 4.5 and pH 6.5 Medium

NITROSTAT 0.3 MG TABLETS (LOT 80287V)

Average % label claim nitroglycerin dissolved (n = 12)

minutes	water	pH 4.5	pH 6.5
1	37	53	44
3	95	82	91
5	98	91	94
7	99	93	94
10	99	95	94

Table 9: Comparison of Dissolution Results Between Water, pH 4.5 and pH 6.5 Medium

NITROSTAT 0.4 MG TABLETS (LOT 808O7V)

Average % label claim nitroglycerin dissolved (n = 12)

minutes	water	pH 4.5	pH 6.5
1	38	39	39
3	96	94	95
5	97	98	98
7	97	98	99
10	97	99	99

Table 10: Comparison of Dissolution Results Between Water, pH 4.5 and pH 6.5 Medium

NITROSTAT 0.6 MG TABLETS (LOT 80387V)

Average % label claim nitroglycerin dissolved (n = 12)

minutes	water	pH 4.5	pH 6.5
1	67	67	65
3	95	94	94
5	96	98	98
7	96	99	98
10	97	100	99

Based on the above results the sponsor is proposing the following method and specifications:

Dosage Form, Strength:	Compressed tablet, 0.3, 0.4, 0.6 mg
Dissolution Apparatus:	USP, Apparatus II (paddle)
Speed of Rotation:	50 rpm
Dissolution Medium:	pH 6.5 phosphate buffer at 37° ± 0.5°C
Volume:	500 ml
Sampling Time:	8 minutes

Dissolution analytical method:

Dissolution Specifications: NLT ___% at ___minutes

COMMENTS: Based on the in vitro dissolution data submitted to the NDA the dissolution specification of Q___ % at___ minutes is satisfactory.

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CLINICAL PHARMACOLOGY &BIOPHARMACEUTICS REVIEW
PHARMACOMETRICS REVIEW

NDA 21,134 **Submission Date:** June 4, 1999

Drug Name:	Nitrostat
Formulation:	Sublingual Tablets
Sponsor:	Parke-Davis Pharmaceutical Research
Submission:	"A Single-Dose Pharmacokinetic and Pharmacodynamic Study Comparing Newly Developed Nitroglycerin Compressed Tablets and Currently Marketed Nitrostat Tablet in Healthy Volunteers"
Consult:	Population Pharmacokinetic/Pharmacodynamic Analysis
Pharmacometrics Specialist:	Elena V. Mishina, Ph.D.

Preamble/Background:
Primary Clinical Pharmacology &Biopharmaceutics review of NDA 21,134 indicates that the new formulation of nitroglycerin is bioequivalent to the marketed Nitrostat tablets with respect to the two active metabolites, 1,2-glycerindinitrate (1,2-GND) and 1,3-glycerindinitrate (1,3-GND) and is not bioequivalent with respect to the parent drug, nitroglycerin. In the same bioequivalence study, the sponsor has measured pharmacodynamic effect on the digital pressure waveform during the period of expected maximal antianginal effect of the drug in 36 healthy volunteers. PK/PD modeling of the rich data file could give supportive evidence for the comparison of effects of newly developed and marketed formulation of nitroglycerin. Bioinequivalence between the new and the marketed formulations with respect to nitroglycerin has been observed with other nitroglycerin formulations (patches in particular) and was attributed to the high inter- and intrasubject variability and the difficulties of the measurements due to the short half-life of nitroglycerin in plasma

Question based review approach to the bioequivalence study

Question:
What is the impact of bioinequivalence between newly developed nitroglycerin compressed tablets and currently marketed nitrostat tablet on the pharmacodynamic effect?

In order to answer on this question, population pharmacokinetic/pharmacodynamic analysis of nitroglycerin was performed.

Objectives:
To develop a pharmacokinetic population model for sublingual nitroglycerin
To investigate the influence of covariates on pharmacokinetic of nitroglycerin
To develop a pharmacokinetic/pharmacodynamic model
To compare the pharmacodynamic effects of the 2 studied nitroglycerin formulations (administered as 3 treatments)

Methods:
Data from a single dose, open-label, randomized, 3-way cross-over pharmacokinetic and pharmacodynamic study comparing newly-developed nitroglycerin compressed tablets and currently marketed nitrostat tablet in healthy volunteers (Protocol 782-16) were used for the population pharmacokinetic/pharmacodynamic analysis of nitroglycerin.
Thirty-seven subjects entered the study, 36 subjects completed the study with total 5508 pharmacokinetic (nitroglycerin and 1,2-GDN and 1,3-GDN concentrations) and 2268 pharmacodynamic (ratio (SDR) between systolic BP and diastolic BP calculated based on digital plethysmography) measurements.

Reference product:
0.6 mg marketed Nitrostat tablets lot # CJ0900997 (coded as treatment 1), one tablet was administered sublingually and allowed to dissolve.

Test Products:
0.3 mg nitroglycerin compressed tablets lot #CV0720897, two tablets (treatment 2) administered sublingually and allowed to dissolve.
0.6 mg nitroglycerin compressed tablets lot #CV0730897, one tablet (treatment 3) administered sublingually and allowed to dissolve.

Washout period: one week between treatments.

Pharmacokinetic data:
Plasma samples were obtained serially for 240 minutes after each treatment and assayed for nitroglycerin as well as for 1,2-GDN and 1,3-GDN by method, lower limits of quantitation were 13 pg/mL for nitroglycerin, and 0.1 ng/mL for the metabolites. Details of the assay as well as the sampling times are discussed in the original OCPB review (Dr. Fadiran).

Pharmacodynamic Data:
The effect of nitroglycerin on the peripheral arterial circulation was measured using digital plethysmographic methods. The end-point was real time systolic BP : diastolic BP ratio (SDR), ratio of the pulse pressure value to the diastolic portion of the BP waveform value. The data were acquired for 5 minutes before and 15 minutes after the dose of nitroglycerin, the post-dose interval during which the parent compound would be expected to exert its maximal vasodilatatory effect.

PK/PD analysis was conducted using NONMEM. Due to the considerable homogeneity of this study population (all subjects were normal healthy volunteers), the body weight (WT) was the only relevant covariate to evaluate based on bayesian posthoc estimates of the PK parameters.
Results:

Pharmacokinetics:
Nitroglycerin concentrations vs time profiles were best described by the one-compartmental model with first order absorption fitted simultaneously for all three treatments. Inspection of nitroglycerin concentration vs time plots showed that there were few subjects for whom two

compartmental model with absorption may be more suitable. Therefore, a two-compartmental model with absorption was tested as well. This model was rejected based on unreasonable value of inter-compartmental blood flow ($8.16*10^6$ L/min). The parameters estimated for the one-compartmental model without covariates are shown in Table 1. The inter-individual error was modeled with a log-normal variance model and the residual error was modeled as a combined additive (ADD), with coefficient of variation of 0.457 nmol/L and a proportional model (CCV), with a coefficient of variation of 83.8%.

Table 1. Pharmacokinetic Parameters of Nitroglycerin

Parameter	Value	Inter-individual variability, %	CV of estimate, %
OBJ	1895		
CL	11.3	45.06	11.68
V	74.9	73.89	18.29
KA	0.836	89.89	15.43
ALAG	1.78		3.59
BIO2	1.26		10.79
BIO3	1.36		20.81
CCV	0.702	83.8	16.52
ADD	0.457		63.02

where CL is clearance
V is volume of distributin
KA is the rate of absorption
ALAG is a lag-time
BIO2 and BIO3 are the fractions of treatment 2 and treatment 3 (respectively) available to the systemic circulation in comparison with treatment 1 (availability of test treatment 1 is assumed to be equal 1)
CCV is proportional residual error
ADD is additive residual error.

Demographic characteristics of the subjects involved in this study were quite homogenous (healthy volunteers, only 3 females out of 36 subjects, weight range from 60.5 to 101.8 kg and age range from 18 to 34 years). Only body weight was assessed as a covariate in this model. The statistical significance of covariate influence on pharmacokinetic parameters was evaluated by the change in the log likelihood value (OBJ) obtained for the reduced (without covariate) and full (with covariate) model. The change in objective function of 7 units (alpha = 0.01) was considered to be significant. The change in OBJ with the use of body weight as a covariate was 113 and pharmacokinetic parameter estimates are shown in Table 2. The correlation of the volume of distribution and WT as covariate was significant:

V(L) = 86.9 + 2.48 (WT-77.3),

Where WT is individual subject's body weight and 77.3 is median value of body weight for the studied popuplation.

Figure 1 (pages A-C) show the individual plots for all 36 subjects with individual predicted nitroglycerin concentrations.

Figure 1. Nitroglycerin Plasma Concentrations vs Time

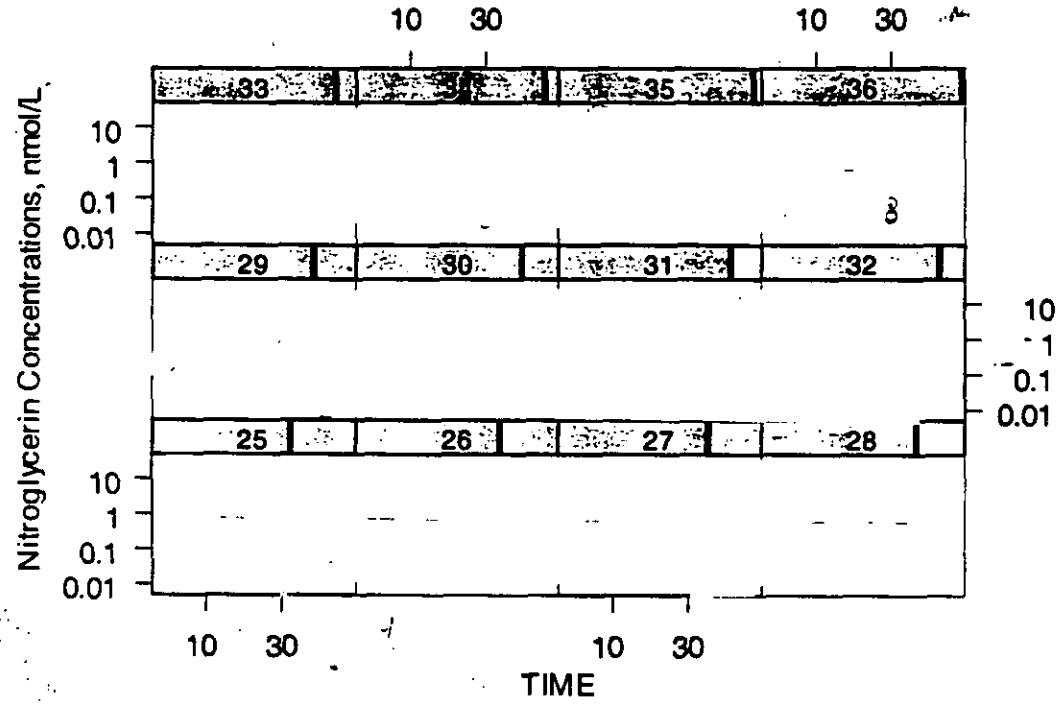

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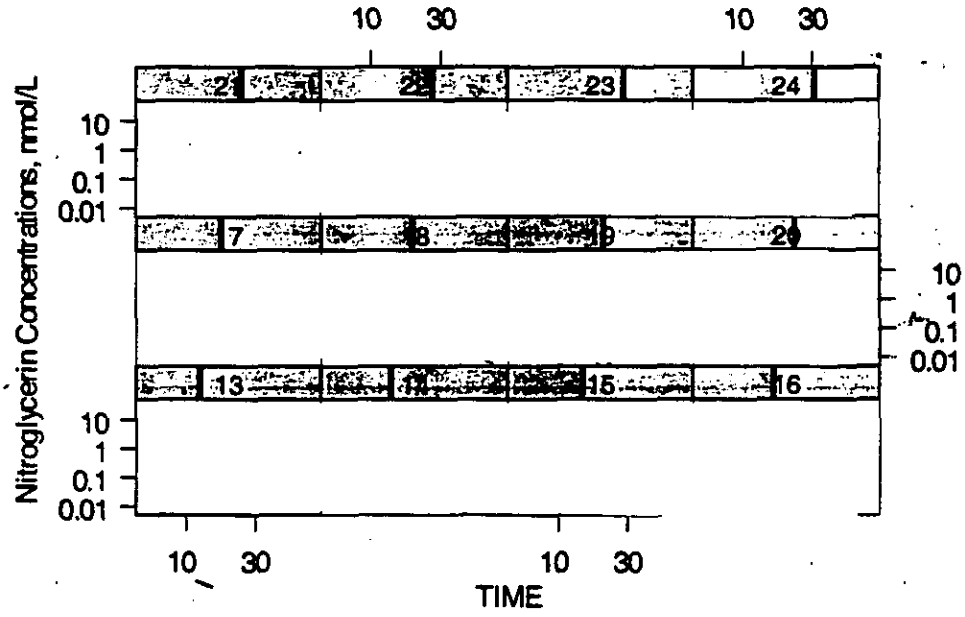
Figure 1. Nitroglycerin Plasma Concentrations vs Time



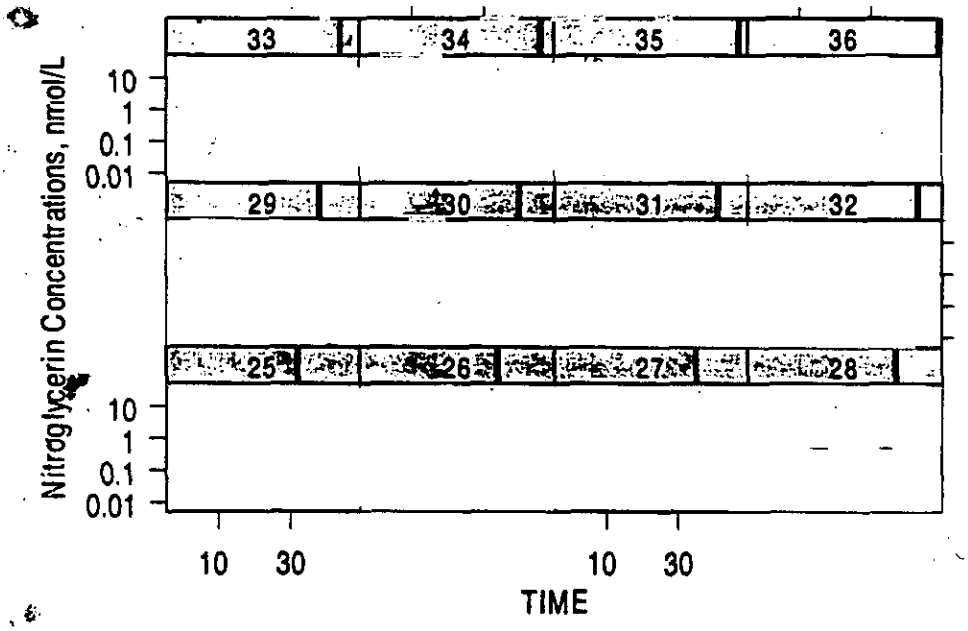
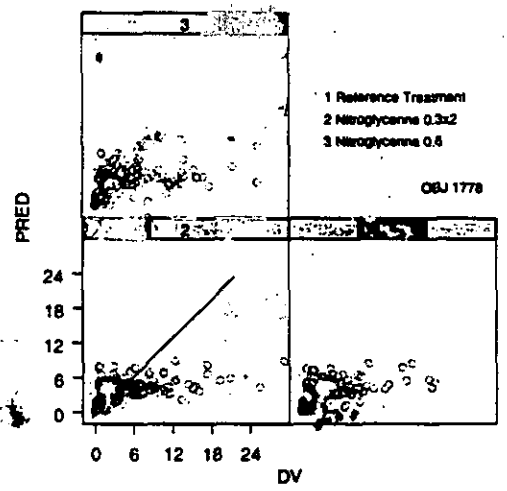


Table 2. Full Model Pharmacokinetic Parameters for Nitroglycerin

PARAMETER	VALUE	Inter-individual variability, %	SE of estimate, %
OBJ	1778		
CL	10.0	42.31	10.30
V	86.9	80.00	18.41
KA	0.906	93.38	16.56
ALAG	1.81		2.38
BIO2	1.06		8.16
BIO3	1.25		18.80
CCV	0.851	92.2	9.44
ADD	0.0928		41.27
BWT	2.48		43.55

In the scatter plots of predicted nitroglycerin concentrations vs observed for all three treatments (Figure 2, A-C) the observed skewness most likely was related to underestimation of drug concentrations.

Figure 2. PREDICTED vs OBSERVED NITROGLYCERIN CONCENTRATION



However, detailed examination of nitroglycerin plasma concentration data revealed that there were concentration measurements above 25 nmol/L for only 6 data points and above 15 nmol/L for the additional 10 data points from 868 observations (in total less than 3% of data measurements). Exclusion of the first 6 measurements as possible outliers led to the 134 units decrease of OBJ, and exclusion of the additional 10 data points showed 163 units decrease of OBJ and improvement in the predicted vs observed nitroglycerin plasma concentrations (Figure 3, A-C and Table 3).

Figure 3. PREDICTED VS OBSERVED NITROGLYCERIN CONCENTRATION

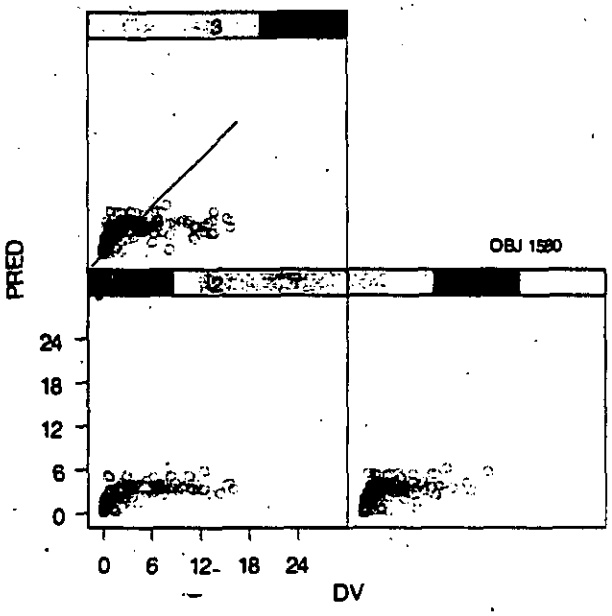


Figure 4. Nitroglycerin PK: IPRED vs CONC

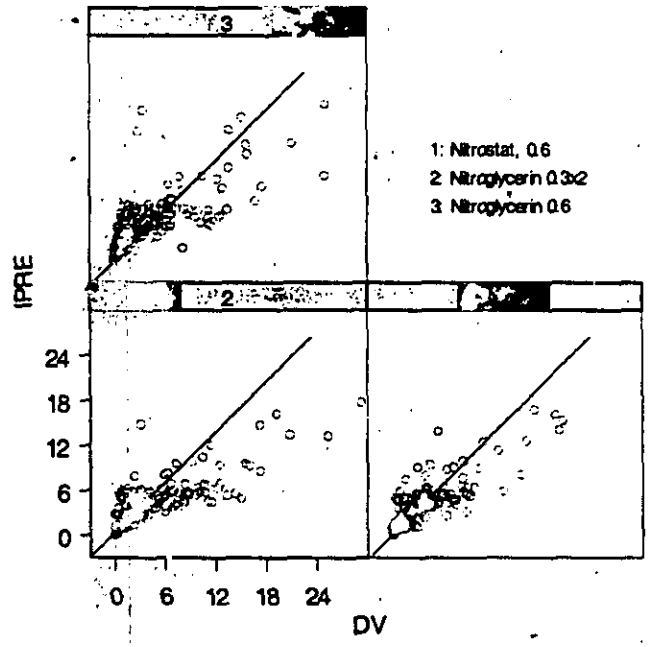


Table 3. Pharmacokinetic Parameters for Nitroglycerin with Outlier Exclusion

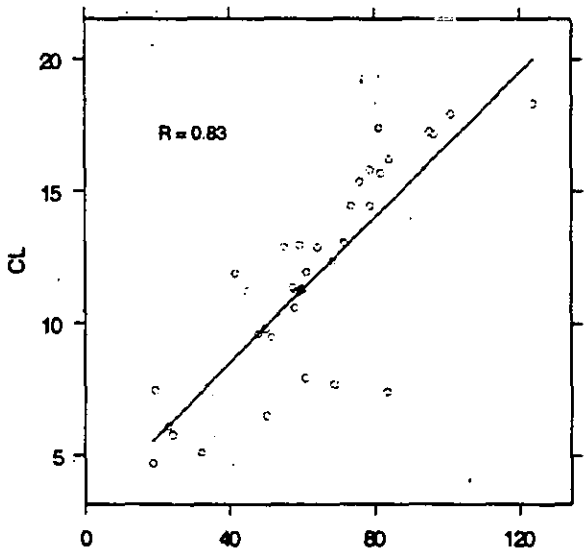
PARAMETER	VALUE	Inter-individual variability, %	SE of estimate, %
OBJ	1580		
CL	10.5	32.86	11.71
V	44.8	33.02	42.63
KA	0.165	65.50	23.15
ALAG	1.51		11.26
BIO2	0.949		9.42
BIO3	1.11		17.39
CCV	0.949	97.42	6.27
ADD	0.0595		26.22
BWT	1.85		52.27

The equation for the correlation of volume of distribution and body weight for this fit was

$$V(L) = 44.8 + 1.85\ (WT-77.3)$$

Although goodness of fit was confirmed by a symmetric distribution of weighted residuals vs time, which is shown in Figure 4, choosing the exclusion of non-confirmed outliers may cause biases in pharmacodynamic model. Moreover, for this last fit fraction of drug bioavailable to the systemic circulation for the treatment 2 was estimated less then for treatment 1, which is not supported by the comparison of mean AUC and C_{max} values.

Figure 5. Relationship between CL & V



Clearance and volume of distribution were correlated with correlation coefficient (R) of 0.78 for all studied population and only slight improvement was achieved (R = 0.83) for the subject data

with exception of outliers (Figure 5). Therefore, for the development of population PK/PD full model (Table 2) was selected.

Pharmacodynamics:

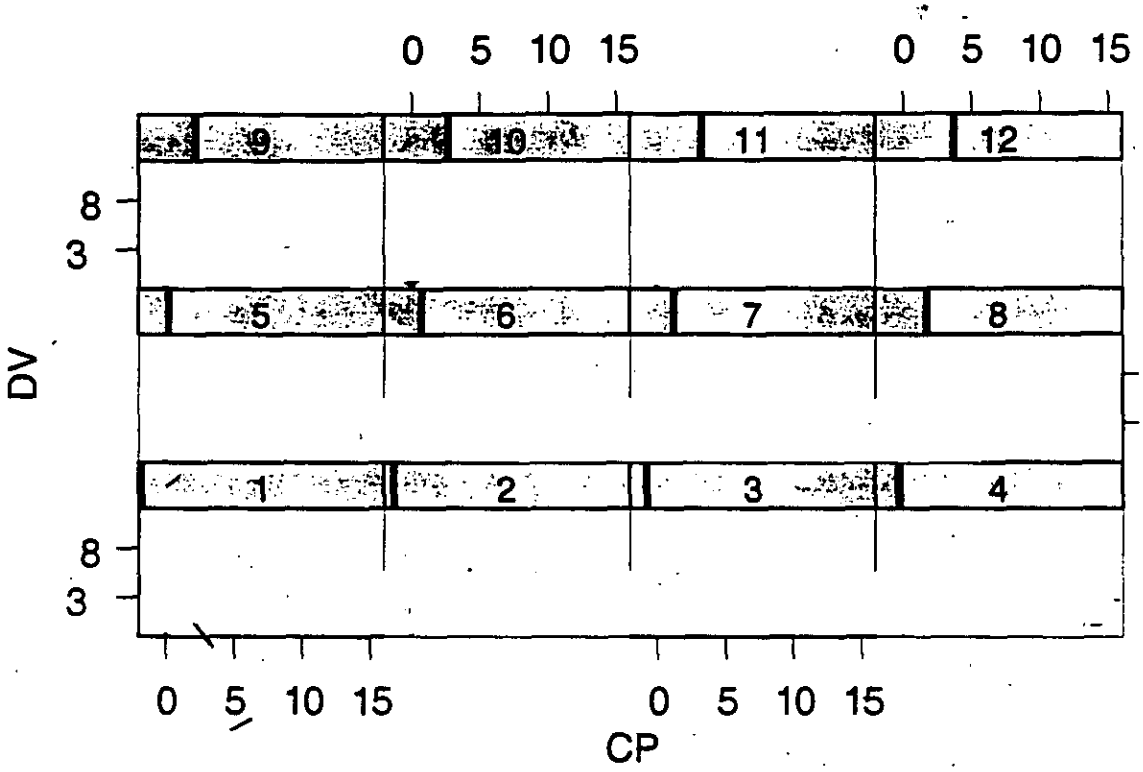
Both an E_{max} and a linear PK/PD models with baseline effect were evaluated. For the E_{max} model the data were selected to account for the observation of nitroglycerin plasma concentrations and pharmacodynamic measurements at the same time points. This model did not have good correlation between predicted and observed data. Then the individual predicted pharmacokinetic parameters were fixed for both E_{max} and linear models and pharmacodynamic data were fitted separately for each treatment for comparison. Nitroglycerin concentrations depend on the fraction of each treatment absorbed to systemic circulation. These relative systemic availability parameters were different for each treatment and estimated as 1 : 1.05 : 1.26 respectively for BIO1, BIO2 and BIO3 for treatments 1, 2, and 3 and fixed for pharmacodynamics. Plasma nitroglycerin concentration was considered as a driving force to the peripheral vasodilatatory effect. Based on the rule of parsimony, linear model was chosen over an E_{max} model. The increase of peripheral vasodilatory effect was directly correlated with the concentration of nitroglycerin

$$EFFECT = BSLN + K_{EFF}CONC$$

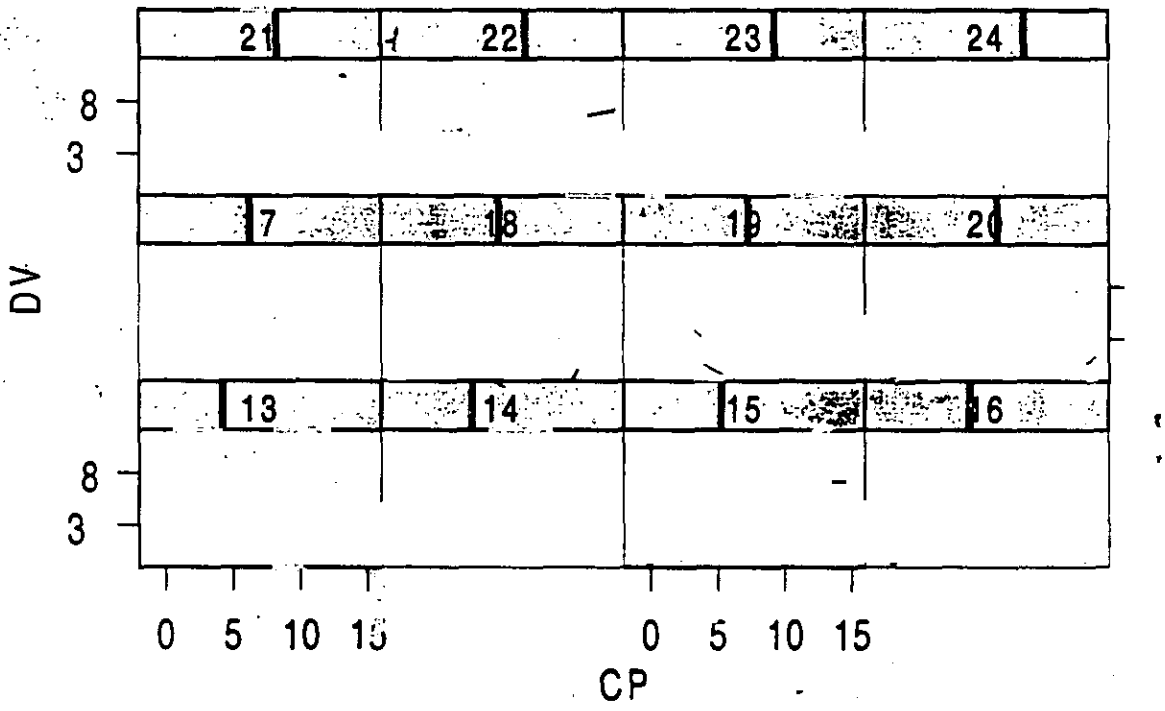
Where EFFECT is SDR values, BSLN is the effect at baseline, Keff is the regression slope, and CONC is nitroglycerin concentration.

The observed and individual predicted effect vs nitroglycerin concentrations plots are shown in Figures 6-9 (pages A-C for treatments 1-3).

Figure 6. Individual Effect vs Nitroglycerin Concentration Plots

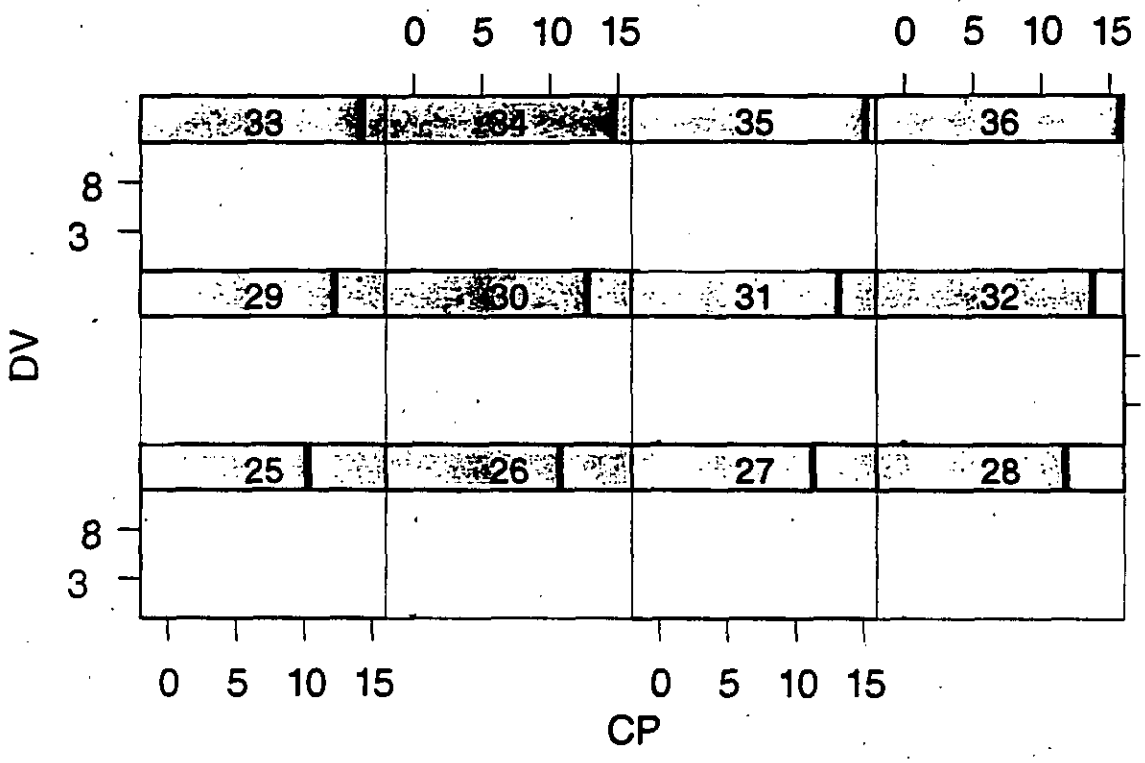


TREATMENT 1 pages A-C



TREATMENT 1 pages A-C

Figure 6. Individual Effect vs Nitroglycerin Concentration Plots



TREATMENT 1 pages A-C

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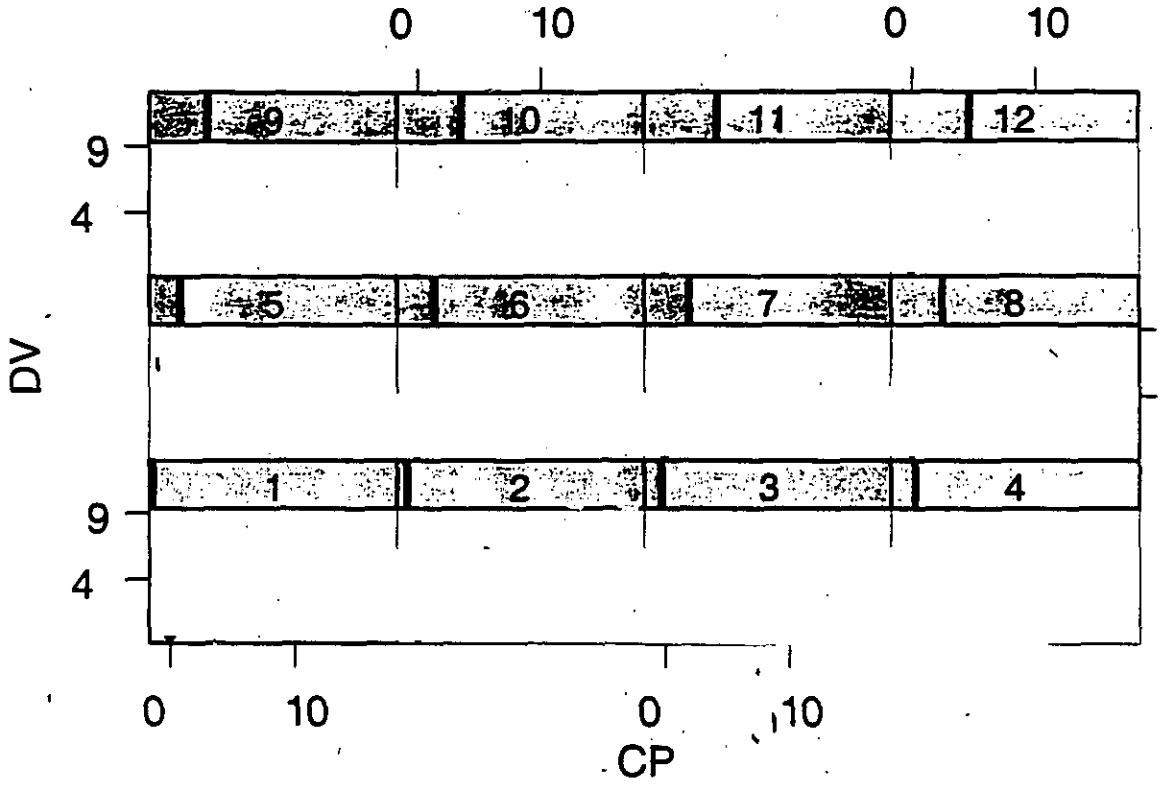
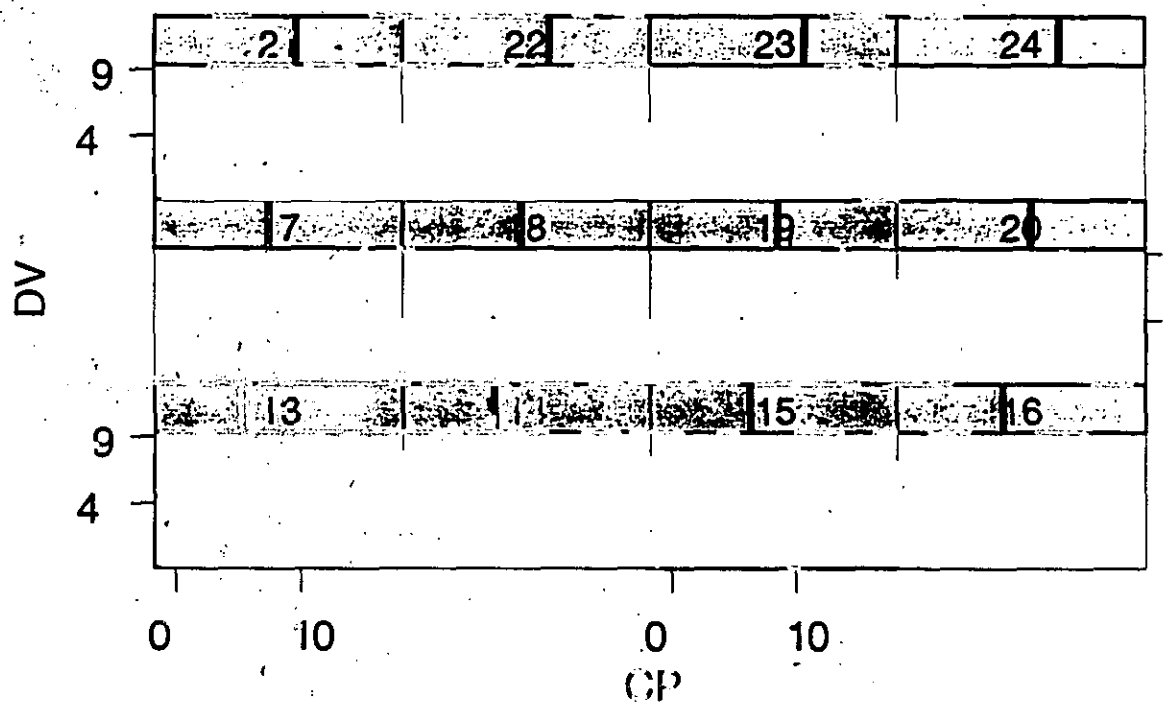
Figure 6. Individual Effect vs Nitroglycerin Concentration Plots

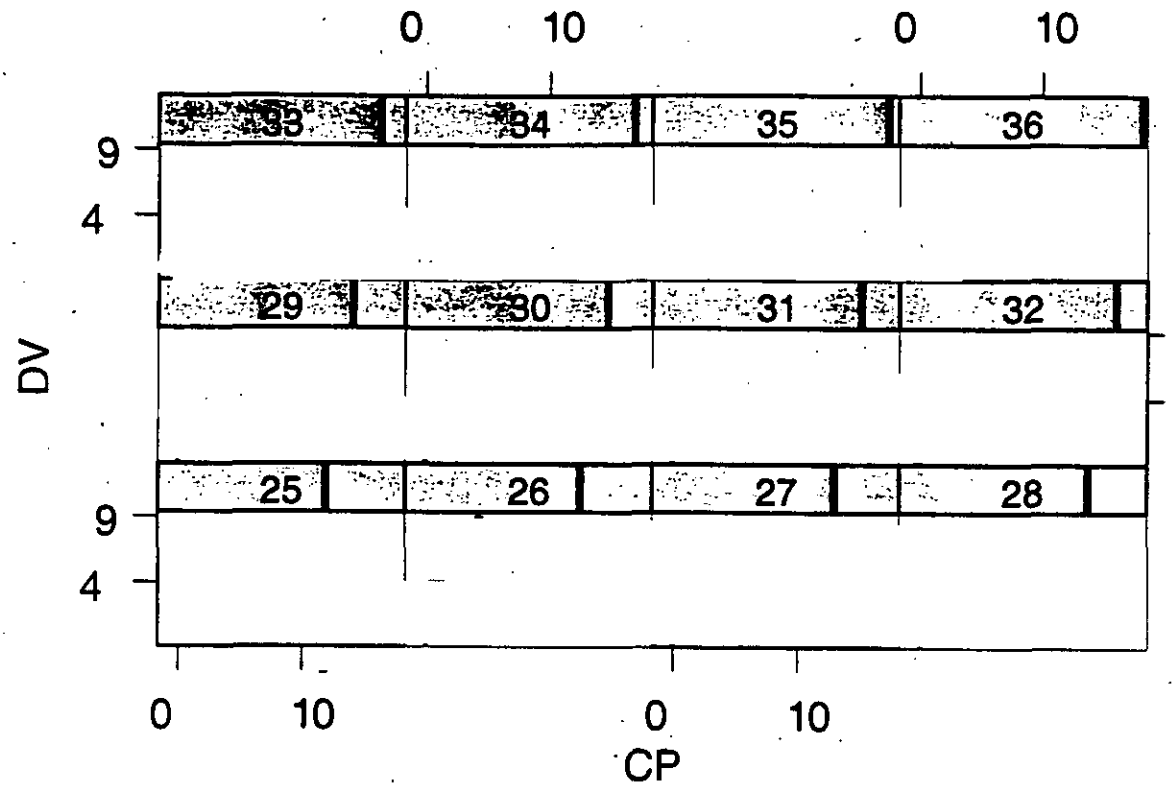


TREATMENT 2 pages A-C



TREATMENT 2 pages A-C

Figure 6. Individual Effect vs Nitroglycerin Concentration Plots



TREATMENT 2 pages A-C

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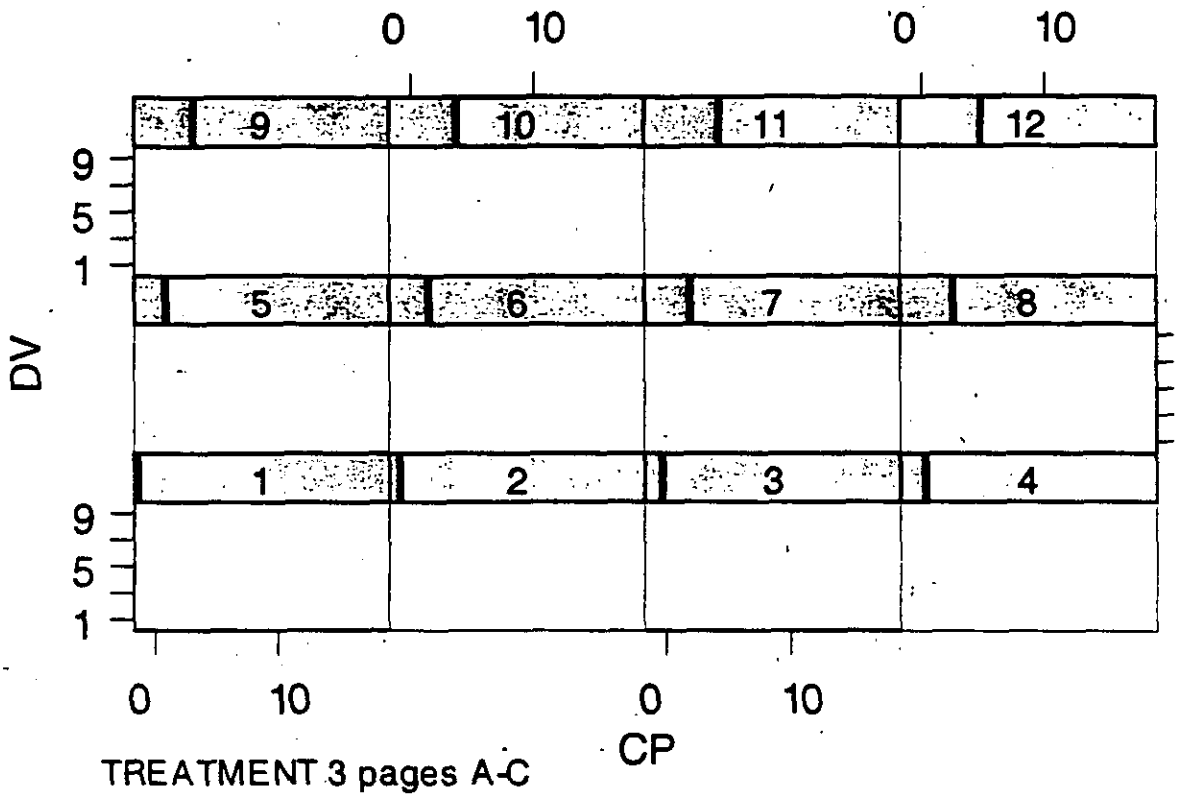
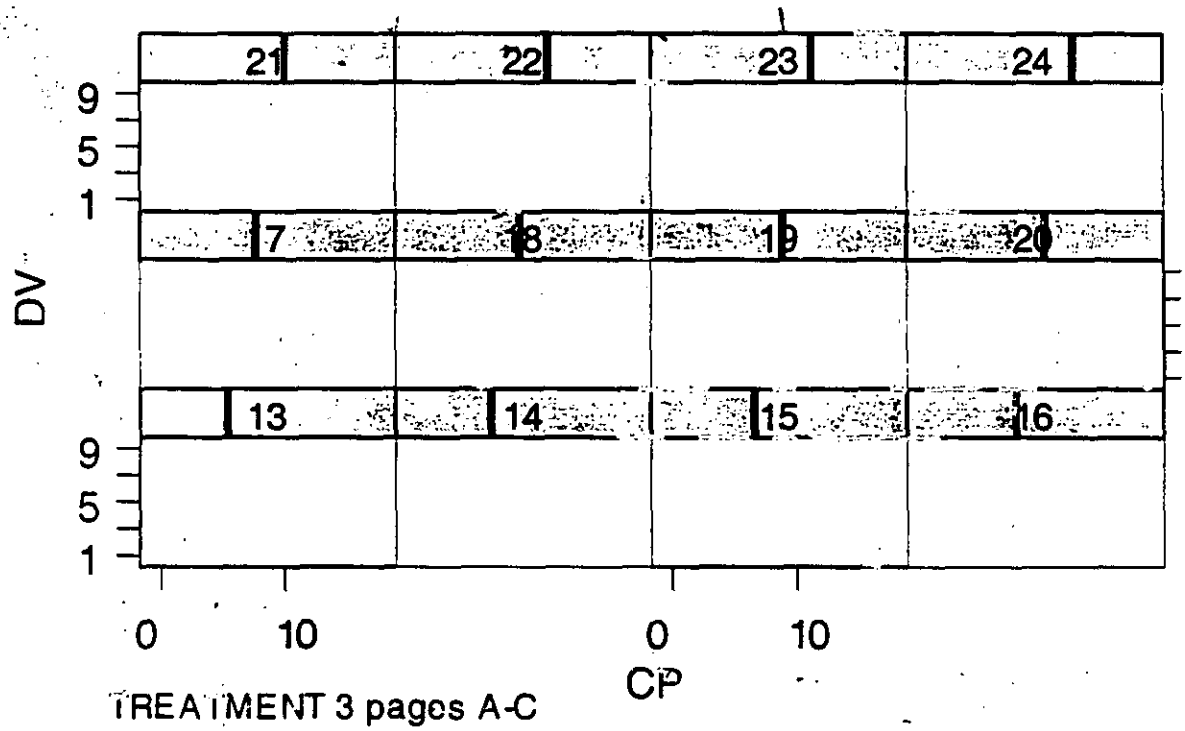
Figure 6. Individual Effect vs Nitroglycerin Concentration Plots

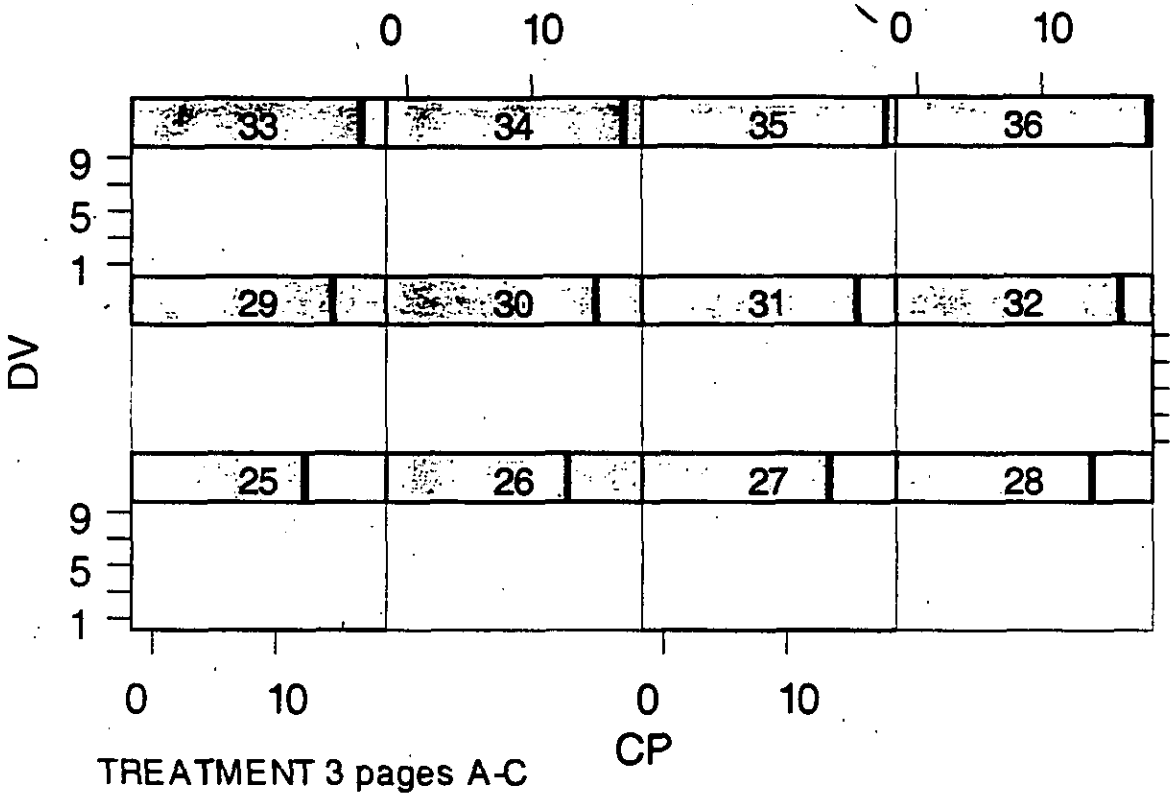


TREATMENT 3 pages A-C



TREATMENT 3 pages A-C

Figure 6. Individual Effect vs Nitroglycerin Concentration Plots



TREATMENT 3 pages A-C

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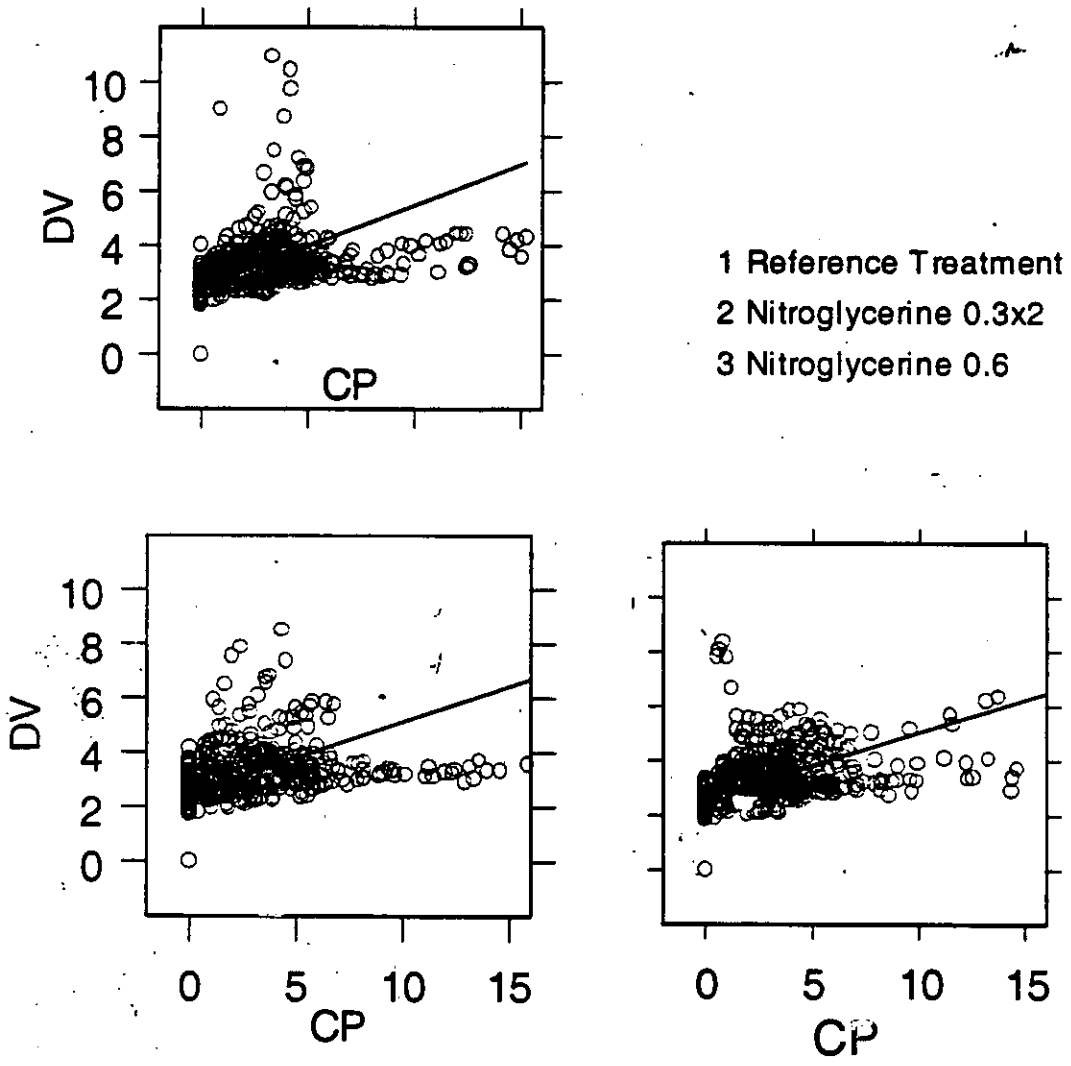
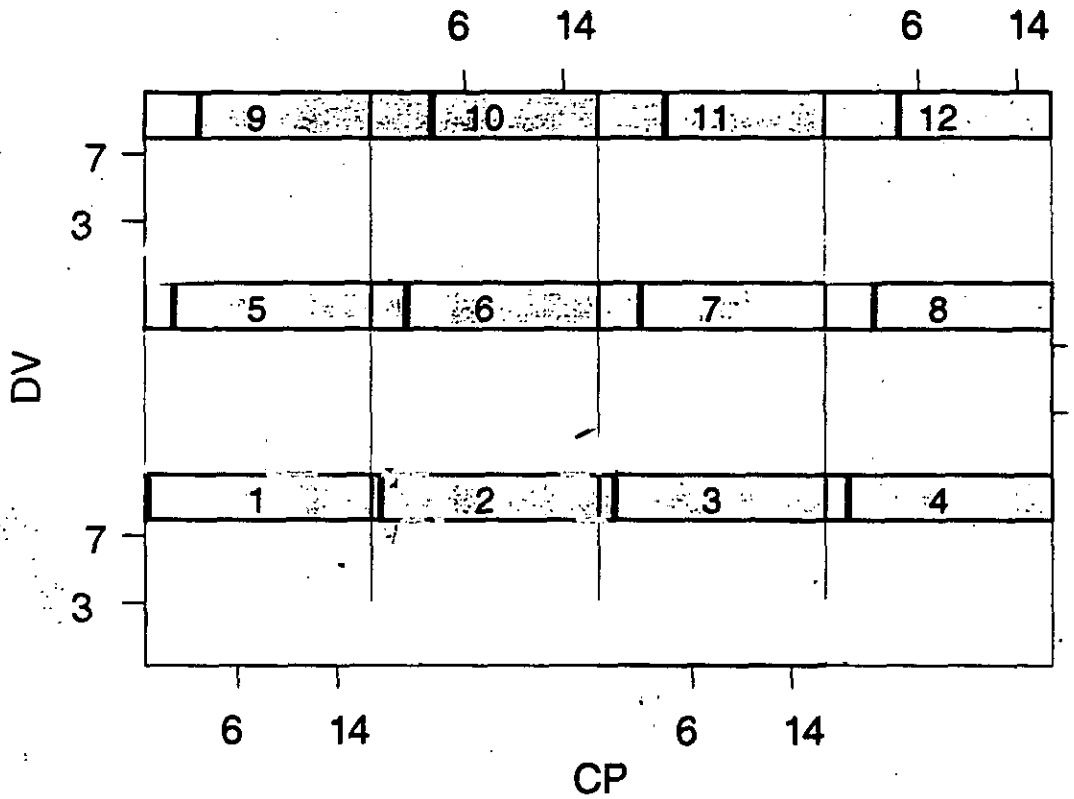
The correlation of the observed and population predicted values of the real time systolic BP : diastolic BP ratio (SDR) are shown in Figure 7.

Figure 7. Effect vs Nitroglycerin Concentration for the Population



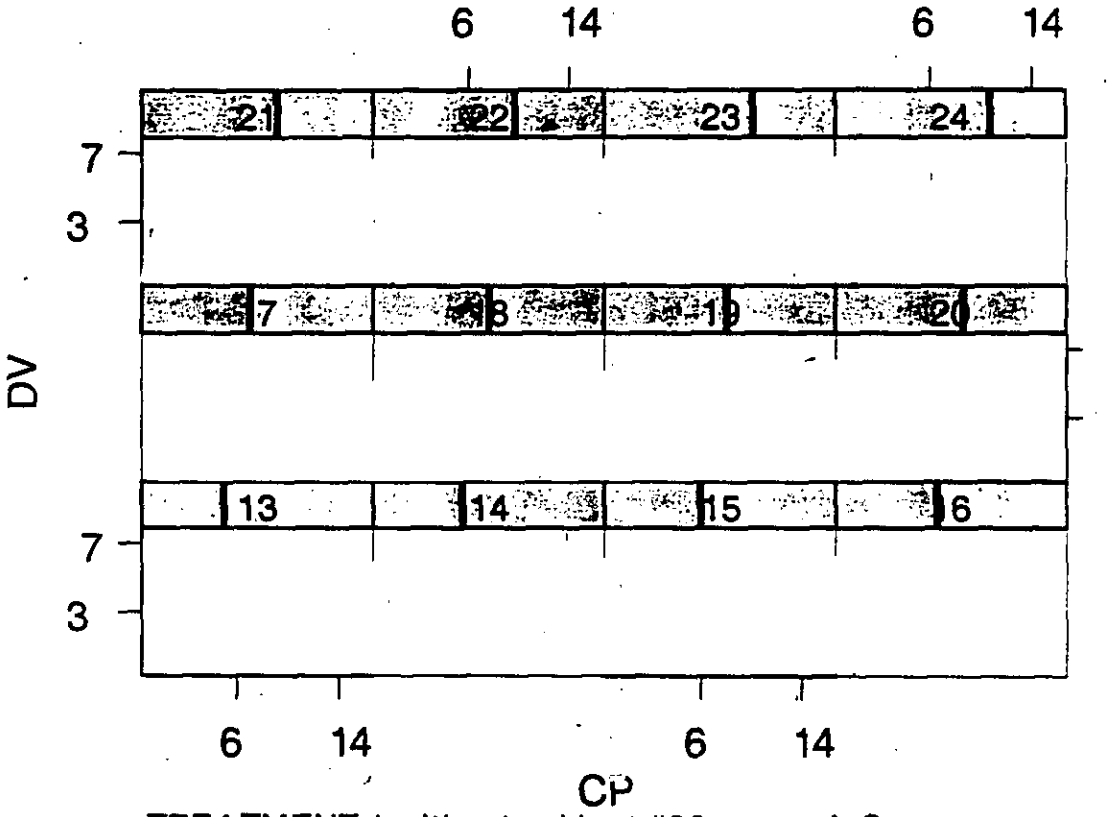
Inspection of effect-concentration plots demonstrated that subject #26 (treatments 1 and 2) and subject #8 (treatment 3) had unusual effect vs concentration profiles. Exclusion of these subjects led to a significant improvement of the goodness of fit.
Individual subjects effect vs nitroglycerin concentration plots with individual predicted curves are shown in Figure 8 (as an example for the treatment 1).

Figure 8. Individual Effect vs Nitroglycerin Concentration Plots

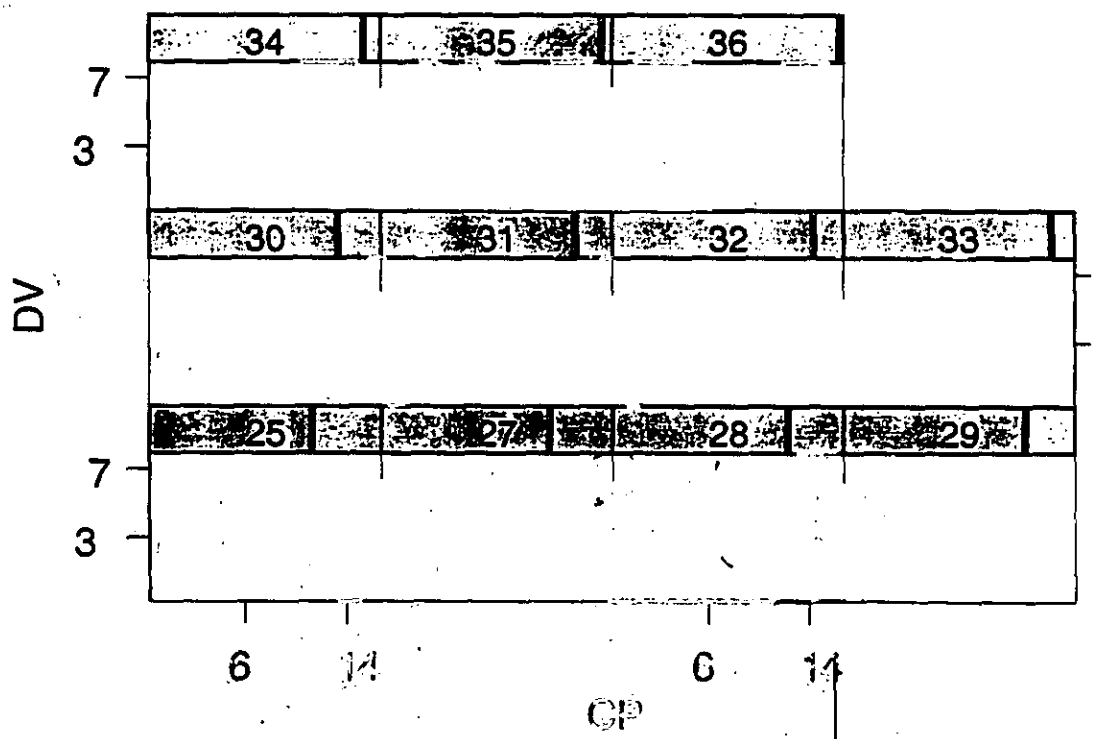


TREATMENT 1 without subject #26 pages A-C

Figure 8. Individual Effect vs Nitroglycerin Concentration Plots



TREATMENT 1 without subject #26 pages A-C



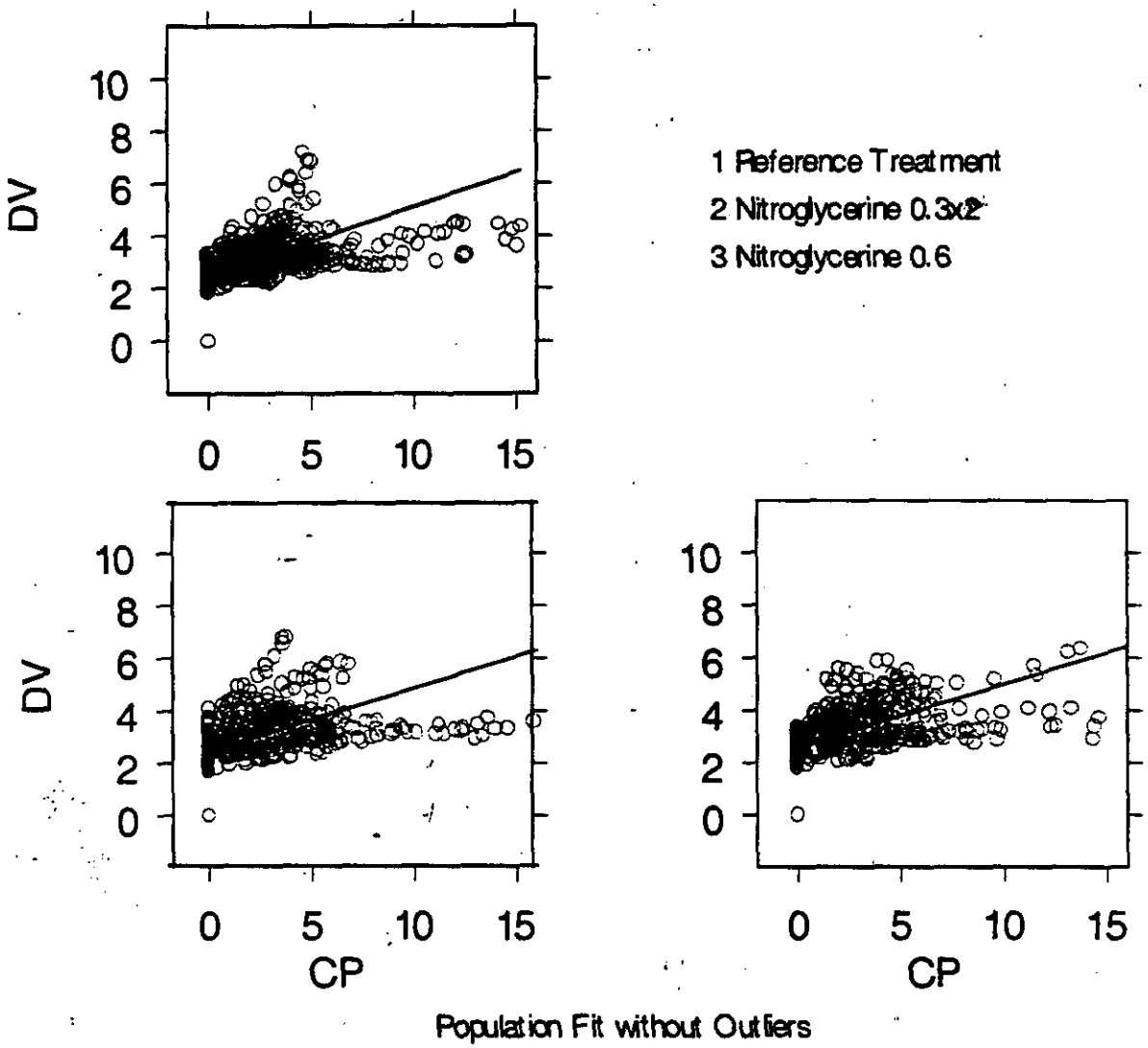
The decreased inter-individual and residual variabilty of parameter estimates values are shown in Table 4.

Table 4.

Parameter	Value	(STD)	CV of estimate, %	Inter-individual Variability, %	CV of estimate, %	Residual Variability, %	CV of estimate, %
TREATMENT 1							
OBJ	-538						
Kef	0.301	0.049	16.41	98.08	35.45	35.78	54.92
BSLN	2.47	0.040	1.62	8.49	32.64		
PAT #26 OMITTED							
OBJ	-1061						
Kef	0.262	0.033	12.44.	72.66	12.44	23.83	15.97
BSLN	2.47	0.062	1.66	9.31	1.66		
TREATMENT 2							
OBJ	-577						
Kef	0.261	0.033	12.80	76.68	31.29	34.35	40.34
BSLN	2.5	0.062	2.46	14.49	26.00		
PAT #26 OMITTED							
OBJ	-889						
Kef	0.239	0.026	10.71	62.69	27.99	27.04	23.39
BSLN	2.48	0.060	2.40	14.14	29.15		
continued							
TREATMENT 3							
OBJ	-85						
Kef	0.24	0.0252	10.50	57.71	10.50	50.99	47.31
BSLN	2.63	0.0716	2.72	14.83	2.72		
PAT #8 OMITTED							
OBJ	-495						
Kef	0.24	0.025	10.58	60.25	10.58	37.55	27.94
BSLN	2.58	0.049	1.93	10.34	1.93		

Predicted vs observed effect values for each treatment with exclusion of outliers are depicted in Figure 9.

Figure 9. PRED vs OBS Nitroglycerin Concentration without Outliers



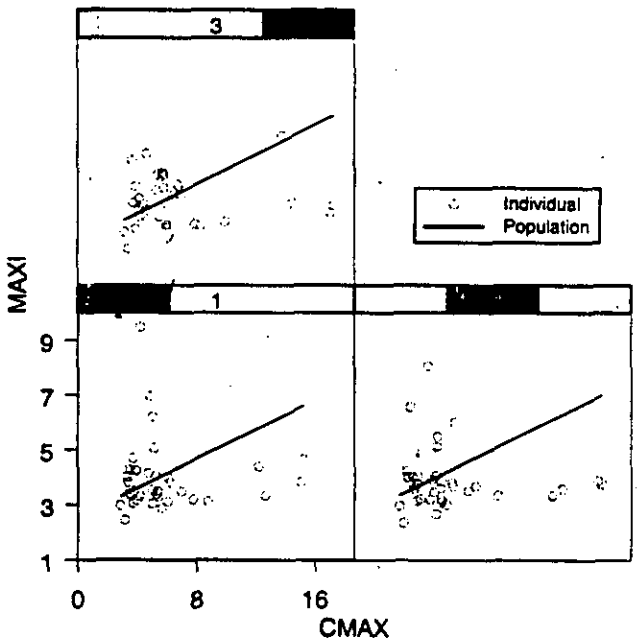
Additionally, the vasodilatory effect vs nitroglycerin concentration data from all three treatments were combined and fitted simultaneously to the linear model to obtain general parameter estimates and individual predictions. Table 5 shows that the inter-individual and residual variabilities were less than variabilities from each treatment for each treatment when fitted alone.

Table 5. Parameter Estimation for the Combined Pharmacodynamic Model

	Parameter Value	STD	CV,%	Inter-individual Variability, %	CV,%	Residual Variability, %	CV,%
Kef	0.268	0.022	8.13	82.6	27.71	41.1	29.94
BSLN	2.540	0.035	1.36	13.2	27.37		

In the posthoc output file, observed C_{max} values were used to estimate individual and population effect. Comparison by treatment is shown it Table 6.
Using the above model, the pharmacodynamic effects corresponding to the peak plasma concentrations were predicted by the posthoc estimates for each individual subject. The predictions for each subject are shown in Table 6 and Figure 10.

Figure 10. RELATIONSHIP BETWEEN MAXIMAL EFFECT AND NITROGLYCERIN PLASMA CONCENTRATION



The results show that the pharmacodynamic effects obtained for each treatment are similar. Thus, the conclusion from this data analysis is that the observed differences in plasma concentrations do not result in differences in the pharmacodynamic effects. This fact can be probably explained by the shallow nature of the PK/PD relationship for this particular case (small k_{eff} values). Additionally, although the inter-patient variability in C_{max} values was high, it does not reflect the high variability in the effect. Statistical analysis of individual estimated effect at C_{max} shows that at present coefficient of variations (21-32%) the difference between treatments is statistically insignificant.

Table 6. Estimation of Maximal Effect Based on Individual Predicted And Population Predicted Model

Treatment 1					
ID	KEF	BSLN	CMAX	MAXI	MAXP
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					
24					
25					
26					
27					
28					
29					
30					
31					
32					
33					
34					
35					
36					
Mean	0.304	2.471	5.837	3.968	4.098
STD	0.294	0.213	3.156	1.299	0.845
CV	96.6	8.6	54.1	32.7	20.6
Range					

Treatment 2					
ID	KEF	BSLN	CMAX	MAXI	MAXP
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					
24					
25					
26					
27					
28					
29					
30					
31					
32					
33					
34					
35					
36					4.102
Mean	0.266	2.501	6.363	3.906	4.239
STD	0.205	0.334	3.472	1.105	0.929
CV	77.4	13.3	54.6	28.3	21.9
Range					

Treatment 3					
ID	KEF	BSLN	CMAX	MAXI	MAXP
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					
24					
25					
26					
27					
28					
29					
30					
31					
32					
33					
34					
35					
36					
Mean	0.252	2.611	6.520	4.058	4.281
STD	0.144	0.384	3.604	0.877	0.965
CV	57.1	14.7	55.3	21.6	22.5
Range					

Conclusion:

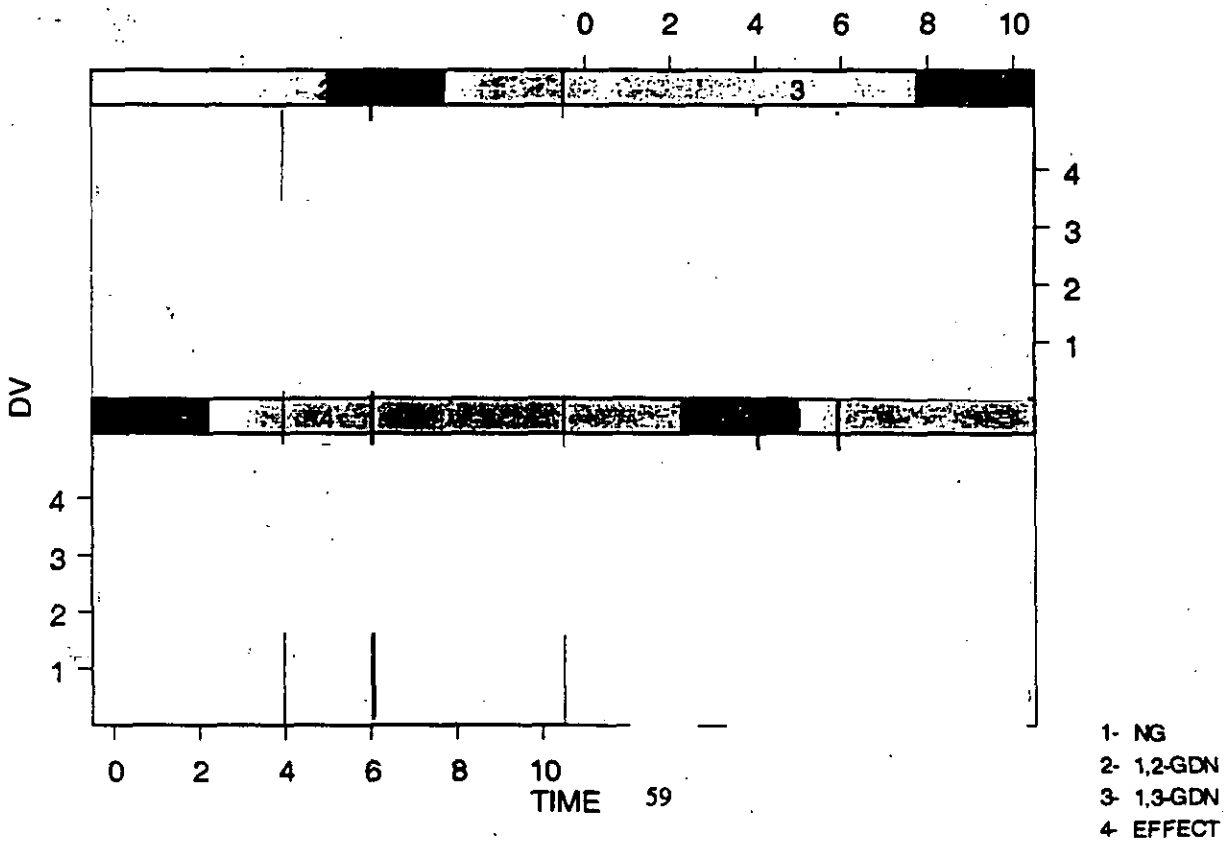
Although the new nitroglycerin formulation has not met the bioequivalence criteria for both Cmax and AUC for nitroglycerin, comparison of the pharmacodynamic effects at peak plasma concentrations obtained for each treatment separately showed that the difference in effect was insignificant; therefore, all three treatments can be considered similar by the effect.

Comments:

The sponsor has not analyzed the relationship between plasma nitroglycerin concentration and the pharmacodynamic effect. The sponsor analyzed the effect vs time data and presented the comparison of the SDR measurements at 100%, 75%, 50% and 25% of maximal effect at the corresponding time points. Please see the primary reviewer (Dr. Fadiran) review.
The population PK/PD model developed by the FDA reviewer shows that the peripheral vasodilatory effect of nitroglycerin was directly proportional to its plasma concentrations.
The impact of nitroglycerin metabolites (1,2-DNG and 1,3-DNG) on this pharmacodynamic measurement was not evaluated according to the following:

Maximum effect of peripheral vasodilation was observed from 4.9 to 5.9 min on average, which is correlated with the T_{max} for nitroglycerin (range from 6.2 to 7.2 min). In this time interval, plasma concentrations of both metabolites was just above the detection limit of 0.1 ng/mL and reached T_{max} at 12.6 – 13.4 min (1,2-DNG) and 15.5 – 17.2 min (1,3-DNG), Figure 11.

Figure 11, PK & PD, PATIENT 1



The correct way to compare EC50 for the parent drug and metabolites is to administer them separately and to obtain the effect measurements. Such data were not available for analysis and thus the contribution of the metabolites to the overall activity could not be assessed. Moreover, literature data show that metabolites have about 10% of activity measured in vitro.
For all the above reasons, it the opinion of the reviewer that the contribution of the metabolites to this pharmacodynamic effect (peripheral vasodilation measured by digital plethysmography) is insignificant and the development of model which includes metabolites concentration is not worthwhile to pursue with the available data.

Recommendation:

The population pharmacokinetic/pharmacodynamic data analysis performed by the FDA for study 78216 showed that the newly developed nitroglycerin compressed tablets and the currently marketed nitrostat tablet produce equivalent pharmacodynamic effects on peripheral vasodilation as measured by digital plethysmography. Although the new nitroglycerin formulation has not met bioequivalence criteria with Nitrostat both for Cmax and AUC, this nonequivalence in plasma concentrations does not result in differences in the pharmacodynamic effect.

/S/ Date 2/23/00

Elena Mishina, Ph. D.
Pharmacometrics Specialist

/S/ 2/23/1000

RD/FT Patrick Marroum, Ph. D.

cc list: NDA 21-134, HFD-110,
Williams (HFD-110),
Chen (HFD-110),
HFD-860 (Fadiran, Mehta, Mishina),
BIOPHARM - CDR