CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19922

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

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CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA 19-922
CORLOPAM
Fenoldopam mesylate, solution for intravenous infusion
Sponsor: Neurex Corpration
Old submission date: 12/12/1988
New submission dates: 06/21/96, 8/13/96, 8/14/96, 10/8/96, 11/21/96, 11/22/96, 12/20/96, 1/27/97, 2/4/97, 2/6/97, 2/11/97, 3/28/97, 4/8/97, 4/28/97, 5/2/97, 5/7/97
Reviewer: Ahmed El-Tahtawy, Ph.D.

SYNOPSIS

Fenoldopam mesylate (6-chloro-2, 3, 4, 5-tetrahydro-l-(4-hydroxy phenyl)-1H-3-benzazapine-7, 8-diol, methanesulfonate, hereafter referred to as fenoldopam, is a systemic and renal vasodilator which stimulates postsynaptic dopamine DA_1 receptors. Corlopam® is a racemic mixture with the R-enantiomer is responsible for the biological activity of this drug. The S-isomer is essentially inactive. Fenoldopam has no significant alpha-adrenergic, beta-adrenergic, or DA_2-receptor agonist activity, and it exhibits no central nervous system effects. The rationale for the clinical use of intravenous (IV) fenoldopam is based on its systemic vasodilatory properties that suggest that it may be effective in the acute lowering of blood pressure. The initial recommended dose is 0.24 ug/Kg/min as a constant-rate IV infusion. The dose can be titrated to achieve the desired effect provided that the change in infusion rate does not exceed 0.24 ug/Kg/min every 20 minutes.

This NDA was originally filed by on December 12, 1988. The application was reviewed and found to be deficient. The absence of adequate and well-controlled clinical trials in the target population, and consequently, lack of information on how to administer the drug to the target population was the basis for the deficiency. A non-approval letter was issued on November 15, 1991 and the application was withdrawn by the sponsor on February 4, 1993. Neurex acquired the rights to this product in 1994 and resubmitted the application on June 25, 1996. It was agreed that none of the original data need to be resubmitted.

Two additional clinical PK/PD studies were recommended to be submitted. The first study (94-007) was a pilot study designed to define the dose range that should be studied in the definitive PK/PD study. Fenoldopam was administered as an i.v. infusion over 48 hours with regular monitoring of blood pressure and heart rate. The conclusion of this pilot study was that the infusion rate of 1.6 ug/Kg/min is excessive and results in serious side effects. The second study (94-005) was conducted in 33 patients to investigate the PK/PD relationship of fenoldopam concentration to blood pressure and heart rate. In this study, the subjects were randomized to receive constant infusions of either placebo or one of several fixed doses of fenoldopam, ranging from 0.04 to 0.8 ug/Kg/min, for a total of a 48-hours. A linear and non-linear PK/PD models were developed in an attempt to predict a dosing regimen that would be effective in treating hypertension. However, due to the large interpatient variability, the small sample size, and lack of covariates that may explain the observed variability, the PK/PD models have limited utility and should be used only to predict an initial dose and treatment regimen.

The population PK/PD modeling was particularly useful in delineating the following:

1. there is a minimal lag time between the fenoldopam concentration and response.

2. Tolerance may develop during the infusion. Nonlinear PK/PD models predict a long $t_{1/2}$ for tolerance (as long as 110 hours).

3. There is a large unexplained intersubject variability in response, which may indicate that different patients may respond quite differently to the same dose and concentration. Caution and titration are warranted.

4. The population approach argued that the concentration-response curve could be a composite of two additive nonlinear responses. Combining data across patients enabled us to identify the multiple response phenomenon and the non-linearity of the response at the very low and high concentration.

Based upon the rapid lowering of blood pressure following the initiation of infusion, there appears to be minimum lag between fenoldopam administration and blood pressure lowering effect. Given this information, and the very short t1/2, we believe that dose adjustment is best accomplished based on achievement of intended therapeutic effect following the initial dose determined via the PK/PD model.

Another clinical trial of PK/PD of intravenous Fenoldopam in emergency hypertensive patients (Protocol Number 94-006) was carried out. The difference in the parameter estimates for the PK/PD model from the previous study (94-005) could be explained by one or more of the following factors:

- Different patients characteristics i.e. emergency HT Vs moderate HT.
- Absence of placebo arm.
- Sparse and sporadic blood sampling.
- The clinical setting for emergency situations mandate care for the patient to take precedence over data collection .
- Inaccurate recording of time for PK or PD response may occur in emergency environment.

The population approach was useful in dealing with these difficulties and the predictions of concentration and effect are very close to the predictions of the PK/PD model developed for study 94-005 in the mild hypertension study. The major difference between the mild and the emergency HT population lies in the fast development of tolerance in the latter population.

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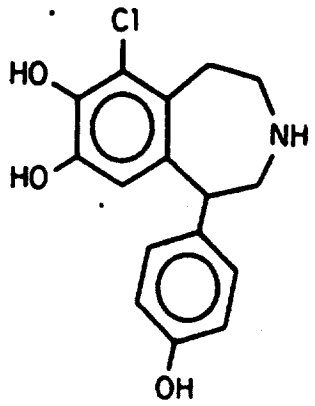
- Original NDA: Pharmacokinetic Section reviewed by Suresh Mallikaarjun, Ph.D.

- Resubmission: Pharmacokinetic Section reviewed by Ahmed El-Tahtawy, Ph.D.

The following is a combined summary of the original and resubmitted data on pharmacokinetics and pharmacodynamics of fenoldopam. The resubmission consisted of data in mild hypertensives. A study in severe hypertensives is currently ongoing and will be analysed upon submission.

DESCRIPTION

Fenoldopam is a benzazepine compound with the following structure:



• CH_3SO_3H

It is a selective postsynaptic dopaminergic (DA1) receptor agonist and has minimal activity at α- or β- adrenergic DA2 receptors. Fenoldopam presumably decreases blood pressure in animals through a direct action on one or several of the ***dopamine$_1$-type*** receptors. Fenoldopam also binds to and antagonizes ***alpha$_2$ adrenergic receptors,*** at concentrations not that dissimilar from those attained with infusion rate of 1 ug/Kg/min. Fenoldopam also binds to and

antagonizes ***alpha$_1$ adrenergic*** receptors but only with binding constants substantially weaker than those of the dopamine$_1$ or alpha$_2$ adrenergic receptors.
It is a rapid acting vasodilator and is proposed to be used in the treatment of hypertension. It will be supplied in ampoules of 1 ml aqueous solution containing fenoldopam mesylate equivalent to 10 mg fenoldopam.

PHARMACOKINETICS:

Healthy Volunteers: Following a 1 ug/Kg/min infusion for 2 hours in 12 healthy volunteers (Study. A-21 UK), the mean Cmax was 26 ng/ml (C.V. 16%), the mean clearance was 41.5 ml/min/Kg (about 2.9 L/min) (C.V. 17%) and the mean VDss was 500 ml/Kg (C.V. 24%). On compartmental analysis, the mean α-half-life was 6 minutes, with 97 % of the AUC accounted for by this phase, and the β-half-life was 60 minutes with 3 % of the AUC described by this phase. The protein binding was about 88 %.

Hypertensive Patients: In study L-36, 21 patients were given successive infusions every 15 minutes from 0.025 to 1.5 µg/Kg/min. The mean concentrations at the end of 0.1 and 0.5 µg/Kg/min infusions were 3.5 and 15.5 ng/ml. In the same study, 9 hypertensive patients were administered single doses of 0.25, and 0.375 µg/Kg/min, and the mean clearances were about 30 ml/min/Kg (2.1 L/min); the mean Css were 8.5 and 13.9 ng/ml respectively. The variability, estimated by the %C.V., for clearance ranged from 15 to 35 %, and for Cmax ranged from 16 to 28 %.

In Study 94-005, where mild hypertensive patients were tested, the pharmacokinetics of fenoldopam were well characterized by a one-compartment model. NONMEM program was utilized to separately fit the kinetics of racemic fenoldopam, R-fenoldopam, and S-fenoldopam. Racemic fenoldopam plasma concentrations were determined for all patients across all dose levels (0.04, 0.1, 0.4, and 0.8 ug/Kg/min). The plasma concentrations of R-fenoldopam, S-fenoldopam, 7-methoxyfenoldopam and 8-methoxyfenoldopam were measured at selected time points in only 9 patients who received fenoldopam infusion at either the 0.4 or the 0.8 ug/Kg/min dose levels.

The average clearance (CL) and half-life ($t_{1/2}$) of racemic fenoldopam in the 25 patients were 2.6 L/min and 4.6 min, respectively. The short half-life results in steady-state (SS) concentrations

being reached in approximately 20 min. The Css were proportional to the infusion rate (Fig. 2), and ranged from 1.5 ng/ml for 0.04 ug/Kg/min to 30 ng/ml for 0.8 ug/Kg/min. Upon discontinuing the infusion, fenoldopam concentration decay was very rapid due to high clearance of the drug.

The CL of R-fenoldopam (3.4 L/min) was larger than that of S-fenoldopam (1.9 L/min) and, therefore, the R-enantiomer reaches lower steady-state concentrations. The difference in elimination half life of racemic fenoldopam and the entantiomers are not significantly different as the 95% confidence intervals for the half-lives are overlapping. The $t_{1/2}$ of R- and S-fenoldopam were similar (6.3 min and 6.1 min , respectively). The $t_{1/2}$ of 7- and 8-methoxyfenoldopam (13.2 min and 12.5 min, respectively) were longer than for racemic fenoldopam (4.6 min).

Only the patients' body weights and their baseline values (systolic blood pressure, diastolic blood pressure heart rate) were tested for influence on the kinetic parameters of the PK models (K, V). Neither body weight nor baseline had influence on the PK parameters. The population clearance rate of racemic fenoldopam (2.6 L/min) suggests that a steady state concentration of 20 ng/mL in an average person may require an infusion of about 3.3mg/hr (about 55 ug/min).

Renal Impairment (CAPD): Eight patients undergoing peritoneal dialysis (Study A- 35) were administered IV infusions of 0.1 µg/Kg/min for 30 minutes followed by 0.2 µg/Kg/min for 4.5 hours. The mean Css after 0.1 and 0.2 µg/min/Kg infusions were 2.8, and 4.8 ng/ml respectively. The clearance values are 41.7 and 36.9 ml/min/Kg after 0.1 and 0.2 µg//Kg/min infusions and are similar to those in normals.

Hepatic Impairment: The results of study L-51 indicated that the mean clearance in 7 hepatically impaired patients after administration of either 0.1 or 0.2 µg//Kg/min of fenoldopam for 5 hours, was 44.6 ml/min/Kg (C.V. 20%), a value very similar to that observed in normal subjects (41.5 ml/min/Kg from Study A-21 UK).

Congestive heart failure:

The mean clearance in 15 CHF patients (Study L-47) was 40.93 ml/min/Kg (C.V. 28%), which is similar to clearance in normal healthy volunteers.

METABOLISM:

Oral fenoldopam undergoes extensive first-pass and systemic metabolism to a variety of sulfate, glucuronide and methoxy metabolites. Urinary excretion of methoxy metabolites was in the glucuronide form.

In-Vitro: The FDA's Division of Clinical Pharmacology (R. Klecker and J. Collins) investigated the metabolism of fenoldopam and its metabolites in human liver slice, microsomal and cytosolic preparations. Details of the study are found in Appendix II. The purpose of their study was to compare the relative rates of glucuronidation, sulfation and methylation of fenoldopam enantiomers and metabolites. There was no evidence of metabolism of fenoldopam by cytochrome P450. R-fenoldopam was metabolized to fenoldopam-8-sulfate (8-SO4), 7-methoxy fenoldopam (7-MeO), 8-methoxy fenoldopam (8-MeO) and 2 glucuronidated products. The 7-MeO formed with incubation of R-isomer in human liver slices was further metabolized to an unknown sulfated product. S-isomer was metabolized to fenoldopam-7-sulfate (7-SO4), a second unknown sulfated product, 7-MeO, 8-MeO and 2 glucuronidated products. Metabolism of S-and R- isomers in human liver slices to 7-MeO occurred at the same rate while further metabolism of 7-MeO was stereo-specific and was slow for the S-isomer of 7-MeO. The parallel pathways of fenoldopam metabolism lessen the possibility of drug-drug interactions .

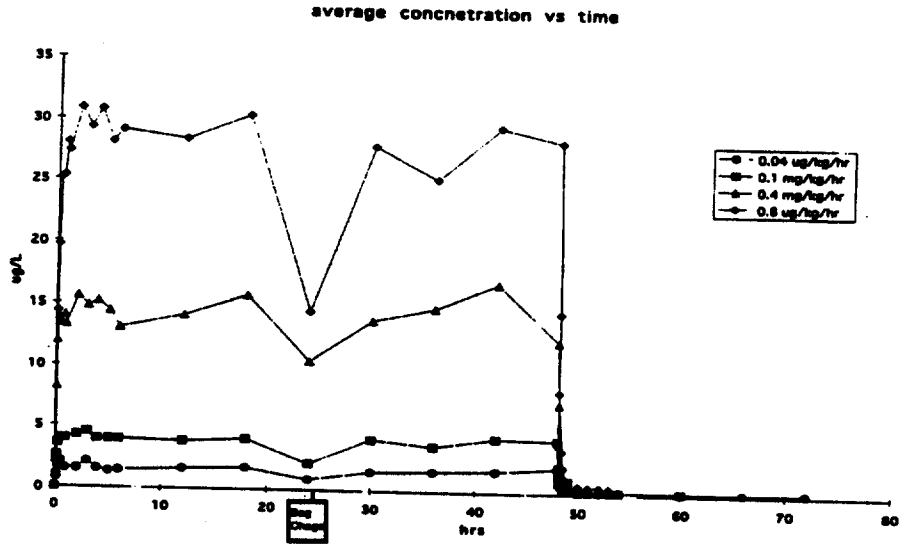
In-Vivo: Four subjects received 3.2 to 4.2 mg IV doses of 14C labeled fenoldopam over 30 minutes in study UK/01/07. The recovery was complete, with 89% of the dose recovered in the urine, and 11% in the feces. The metabolites identified in the urine were the 7-methoxy conjugates (sulfate + glucuronide) (11 %), 8-methoxy conjugates (17.4%), and fenoldopam conjugates (17.2%). Overall, fenoldopam was extensively metabolized with only about 4-6% of the dose being recovered as unchanged drug (UK/01/07, A-21/UK).

A population PK model was used to simultaneously fit racemic fenoldopam and its methoxymetabolites (7-MeO, 8-MeO). These two metabolites accounted for 85% of the clearance of racemic fenoldopam, which may indicate that 7-MeO, 8-MeO products are the major metabolites of fenoldopam.

DOSE PROPORTIONALITY:

On administration of 3 single doses between 0.025-0.5 µg//Kg/min in a crossover manner to three normal volunteers (L-34), the Css appeared to be proportional to the dose. However, the small sample size precluded any definitive conclusions on dose proportionality from this study. The sponsor pooled the data from studies A-21, L-34 and L-64 and the plot of Css against rate of infusion appeared to indicate linearity between 0.025 to 1.0 µg/Kg/min . Based on information from these studies and the dose-ranging PK/PD study, 94-005, dose proportionality can be concluded upto 1 ug/Kg/min.

Based on the results of study # 94-05 in a mild-moderate hypertensive population, the kinetics of fenoldopam at infusion rates of up to 0.8 ug/kg/min, are well behaved. At the start of the infusion, the concentration of fenoldopam rapidly rises, leading to apparent steady concentrations. The kinetic T1/2 of fenoldopam to reach this steady state is approximately 5 minutes. Over a 20-fold difference in infusion rate, the steady state fenoldopam concentrations are linearly related to these rates. (There is a dip in concentrations at 24-hours, corresponding when the infusion bag was changed).



Infusion rate versus concentrations.

ANALYTICAL METHOD:

In the new resubmission, the firm has supplied the requested information regarding

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PK/PD IN HEPATICALLY IMPAIRED PATIENTS:

The sponsor examined the relationship between plasma concentrations and systolic BP, diastolic BP, and heart rate in hepatically impaired patients (Study A-20). 12 patients were administered 4 successive infusions of fenoldopam of 0.05, 0.5, 1.0, and 1.6 ug/Kg/min spaced 30 min apart. The Emax and EC50 for the parameters are listed below:

	Systolic BP	Diastolic BP	Heart Rate
EMAX(%)	-41.7 ±10.1	-47.5 ± 8.7	22.9 ±3.0
EC50 (ng/Ml)	20.0 ±10.1	12.1 ±5.6	2.76 ± 1.54

EMAX(%) - Percent reduction from baseline.

The sponsor concluded that although mean clearances decreased with increasing infusion rates, the mean clearance of hepatically impaired population was similar to healthy volunteers.

SUMMARY OF PK/PD ANALYSIS IN HYPERTENSIVE PATIENTS (STUDY 94-005):

PK/PD data

Twenty-five hypertensive patients received continuous infusion of racemic fenoldopam (0.01-0.8 µg/Kg/min) for 48h. Seven patients received placebo during the whole treatment period.

The number of patients randomly assigned to different treatment groups were as follows:

- Six patients for 0.8 ug/Kg/min group.
- Five patients for 0.4 ug/Kg/min group
- Seven patients for 0.1 ug/Kg/min group.
- Seven patients for 0.04 ug/Kg/min group.
- One patients for 0.01 ug/Kg/min group.
- Seven patients for 0.0 ug/Kg/min group.

Blood samples for kinetic analysis were collected at 0, 5, 10, 30, 45, 60, 120, 180, 240, 300 and 360 minutes after the initiation of the infusion and every 6 hours thereafter till 48 hours. Blood samples were also collected at 0, 5, 10, 30, 45, 60, 120, 180, 240, 300 and 360 minutes and every 6 hours for 24 hours after completing the infusion. Blood pressure and heart rate were continuously monitored 24 hrs before the infusion, during the infusion, and for 24 hrs after the end of the infusion. During the initial placebo infusion day, blood pressures and heart rates were recorded at approximately 15 minute intervals. During the initial hour of active infusion these vital signs were measured at 5 minute intervals for the first hour, followed by measurements every 15 minute for the remaining 48-hours. Upon discontinuation of the infusion on day 4, vital signs were again measured every 5 minutes for the first hour, followed by measurements every 15 minutes for the remaining 24 hours. Baseline was first calculated as the mean of all measurements between 24 h and 1 hr before the start of the infusion. The effect of treatment was calculated as the difference between the measurement after the infusion and the baseline value. It was suggested by the supervisory medical officer that analysis of drug effect should be conducted after baseline & placebo correction, rather than using only average baseline corrected values. The average baseline subtracted response did not account for the diurnal blood pressure pattern and the placebo effect.

The new analysis utilized the seven patients who received placebo to calculate an average placebo profile that was used as a correction for the other 25 patients. The placebo data were fitted to polynomial equations to simulate the circadian rhythm. The average placebo effect served as baseline with circadian rhythm. The PD response was calculated as the difference of the observed effect minus the average predicted placebo effect for each data point.

The PD measurements were averaged according to the following schedule to reduce the disparity between the PK and PD number of measurements (PD measurements were more frequent, ratio≅10:1). For the first 30 minutes after the start of infusion and end of the infusion all PD effects were used; from 30-45 min and from 45-60 min the average was used at the midpoint of the interval; thereafter averages over 30 min intervals were placed at the midpoints until 6 h after the start or after the end of the infusion; thereafter averages over 3 h were used.

Population PK/PD Analysis

For PK/PD modeling, Emax, Hill Equation, Effect Compartment were tested and rejected. Initially, the linear model with E_0 (intercept) and SL (slope) was the only model supported by

the data. This model for the effect of racemic fenoldopam on DBP estimates a 0.7 mmHg decrease in DBP for each ng/mL of racemic fenoldopam (value of 0.7 applies to a patient of 75 Kg). SL was influenced by a patient's body weight, and a patient with body weight "x" Kg had a slope of SL*"x"/75. The slope also changed exponentially with time. The model estimated tolerance to fenoldopam with a half-life of 25 h. So for a 90 Kg patient who achieved 20 ng/ml SS blood concentration(C) the effect could be:

E=9.0 + [0.7*(WT/75)*Exp(-0.028*Time)]*C.

For example, a 90 Kg patient could have his DBP decrease by 25 mmHg after 2 hours of infusion at 3.31mg/hr (0.61 ug/Kg/min).

The linear PK/PD relationship was not very satisfactory from the clinical point of view. This model predicts a 9 mm Hg reduction of diastolic blood pressure at zero concentration (intercept was estimated to be 9.00 mmHg). The sponsor claimed that the high variability of effect at low concentration made it impossible to model the response to any continuous relationship.

While, the firm's explanation was verified by our analysis of the data which was extremely variable and underpowered, the reviewer tried to model the data using different linear and non-linear function (Emax, loglinear, polynomial, parabolic,..). The linear model outperformed all the models that were tested. Segmental linear models were also tried to force the E0 to Zero intercept without much success. The conc/response was, however, best described by a composite of 2 nonlinear functions (Appendix IV for more details). This model argues for a dual effect depending on the concentration.

E=[21*C/(6.31+C) + 2.66*C/(0.13+C)]*WT/75*EXP(-0.0065*TIME)
For the above patient, the predicted decrease of DBP would be 22 mmHg after 2 hours and 19 mmHg after 24 hours. Although, the predictions of the alternative model is very close to the linear model it differs in the following:

1. A net effect of zero at concentration of zero.

2. A much longer tolerance half life. The estimated tolerance t1/2 is about 110 hours which agrees very well with most of the patients' observations.

3. This model may have less bias at the extreme of concentration and effect relationship.

These two PK/PD models are useful, and either could be applied to estimate an initial infusion rate for racemic fenoldopam. Due to the large variability in the PK/PD parameters and the lack of covariates that may explain these variabilites, this model may not be the optimal model for predicting the effect for different patients. This model could serve as a tool for predicting an initial infusion rate which could be adjusted based on the actually observed changes in DBP. These adjustment should be made only after steady state is reached i.e. 20-25 minutes. The short half-life of fenoldopam assures a rapid steady-state and allows for a frequent dose adjustments.

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In conclusion, the clinical implication of the PK/PD anaylsis can be summerazied as follows:

1. Defines the concentration-effect relationship of fenoldopam in mild-moderate hypertensive so that a set of specific instructions can be written for the use of fenoldopam in this population.
2. Determines the appropriate intial dose for patients.
3. The appropriate interval to allow before dosing changes.
4. No lag time between decrease of blood pressure and onset of infusion.
5. The effect at steady state is relatively stable so that during 48-hours of infusion, adequate response remains to distinguish active infusion from placebo.
6. A very mild tolerance to effect may develope. The T1/2 of tolerance to decrease in blood pressure was estimated to be 102 hours.
7. Upon discontinuation of drug there is a rapid decline in serum concentrations of fenoldopam with a corresponding rapid decline in effect. There was no evidence of rebound upon discontinuation of medication.

Summary of Pharmacodynamic and Pharmacokinetic Study of Intravenous Fenoldopam in Emergency Hypertensive Patients: Protocol Number 94-006

Ninety-four patients were enroled in 21 centers. They were randomized to four different initial infusion rates of fenoldopam: 0.01, 0.03, 0.1, and 0.3 µg/kg/min. Upward dose titrations were allowed during the first 4 hours, and upward and downward titrations were permitted thereafter until the scheduled end of the infusion at 24 h.

PK Data

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Certain patients received intravenous fenoldopam as one constant-rate infusion lasting for 24 h; others also received a continuous infusion of fenoldopam but the rate was changed upwards and/or downwards according to therapeutic need. The starting infusion rates were double-blinded and randomized to four rates: 0.01, 0.03, 0.1, and 0.3 µg/kg/min. The attending physicians titrated the infusions blindly. Blood samples for the determination of racemic fenoldopam plasma concentrations were drawn sporadically (2 to 7 samples) during the 24 h infusion at roughly the times 0.5, 1, 4, 8, and 12 h into the infusion. After the end of the infusion, 4 blood samples were drawn in most patients during the first hour. Late samples (24 h to 48 h after the end of the infusion) were also collected, but only few contained measurable plasma concentrations. Concentrations below the limit of quantitation were not set to zero, but were left out instead.

PD Data

Supine diastolic blood pressure measurements (DBP) and also measurements of heart rate during the first hour of fenoldopam infusion were recorded with their time points in the PD data file. After the first hour, hourly averages of usually four measurements were entered in the PD data file. Also the time points of measurements were averaged. The last entry for each patient was determined by the end of PD measurements or by the start of a diuretic or an antihypertensive drug, whichever occurred first. For some patients (n=13), the last PD measurements in the PD data file happened after the end of the fenoldopam infusion. For each listed time point in the PD data file, an individual racemic fenoldopam plasma concentration (CPR) was predicted using the final PK model.

PK model

A one-compartment PK model (ADVAN1 of the NONMEM PREDPP library) was the initial choice. Also a two-compartment PK model (ADVAN3 TRANS3) was tested. The influence of all covariates on the structural PK parameters with interindividual error terms was investigated. Continuous covariate data (COV) were tested in exponential format, Dichotomous covariates were tested in conditional format. The independent variable of the PD model is the individual predicted plasma concentration of fenoldopam (CPR) at the time of the PD measurement (dependent variable); i.e., the time of the diastolic blood pressure. Baseline DBP was not subtracted from the measurements after the start of the infusion, since no placebo data could be collected in this study of hypertensive emergencies. Baseline was instead modeled, and 24 h clock time and a data item on the sleep/wake cycle were tested as covariate information in order to account for possible circadian variations in DBP.

The following model types were tested:

- Average response model
- Linear PD model
- Emax-type PD model

A possible time delay between CPR and reduction in DBP was modeled with a delay factor to account for a gradual loss of effect (tolerance) while CPR was constant. Onset and offset are empiric factors which incorporate temporal changes into the PD relationship with the aim to improve the goodness-of-fit. The influence of continuous and dichotomous covariates on structural parameters with interindividual error was tested using the same relationships which are listed in the paragraph on PK models.

PK Results:

At the end of the univariate search, none of the factors influenced the structural PK parameters

with interindividual error. The final PK model, its individual predictions of racemic fenoldopam plasma concentrations (CPR) at the time points of PD measurements are used as the independent variable in the PD models. The estimated parameter values of the Model are listed in the followingTable .

Population Parameter Estimates Obtained for racemic fenoldpam

(correspondin table for stud. 94-005 on p 2

Parameter		Estimate	95% CI
K:			
θ_1	1/hr	3.64	2.09-4.83
V:			
θ2	L	56.3	31.3-81.3

% Coefficient of Variation (95%C.I.)			
Intersubject Variability:		Residual Variability:	
ω_K	110% (53.1-146%)	σ_1(Exp.)	54.2%(42.0-64.2%)
ω_V	116% (66.9-149%)	σ_2(fixed)	1.41 ng/ml

[a] K stands for the first-order rate constant of elimination of a one-compartment PK model. V stands for the volume of distribution. The variances of random effects are listed as their square roots which express a "percent coefficient of variation", when the error term was exponential, or a "standard deviation" with the units of the parameter whose error is estimated, when the error term was additive. The precision of all parameter estimates of fixed and random effects is presented as a 95% confidence interval which is calculated from the standard error of the estimate.

PD results

Baseline blood pressure was not subtracted but estimated by the PD model. The TIME after the start of the infusion was a factor which was tested before any other covariate information. TIME was used to address the important questions of onset and offset of the reduction in DBP. The influence of covariate data items such as sleep and clock time or body weight was tested on structural model parameters with interindividual error such as baseline (BL) and a potency (C50). As nonwhite patients were predominantly Afro-American, the baseline (BL) estimate reflects more severe hypertension at the start of the infusion in this group of patients. The onset of the effect on DBP is biphasic. An initial rapid decline follows the increase in the fenoldopam plasma concentrations for an average period of 1.9 h. Thereafter, the onset factor continues to reduce the DBP with a half-life of 7.3 h. Simultaneously, the offset factor is building up after the start of the infusion with a half-life of 12.9 h during wake hours and a half-life of 14.5 h during sleep hours. The PD model follows the time course of the actual DBP measurements well. The nadir of the DBP drop is reached between 12 h and 14 h into the constant rate infusion.

Discussion & Conclusion:

The PK analysis of the concentration-time data demonstrates that racemic fenoldopam, is eliminated rapidly with a half-life of 12.0 min and a clearance of about 200 L/h. The PK model had to fit fairly variable concentration-time data which were collected from patients suffering

from hypertensive emergencies. It is likely that a portion of the variability was caused by inaccurate recording of time in this clinical setting where care for the patient had precedence over data collection.

The occurrence of tolerance with a half-life of 12.9 h during wake hours (14.5 h during sleep) diminishes part of the effect. The use of TIME in the current PD models is mainly empiric, and does not elucidate the underlying mechanisms. The onset and offset factors in the final PD model fulfill their role mainly by improving the goodness-of-fit, and they are helpful in the design of an initial dosage regimen. RACE was the only covariate factor which influenced the PD model apart from TIME and sleep. Nonwhite patients, who were predominantly black, had a higher baseline level than white patients. The search for important covariate factors in the PD analysis was not impeded, like the search in the case of the PK analysis, by ill-defined models, and it can be stated unequivocally that body weight, gender, age, and end-organ disease did not influence the concentration-effect relationship of fenoldopam.

The difference in the parameter estimates for the PK/PD model from the previous study (94-005) could be explained by one or more of the following factors:

- Different patients characteristics i.e. emergency HT Vs moderate HT.
- Absence of placebo arm.
- Sparse and sporadic blood sampling.
- The clinical setting for emergency situations mandate care for the patient to take precedence over data collection .
- Inaccurate recording of time for PK or PD response may occur in emergency environment.

The population approach is always recommended for such situations, but successful modeling needs more controlled conditions and accurate recording of measurements. The PK/PD model was useful in delineating that no covariates, including patient weight, influence the PK of fenoldopam; and, only RACE and sleep influence the PD model. In addition, the PK/PD model suggest that an intial infusion rate (10ug/min) which produces an average steady-state of 3 ng/ml should produce an average response of about 5mmHg reduction in SBP. That initial dose could be titrated upwards and downwards as needed.

Dual Effect Population PK/PD

In-house analysis of the data (94-006) using NONMEM was conducted by the reviewer. We, again, found the conc-response was best described by a composite of 2 nonlinear functions.

E=[(Baseline-Ex1)*C*ONSET/(EC501+C) + (Baseline-Ex2)*C/(EC502+C)] *
EXP (-Tol*TIME)

This model argues for a dual effect depending on the concentration. This equation for this model is what would be observed for a system characterized by two operational classes of receptors. The model, also, predicted that tolerance to effect will develop with a half-life of 13 h. This model argues for dual response with one response which is immediate and another that is more gradual in nature.

$$\text{Effect} = \frac{(127-7.93)*\text{Conc}*1-\text{EXP}(-0.284*\text{Time})}{(0.133 + \text{Conc})} + \frac{(127-85.2)*\text{Conc}}{(23.9 + \text{Conc})} \times *(\text{EXP}(-0.0541*\text{Time})$$

Concentration is in units of ng/ml
Time in hours.

Example of the application of the final Model:
For a patient who achieved 20 ng/ml SS blood concentration the effect could be: 21 mmHg. i.e. the patient could have his DBP decreased by 21 mmHg after 1hours of infusion at 3.31mg/hr (0.61 ug/Kg/min). The predictions of this model is very close to the dual effect model devloped for study 94-005 in the mild hypertension study. The major difference between the mild and the emergency HT population lies in the fast development of tolerance in the latter population.

General

Comments ~~to be sent to the sponsor~~:

1. The study design for the main PK/PD study(94-005) was not optimal to establish a definite relationship between plasma concentration and blood pressure. The main reason for that deficiency may be the small number of patients in each treatment group. That was further complicated by the presence of large intersubject variability. The population PK/PD analysis was very valuable, but its success was compromised by the lack of covariates in the modeling and the final selection of the optimal model. The patients demographics could have lessened and explained the high data variability.

2. The Pharmacokinetic section of the label should contain subsections for drug distribution, metabolism, elimination, and special population. The population (average) parameter values should be used in the corresponding sections.

Labeling Comments:

1. In moderately hypertensive patients, The initial recommend dose of 0.24 ug/Kg/min may seem excessive. That dose would produce a blood concentration of 18 ug/L in an average 75 Kg patient. The blood concentration would decrease DBP by over 20 mmHg, using the PK/PD models (linear or nonlinear). It may seem more prudent to start the infusion using a smaller initial dose, e.g. 0.1 ug/Kg/min or less.

2. The maximum recommended dose of 1.67 ug/Kg/min seems also to be excessive in the same population of patients. As a matter of fact, that dose was used in the pilot study (94-

007) and was excluded in the dose range of main PK/PD study. The maximum dose that has been used in mild hypertensive patients(94-005) was 0.8 ug/Kg/min and should be recommended as the maximum tolerated dose.

Specific labeling changes were discussed with the Supervisory medical officer (Avi Karkowski). The changes are attached.

RECOMMENDATION:

This current submission is acceptable provided the requested changes to the proposed labeling are made. The comments should be forwarded to the sponsor.

Ahmed El-Tahtawy, R.Ph., Ph.D.
Pharmacokineticist, Pharmaceutical Evaluation I

FT Initialed by A. Parekh, Ph.D. ---------- Ameeta Parekh 9/25/97
(draft to clinical Division earlier)

CC: NDA 19-922
HFD-110 (McDonald, Karkowski)
HFD-860 (El-Tahtawy, Malinowski, Parekh)
Chron, Drug, Review Files (CDR, B. Murphy, HFD 870).

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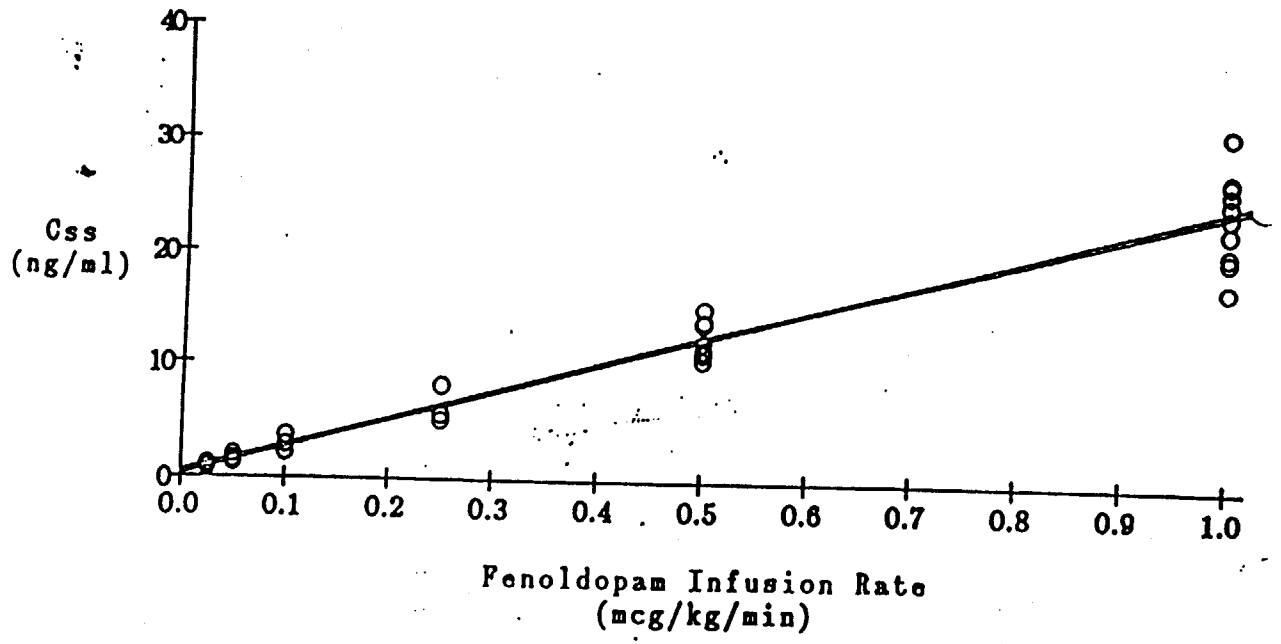
Figure 1

Steady-State Plasma Concentrations of Fenoldopam as a Function of the Fenoldopam Infusion Rate in Healthy Volunteers
Protocols L-34, L-64, A-21

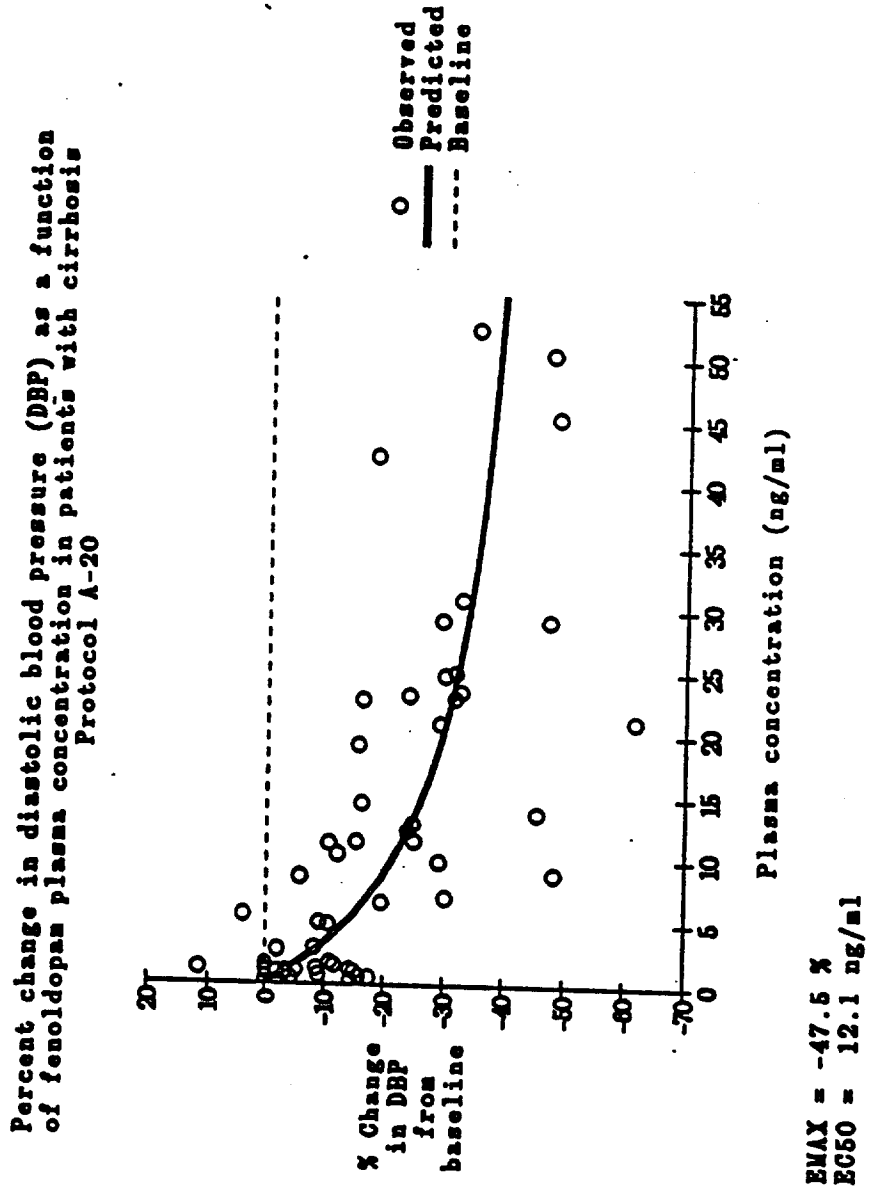


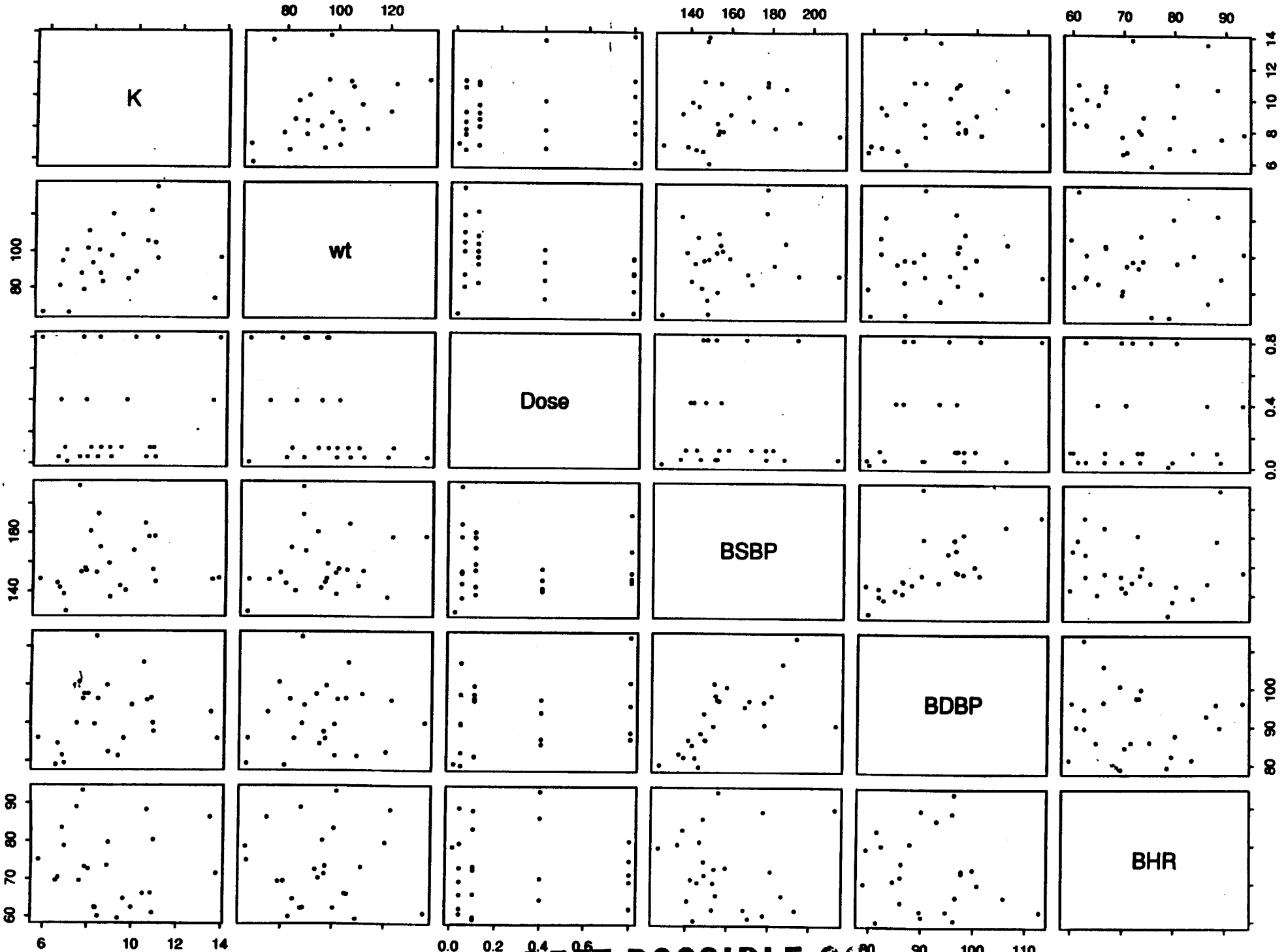
regression line: 24.0*X + 0.38 (R-squared=0.94)

n=36

FIGURE (1)

FIGURE 3





APPENDIX I

A Pharmacodynamic and Pharmacokinetic Study of Intravenous Fenoldopam in Hypertensive Patients

Protocol Number 94-005

A Pharmacodynamic and Pharmacokinetic Study of Intravenous Fenoldopam in Hypertensive Patients

Protocol Number 94-005

PRINCIPAL INVESTIGATORS:

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OBJECTIVE

To define the pharmacokinetic behaviour of fenoldopam infusion.
To determine the relationship between plasma fenoldopam concentrations and blood pressure.
To determine whether the effect is maintained throughout a 48-hour infusion.
To assess recovery and rebound effects.
To establish a dose-response curve.

Study Design:

Multicenter, randomized, placebo-controlled, double-blind study

Washout	Day 1	Day 2	Day 3	Day 4
DBP monitored	24 hrs vehicle-only IV infusion	IV fenoldopam 24 hrs at 0.04, 0.1, 0.4, or 0.8 ug/Kg/min, or placebo	IV fenoldopam 24 hrs at 0.04, 0.1, 0.4, or 0.8 ug/Kg/min, or placebo	24 hours vehicle-only IV infusion

Demographics:

Of the population treated with fenoldopam, 92% was male and 8% was female; 57.7% was Caucasian and 34.6% was Black, 3.8% was Asian and 3.8% was Hispanic; the mean age was 50.4; and the mean weight was 94.9 Kg.

Dosage Regimen:

All patients were to receive a vehicle-only infusion of 5% dextrose in water on Day 1. Patients were to receive infusions of placebo or one of 4 dose levels of fenoldopam for the 48-hour period of Days 2 and 3. A fifth dose level at 0.01 ug/Kg/min was created due to a pharmacy

error for one patient.Thirty-two of the 33 patients who entered the active-treatment phase of the study completed the entire 4-day study period. Seven of the 33 patients received 0.0 ug/Kg/min (placebo), 1 patient received 0.01 ug/Kg/min fenoldopam, 7 patients received 0.04 ug/Kg/min fenoldopam, 7 patients received 0.1 ug/Kg/min fenoldopam, 5 patients received 0.4 ug/Kg/min fenoldopam, and 6 patients received 0.8 ug/Kg/min fenoldopam. Only patient 2007 in the 0.4 ug/Kg/min dose group failed to complete the entire study. This patient discontinued the study on Day 3 (at 31 hours and 48 minutes after initiation of IV fenoldopam) due to inadequate IV access.

Treatments Administered:

On Day 1, patients were administered a 24-hour infusion of vehicle-only solution. Frequent measurements of blood pressure and heart rate were collected and a urine sample was also taken, as well as a 12-lead ECG measurement.

On Day 2 and Day 3 (48 hours total), the infusions of fenoldopam and placebo began. Blood pressure was monitored every 5 minutes for the first hour and then every 15 minutes for the remainder of the 48-hour period. The infusion was to be discontinued if the patient developed intolerable symptoms or if blood pressure fell to levels that were a concern to the investigator(s). Constant-rate, fixed-dose, infusions of IV fenoldopam and placebo continued for 48 hours throughout Days 2 and 3. Blood samples (8 mL each) for plasma fenoldopam concentration were obtained at 0, 5, 10, 20, 30, 45, 60, 120, 180, 240, 300, and 360 minutes after the initiation of drug infusion, and every 6 hours thereafter (12, 18, 24, 30, 36, 42, and 48 hours). The amount of blood drawn during this study was approximately 400 mL per patient.

On Day 4, the fenoldopam and placebo infusions were discontinued. Blood pressures and heart rates were monitored every 5 minutes for the first hour and then every 15 minutes for the remainder of the 24-hour period (Day 4) in which all patients received an infusion of vehicle only.

Protocol Deviations

A total of 3 randomization errors occurred in this study. 2 patients (1002 and 1003 were misrandomized. Patient 1002 was randomized to receive placebo but instead received 0.8 ug/Kg/min, and patient 1003 was randomized to receive 0.4 ug/Kg/min fenoldopam infusion but instead received placebo. A third patient was also misrandomized due to a transcription error by ; patient 3001 was randomized to receive 0.4 ug/Kg/min fenoldopam infusion but instead received 0.04 ug/Kg/min.

A fourth patient (2011 received 0.01 ug/Kg/min fenoldopam instead of the randomization assignment of 0.1 ug/Kg/min due to an error by the pharmacist at the study site. As a result, 5 dose levels of fenoldopam were actually administered in this study, instead of the 4 dose levels specified in the protocol.

The primary efficacy endpoint for this study was to be the changes from baseline (Day 1) in DBP, SBP, and heart rate to those measurements during Infusion Days 2 and 3.

The pharmacodynamic effects were defined as follows:
The pharmacologic effect was defined as a negative change in mean SBP, mean DBP, and a positive change in the mean heart rate when measurements of these same parameters from Day 2 and Day 3 were compared to measurements collected on Day 1.

The pharmacologic tolerance was defined as a positive change in the mean SBP, mean DBP, and a negative change in mean heart rate when these same parameters from Day were compared to measurements collected on Day 2.

The appearance of recovery from the effects of a 48-hour infusion of constant-rate, fixed-dose, IV fenoldopam, was defined as a positive change in mean SBP, mean DBP, and a negative change in mean heart rate when data from Day 4 were compared to measurements of these same parameters collected on Day 3.

The appearance of a rebound effect to the administration of a 48-hour infusion of constant-rate, fixed-dose, IV fenoldopam, was defined as a sustained (30 min), positive change above 30 mmHg in mean SBP, mean DBP, and a negative change below 30 bpm in mean heart rate when measurements from Day 4 were compared to measurements of these same parameters collected on Day 1.

Population Modeling and analysis
Basic Model:
A one compartment open model with first order absorption and elimination from the central compartment was found to best describe the plasma concentration/time data.

The interindividual variability in the pharmacokinetic parameters (K, V) was modeled according to the proportional error model:

$$K_j = \tilde{K}_j * (1+\eta_j^K)$$

where,

K_j = the true value of elimination rate in the jth subject

$\tilde{K}_j$ = the typical value of elimination rate in the jth subject

η_j^K = the difference between the true value of clearance in the jth subject and the predicted value; the η_j^K's are independent, identically distributed statistical errors with a mean of 0 and a variance equal to ω^2_K

The residual variability, representing a composite of model misspecification, assay variability, and intraindividual variability, was modeled as a constant coefficient of variation error model during the infusion and as an additive before and after the infusion

$$C_{pij} = \hat{C}_{pij} + (1 + \varepsilon_{ij})$$

where:

C_{pij} = the true value of the jth plasma concentration in the jth subject.

$\hat{C}_{pij}$ = the ith plasma concentration in the jth subject predicted using the pharmacokinetic model.

ε_{ij} = random variable which represents the difference between the ith measured plasma concentration in the jth subject and the plasma concentration predicted from the pharmacokinetic model; the ε_{ij}'s are independent, identically distributed statistical errors with a mean of 0 and a variance equal to σ^2.

Model Building:

The evaluation of the influence of subject demographic on the pharmacokinetic parameters was performed in 3 steps:

The basic model is selected based on a significant difference in the objective function(OBJ) and by the random pattern of residual plots.

Covariates were plotted against the WRES of the basic model. For each pharmacokinetic parameter, full models were developed by the addition of each of the covariates to the basic model. The additions of significant covariates was done one by one till a full model is reached.

Reduced models were developed by stepwise deletion of each factor from the full model.

The change in the objective function obtained upon addition of all factors to the basic model (difference between the full and basic model) and upon deletion of a factor at a time from the full model (the difference from the reduced model and the full model) was used to assess whether the parameter was associated with a statistically significant improvement in the fit. The objective function is a statistic computed by the NONMEM program that is proportional to minus twice the log likelihood of the data. The difference is asymptotically distributed χ^2 with one degree of freedom when one parameter is deleted from the model, i.e., when a parameter was fixed to zero (the null hypothesis value). The final model will retain only the factors which significantly affect the pharmacokinetic parameters.

Results:
Neither the patients' body weights nor their baseline values in systolic blood pressure, diastolic blood pressure or heart rate influenced any of the kinetic parameters of the PK models of racemic fenoldopam or of the two enantiomers.

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Population Parameter Estimates Obtained for racemic fenoldpam

Parameter		Estimate	95% CI
K:			
θ_1	1/hr	9.05	6.65-11.5
V:			
$\theta 2$	L	17.4	13.2-21.6

% Coefficient of Variation (95%C.I.)

Intersubject Variability:		Residual Variability:	
ω_K	27.4% (14.2-36.1%)	σ_1(Add.)	2.0 ng/ml(0.8-2.6)
ω_V	22.2% (5.2-31.1%)	σ_2(prop.)	23.5% (0.0-33.3%)

The population average $t_{1/2}$ for racemic fenoldpam is 4.6 min.
The population average CL for racemic fenoldpam is 2.6 L/min (V.K).

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Population Parameter Estimates Obtained for R-fenoldpam

Parameter		Estimate	95% CI
K:			
θ_1	1/hr	6.59	5.84-7.33
V:			
θ2	L	61.7	50.2-73.2

% Coefficient of Variation (95%C.I.)			
Intersubject Variability:		Residual Variability:	
ω_V	21.8% (7.48-30.0%)	σ_1(prop.)	19.3% (13.2-23.9%)

The population average $t_{1/2}$ for R-fenoldpam is 6.3 min.
The population average V for R-fenoldpam is 30.9 L (V/2).
The population average CL for R-fenoldpam is 3.39 L/min (V.K/(2)).

Population Parameter Estimates Obtained for S-fenoldpam

Parameter		Estimate	95% CI
K:			
θ_1	1/hr	6.77	5.73-7.81
V:			
θ2	L	34.1	27.6-40.6

% Coefficient of Variation (95%C.I.)			
Intersubject Variability:		Residual Variability:	
ω_V	20.1% (8.83-27.0%)	σ_1(prop.)	19.3% (13.8-23.5%)

The population average $t_{1/2}$ for S-fenoldpam is 6.1 min.
The population average V for S-fenoldpam is 17.1 L (V/2).
The population average CL for S-fenoldpam is 1.92 L/min (V.K/(2)).

The R-enantiomer of fenoldpam exhibited approximately a two-fold increase in volume of distribution than the S-enantiomer. Plasma clearance of R-enantiomer was also higher than that of S-entantimer. The PK paramters in this study were similar to those seen in previous healthy volunteers studies.

Population Parameter Estimates Obtained for simultaneous analysis of racemic fenoldpam and its two metabolites

Parameter		Estimate	95% CI
K12:			
θ_1	1/hr	3.82	2.34-5.30
K20:			
θ_2	1/hr	3.03	2.09-4.00
K13:			
θ_3	1/hr	4.10	2.60-5.60
K30:			
θ_4	1/hr	3.51	1.92-5.10
Vfen:			
θ5	L	16.8	12.0-21.6
Vmet:			
θ6	L	43.1	43.1-72.9

K12, K20, K13, and K30 are the micro rate constants for the metabolism of racemic fenoldpam to 7-methoxyfenoldpam (K12) and to 8-methoxyfenoldpam (K13) and for the elimination (K20 and K30) of the two metabolites.
Vfen, is the volume of distribution for fenoldpam.
Vmet, is the common parameter for the volume of distribution for either of the metabolites.

% Coefficient of Variation (95% C.I.)

Intersubject Variability:		Residual Variability:	
ω_{vfen}	16.9% (3.0-74.9%)	$\sigma_{1(Add.fen)}$	3.48 ng/ml(2.10-4.45)
ω_{vmet}	23.5% (5.7-33.7%)	$\sigma_{2(prop.fen)}$	12.2% (10.3-13.9%)
		$\sigma_{3(prop.7met)}$	25.5% (17.1-31.8%)
		$\sigma_{4(prop.8met)}$	36.2% (31.6-40.2%)

The population average $t_{1/2}$ for 7-methoxyfenoldpam is 10.9 min.
The population average $t_{1/2}$ for 8-methoxyfenoldpam is 10.1 min.
The population average CL for 7-methoxyfenoldpam is 1.1 L/min (Vfen.K12).
The population average CL for 8-methoxyfenoldpam is 1.1 L/min (Vfen.K13).

Pharmacokinetic/Pharmacodynamic:

The FDA reviewers requested the placebo data (7 patients) to be used to calculate an average placebo profile to serve as a baseline for the 25 patients for whom data had been collected after active treatment. The placebo data separated into three 24 h periods was fitted by three

polynomial equations (using NONMEM Version IV) in order to simulate the circadian rhythm. The scatterplot of the raw data and the fitted average curves are shown in Figure 1. The average placebo models for the three PD responses (SBP, DBP, and HR) were used to predict baseline values for all time points at which PD responses were measured in 25 patients receiving active treatment.

The PD responses to be fitted were calculated as the difference of the observed effect minus the average predicted placebo effect which served as baseline with circadian variation. A positive value for the change in SBP and DBP during treatment with fenoldopam indicates a reduction in blood pressure from the predicted baseline value. A positive value for the change in HR indicates an increase in heart rate over the predicted baseline value.

Decrease in Diastolic Blood Pressure Caused by Racemic Fenoldopam

For PK/PD modeling, only the linear model with EO (intercept) and SL (slope) was supported by the data. (Emax, Hill Equation, Effect Compartment were tested and rejected.) The final model for the effect of racemic fenoldopam on DBP estimates a 0.7 mmHg decrease in DBP for each ng/mL of racemic fenoldopam. SL was influenced by a patient's body weight, and the value of 0.7 applies to a patient of 75 Kg. A patient with body weight "x" Kg had a slope of SL*"x"/75. The slope also changed exponentially with time. The model estimated a half-life of 25 h. Of the total decrease in DBP predicted by the model, 9 mmHg (E0) were independent of the plasma concentration of racemic fenoldopam. An interindividual variance for SL could not be determined by the model, but E0 differed between patients with a standard deviation of 9 mmHg. The residual variability of the PD model had a standard deviation of 7 mmHg. The final model is not supported by a valid explanation of the influence of WT on potency of the drug. WT may account for much of the unexplained variabilty in the PK/PD model or it can be an indicator or a surrogate for a missing covariate. A larger study with covariates included in the PK/PD analysis could provide a better answer and explaination.

An alternative population model for the conc/response was attempted by the reviewer. The PK/PD model is best described by a composite of 2 nonlinear functions (Appendix IV for more details). This model argues for a dual effect depending on the concentration.

Population PK/PD Parameter Estimates for Reduction in Diastolic Blood Pressure

Parameter		Estimate	95% CI
E0:			
θ_1	mmHg	9.45	5.86-13.04
Tol:			
θ2	1/h	.0282	0.018-0.038
SL:			
θ3	mmHg/(ng/mL)	.716	0.556-0.876

The slope has a tolerance with a half-life of 25 h.

	% Coefficient of Variability (95% CI)		
	Intersubject Variability:		Residual Variability: SD
ω_{E0}(Add)	8.5 mmHg (5.41-10.75)	σ(Add.)	6.80mmHg(6.20-7.36)

Final Model:
E=E0+[SL*WT/75*EXP(-TOL*TIME)]*CONC

The final model predicts that the potency (SL) of fenoldopam is influenced by the patient's body wt. For example, a 90 Kg. Patient would have a SL of 0.86 mmHg/(ng/mL) instead of 0.716 mmHg/(ng/mL) for a 75 Kg patient.

The final model also, predicts that the slope changed exponentially with time. The model estimated tolerance to fenoldopam with a half-life of 25 h. So for a 90 Kg patient who achieved 20 ng/ml SS blood concentration the effect could be:
9.0 + [0.7*(90/75)*Exp(-0.028*Time)]*20.
For example, a 90 Kg patient could have his DBP decrease by 25 mmHg after 2 hours of infusion at 3.31mg/hr (0.61 ug/Kg/min). After 24 hrs of infusion the patient's DBP may decrease by only 18 mmHg given the blood concentrations remain the same at 20 ng/ml.

The PK/Pd model may be applied to estimate an initial infusion rate for racemic fenoldopam. Due to the large varaibility in the PK/PD parameters and the lack of covariates that may explain these variabilites, this model may not be the optimal model for predicting the effect for different patients. This model could serve as a tool for predicting an initial infusion rate which could be adjusted based on the actually observed changes in DBP. These adjustment should be made only after steady state is reached i.e. 20-25 minutes. The short half-life of fenoldopam assures a rapid steady-state and allows for a frequent dose adjustments

Increase in Heart Rate Caused by Racemic Fenoldopam

The final model for the effect of racemic fenoldopam on HR estimates an increase in HR of 19 bpm when racemic blood concentration is 20 ng/ml (i.e. 1bpm for each ng/mL). This linear PD model with slope, SL, was superior to Emax-type models. Also, an effect compartment was not supported by the data. Neither a patient's body weight, nor sleep, nor the infusion rate influenced SL. The slope was reduced exponentially with time. The model estimated a half-life of 51 h. No portion of the predicted increase in HR was independent of the racemic fenoldopam

concentration. There was considerable interindividual variability in SL, and the model estimated a coefficient of variation of 139%. The residual variability of the PD model had a standard deviation of 9 bpm.

Population PK/PD Parameter Estimates for Reduction in Heart Rate

Parameter		Estimate	95% CI
SL:			
θ1	bpm/(ng/mL)	.993	0.340-1.645
Tol:			
θ2	1/h	.0136	0.018-0.038

The slope has a tolerance with a half-life of 51 h.

	% Coefficient of Variability (95% CI)		
	Intersubject Variability:		Residual Variability:
ω_{sl}	139(58-188)	σ(Add.)	8.80 bpm(7.57-9.88)

Final Model:
E=[SL*EXP(-TOL*TIME)]*CONC

There is no apparent rebound hypertension after the end of the infusion. Patient demographic factors were not investigated, except for body weight, in this small group of 25 patients of whom 23 were male.

Potenial use of the PK/PD model for therapy:

The PK/PD model of DBP and racemic fenoldopam predicts the following:

1. Body wieght did not affect the clearance of fenoldopam and thus should not be used to guide fenoldopam infusion rate selection.

2. To achieve a SS concentration of ≅ 20ng/mL in an average person you may require an infusion of 3.31mg/hr.

3. The potency of fenoldpam decline, with a half-life of about 25 hr.

4. Determination of an initial infusion rate for an average patient to reach a predetermined effect.

5. Large variability in the pharmacologic response may indicate that titration of the infusion rate may be required. Fenoldopam allows fairly frequent adjustments with a minimal interval of 20 minutes, since the short half-life assures that steady-state will be reached rapidly.

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APPENDIX II

METABOLISM OF FENOLDOPAM AND ITS METABOLITES IN HUMAN LIVER MICROSOMES, CYTOSOL AND SLICES

Food and Drug Administration
CDER, OTR, Division of Clinical Pharmacology

Department of Health and Human Services
U.S. Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Rockville, MD 20857

December 6, 1995
Bonnie Horner
Senior Director, Neurex Corporation
Regulatory Affairs
3760 Haven Avenue
Menlo Park, CA 94025-1012

Dear Ms. Horner;

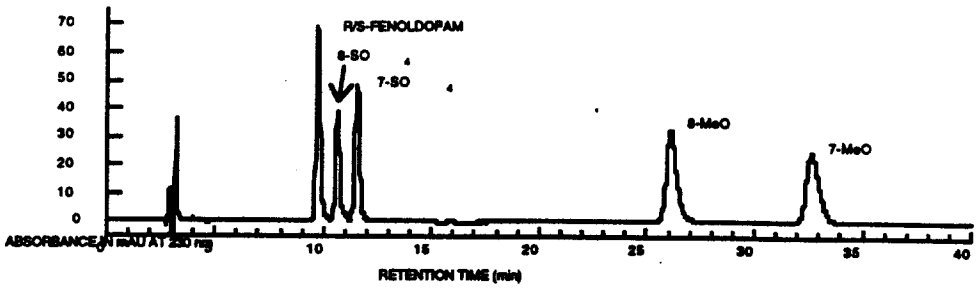
I wanted to let you know that I had the opportunity to perform the first set of experiments with fenoldopam in human liver microsomes, cytosol and fresh slices. Human liver tissue, medically unsuitable for transplantation, was obtained from the Washington Regional Transplant Consortium (WRTC, Washington, DC) or the International Institute for the Advancement of Medicine (IIAM, Exton, PA). R/S-fenoldopam, R-(+) Fenoldopam (R-Fen), S-(-) fenoldopam (S-Fen), fenoldopam-7-sulfate (7-SO4), fenoldopam-8-sulfate (8-SO4), 7-methoxy fenoldopam (7-MeO) and 8-methoxy fenoldopam (8-MeO) were sent to me from Dr. Kevin Ballard of Baylor College of Medicine, Houston, TX. I did not receive the any glucuronidated fenoldopam compounds.

Microsomes and cytosol were prepared by differential centrifugation using standard techniques from liver samples obtained through WRTC. Liver slices were obtained from IIAM. Sample incubations were performed using a NADPH-generating system. I incubated with standard donor species to investigate glucuronidation (uridine 5'-diphosphoglucuronic acid, UDPGA), sulfation (adenosine 3'-phosphate 5'-phosphosulfate, PAPS) and methylation (S-adenosyl-L-methionine, SAM) of fenoldopam.

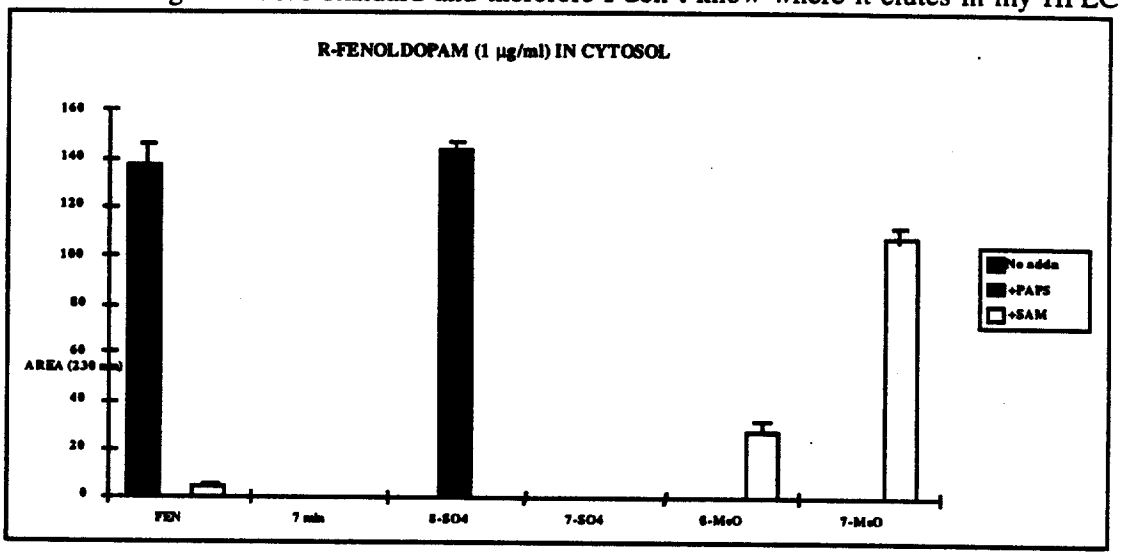
Experiments were performed on single preparations or mixtures of microsomes or cytosols from three human livers. Fenoldopam incubations were 60-70 min and contained 1 or 10 _g/ml fenoldopam. Fresh liver slices were available during the last two months and I incubated liver slices with all the fenoldopam compounds for 60 min.

Incubation samples were extracted by adding 5 to 10 volumes of acetonitrile (containing 1 _l/ml of acetic acid) to 1 volume of sample. The sample was centrifuged at 12,000g for 10 min, and the supernatant was transferred to a separate tube and dried under vacuum. Extracts were analyzed by HPLC.
Chromatogram shows the fenoldopam peaks of interest for the isocratic separation.

Fenoldopam and metabolites were separated on a Zorbax 300SB-C_8 column (4.6 mm x 25 cm) with similar guard column, Mac-Mod Analytical, Inc, Chadds Ford, PA. Flow rate is 1 ml/min of a mobile phase consisting of 9% acetonitrile, 0.1 % trifluoroacetic acid and 0.15% triethylamine, apparent pH 2.5-2.7. The run times were reduced in later experiments by utilizing a linear gradient up to 15% acetonitrile over 20 min. A pilot UV wavelength of 230 nm was used in addition to diode array detection which obtained confirming spectra of the peaks on the fly.



No metabolism mediated by cytochrome P-450 was observed. Most notable is the loss of the R-fenoldopam when the sulfate donor PAPS is added. Smaller losses of each isomer occurred in incubations containing UDPGA and SAM. Disappearance of the parent peak area resulted in the appearance of peaks which eluted with retention times similar to the retention times of the sulfate and methoxy metabolites. No additional peaks were observed after incubation with UDPGA. I don't have a glucuronide standard and therefore I don't know where it elutes in my HPLC system.



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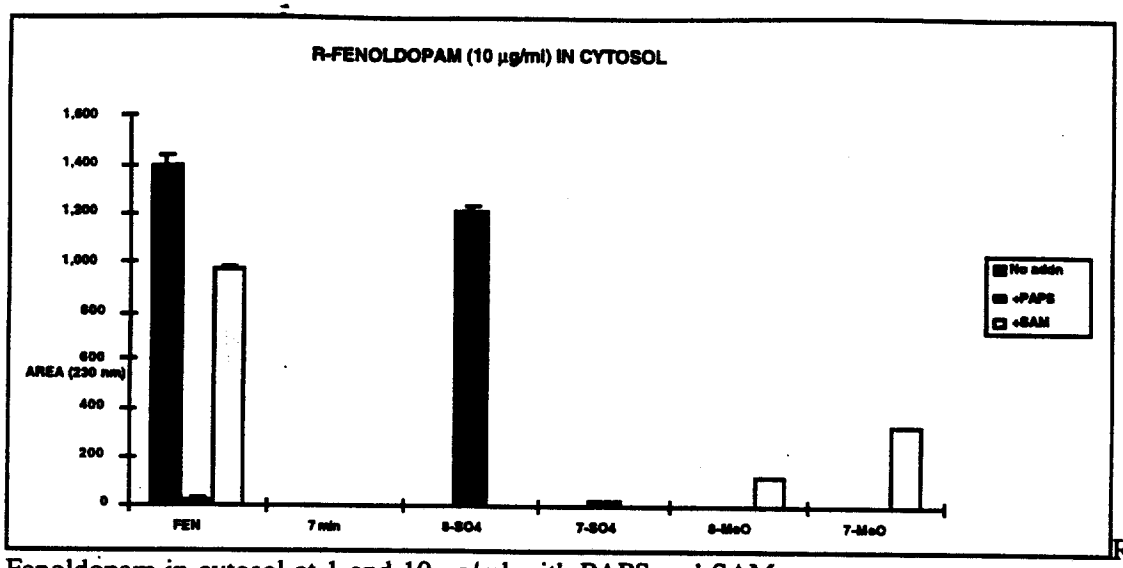
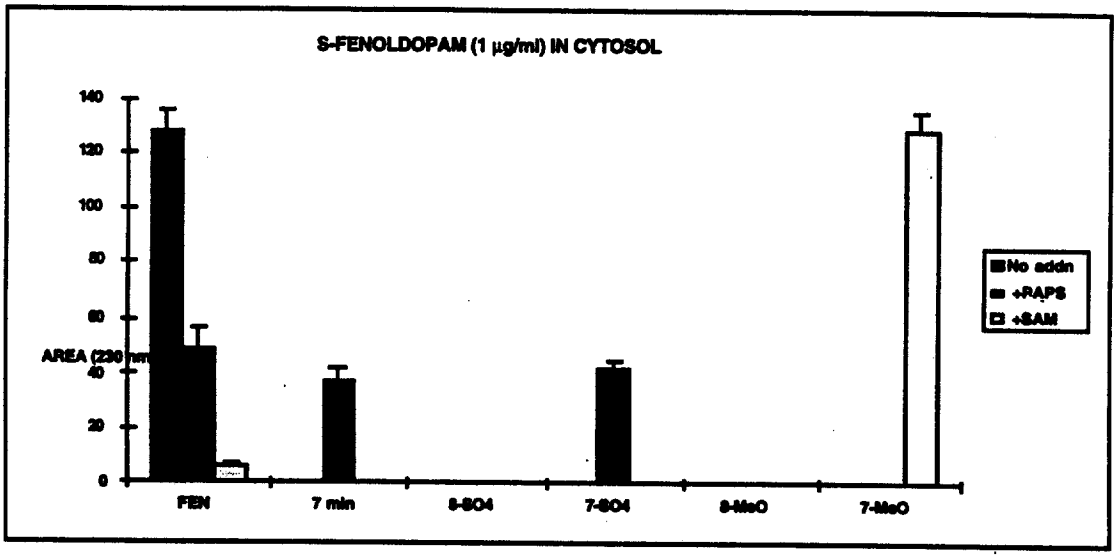
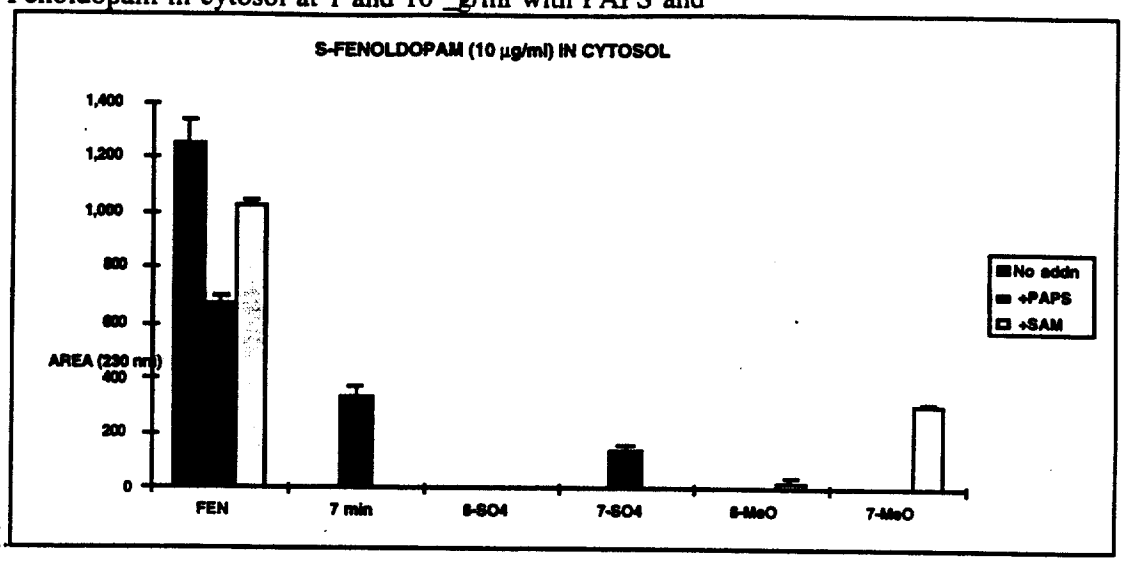


R-(+) Fenoldopam in cytosol at 1 and 10 _g/ml with PAPS and SAM.

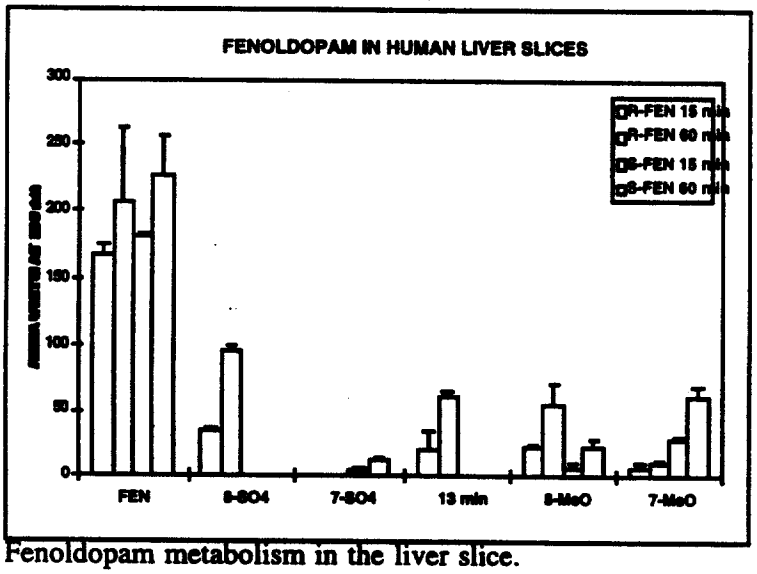
In the absence of cofactors, there was little disappearance of parent after a 60-min incubation of R-fenoldopam at 1 and 10 _g/ml in human liver cytosol. Addition of PAPS to the incubation gave the same pattern of results for both concentrations of R-fenoldopam, i.e., the parent was completely consumed, and the major product formed was the fenoldopam-8-sulfate. With incubation of SAM at 1 _g/ml the parent was completely consumed while at 10 _g/ml about 75% of the parent remained. At both R-fenoldopam concentrations, the proportion of 8-methoxy fenoldopam to 7-methoxy fenoldopam was the same.



S-(-) Fenoldopam in cytosol at 1 and 10 _g/ml with PAPS and SAM



In the absence of cofactors, there was little disappearance of parent after a 60-min incubation of S-fenoldopam at 1 and 10 _g/ml in human liver cytosol. Addition of PAPS to the incubation gave slightly different results for S-fenoldopam compared with R-fenoldopam. Most notable compared to R-fenoldopam was the appearance of the unknown metabolite at 7 min, the presence of fenoldopam-7-sulfate and the complete absence of fenoldopam-8-sulfate. With incubation of SAM at 1 and 10 _g/ml the results were similar to the R-fenoldopam incubation except that the proportion of 8-methoxy fenoldopam to 7-methoxy fenoldopam was smaller.



Fenoldopam metabolism in the liver slice.

There was an increase in the amounts of the parent fenoldopam and fenoldopam metabolites inside the liver slice from 15 to 60 min. As expected from the earlier *in vitro* experiments R-fenoldopam was metabolized to 8-SO4, 8-MeO and 7-MeO. However, the amount of 7-MeO was less than predicted and there was an unknown peak discovered (labeled 13 min) which had a spectrum identical to fenoldopam. Based on chromatographic data, only one of the reference metabolites of fenoldopam (7-MeO) was metabolized during incubation with liver slices. The product of the 7-MeO incubation was found at 13 min.

As expected from the earlier *in vitro* experiments S-fenoldopam was metabolized to 7-SO4, 8-MeO and 7-MeO. Although not shown above, the unknown peak observed at 7 min in the cytosol incubation was also found in the liver slices.

Conclusions:

The above data were obtained from the first set of experiments, and will be replicated. In order to obtain adequate sensitivity, the fenoldopam concentrations used in these experiments were higher than plasma concentrations found in clinical use. Nonetheless, these conditions generated the same products found in vivo, indicating that methylation and sulfation are the dominant metabolic pathways. As with dobutamine and isoproteronol, fenoldopam should not be subject to the inhibitors and inducers seen with cytochrome P-450 enzymes.

I don't have enough evidence of glucuronidation to implicate it as a major pathway. Incubation of fenoldopam in parallel with a positive control for glucuronidation would be useful to confirm experimental technique.
Human liver slices are more representative of the *in vivo* setting and gave similar results as the microsome and cytosol experiments with one unexpected peak which may result from the secondary metabolism of 7-MeO.

It is interesting to note that the pattern of sulfation and methylation is dependent upon which fenoldopam isomer is incubated. With the addition of PAPS to cytosol preparations, R-fenoldopam was only metabolized to fenoldopam-8-sulfate while S-fenoldopam was metabolized to an unknown species (referred to as 7-min peak) and fenoldopam-7-sulfate. With the addition of SAM to cytosol preparations, both stereo isomers produced 8-methoxy and 7-methoxy fenoldopam. However, in the slices R-fenoldopam produced much less 7-MeO than did S-fenoldopam. R-fenoldopam and 7-MeO, in slices, produced an unknown peak at 13 min. It is likely that the 13-min peak results from the secondary metabolism of R-7-methoxy fenoldopam to a yet undetermined product.

Future studies include replication of the above experiments. Donating cofactors will be studied separately as well as in combination to try to obtain an overall metabolic profile. I will attempt a further characterization of the unknown HPLC peaks found in the chromatograms from the liver sample incubations.

The stereochemistry of fenoldopam is interesting as it relates to sulfation and methylation. Eventually, I would like to submit the data for publication with emphasis on the *in vitro* metabolism of fenoldopam in human samples.

I hope you find the data interesting and useful and I look forward to your response regarding the data and future publication.

Ray Klecker
Food and Drug Administration
CDER, OTR, Division of Clinical Pharmacology

cc: Dr. Jerry Collins, FDA
Mr. David Roeder, FDA

Department of Health and Human Services
U.S. Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Rockville, MD 20857

April 1, 1996
Bonnie Horner
Senior Director, Neurex Corporation
Regulatory Affairs
3760 Haven Avenue
Menlo Park, CA 94025-1012

Dear Ms. Horner;

I am updating you on additional experimental work that was performed since I last sent you a report on December 6, 1995. The first report provided results from initial metabolic experiments with fenoldopam in human liver microsomes, cytosol and fresh slices. I replicated the initial findings from human liver cytosol and fresh slices and began experiments to determine the values for Km and Vmax for each of the products produced. I have also used microsomes to explore glucuronidation.

Abbreviations used: R/S-fenoldopam (R/S-FEN), R-(+) fenoldopam (R-FEN), S-(-) fenoldopam (S-FEN), fenoldopam-7-sulfate (7-SO4), fenoldopam-8-sulfate (8-SO4), 7-methoxy fenoldopam (7-MeO) and 8-methoxy fenoldopam (8-MeO), sulfur donor, adenosine 3'-phosphate 5'-phosphosulfate (PAPS), methyl donor S-adenosyl-L-methionine (SAM), glucuronide donor, uridine 5'-diphosphoglucuronic acid (UDPGA) and bovine serum albumin (BSA).

Human liver tissue, medically unsuitable for transplantation, was obtained from the Washington Regional Transplant Consortium (WRTC, Washington, DC) or the International Institute for the Advancement of Medicine (IIAM, Exton, PA). Microsomes and cytosol were prepared by differential centrifugation using standard techniques from liver samples obtained through WRTC. Liver slices were obtained from IIAM and In Vitro Technology, Columbia, MD.

The major pathways of metabolism of fenoldopam were by sulfation, glucuronidation or methylation. The sulfation and methylation occurred at the 7- and 8-hydroxyl positions with additional sulfation suspected to the phenyl-hydroxyl. Glucuronidation probably occurred at the same sites, however, I did not have any glucuronidated standards. The sulfated, glucuronidated and methylated products produced were dependent upon the isomer of fenoldopam used and of course whether a sulfate (PAPS), glucuronide (UDPGA) or methyl (SAM) donor was used. The metabolism process was determined using 10 _g/ml of the methanesulfonate (salt) of R-FEN or S-FEN and was equivalent to 25 _M using the total molecular weight given on the SmithKline Beecham Pharmaceuticals Investigational Use Data Sheet.

Three of the fenoldopam metabolite reference compounds I received, 8-SO4, 7-SO4 and 8-MeO were not metabolized in the presence of PAPS or SAM. However, 7-MeO was metabolized when incubated with the sulfur donor PAPS. I suspect that the R-7-MeO was sulfated at the phenyl-hydroxyl while the S-7-MeO was not. Evidence for the isomer selectivity was provided by incubation with human liver slices described later.

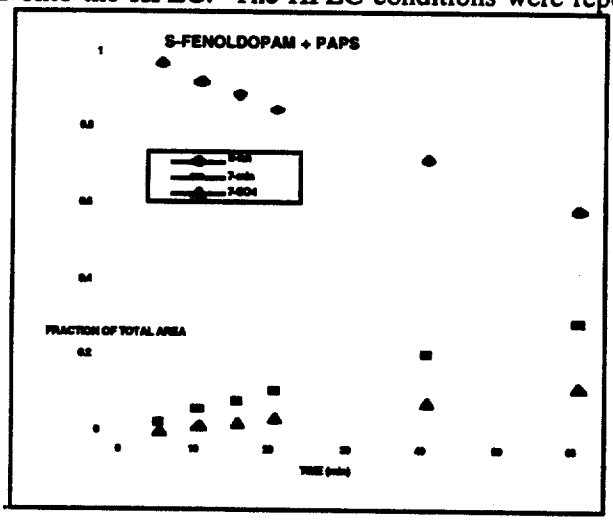
Experimental conditions:
Cytosol Incubations:
Buffer: 100 mM Sodium phosphate,1 mM EDTA, 5 mM MgCl2, pH 7.4
Each sample incubation was performed in buffer at a final volume of 0.25-0.3 ml.

The cytosol fraction of 3 human livers was pooled and each sample incubation contained 0.5 mg cytosolic protein. Drug and donor cofactors were dissolved in 2.25% BSA in buffer resulting in final BSA concentration of 0.45% BSA. Reaction was stopped with addition of 3 ml acetonitrile.

Microsome Incubations:
Buffer: 100 mM Sodium phosphate,1 mM EDTA, 5 mM MgCl2, 2.25% BSA, pH 7.4 UDPGA, 1 mM, was added as the glucuronide donor. Each sample incubation was performed at a final volume of 1 ml for 2 hours in duplicate.

For liver slices:
Two liver slices, 10-15 mg, were incubated in each well containing 0.5 ml Krebs's-Henseleit Buffer with 2.25% BSA, pH 7.5. The reaction was stopped by placing the 24-well plate on ice. Slices were homogenized by adding 200 _l water, extraction beads and providing vigorous vibration using a bead beater. The homogenate was extracted with 1.5 ml acetonitrile containing 1.5 _l acetic acid. Media, 200 _l, from each well was extracted with1.5 ml acetonitrile containing 1.5 _l acetic acid.

Each extract was centrifuged, the supernatant transferred to a second tube and dried under vacuum. The dried extract was dissolved in 50-75 _l of HPLC mobile phase and up to 25 _l was injected onto the HPLC. The HPLC conditions were reported in a previous communication,



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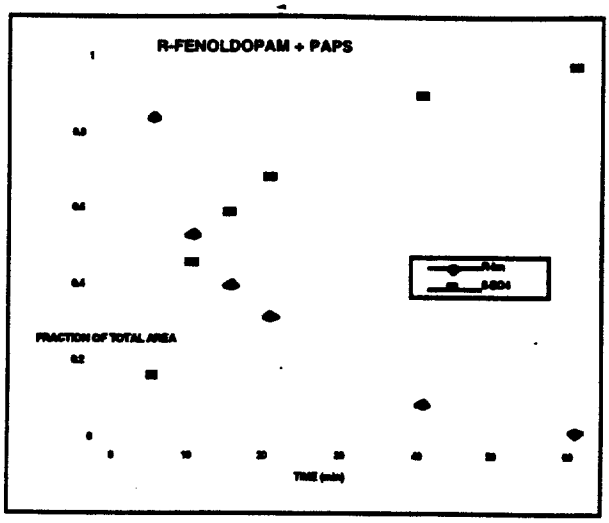

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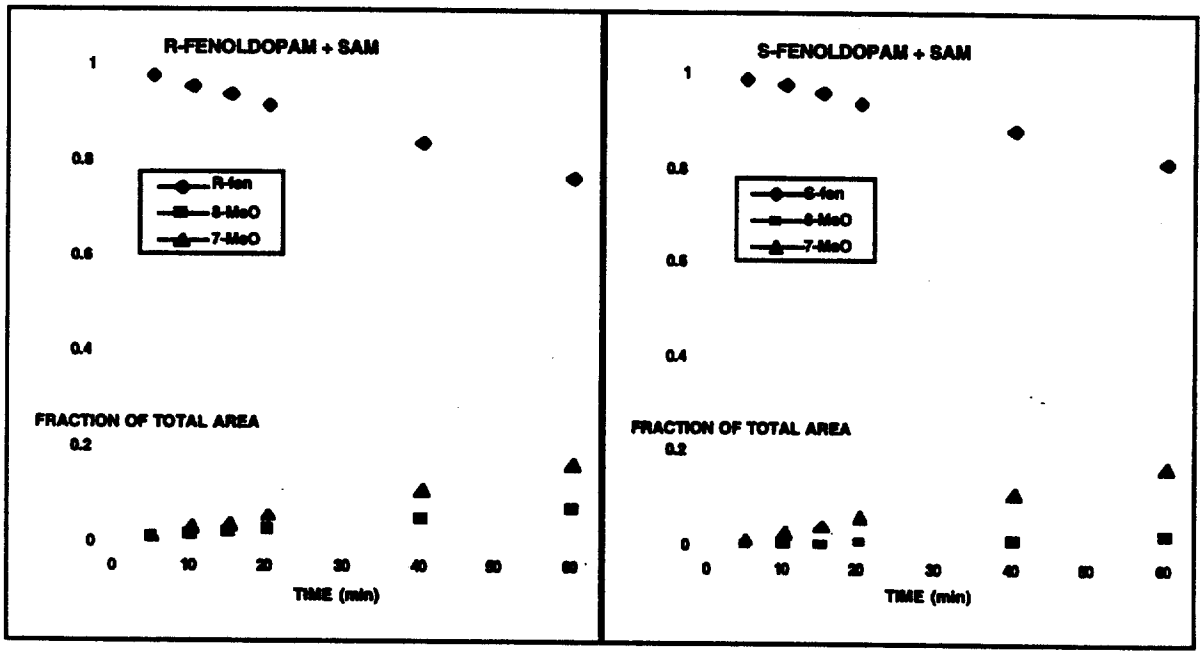
Metabolic incubations were performed in a mixture of the cytosolic preparations from 3 human livers. The rate of sulfation of R-FEN to 8-SO4 was rapid and proceeded to completion within the 60-min incubation, Figure 1. S-FEN was metabolized at a much slower rate to yield 2 products, an unknown peak with retention time of 7 min and 7-SO4, Figure 2. Although I have not identified the 7-min peak, I suspect that the 7-min peak arose from the sulfation of S-FEN at the phenyl-hydroxyl position. The rate of production of both S-FEN products was linear throughout the 60-min incubation.



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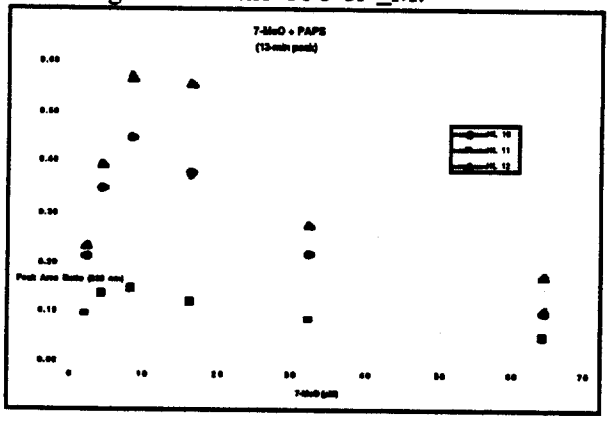
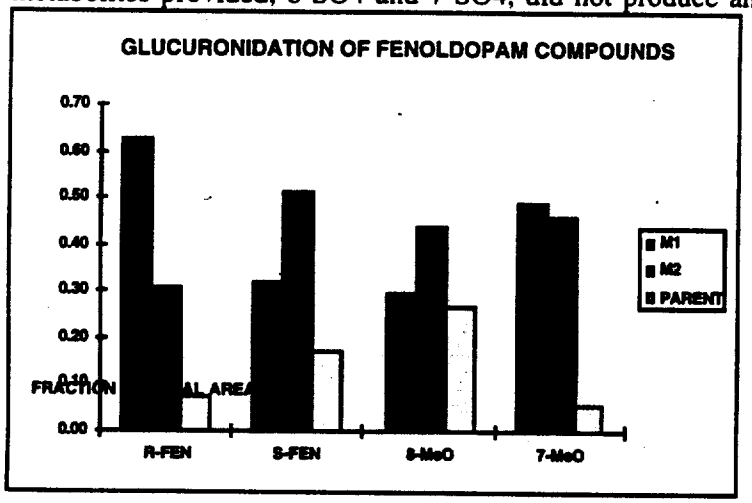
For the cytosol fraction the rate of methylation to the 7-or 8-hydroxyls of each fenoldopam isomer was slower than the rate of sulfation but was linear throughout the 60-min incubation, Figures 3 & 4. Both isomers of fenoldopam produced similar amounts of 7-MeO during the 60-min incubation. The amount of 8-MeO produced during the R-FEN incubation was about half that of 7-MeO while the amount of 8-MeO produced during the S-FEN incubation was only about an eighth of the amount of 7-MeO. These were the only methylated products found as peaks in the HPLC chromatograms.

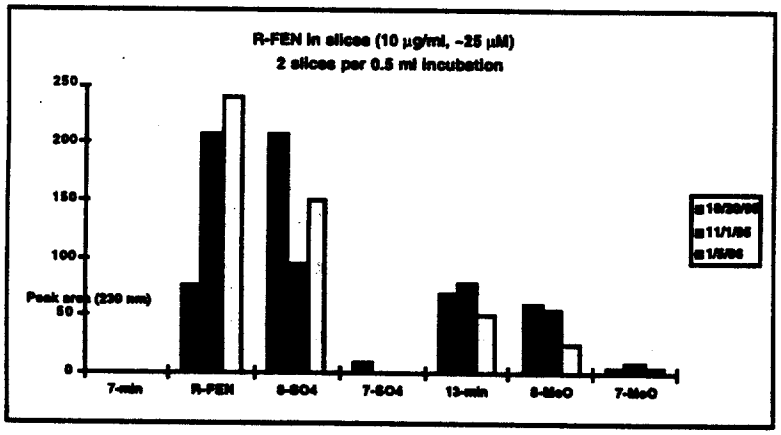
I performed some work toward determining the Km for the sulfated and methylated metabolites of R-FEN and S-FEN. Km determination of each species required optimization of incubation times and concentrations of drug and protein. I was not able to optimize the experimental conditions to my satisfaction and cannot report specific values for Km of each metabolite with certainty. It did appear that the Km for methylation was in the units of _M whereas the Km for sulfation was about 10-fold greater in the 10's of _M.



The 7-MeO reference compound was sulfated in the presence of PAPS, but the reaction kinetics were complex. I obtained unexpected inhibition results relating to the sulfation of 7-MeO (which I assumed to be a racemate of R- and S-7-MeO) for a 10-min incubation, Figure 5. It was speculated from the human liver slice experiments that the rate of sulfation of R-7-MeO was faster than the rate of sulfation of S-7-MeO. A chiral separation would be necessary in determining any isomer preference for sulfation. The inhibitory effect was not observed when a larger amount of enzyme (ie. cytosol) was used in the incubation. Investigation into the inhibition by 7-MeO on the other sulfated products was not attempted.

Recent experiments with duplicate samples have demonstrated glucuronidation of fenoldopam and metabolites. Without BSA in the medium there was little or no glucuronidation. However, with 2% BSA in the incubation medium the glucuronidation of 20 _M substrate was nearly depleted after 2 hours, Figure 6. When glucuronidation occurred it produced two products, M1 and M2, for each substrate. The products, M1 and M2, were different for each substrate. The sulfated metabolites provided, 8-SO4 and 7-SO4, did not produce any glucuronide product.

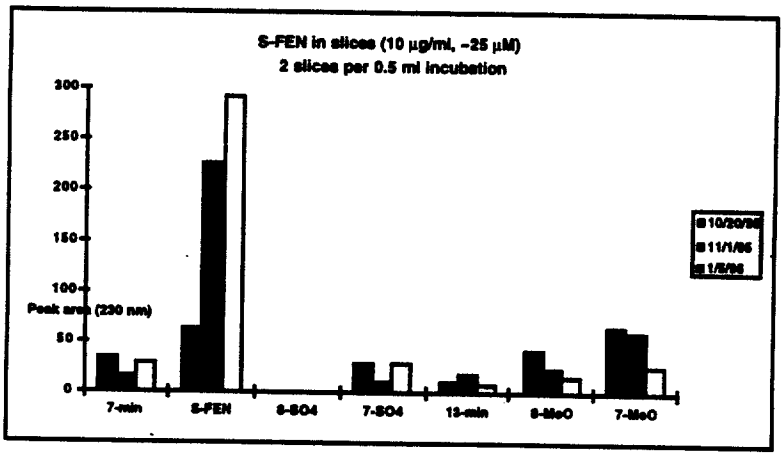




Three human liver slice experiments have been completed to date. The metabolic process required transport of fenoldopam into the slice, metabolism and possible efflux of metabolites out of the slice. The first incubation was exploratory without replicates while the second and third

incubations were performed in triplicate. The metabolic results were qualitatively similar from the slice extracts for all three of the livers, Figures 7 & 8. The metabolism of fenoldopam in liver slice incubations gave the products expected based on the cytosol incubations.

The major product produced during the R-FEN incubation was 8-SO4, Figure 7. Minimal amounts of 7-MeO were produced during the R-FEN incubation while in its place the proposed metabolite of R-7-MeO, the 13-min peak, was produced. The amount of 8-MeO and the 13-min peak produced was about _ amount of the 8-SO4. There were other small peaks eluting early in the HPLC chromatograms that contributed only a few percent of the total area and might have resulted from glucuronidation of fenoldopam or its primary metabolites.



Sulfation of S-FEN in the slices was much slower than R-FEN, Figure 8. There were two sulfated products produced during the incubation, the 7-min peak and 7-SO4. However, the major product produced during the S-FEN incubation was 7-MeO with minimal production of the 13-min peak. There were other small peaks eluting early in the HPLC chromatograms that contributed as much as 10% of the total area and might have resulted from glucuronidation of fenoldopam or it's primary metabolites.

Conclusions:

The metabolic products of fenoldopam observed in the human liver slices correlated well with the expected pattern of metabolic products found in the microsome and cytosol fractions and the limited information from clinical studies.

There was sulfation of R-FEN and S-FEN at different rates and to different products. The sulfation of R-FEN to 8-SO4 was the dominant metabolic route in both cytosol and liver slices. The sulfation of S-FEN to the 7-min peak and 7-SO4 was slower in the liver slices than in the cytosol.

There was methylation of R-FEN and S-FEN at different rates but to similar products. Both fenoldopam isomers produced an equal amount of 7-MeO in the cytosol incubations. The formation 8-MeO from S-FEN was slower than from R-FEN. The pattern of metabolism was similar for slices except in the R-FEN incubations, in which it was presumed that the 7-MeO was further metabolized in the slice to the 13-min peak. The 13-min peak could be produced by incubating 7-MeO (believed to be R/S-7-MeO) with the sulfur donor.

There was glucuronidation of R-FEN and S-FEN in microsomes when 2% BSA was added to the incubation. Peaks in the liver slice experiments eluted with retention times similar to those of the products found in the glucuronide experiments in microsomes. It is likely that these peaks were

glucuronides of the parent drug or primary metabolites. It appeared that the glucuronidation of R-FEN may be only a few percent of the total area in the slice and media while for S-FEN it may be as much as 10% of the total area in the slice and media. Glucuronidation of S-FEN in liver slices proceeded at about the same rate as the sulfation.

The metabolism of fenoldopam in human derived *in vitro* samples has been very interesting. Incubating microsome and cytosol samples with appropriate donating species were good predictors of the metabolic pathways of fenoldopam and to some extent the incubations were predictive of the relative rates of metabolism in an *in vivo* setting such as the liver slices. Incubations of fenoldopam in liver slices produced the same products found clinically. In addition, there were two more products found in the slices that were not identified in patients. It is believed that these were additional conjugations with sulfate.

Although I had hoped to determine the kinetic rates for the different metabolic products of fenoldopam, I have found that it would require a substantial investment of time that I cannot presently afford. A few more replicates are required to complete the loose ends of the project and then I will begin preparing a manuscript for publication. I have not yet identified the audience or journal and do not anticipate that it will include any information that you haven't seen in this communication or the 12/6/95 report.

Ray Klecker
Food and Drug Administration
CDER, OTR, Division of Clinical Pharmacology

cc: Dr. Jerry Collins, FDA
Mr. David Roeder, FDA

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APPENDIX III

ANALYSIS AND STABILITY OF FENOLDOPAM IN PLASMA SAMPLES

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APPENDIX IV

Additional Analysis of Fenoldpam PK/PD data

- Dual Effect Population PK/PD
- Population PK/PD At Steady State
- Simulation of 100 patient's response profiles

Dual Effect Population PK/PD

The initial fit of this data was to a linear model. This model was initially chosen after rejecting Emax, Hill equation, and Effect-Compartment models which did not improve the fit to the pharmacokinetics-pharmacodynamic data.

$$E = 9.0 + [0.7 * weight/75)* Exp(-0.028*Time)]*Concentration$$

This model contains a time dependent factor to account for tolerance. This model, however, was rejected and failed the credibility test of the supervisory medical officer. The relatively large reduction in DBP at zero concentration of fenoldopam was not clinically acceptable.

The linear PK/PD model suggested by the firm reasonably fit the data. Its main advantage was its simplicity and parsimony; on the other hand, its major weakness was the assumption that effect will increase with concentration indefinitely. Additionally, the linear fit estimated an intercept (concentration-independent effect) of 9.0 mmHg.

We tried to model the data using different non-linear function (Emax, loglinear, polynomial, parabolic,..). The linear model outperformed all of these models. The following step was to try segmental models. The two linear segmental model was again outperformed by the linear model. Only, when two nonlinear segmental models were tried we succeeded in fitting the conc-response data. The conc-response was best described by a composite of 2 nonlinear functions.

$$E=[Ex1*C/(EC501+C) + Ex2*C/(EC502+C)\ ]*WT/75*EXP(Tol*TIME)$$

This model argues for a dual effect depending on the concentration. This equation for this model is what would be observed for a system characterized by two operational classes of receptors, one a high affinity-low capacity receptor and the other a high capacity low affinity receptor. The model ,also, predicted that a mild tolerance to effect will develop with a half-life of 102 h. This model finds no lag between concentration and onset of dynamic effects.

$$Effect = \left[\frac{21*Concentration}{(6.31 + Concentration)} + \frac{2.66*Concentration}{(0.13 + Concentration)} \right] \times \frac{(Weight)}{75} * (EXP(-0.0065*Time)$$

Concentration is in units of ng/ml
Weight in Kg
Time in hours.

Population PK/PD Parameter Estimates for Reduction in Diastolic Blood Pressure

Parameter	Estimate	(90% CI)
Ex1:		

θ_1	mmHg	21.0	11.73-30.27
EC501:			
θ_1	ng/ml	6.31	1.86-10.77
Ex2:			
θ_1	mmHg	2.66	-1.20-6.52
EC502:			
θ_1	ng/ml	.13	0.036-0.224
Tol:			
θ2	1/h	0.0065	0.0026-0.0103

% Coefficient of Variability

Intersubject Variability:	SD		Residual Variability:	SD
ω_{Ex1}(Add)	10.34 (5.08-13.72)		σ(Add.)	10.04 (9.03-11.07)

Example of the application of the final Model:
For a 90 Kg patient who achieved 20 ng/ml SS blood concentration the effect could be:
E=[21*20/(6.31+20) + 2.66*20/(0.13+20)]*90/75*EXP(-0.0065*2)

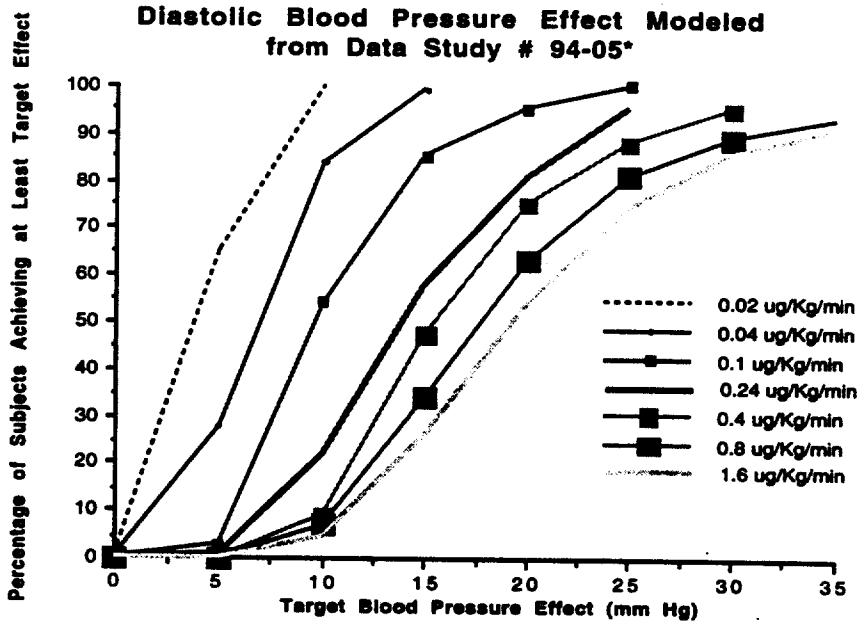
The patient could have his DBP decreased by 22 mmHg after 2 hours of infusion at 3.31mg/hr (0.61 ug/Kg/min). After 24 hrs of infusion the patient's DBP may decrease by only 19 mmHg given the blood concentrations remain the same at 20 ng/ml.

Although, the predictions of the alternative model is very close to the linear model, the C-E curve start at the origin i.e. a net effect of zero at concentration of zero. In addition, The alternative model predicted a much longer tolerance half life. The estimated $t_{1/2}$ for tolerance is about 106 hours which agrees very well with most of the patients' observations.

These two PK/Pd models are useful, and either could be applied to estimate an initial infusion rate for racemic fenoldopam. Due to the large variability in the PK/PD parameters and the lack of covariates that may explain these variabilities, this model may not be the optimal model for predicting the effect for different patients. This model could serve as a tool for

This model could serve as a tool for selecting an initial infusion rate which could be adjusted based on the actually observed changes in DBP. These adjustment should be made only after steady state is reached i.e. 20-25 minutes. The short half-life of fenoldopam assures a rapid steady-state and allows for a frequent dose adjustments.
Based on the population PK/PD model, we can predicted a certain concentration and effect after a given dose. It is also possible to estimate the percentage of the population reaching a specific DBP effect . The PK/PD model presumed a 90 Kg man with reading made at approximately 1 hour. Each curve represent the mean and SD of response for 100 simulated patients at a certain infusion rate of fenoldopam using the population PK/PD dual effect model. The curves with symbols represent infusion actually studied, the doses without symbols are modeled to simulate the minimal effective dose and the maximum tolerated dose. the cumulative probability of patients are shown in the following Table and illustrated in the accompyaing Figure.

As an example, at the infusion rate recommend by the firm (0.24ug/Kg/min) 22%, 58%, and 95% of the patients may achieve a target effect of 10, 15, and 25 mm Hg or less. At 0.04ug/Kg/min, almost all patients will achieve an effect <15 mm Hg, and about 28% will achieve an effect of 5 mmHg or less. 0.02 may be ruled out as the minimal effective dose as 65% of the patients would not even achieve a target effect of 5 mm Hg. Similarly, 1.6 ug/Kg/min should not be recommended as the maximum dose due to lack of gain of effect over 0.8ug/Kg/min, and the increase of reported side effects.



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Corlopam Mesylate (Fenoldopam®) Intravenous Formulation For Hypertension

Cumulative Distribution of Effect (Reduction in DBP), Simulated for 100 Patients/Dose									
Dose ug/kg/min	Average Effect	Effect							
		<5	<10	<15	<20	<25	<30	<40	<45
0.02	5	65 %	100 %						
0.04	6	28 %	84 %	99 %					
0.1	11	3 %	54 %	85 %	95 %				
0.24	15	1 %	22 %	58 %	81 %	95 %			
0.4	17	0 %	9 %	47 %	75 %	88 %	95 %		
0.8	20	0 %	7 %	34 %	63 %	81 %	89 %	97 %	
1.6	22	0 %	5 %	26 %	54 %	74 %	86 %	96 %	98 %

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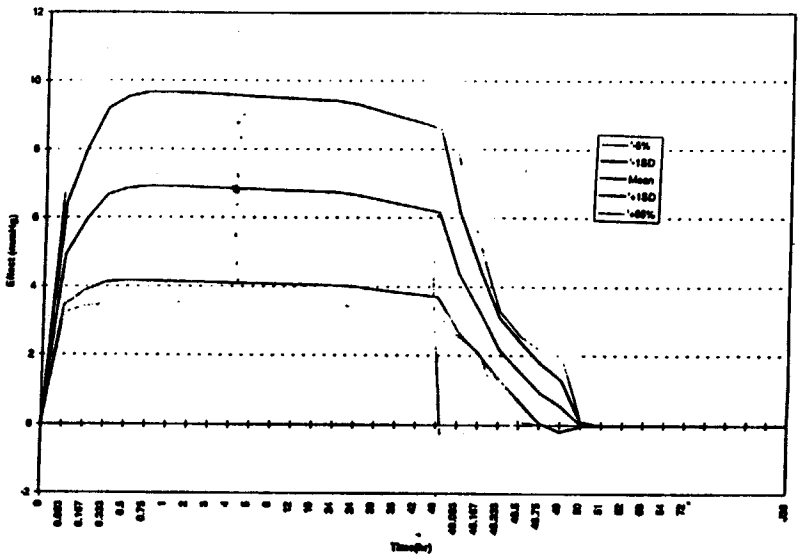
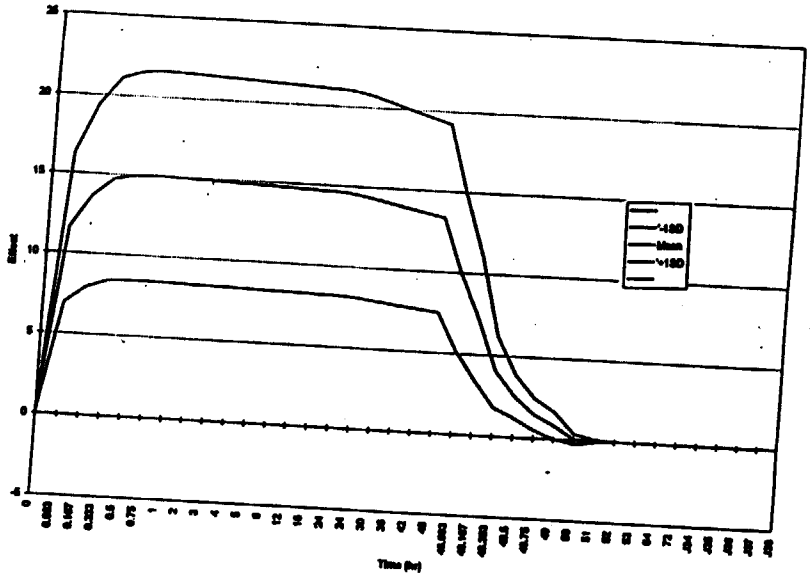
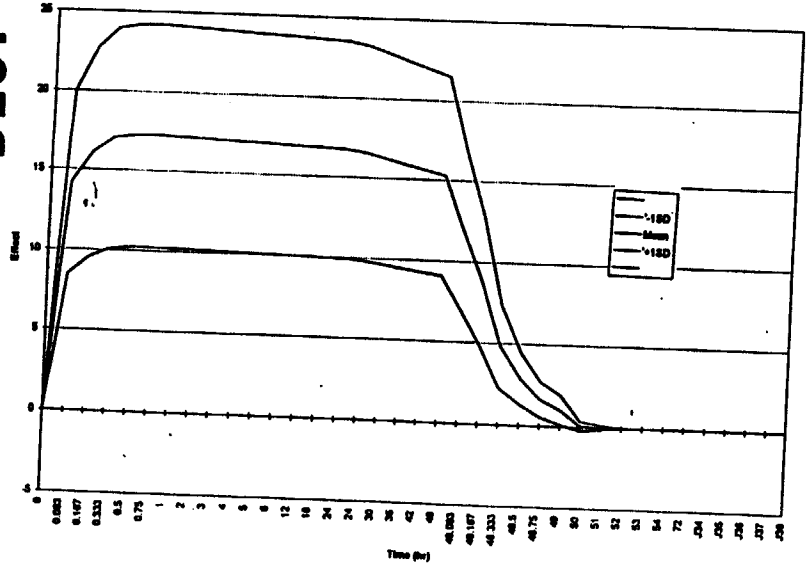
Predicted Diastolic Blood Pressure Effect for 0.04 ug/kg/min



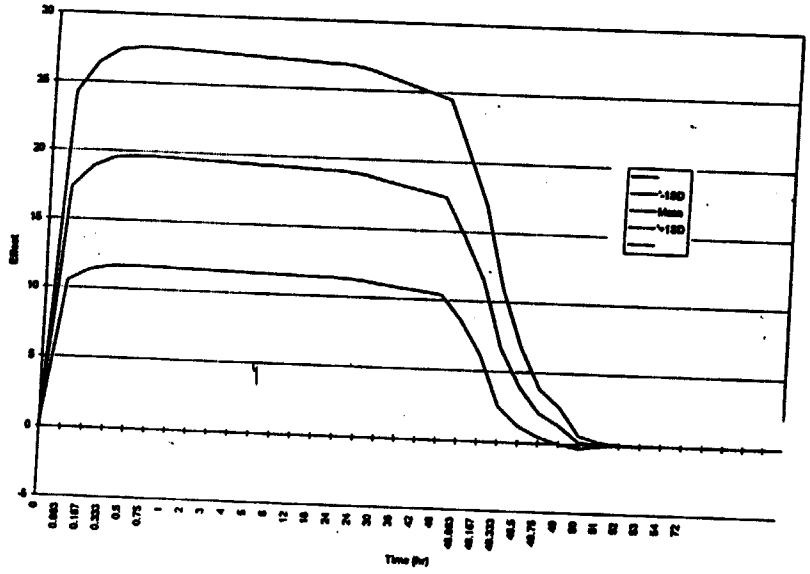
Predicted Diastolic Blood Pressure Effect for 0.24 ug/kg/min



Predicted Diastolic Blood Pressure Effect for 0.4 ug/kg/min



Predicted Diastolic Blood Pressure Effect for 0.8 ug/kg/min



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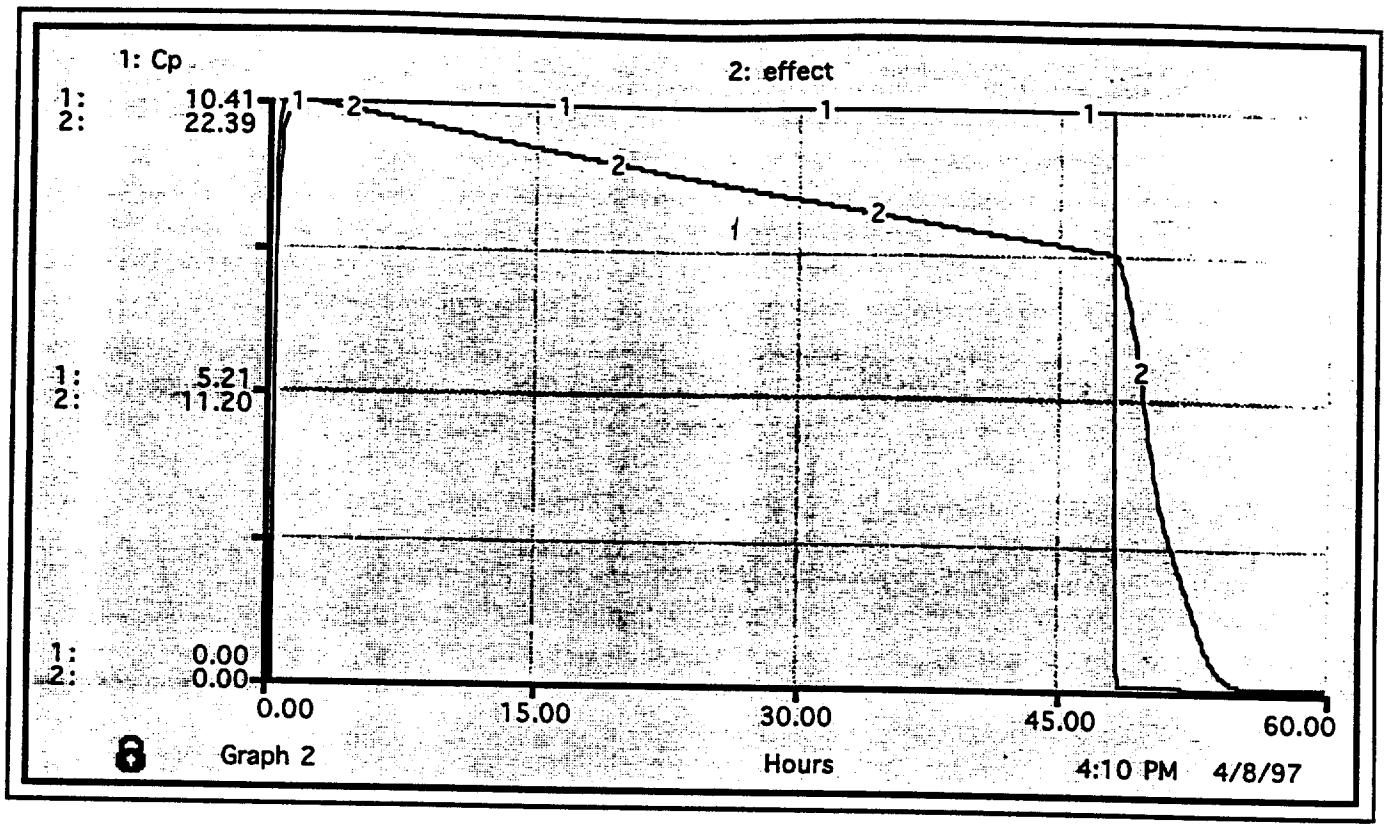

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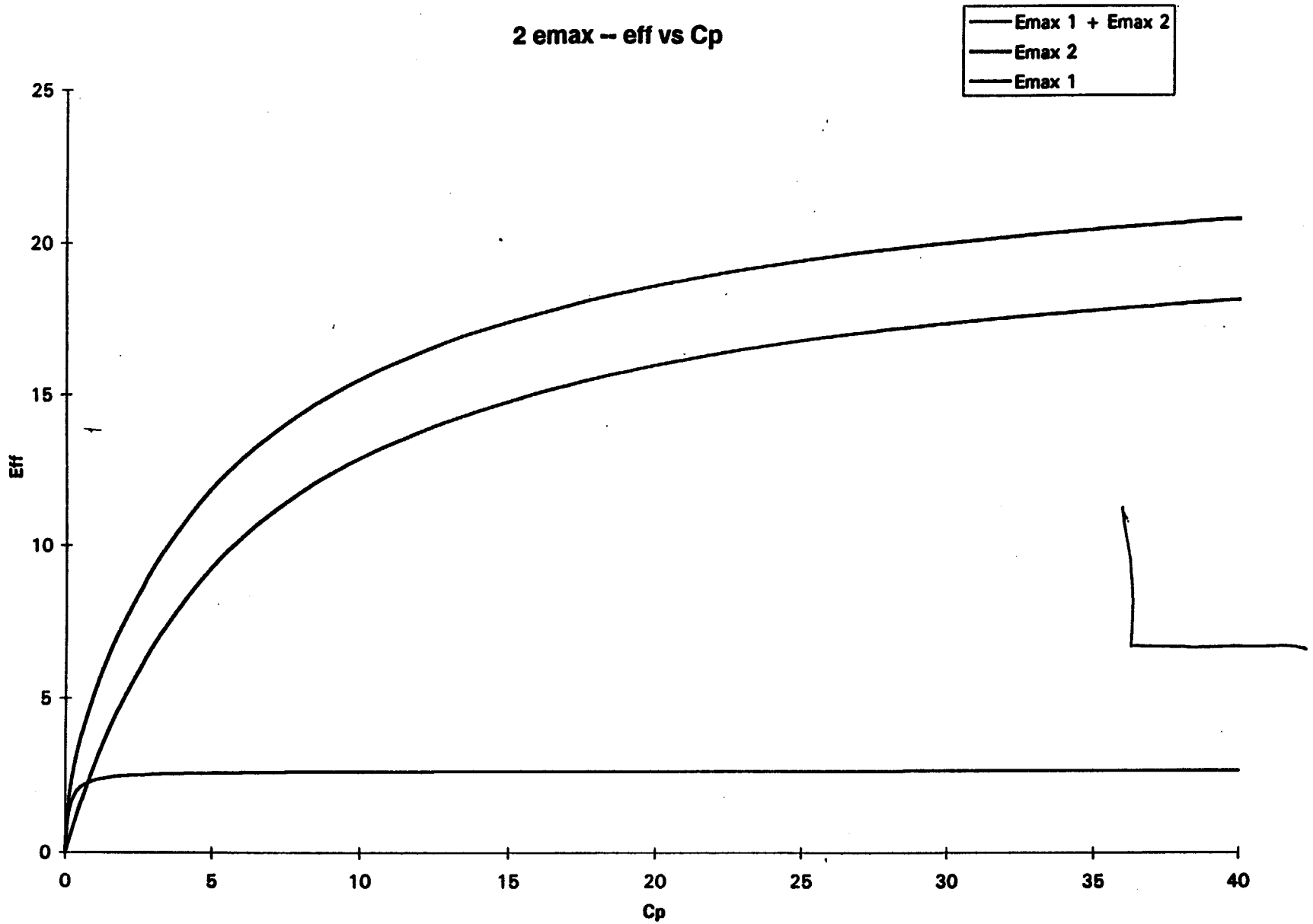
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APPENDIX V

A Pharmacodynamic and Pharmacokinetic Study of Intravenous Fenoldopam in Emergency Hypertensive Patients

Protocol Number 94-006

A Pharmacodynamic and Pharmacokinetic Study of Intravenous Fenoldopam in Hypertensive Patients

Protocol Number 94-006

Ninety-four patients were enroled in 21 centers. They were randomized to four different initial infusion rates of fenoldopam: 0.01, 0.03, 0.1, and 0.3 µg/kg/min. Upward dose titrations were allowed during the first 4 hours, and upward and downward titrations were permitted thereafter until the scheduled end of the infusion at 24 h. Despite a primary clinical endpoint at 4 h into the infusion, the study included all the important design elements of a "Learning Study". It lent itself, therefore, well to the population analysis approach to answer the following questions:

- Do fenoldopam plasma concentrations respond quickly to adjustments of the infusion rate?
- Does the reduction in diastolic blood pressure (DBP) follow suit in these patients with hypertensive emergencies? Is there a time delay between fenoldopam plasma concentrations and the reduction in DBP?
- Under kinetic steady-state of fenoldopam plasma concentrations, does the reduction in DBP remain constant?
- Can covariate factors be identified which influence the dose-concentration and/or the concentration-effect relationship? Do certain patient populations require separate dosing schedules?
- Can dose titrations which are solely guided by the therapeutic outcome (reduction in DBP) lead to the desired therapeutic effect?

PK Data

The infusion rate for the PK analysis (RATE with units mg/h) was calculated from AMT divided by the duration with units h. Certain patients received intravenous fenoldopam as one constant-rate infusion lasting for 24 h; others also received a continuous infusion of fenoldopam but the rate was changed upwards and/or downwards according to therapeutic need. Some patients had up to 11 changes in their infusion rate. These dosing histories were recorded in the data file for the NONMEM PK analysis as precisely as the raw data allowed. The starting infusion rates were double-blinded and randomized to four rates: 0.01, 0.03, 0.1, and 0.3 µg/kg/min. The attending physicians titrated the infusions blindly, indicating to the research pharmacies the factor by which they wanted the infusion rate to change. The pharmacies executed the orders up to a ceiling of 1.2 µg/kg/min prescribed by the protocol. Blood samples for the determination of racemic fenoldopam plasma concentrations were drawn sporadically (2 to 7 samples) during the 24 h infusion at roughly the times 0.5, 1, 4, 8, and 12 h into the infusion. After the end of the infusion, 4 blood samples were drawn in most patients during the first hour. Late samples (24 h to 48 h after the end of the infusion) were also collected, but only

few contained measurable plasma concentrations. Concentrations below the limit of quantitation were not set to zero, but were left out instead.

PD Data
Supine diastolic blood pressure measurements (DBP) and also measurements of heart rate (which were not used in this PD analysis) during the first hour of fenoldopam infusion were recorded with their time points in the PD data file. After the first hour, hourly averages of usually four measurements were entered in the PD data file. Also the time points of measurements were averaged. The last entry for each patient was determined by the end of PD measurements or by the start of a diuretic or an antihypertensive drug, whichever occurred first. For some patients (n=13), the last PD measurements in the PD data file happened after the end of the fenoldopam infusion.

For each listed time point in the PD data file, an individual racemic fenoldopam plasma concentration (CPR) was predicted using the final PK model, the fenoldopam dosing history (from the PK data file), and the optimal individual PK parameters, K_i and V_i .

PK model
Like in the analysis of an earlier study of intravenous fenoldopam (Study 94-005), a one-compartment PK model (ADVAN1 of the NONMEM PREDPP library) was the initial choice. Also a two-compartment PK model (ADVAN3 TRANS3) was tested. In the case of the one-compartment model, interindividual error terms ('s) were attached to the rate constant of elimination (K) and to the volume of distribution (V). In the case of the two-compartment model, 's were estimated for clearance (CL) and the volume of the central compartment (V1). Both exponential and additive residual error terms ('s) were estimated.

The influence of all covariates on the structural PK parameters with interindividual error terms was investigated. Continuous covariate data (COV) were tested in exponential format, Dichotomous covariates were tested in conditional format.

The independent variable of the PD model is the individual predicted plasma concentration of fenoldopam (CPR) at the time of the PD measurement (dependent variable); i.e., the time of the diastolic blood pressure. Baseline DBP was not subtracted from the measurements after the start of the infusion, since no placebo data could be collected in this study of hypertensive emergencies. Baseline was instead modeled, and 24 h clock time and a data item on the sleep/wake cycle were tested as covariate information in order to account for possible circadian variations in DBP.

The following model types were tested:

- Average response model
- Linear PD model
- Emax-type PD model

A possible time delay between CPR and reduction in DBP was modeled with a delay factor to account for a gradual loss of effect (tolerance) while CPR was constant. Onset and offset are empiric factors which incorporate temporal changes into the PD relationship with the aim to improve the goodness-of-fit. These factors are not based on mechanistic insights which this clinical study could not offer. The influence of continuous and dichotomous covariates on structural parameters with interindividual error was tested using the same relationships which are listed in the paragraph on PK models.

PK Results:
At the end of the univariate search, none of the factors influenced the structural PK parameters with interindividual error. The final PK model, its individual predictions of racemic fenoldopam plasma concentrations (CPR) at the time points of PD measurements are used as the independent variable in the PD models. The estimated parameter values of the Model are listed in the followingTable .

Population Parameter Estimates Obtained for racemic fenoldpam

Parameter		Estimate	95% CI
K:			
θ_1	1/hr	3.64	2.09-4.83
V:			
θ2	L	56.3	31.3-81.3

% Coefficient of Variation (95%C.I.)			
Intersubject Variability:		Residual Variability:	
ω_K	110% (53.1-146%)	σ_1(Exp.)	54.2%(42.0-64.2%)
ω_V	116% (66.9-149%)	σ_2(fixed)	1.41 ng/ml

[a] K stands for the first-order rate constant of elimination of a one-compartment PK model. V stands for the volume of distribution. The variances of random effects are listed as their square roots which express a "percent coefficient of variation", when the error term was exponential, or a "standard deviation" with the units of the parameter whose error is estimated, when the error term was additive. The precision of all parameter estimates of fixed and random effects is presented as a 95% confidence interval which is calculated from the standard error of the estimate.

PD results
The aim of the PD analysis was to describe the relationship between the measured diastolic blood pressure (DBP as dependent variable) and the individual predicted plasma concentration of racemic fenoldopam (CPR as independent variable). Both linear and saturable (Emax-type) PD models were considered. Baseline blood pressure was not subtracted but estimated by the PD model. The TIME after the start of the infusion was a factor which was tested before any other covariate information. TIME was used to address the important questions of onset and offset of the reduction in DBP. The influence of covariate data items such as sleep and clock time or body weight was tested on structural model parameters with interindividual error such as baseline (BL) and a potency (C50). As nonwhite patients were predominantly Afro-American, the baseline (BL) estimate reflects more severe hypertension at the start of the infusion in this group of patients. The onset of the effect on DBP is biphasic. An initial rapid decline follows the increase in the fenoldopam plasma concentrations for an average period of 1.9 h. Thereafter, the onset factor continues to reduce the DBP with a half-life of 7.3 h. Simultaneously, the offset factor is building up after the start of the infusion with a half-life of 12.9 h during wake hours and a half-life of 14.5 h during sleep hours. The PD model follows the time course of the actual

DBP measurements well. The nadir of the DBP is reached between 12 h and 14 h into the constant rate infusion.

Discussion & Conclusion:

The PK analysis of the concentration-time data demonstrates that racemic fenoldopam, is eliminated rapidly with a half-life of 12.0 min and a clearance of about 200 L/h. The PK model had to fit fairly variable concentration-time data which were collected from patients suffering from hypertensive emergencies. It is likely that a portion of the variability was caused by inaccurate recording of time in this clinical setting where care for the patient had precedence over data collection. The current PK analysis served two objectives: (I) to provide predicted concentrations for the PD model and (II) to investigate the influence of patient demographic factors and other covariate information on the dose-concentrations relationship. The former objective was achieved by the Bayesian prediction of individual PK parameters. The latter objective is supported by the plots of WRES against each covariate factor. None of the plots displayed, to the naked eye, a trend or tendency. For example, one can safely conclude that body weight does not influence the pharmacokinetics of fenoldopam, and that recommendations for the initial infusion rate in adult patients could be given independent of their body weight.

The concentration-effect relationship of racemic fenoldopam was not independent of temporal factors. The investigation of diurnal factors, as represented in clock time and the wake/sleep cycle, revealed only a weak influence of sleep on the offset factor. Specifically, the baseline estimate of the DBP was not influenced by clock time or sleep. It seemed that hypertensive emergencies treated with fenoldopam in a hospital setting were not influenced by circadian changes. On the other hand, time since start of the infusion had an important impact on the effect of racemic fenoldopam plasma concentrations. The initial, rapid, but partial response, followed by a more gradual onset which leads to the full effect may offer a safety feature for the first 8 h of the infusion. The occurrence of tolerance with a half-life of 12.9 h during wake hours (14.5 h during sleep) diminishes part of the effect. The use of TIME in the current PD models is mainly empiric, and does not elucidate the underlying mechanisms. The onset and offset factors in the final PD model fulfill their role mainly by improving the goodness-of-fit, and they are helpful in the design of an initial dosage regimen. The final PD model should, however, not be extrapolated beyond the limits set by the available data.

RACE was the only covariate factor which influenced the PD model apart from TIME and sleep. Nonwhite patients, who were predominantly black, had a higher baseline level than white patients. The search for important covariate factors in the PD analysis was not impeded, like the search in the case of the PK analysis, by ill-defined models, and it can be stated unequivocally that body weight, gender, age, and end-organ disease did not influence the concentration-effect relationship of fenoldopam.

The potency of racemic fenoldopam plasma concentrations is reflected in the C50 parameter. Now, the question arises whether the design of the clinical study covered the range of active concentrations well. Based on the average PK model, an infusion rate of 10 µg/min (or 0.143 µg/kg/min for a 70 kg patient) would lead to a steady-state concentration of 3.08 ng/mL, the average C50 estimate of the PD model. From a clinical point of view, infusion rates of 0.01 µg/kg/min led to reductions in DBP which were not therapeutic. The large interindividual variability of C50 works against the definition of a standard initial infusion rate which can be effective in reducing DBP to therapeutic levels in all patients. Instead, an initial infusion rate which produces an average steady-state of 3 ng/mL could be recommended, and adjustments could be made as need arises.

The difference in the parameter estimates for the PK/PD model from the previous study (94-005) could be explained by one or more of the following factors:

- Different patients characteristics i.e. emergency HT Vs moderate HT.
- Absence of placebo arm.
- Sparse and sporadic blood sampling.
- The clinical setting for emergency situations mandate care for the patient to take precedence over data collection .
- Inaccurate recording of time for PK or PD response may occur in emergency environment.

The population approach is always recommended for such situations, but successful modeling needs more controlled conditions and accurate recording of measurements. The PK/PD model was useful in delineating that no covariates, including patient weight, influence the PK of fenoldopam; and, only RACE and sleep influence the PD model. In addition, the PK/PD model suggest that an intial infusion rate (10ug/min) which produces an average steady-state of 3 ng/ml should produce an average response of about 5mmHg reduction in SBP. That initial dose could be titrated upwards and downwards as needed.

Dual Effect Population PK/PD

In-house analysis of the data (94-006) using NONMEM was conducted by the reviewer. We, again, found the conc-response was best described by a composite of 2 nonlinear functions.

E=[(Baseline-Ex1)*C*ONSET/(EC501+C) + (Baseline-Ex2)*C/(EC502+C)] * EXP (-Tol*TIME)

This model argues for a dual effect depending on the concentration. This equation for this model is what would be observed for a system characterized by two operational classes of receptors. The model, also, predicted that tolerance to effect will develop with a half-life of 13 h. This model argues for dual response with one response which is immediate and another that is more gradual in nature.

$$\text{Effect} = \left[\frac{(127-7.93)*\text{Conc}}{(0.133+\text{Conc})}*1-\text{EXP}(-0.284*\text{Time}) + \frac{(127-85.2)*\text{Conc}}{(23.9+\text{Conc})}\right] \times *(\text{EXP}(-0.0541*\text{Time})$$

Concentration is in units of ng/ml
Time in hours.

Example of the application of the final Model:
For a patient who achieved 20 ng/ml SS blood concentration the effect could be: 21 mmHg. i.e. the patient could have his DBP decreased by 21 mmHg after 1hours of infusion at 3.31mg/hr (0.61 ug/Kg/min). The predictions of this model is very close to the dual effect model devloped for study 94-005 in the mild hypertension study. The major difference between the mild and the emergency HT population lies in the fast development of tolerance in the latter population.

This model could serve as a tool for selecting an initial infusion rate based on the desired response. The initial infusion rate could be adjusted based on the actually observed changes in DBP. These adjustment should be made only after steady state is reached i.e. 20-25 minutes.

Table 6 Final PD model (Model 18.3)[a]

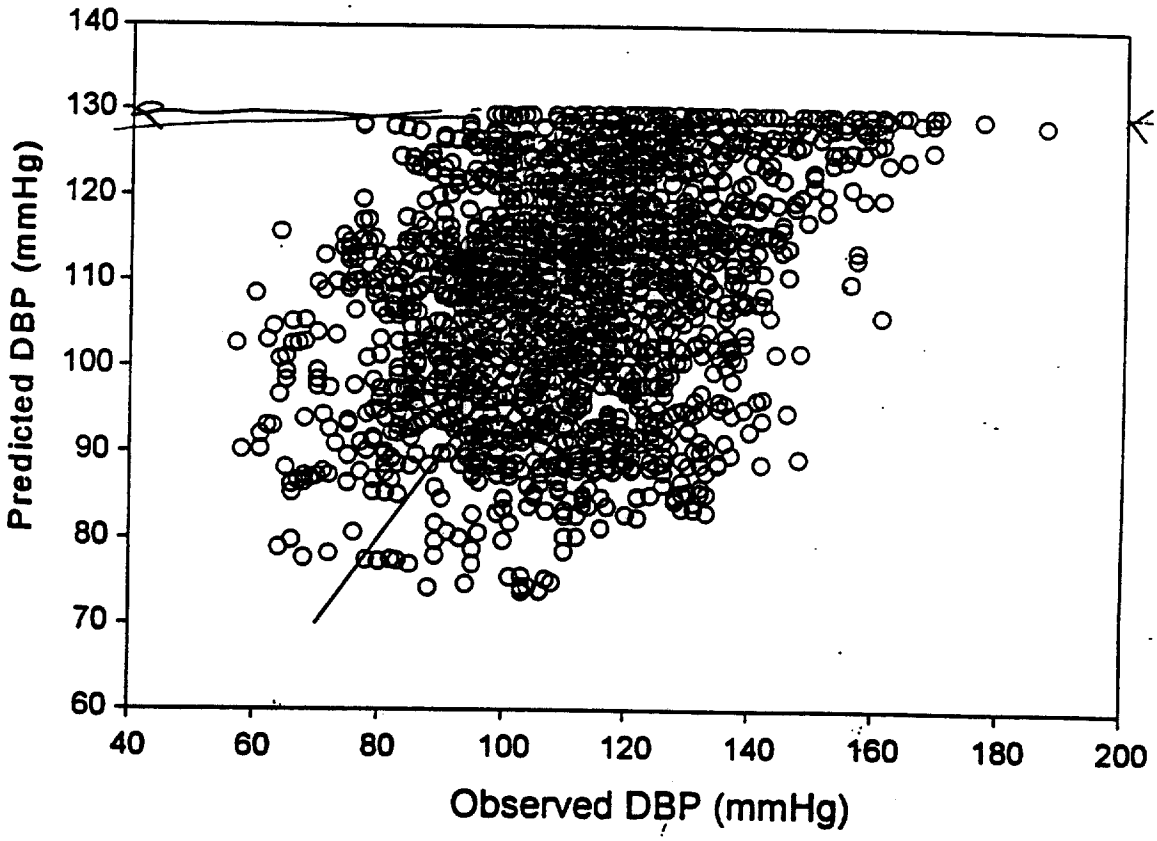
Parameter	Units	Relationship
T1	h	θ_7 for $TIME - \theta_7 < 0$ $TIME$ for $TIME - \theta_7 \geq 0$
ONS	-	$1 - EXP(-\theta_4 \cdot T1)$
K_{off}	1/h	$\begin{pmatrix} \theta_5 \text{ for wake hours} \\ \theta_6 \text{ for sleep hours} \end{pmatrix} \cdot EXP(\eta_3)$
OFF	-	$EXP(-K_{off} \cdot TIME)$
BL	mmHg	$\begin{pmatrix} \theta_1 \text{ for whites} \\ \theta_2 \text{ for nonwhites} \end{pmatrix} \cdot EXP(\eta_1)$
C50	ng/mL	$\theta_3 \cdot EXP(\eta_2)$
EFF	mmHg	$BL \cdot ONS \cdot OFF \cdot \frac{CPR}{C50 + CPR}$
$\hat{E}$	mmHg	$BL - EFF$
E	mmHg	$\hat{E} + \epsilon$

Parameter	θ_1	θ_2	θ_3	θ_4
Estimate	117	130	3.08	0.0955
95% C.I.	109 to 125	126 to 134	1.43 to 4.73	0.0803 to 0.111
Parameter	θ_5	θ_6	θ_7	ω_1^2
Estimate	0.0537	0.0479	1.88	11.5%
95% C.I.	0.0411 to 0.0663	0.0353 to 0.0605	1.55 to 2.21	9.23% to 13.4%
Parameter	ω_2^2	ω_3^2	σ^2	
Estimate	175%	77.8%	8.3 mmHg	
95% C.I.	132% to 210%	48.4% to 98.9%	7.7 mmHg to 8.9 mmHg	

[a] ONS stands for the factor governing the onset of the effect of racemic fenoldopam on the diastolic blood pressure (DBP). OFF denotes the factor for the offset or tolerance. BL stands for the baseline DBP, and C50 is the concentration of racemic fenoldopam which causes half-maximal effect. At a given TIME and concentration (CPR, the individual prediction of the final PK model, Model 1.30), BL is reduced to a certain degree (EFF). The model-predicted and the observed DBP are denoted as $\hat{E}$ and as E, respectively. Structural

arameters or "fixed effects" are denoted as θ. Interindividual "random effects" are represented as η's; their ariance, ω^2, is estimated. Also the variance, σ^2, of the residual "random effect", ϵ, is estimated. The ariances of random effects are listed as their square roots which express a "percent coefficient of variation", hen the error term was exponential, or a "standard deviation" with the units of the parameter whose error is stimated, when the error term was additive. The precision of all parameter estimates of fixed and random ffects is presented as a 95% confidence interval which is calculated from the standard error of the estimation.

igure 4 Scatterplot for goodness-of-fit of final PD model (Model 18.3). The predicted DBP of the ordinate are the average predicted diastolic blood pressures of Model 18.3 with all random variables set to their population mean; i.e., zero. The observed DBP stem from the DV data item of the data file, `fen_6_05.txt`, used in this PD analysis. The line of identity is included in the graph.



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NDA 19-922

SUBMISSION DATE: Dece...

Fenoldopam (Corlopam®)
10 mg/mL vials IV

REVIEWER: Suresh Mallikaarjun, Ph.D.

TYPE OF SUBMISSION: Original NME

SYNOPSIS: The sponsor has studied the pharmacokinetics of fenoldopam in normal and hypertensive patients, the metabolism and excretion of the drug, and has examined the dose proportionality of fenoldopam to include the dosing range covered in the proposed package insert. Acceptable studies have been performed in renal impairment, hepatic impairment and CHF patients. Although the sponsor did provide information regarding pharmacokinetic-pharmacodynamic (PK-PD) relationships in patients with hepatic impairment, no information has been submitted on PK-PD relationships in normal or hypertensive patients.

The major concern with this NDA is that the sponsor has not provided study validation information for any of the studies submitted to the Division of Biopharmaceutics.

RECOMMENDATION:

The NDA 19-922 for fenoldopam (Corlopam®) is not acceptable for meeting the requirements of the Division of Biopharmaceutics, due to lack of assay validation information (See Deficiency 1).

Please convey the Recommendation, Deficiency, and Comments 1-8 to the sponsor.

TABLE OF CONTENTS:

Appendix I (Study Summaries)

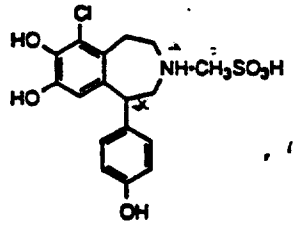
Appendix II:

Note: Appendix II contains more detailed data/information such as dosage formulation, demographic data, individual subject data and pharmacodynamic data. This information is being retained in the Division of Biopharmaceutics, and can be obtained upon request.

Abbreviations:

CV - Coefficient of variation
AUC - Area under the curve from 0 to ∞

BACKGROUND: Fenoldopam is a benzazepine compound with the following structure:



It is a selective postsynaptic dopaminergic (DA_1) receptor agonist and has minimal activity at α- or ß- adrenergic (DA_2) receptors. It is a rapid-acting vasodilator and is proposed to be used in the treatment of hypertension.

Proposed Dosing: The initial dose is 0.1 μg/kg/min by IV infusion, which can be titrated upwards as needed by 0.1 μg increments until an appropriate blood pressure is achieved. Dosage may be adjusted as often as every 10 minutes, depending on the patients clinical status and the urgency of the situation. For most patients, titration to a dosage of 0.1 to 0.4 μg/kg/min produces the target blood pressure.

SUMMARY OF BIOAVAILABILITY/PHARMACOKINETICS/PHARMACODYNAMICS:

I. BIOAVAILABILITY/BIOEQUIVALENCE:

Not applicable, since the product is intended to be administered intravenously.

II. PHARMACOKINETICS:

A. Normal Subjects: Following a 1 μg/kg/min infusion for 2 hours to 12 healthy volunteers (Study A-21 UK), the mean Cmax was 25.9 ng/ml (C.V. 16%), the mean clearance 41.5 ml/min/kg (C.V. 17%), the mean VD_{ss} 499.5 ml/kg (C.V. 24%). On compartmental analysis, the mean α half-life was 6 minutes, with 97% of the AUC described by this phase, and the ß half-life was 60 minutes with 3% of the AUC described by this phase. The protein binding was approximately 88%

B. Hypertensive Patients: In study L-36, 21 patients with hypertension were given successive infusions every 15 minutes from 0.025 to 1.5 μg/kg/min. The mean concentrations at the end of the 0.1 and 0.5 μg/kg/min infusions were 3.52 and 15.52 ng/ml. In the same study, 9 hypertensive patients were administered single doses of 0.25, and 0.375 μg/kg/min, and the mean clearances were 29.8 and 29.6 ml/min/kg respectively (mean C.V. 23%); the mean Css were 8.53 and 13.87 ng/ml respectively (mean C.V. 28%). The clearance values were lower than that observed in other studies.

Variability in PK Parameters: The variability, estimated by the %C.V., for clearance ranged from 15 to 35%, and for Cmax ranged from 16 to 28%.

III. METABOLISM: Four subjects received 3.2 to 4.2 mg IV doses of ^{14}C labeled fenoldopam over 30 minutes in study UK/01/07. The recovery was complete, with 89% of the dose recovered in the urine, and 11% in the feces. The metabolites identified in the urine were the 7-methoxy conjugates (sulfate + glucuronide) (11%), 8-methoxy conjugates (17.4%), and fenoldopam conjugates (17.2%). Overall, fenoldopam was extensively metabolized with only about 4-6% of the dose being recovered as unchanged drug (UK/01/07, A-21/UK).

IV. DOSE AND DOSAGE FORM PROPORTIONALITY: On administration of 3 single doses between 0.025-0.5 μg/kg/min in a crossover manner to three normal volunteers (L-34), the Css appeared to be proportional to the dose. However, the small sample size precluded any definitive conclusions on dose proportionality from this study. The sponsor pooled the data from studies A-21, L-34 and L-64 (study L-64 was not submitted to the Div. of

Biopharm.), and the plot of Css against rate of infusion appeared to indicate linearity between 0.025 to 1.0 μg/kg/min (Fig. 1).
In Study L-36 with hypertensive patients, the sponsor submitted a plot of plasma concentrations versus infusion rate (Fig. 2), which appeared to indicate a linear relationship. However, the sponsor needs to perform statistical analyses on the two data sets to conclude dose proportionality of fenoldopam (See Comment 1).

V. SPECIAL POPULATIONS:

A. Renal Impairment (CAPD): Eight patients undergoing peritoneal dialysis (Study A-35) were administered IV infusions of 0.1 μg/kg/min for 30 minutes followed by 0.2 μg/kg/min for 4½ hours. The mean Css was after 0.1 and 0.2 μg/min/kg infusions were 2.8, and 4.8 ng/ml respectively. The clearance values reported by the sponsor were incorrect and the mean clearances calculated by the reviewer are 41.7and 36.9 ml/min/kg after 0.1 and 0.2 μg/kg/min infusions (See Comment 6). The mean ratio of dialysate to plasma concentration was 0.14, which indicates only a small fraction of the drug is cleared by CAPD.

B. Hepatic Impairment: The results of study L-51 indicated that the mean clearance in 7 hepatically impaired patients after administration of either 0.1 or 0.2 μg/kg/min of fenoldopam for 5 hours, was 44.6 ml/min/kg (C.V. 20%), a value very similar to that observed in normal subjects (41.5 ml/min/kg from Study A-21 UK).
Study A-20 had 12 hepatically impaired patients who were administered 4 successive infusions between 0.05 to 1.6 μg/kg/min spaced 30 minutes apart. The clearances calculated after each infusion were much greater than the other studies, 47-64 ml/min/kg, and this may be due to the short interval (30 minutes) between infusions, leading to nonachievement of steady state for each infusion rate (See Comment A).

C. Congestive heart failure: The mean clearance in 15 CHF patients (Study L-47) was 40.93 ml/min/kg (C.V. 28%), which is similar to clearance in normal healthy volunteers. The individual clearance values and plasma concentrations submitted were illegible and could not be confirmed (See Comment 5).

VI. DRUG INTERACTIONS:

No studies were submitted with reference to drug interactions.

VII. PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS: The sponsor examined the relationship between plasma concentrations and systolic BP, diastolic BP, and heart rate in hepatically impaired patients (Study A-20). The Emax and EC_{50} for the parameters are listed below:

	Systolic BP	Diastolic BP	Heart Rate
EMAX (%)	-41.7 ± 10.1	-47.5 ± 8.7	22.9 ± 3.0
EC_{50} (ng/ml)	20.0 ± 10.1	12.1 ± 5.6	2.76 ± 1.54

EMAX(%) - Percent reduction from baseline.

Although the sponsor submitted PK-PD data in hypertensive patients with no hepatic impairment, no analysis of PK-PD relationships was provided. Dr. Cheryl Graham, Deputy Director, Cardio-Renal Drug Products informed this reviewer that analysis of the PK/PD data on hypertensive patients was not necessary at this stage, since the sponsor had not provided PD data in patients on placebo. However, if in the future PK-PD information is required, the analysis can be performed, since the data will be retained in the Division of Biopharmaeutics.

The PK/PD data submitted by the sponsor is provided in Attachment II.

VIII. FORMULATION: See Appendix II.

IX. DISSOLUTION: Not applicable - IV dosage form.

X. ASSAY: In Vol 1.62 details of the pre-study validation are provided for

GENERAL COMMENTS (Need not be sent to the firm):

A. Linear regression of clearance as a function of the infusion rate in study A-20, indicated a decrease in clearance with increasing infusion rate. The mean clearance at the lowest and highest rates were 63.72 and 46.55 ml/min/kg respectively. However this decline was not apparent in the clearance data from other studies. Also, the calculation of the clearance may be flawed. The equation for IV infusion is:

$$C_t = \frac{k_0}{VK}(1-e^{-kt}) \qquad (1)$$

$$\frac{k_0}{C_t} = \frac{VK}{(1-e^{-kt})} = \frac{Cl_s}{(1-e^{-kt})} \qquad (2)$$

If steady state after IV infusion was not achieved by 30 minutes (duration of infusion), the use of the equation, Cls = k0/C_{ss}, to calculate clearance would be incorrect. When half-lives greater than 6 minutes (the normal half-life) were substituted in equation (2), higher values of clearances were obtained (higher than normal), which were observed in the study.

B. The clearances observed across studies were not very different and were approximately between 40 to 50 ml/min/kg. However the clearances in hypertensive patients were lower and were around 29 ml/min/kg.

C. On Day 1 in Study L-36, although the sponsor claims that the sample at 15 minutes represents the "steady state" levels, since the T½ is about 6 minutes, it would take about 30 minutes to be at steady state. Nevertheless, a plot of all the concentrations obtained as a function of the doses does provide some information on the linearity of fenoldopam.

D. In Study L-51, the estimation of clearance by the sponsor in patient 6 is incorrect, since the plasma levels did not indicate attainment of steady state. However, calculation by the reviewer of clearances using observed C_{ss} levels, rather than plasma levels at a fixed time point, as used by the sponsor, revealed very little difference in the mean clearances.

E. The clearance observed in most studies was around 40-45 ml/min/kg, a value much greater than hepatic blood flow. It is possible that the drug is unstable in blood due to the presence of enzymes and degradation may occur. Fenoldopam has a catechol nucleus and it may be metabolized by COMT (catechol o-methyl transferase) in the blood, thus giving rise to clearance values which are much higher than liver blood flow. The phenolic groups in the catechol nucleus of fenoldopam are methylated to form the 7-O-methyl, and the 8-O-methyl metabolites, which is similar to the methylation of catecholamines by COMT. Also the very short half-life of fenoldopam, 6 minutes suggests that degradation in the blood

may be a possibility.

COMMENTS TO BE SENT TO THE FIRM:

1. The sponsor has not established dose proportionality of fenoldopam conclusively. The pooled data submitted in Vol 1.6, pg 41, Figure 4, and the data from hypertensive patients (Study L-36) should be statistically analyzed to conclude dose proportionality.

2. The sponsor should explain the term "limit of sensitivity", used in Study L-47.

3. The sponsor should provide study validation of the assays used in studies L-47, A-20, L-51 and A-35.

4. The sponsor should provide information, if any, on the stability of fenoldopam in blood or plasma. Also, information on handling and storage of blood samples in the various studies should be provided.

5. The individual clearance values and plasma concentrations submitted in Study L-47 were illegible and could not be confirmed.

6. In the CAPD study (A-35), plasma levels of patients 1 and 4 seem to be higher at a lower infusion rate and vice versa. The sponsor should explain this discrepancy.

Labeling Comments: The final revision of the Pharmacokinetic section of the labeling will be done at the time of approval of the drug.

Pharmacokinetics section

7. The pharmacokinetic parameters of fenoldopam in hypertensive patients should be listed instead of the statement listing PK parameters in normal subjects.

8. A statement to the effect that the mean plasma clearance of fenoldopam in patients with CHF was similar to that in healthy subjects, should be added.

DEFICIENCY:

1. Although Vol 1.62 contains information on different

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Pharmacokinetic Evaluation Branch

Biopharm Day 5/13/91 J. Collins, H. Malinowski, J. Hunt, A. Parekh.

FT initialed by John Hunt JH 5/27/91

cc: NDA 19-922, HFD-110, HFD-426 (Mallikaarjun), Chron, Division, Drug, Reviewer, FOI (HFD-19), PK/PD.

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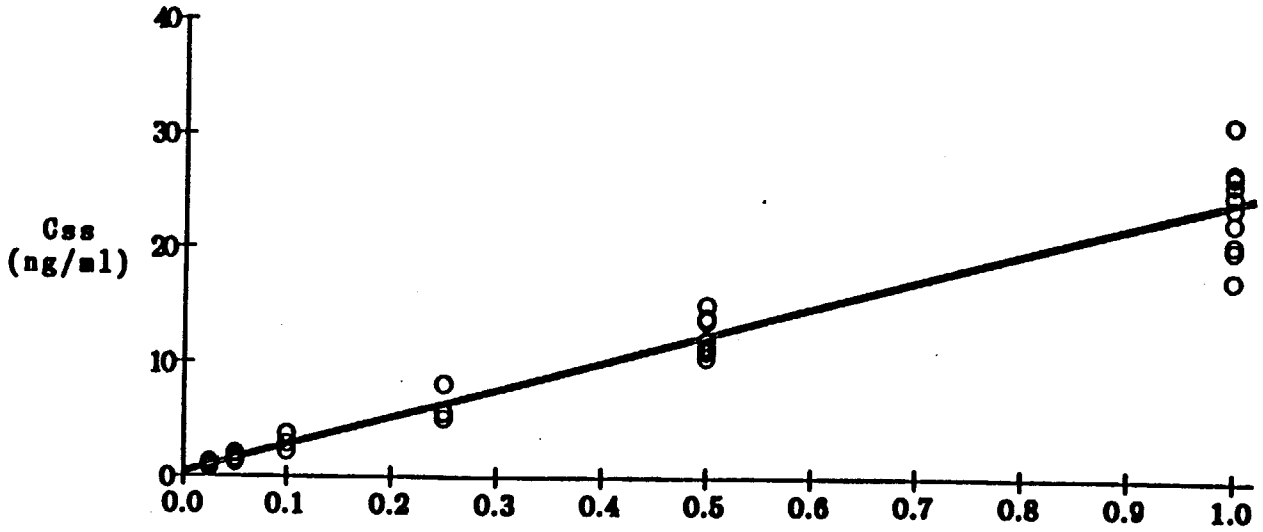
Figure 1

Steady-State Plasma Concentrations of Fenoldopam as a Function of the Fenoldopam Infusion Rate in Healthy Volunteers
Protocols L-34, L-64, A-21



regression line: 24.0*X + 0.38 (R-squared=0.94)

n=36

FIGURE (1).

FIGURE 20

FENOLDOPAM MESYLATE, - PROTOCOL L-30

STUDY DAY 1 - PLASMA CONCENTRATIONS OF FENOLDOPAM AT THE END OF EACH 15 MINUTE INFUSION PERIOD (+/-SD)

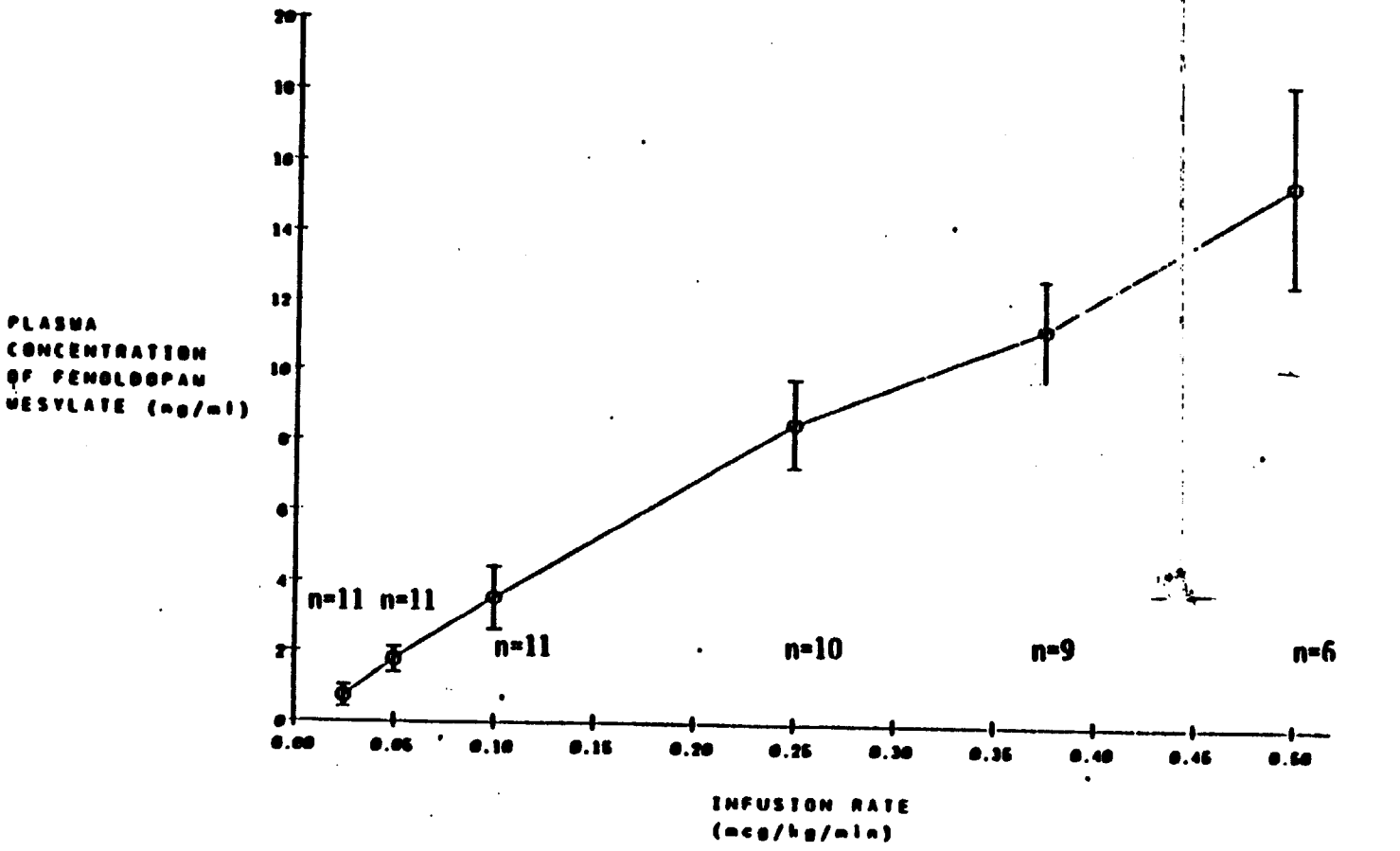


FIGURE (2).

APPENDIX I

SINGLE DOSE STUDY:

STUDY NO. A21-UK VOLUME: 1.66 PAGES: 000120-000263

INVESTIGATOR AND LOCATION:

OBJECTIVES: 1. To provide a preliminary indication of the bioequivalence of 100 mg fenoldopam capsules and 'Tiltab' tablets.
2. To obtain information on the absolute bioavailability of fenoldopam after IV and oral administration.

FORMULATION: i) IV - Ampoules containing 10 mg/ml fenoldopam (Batch No. 1F) were diluted with 5% Dextrose individually for each subject prior to injection.
ii) Tablet - 100 mg fenoldopam (Formula No 1/100AFC1 Batch II).
iii) Capsule - 100 mg fenoldopam (Formula No 4/100WW Batch No. 6).

STUDY DESIGN: Three way crossover involving 12 healthy subjects (6 male, 6 female), aged between 21 and 37 years. The IV dose, 1 mcg/kg/min was administered over 2 hours. Subjects were fasted from the previous night up to 2 hours after stopping the IV infusion. The washout period was at least one week. Plasma samples for the IV dose were drawn freqently up to 6 hours after the start of the infusion (Appendix II). Urine was collected for 24 hours and an aliquot frozen. Blood pressure measurements (systolic and diastolic) were taken up to 2 hours after start of the infusion (Appendix II).

ASSAY:

RESULTS: The mean parameter values are listed below:

	AUC(0-T)	CMAX	CL_s	VD_{ss}	X_u	fu (%)
	ng*hr/ml	ng/ml	ml/min/kg	ml/kg	µg	
N	11	11	11	11	8	8
MEAN	49.44	25.85	41.5	499.5	473.38	5.9
C.V.(%)	16.4	15.5	17.3	23.5	25.9	23.7

By compartmental analysis, the mean α T½ was 6.2 minutes and the mean ß T½ was 1.1 hours. Of the total post-infusion AUC, 97% was described by the α phase, and 3% by the ß phase. A representative figure of plasma concentration vs. time is attached.

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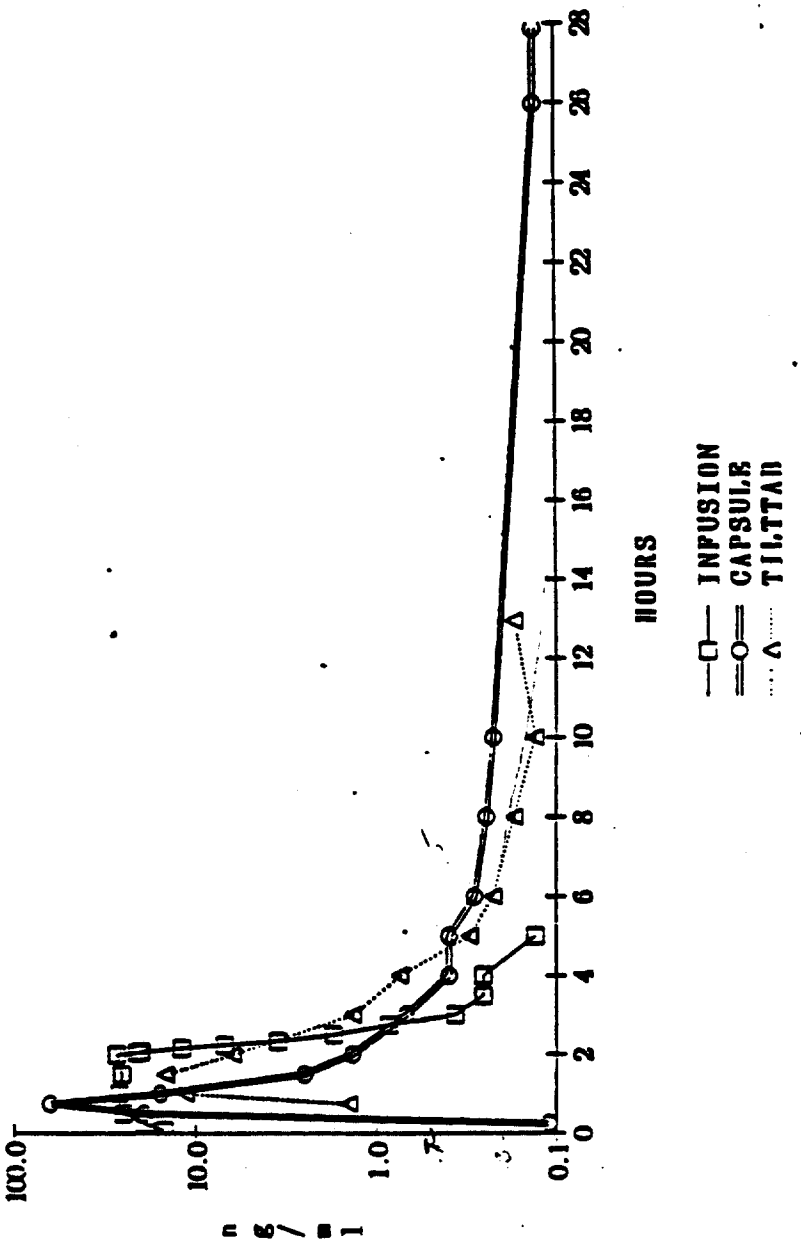
A-21

Figure 4. Plasma fenoldopam concentration versus time profile during and after an 2 hour intravenous infusion of 1.0 ug/kg/min of fenoldopam, oral administration of a 100 mg fenoldopam capsule and oral administration of a 100 mg fenoldopam tablet in Subject #4.



C-14 STUDY:

STUDY NO. UK/01/07 VOLUME: 1.65 PAGES: 260-340

INVESTIGATOR AND LOCATION:

OBJECTIVES: To determine the absorption, distribution and elimination kinetics of 82526 (fenoldopam) and its metabolites after oral and IV administration.

STUDY DESIGN: ^{14}C- fenoldopam mesylate was administered over 30 minutes to 4 subjects as separate single doses between 3.2 to 4.2 mg IV, and 100 mg oral doses in a randomized crossover design, with at least 4 weeks between treatments. Blood samples were drawn at regular intervals up to 168 hours as listed in Appendix II. Urine samples were collected at 4 hour intervals for 12 hours, from 12 to 24 hours, and then every 24 hours for up to 192 hours. Feces samples were collected when voided.

ASSAY:

DATA ANALYSIS: No parameters were calculated.

RESULTS: The individual concentrations are in Appendix II. The mean blood:plasma ratio of fenoldopam was 1:1.1. Measurement of radioactivity indicated a mean of 88.6% excreted in urine, 10.9% excreted in the feces, for a total of 99.5% recovery, with 86% of the dose being excreted in 24 hours. The percent of various metabolites excreted in the urine are listed in Appendix II. The percent of 7-methoxy and the 8-methoxy metabolites excreted after the IV administration was greater (11-17%) than that from the oral route (4.3-5%). Approximately 46% of the IV dose was recovered as fenoldopam and its known metabolites.

CONCLUSIONS: Fenoldopam is extensively metabolized with only about 4% of unchanged drug being excreted in the urine. Elimination of the parent and the metabolites is fairly rapid with more than 85% being excreted in 24 hours.

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DOSE PROPORTIONALITY STUDY:

STUDY NO. L-34 VOLUME: 1.62 PAGES: 000299-000435

INVESTIGATOR AND LOCATION:

OBJECTIVES: To determine the safety, and effect on renal function of IV fenoldopam.

STUDY DESIGN: In Part 2, Regimen B of the study, 3 normal healthy volunteers were administered three fenoldopam doses, 0.025, 0.1 and 0.5 μg/kg/min over 30 minutes in a crossover manner. Blood samples were drawn at 0, 0.5, 1, 1.5, 2, 2.5 and 4 hours after the start of the infusion.

ASSAY: No details were provided.

DATA ANALYSIS: The plasma clearance was calculated by, $Cl_p = ko/C_{ss}$.

RESULTS: The attached table lists the plasma levels and clearances, and the attached figure shows the mean plot of C_{ss} vs. infusion rate.

CONCLUSIONS: From the attached figure, it appears that the C_{ss} increases linearly as a function of the infusion rate. However, due to the small sample size, and the lack of any statistical evaluation it is not possible to conclusively state that the pharmacokinetics of fenoldopam is dose proportional.

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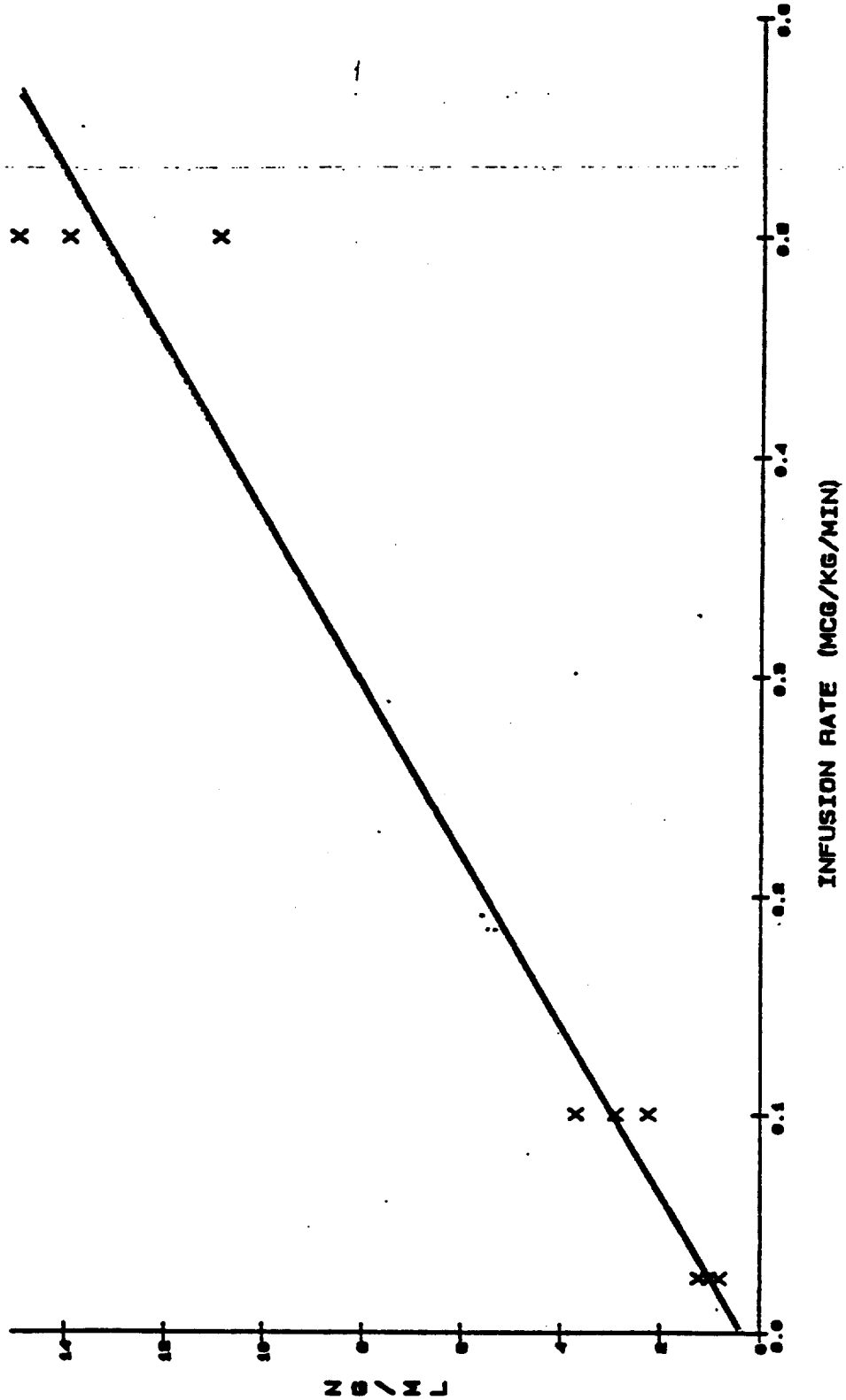
L-54

TABLE 23
PROTOCOL L-34, PHARMACOKINETICS
(NG/ML) PLASMA CONCENTRATION

SUBJ.#	MCG/KG/MIN	'0'	TIME 30	POST 60	DRUG 90	IN 120	MIN 150	240	AVERAGE 30-120MIN	CL(plasma)* ML/MIN/KG	CL(blood)* ML/MIN/KG
S-59											
S-60											
S-61											

* CL(plasma) = TOTAL BODY PLASMA CLEARANCE
  CL(blood) = TOTAL BLOOD CLEARANCE

FIGURE 1
MEAN PLASMA CONCENTRATION (NG/ML)
PROTOCOL L-34, PART 2 REG. A & B



PK STUDY IN HYPERTENSIVE PATIENTS:

STUDY NO. L-36 VOLUME: 1.63 PAGES: 2-468

INVESTIGATOR AND LOCATION:

OBJECTIVES: To evaluate the effects of IV fenoldopam on blood pressure, heart rate and renal function in patients with mild-moderate essential hypertension.

STUDY DESIGN: Twenty one patients (12 female and 9 male) patients with mild to moderate essential hypertension were enrolled in the study. On Day 1, the patients received incremental infusions for 15 minutes ranging between 0.025 to 1.50 μg/kg/min, and blood samples were obtained at every 15 minutes. Of these in 8 subjects, samples were drawn up to 40 minutes after stopping the last infusion. On Day 2, fenoldopam was infused at 0.25 and 0.375 μg/kg/hr for 2 hours in 9 patients, and blood samples were collected at 0.5, 1, 1.5, 2, 2.5 and 3 hours after the start of the infusion.

ASSAY:

DATA ANALYSIS: Plasma clearance was estimated by the equation, $Cl_p = K_o/C_{ss}$. No other parameters were calculated by the sponsor.

RESULTS: The attached table lists the C_{ss} and clearances on Day 2. The following table lists the doses and the mean concentration at the end of each infusion on Day 1:

Study Day 1. Mean Fenoldopam Plasma Concentrations at the End of Each 15 Minute Infusion Period (Infusion Rate mcg/kg/min)

	0.025	0.05	0.10	0.175	0.25	0.375	0.50	1.0
Mean Concentration (ng/ml)	0.79	1.76	3.52	4.55	8.52	11.28	15.52	27.86
n	11	11	11	3	10	9	6	1

CONCLUSIONS: On Day 1, although the sponsor claims that the sample at 15 minutes represents the "steady state" levels, since the T½ is about 6 minutes, it would take about 30 minutes to be at steady state. Nevertheless, a plot of all the concentrations obtained as a function of the doses does provide some information on the linearity of fenoldopam.

L-30

Summary Table 11

Pharmacokinetic Parameters of Fenoldopam
in Hypertensive Patients

Infusion - 0.25 mcg/kg/min

Patient #	C_{ss} (ng/ml)	CL (ml/min/kg)
28		
41		
42		
47		
Mean		
±SD		

Infusion - 0.375 mcg/kg/min

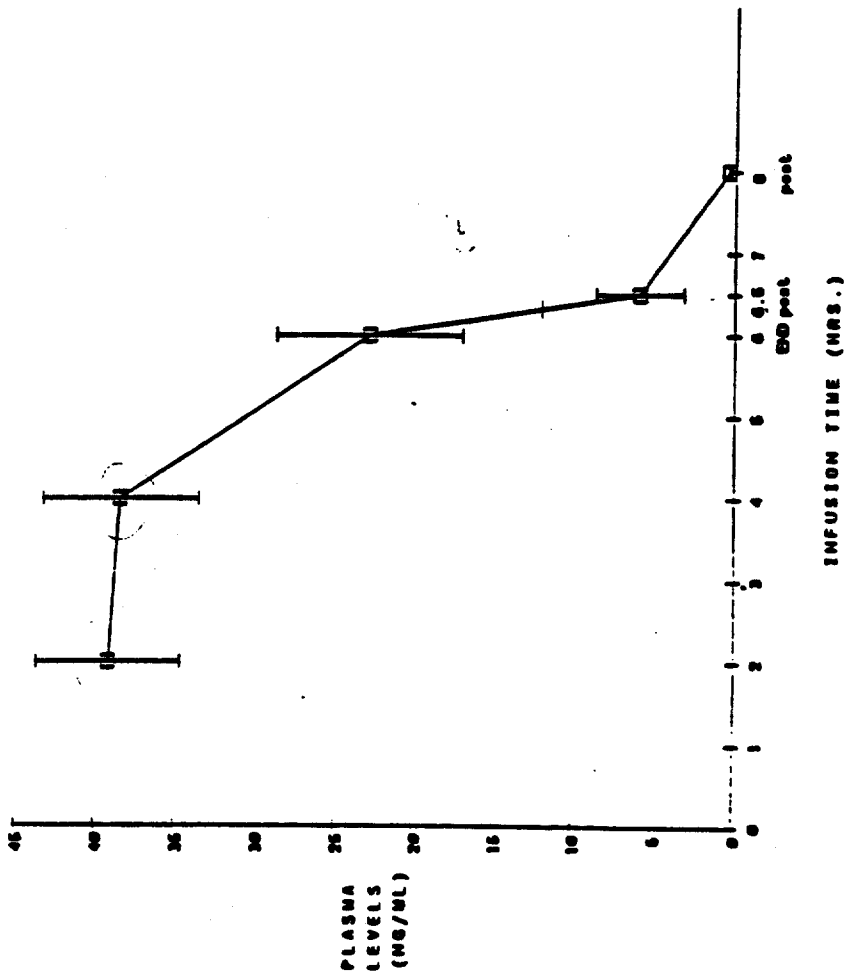
Patient #	C_{ss} (ng/ml)	CL (ml/min/kg)
38		
40		
65		
66		
70		
Mean		
±SD		

C_{ss} The mean of the 60 and 120 minute fenoldopam plasma concentration during infusion (steady-state).
CL clearance

Figure 20

PROTOCOL

FENOLDOPAM PLASMA LEVELS DURING AND FOLLOWING INTRAVENOUS MAINTAINED INFUSION *



* Each point is the mean ± SEM

STUDY IN CHF PATIENTS:

STUDY NO. L-47 VOLUME: 1.64 PAGES: 2-395

INVESTIGATOR AND LOCATION:

OBJECTIVES: To compare IV fenoldopam and sodium nitroprusside on the effects on cardiac and renal function in CHF patients.

STUDY DESIGN: In a randomized crossover design, 8 Class III and 7 Class IV patients were administered either fenoldopam 0.1 to 1.5 μg/kg/min in an incremental manner, or sodium nitroprusside IV infusions as shown below:

Fenoldopam
0.1 μg/kg/min (.001 ml/kg/min) x 10-15 min
0.25 μg/kg/min (0.0025 ml/kg/min) x 10-15 min
0.5 μg/kg/min (0.0050 ml/kg/min) x 10-15 min
1.0 μg/kg/min (0.0010 ml/kg/min) x 10-15 min
1.25 μg/kg/min (0.0125 ml/kg/min) x 10-15 min
1.5 μg/kg/min (0.015 ml/kg/min) x 10-15 min

When an optimal rate was achieved (determined by clinical parameters), the infusion rate was maintained for 4-6 hours. In most cases, the patients were stabilized at 1.5 μg/min/kg. Blood samples were drawn at 2, 4, 6, 6.5 and 8 hours after starting the infusion. The exact duration of each infusion was not provided.

ASSAY:

DATA ANALYSIS: The clearance was calculated by the ratio of the infusion rate to the concentration at 2 and 4 hours.

RESULTS: The mean plasma profile is in the attached figure. The mean clearance was 40.93 ± 11.34 ml/min/kg.

CONCLUSIONS: The concentrations reported on page 123 are illegible and the sponsor needs to provide a legible copy of the data. If the sponsor's analysis is correct, then the clearance of fenoldopam in patients with CHF is very similar to clearance in normal subjects.

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HEPATIC IMPAIRMENT STUDY:

STUDY NO. A-20 VOLUME: 1.66 PAGES: 2-119

INVESTIGATOR AND LOCATION:

OBJECTIVES: To assess the safety and hepatic hemodynamic responses to IV infusions of fenoldopam in patients with compensated and decompensated liver disease.

STUDY DESIGN: 6 male patients and 6 female patients were administered 4 successive IV infusions of fenoldopam of 0.05, 0.5, 1.0 and 1.6 mcg/kg/min spaced 30 minutes apart. Blood samples were drawn prior to the infusion, at the end of each infusion, and 30 minutes after terminating the last infusion. The plasma concentrations of fenoldopam, and its metabolites (the 7- and 8-sulfates) were measured.
Systolic BP, diastolic BP and heart rate were measured at the same times as the blood samples (Appendix II).

ASSAY:

DATA ANALYSIS:

PK: The systemic clearance was calculated as the ratio of the infusion rate to the plasma concentration at the end of the infusion.

PD: The following Emax model was used

$$E = \frac{EMAX * C_p}{EC_{50} + C_p}$$

where E = the percent change from baseline of systolic BP, diastolic BP or heart rate, Emax = the maximum reduction of the effect, EC_{50} = Cp at half the maximal effect, and Cp = plasma concentration.
The data were pooled and fitted to this model and the estimates of Emax and EC_{50} obtained for each effect.

RESULTS: PK: The mean and individual plots of clearances vs. infusion rate is attached. The mean clearances for the infusion rates are listed below:

INFUSION (μg/min/hr) RATE		0.05	0.5	1.0	1.6
CLEARANCE (ml/min/kg)	MEAN	63.72	55.66	50.84	46.55
	STD. DEV	25.17	20.42	19.22	16.94

PD: The following table lists the mean PD parameters from the fit:

Haemodynamic Parameter	Emax (%)	EC50 (ng/ml)	Multiple R-squared
Systolic blood pressure	-41.7 (10.1)*	20.0 (10.1)	0.79
Diastolic blood pressure	-47.5 (8.7)	12.1 (5.6)	0.81
Mean atrial pressure	-42.5 (7.0)	14.0 (5.5)	0.85
Heart rate	22.9 (3.0)	2.76 (1.54)	0.73
Cardiac output	15.9 (4.0)	2.65 (2.73)	0.42
Total systemic resistance	-46.4 (7.0)	8.27 (3.73)	0.83

CONCLUSIONS: The sponsor concluded that although mean clearances decreased with increasing infusion rates, and there was wide intersubject variability, the mean clearance of the hepatically impaired population was similar to healthy volunteers.

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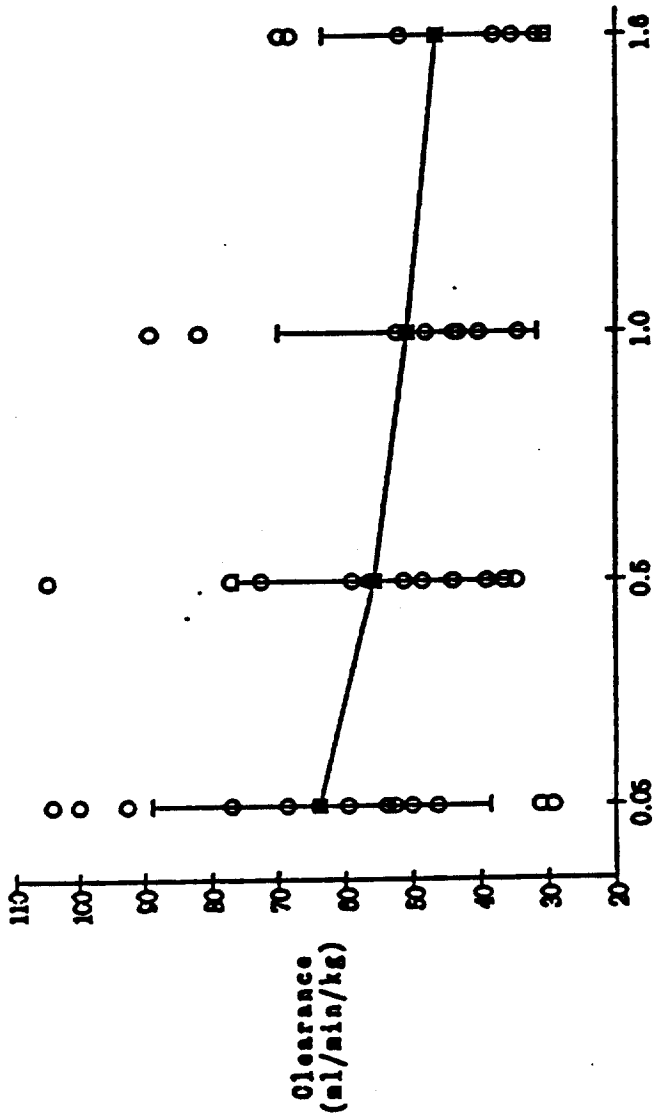
A-20

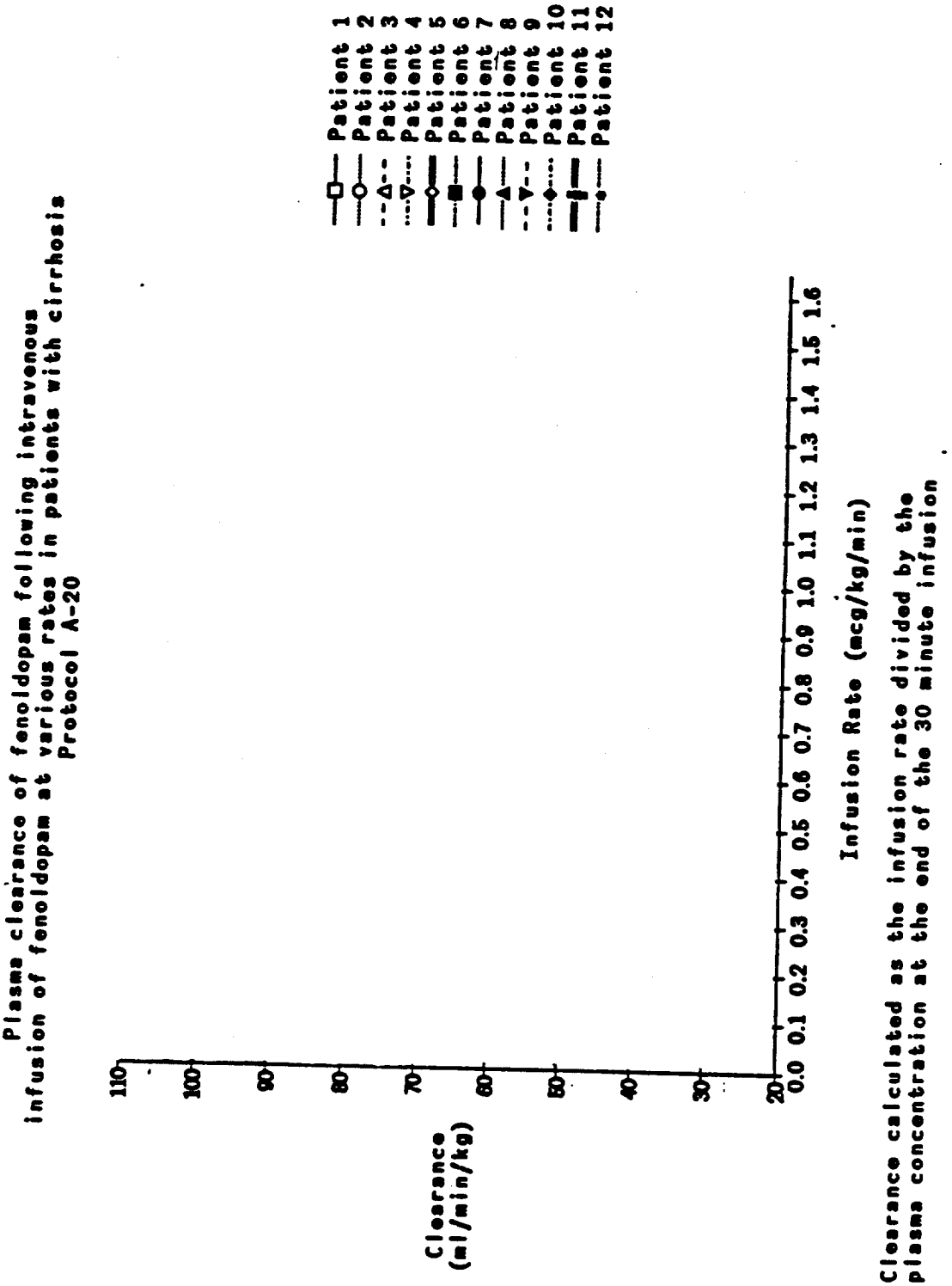
FIGURE 7

Plasma clearance of fenoldopam following intravenous infusion of fenoldopam at various rates in patients with cirrhosis
Protocol A-20



A-20

FIGURE 8



HEPATIC IMPAIRMENT STUDY:

STUDY NO. L-51 VOLUME: 1.65 PAGES: 2-259

INVESTIGATOR AND LOCATION:

OBJECTIVES: To determine the effect of IV fenoldopam on renal hemodynamics and other physiologic parameters in cirrhotic patients.

STUDY DESIGN: Eight males and one female (47 - 62 years old) were administered either 0.1 μg/kg/min (n=3) or 0.2 μg/kg/min (n=6) fenoldopam mesylate over 5 hours. Blood samples were drawn at 0, 1, 2.5, 5, 5.25, 5.5, 6, and 7 hours after starting the infusion.

ASSAY:

DATA ANALYSIS: The clearance was calculated by the ratio of the infusion rate to the concentration at 1 hour.

RESULTS: The samples from 2 patients were lost, and therefore data from only 7 patients was provided. The individual concentrations and clearances are in Appendix II. The mean clearance was 44.6 ml/min/kg

CONCLUSIONS: The estimation of clearance in patient 6 is incorrect, since the plasma levels did not indicate attainment of steady state. Overall, calculation of clearances by the reviewer using observed C_{ss} levels, rather than plasma levels at a fixed time point, as used by the sponsor, revealed very little difference in the mean clearances. The clearance value obtained here, 44.6 ml/min/kg is lower than that from the other hepatic impairment study reviewed (46 - 63 ml/min/kg), but not very different from the value obtained for normal subjects, 41.2 ml/min/kg. This indicates that hepatic impairment probably does not affect the plasma levels of fenoldopam.

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CAPD STUDY:

STUDY NO. A-35 VOLUME: 1.66 PAGES: 269-442

INVESTIGATOR AND LOCATION:

OBJECTIVES: To assess the effects of IV fenoldopam on peritoneal solute and water clearance, plasma renin activity, plasma aldosterone, plasma atrial natriuretic factor, and to determine the pharmacokinetic profile of fenoldopam in patients undergoing continous ambulatory peritoneal dialysis.

STUDY DESIGN: Five male and 3 female patients who had undergone CAPD for at least 3 months, enrolled in this randomized, crossover study. Patients received either an IV infusion of fenoldopam in doses of 0.1 μg/kg/min for 30 minutes increased to 0.2 μg/kg/min for 4½ hours, or placebo for 5 hours.
Blood samples were collected at 0, 0.5, 1, 2, 3, 4 and 5 hours after the start of the infusion. Samples of the dialysate fluid were also collected during this period at 1.5, 2, 3, 4, 5, and 9 hours after starting the infusion. Samples were analyzed for fenoldopam and the 7- and 8-sulfate metabolites.

ASSAY:

RESULTS: The mean clearance of fenoldopam reported by the sponsor was 46.8 ml/min/kg. The dialysate concentration of fenoldopam appeared to be in equilibrium with the plasma concentration after approximately 3 hours after starting the infusion.
The mean ratio of the dialysate concentrations to the plasma concentrations of fenoldopam was 0.14.

CONCLUSIONS: From the data, it appears that the clearance of fenoldopam in CAPD patients is not very different from that of normal volunteers. This is not surprising, since fenoldopam is extensively metabolized and only 4-6% in excreted unchanged in the urine. The ratio of the dialysate to plasma concentrations is very low, and reflects the fact that fenoldopam is highly bound, with a free fraction in the vicinity of 0.14.