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I. Introduction/Thesis.

This document summarizes our rationale for the approval of fenoldopam mesylate (Corlopam®) for the short term intravenous treatment of hypertension, when oral medication is not a reasonable alternative. Although I wrote this document, it was circulated to all members of the review team for their corrections and comments. We do not recommend a specific indication such as hypertensive crisis or peri-operative control of blood pressure. For the former indication, there is, at present, insufficient kinetic and dynamic information to adequately compose dosing instructions, as well as an insufficient data base to assess the risk/benefit relationship of this drug. For the latter indication, there is neither convincing information that treatment of peri-operative hypertension is useful, in general, nor that fenoldopam, in particular, decreases perioperative complications.

II. Historical.

Fenoldopam mesylate was originally submitted as NDA 19,922 on 12 December 1988. A non-approval letter for its use in the treatment of severe hypertension was issued in 15 November 1991. The specifics for the non-approval recommendation can be summarized as follows:

- Clinical trials were either open-labeled or positive-controlled with concurrent anti-hypertensive medications allowed up to randomization or after only short duration of infusion. It was, therefore, not possible to definitively attribute any blood pressure response to drug treatment alone.

- In addition, none of the studies adequately defined the relationship of serum concentration to drug effect in a population remotely related to the targeted population. Consequently, aside from the short term empirical infusion regimens, adequate instructions for increasing or decreasing dosage and the frequency of such changes could not be described.

- Few, if any of those enrolled in the clinical studies, could be verified as having on-going, end-organ compromise such as encephalopathy, intracranial bleeding, pulmonary edema, retinopathy etc. Consequently, there was no guarantee that safety and dosing could be extrapolated from the studied population to the to-be-treated population.

- Fenoldopam infusions were generally administered for only short times. Few subjects were infused with fenoldopam for sufficient durations to assure both continued activity and absence of unanticipated adverse events.

- There was inadequate information that the kinetics of fenoldopam were

well behaved except for the short durations in which the kinetics were studied.

• There was inadequate information to assure that there was adequate guarantees of product sterility.

This Division met several times with Neurex Pharmaceutical (Neurex purchased the rights to Corlopam® from in 1994, after the non-approval letter was issued), to outline the studies that would be sufficient to correct these deficiencies.

This Division recommended that Neurex perform two studies, the first to adequately define the kinetics and dynamics of fenoldopam in a stable hypertensive population, with emphasis on defining the onset and offset kinetics as well as the possible occurrence of tolerance. The second study would apply this information in an emergent hypertensive crisis population, verifying the applicability, in this population, of the dosing instructions derived from mild-moderate hypertensives. In addition, this last study was also to serve as a data base from which to assert safety in this emergent hypertension population.

As of the writing of this summary, Neurex has completed and submitted both a pilot study (study #95-07) and pivotal study (study #94-05) which adequately defines the effect of Corlopam® in mild-moderate hypertensives. The dose response study in an emergent population has been completed, but the data has yet to be submitted to the Division for review. In both of the mild-moderate hypertensive studies, Corlopam® was administered as a constant infusion for two days, bracketed with one day placebo infusions before and after active drug exposure. The first placebo infusion was to define baseline blood pressure; the second infusion to define any post-infusion rebound. The results of the pivotal study, in conjunction with the studies previously submitted, demonstrate that the kinetics of Corlopam® are well behaved; the initial blood pressure response is related to infusion rate/concentration of fenoldopam; the onset of blood pressure effect is rapid; the effects are substantially maintained during at least two days of fenoldopam infusion and blood pressure reverts towards baseline after discontinuation of treatment with no evidence of excessive rebound.

This resubmission was reviewed as a team, consisting of the following members. In addition to the specific responsibilities enumerated below, all reviewers were invited to participate in general discussions.

Dr. Kun Jin	Statistics- Analyzed pivotal study #94-05
Dr. Jim Short	Chemistry
Ms Estela Barry	Pharmacology
Dr. Ahmed Al-Tahtawy	Pharmacokinetic and pharmacodynamic modeling
Dr. Ameeta Parekh	Group Leader Pharmacokinetics and Dynamics

Dr. Steve Rodin	Medical Reviewer
Dr. Abraham Karkowsky	Medical Reviewer
Ms. Zelda MacDonald	Project Manager

III. Chemistry, Manufacturing and Pharmacology.

Fenoldopam mesylate (6-chloro-2,3,4,5-tetrahydro-1-(4-hydroxy phenyl)-1H-3-benazepine-7,8-diol, methanesulfonate) is a benazepine derivative with a single optically active center.

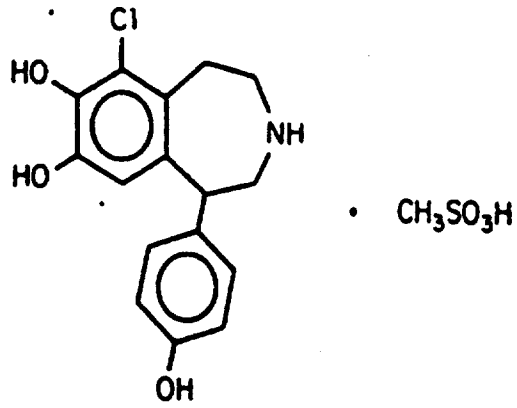

Figure 1. Structure of Fenoldopam

The present procedures of , for the 10 mg/ml; 5 ml ampoule, are adequate to assure sterility of the to-be-marketed product (as per Dr. Uratani, the Agency microbiologist). The EER was found acceptable.

Fenoldopam presumably decreases blood pressure in animals through a direct action on one or several of the ***dopamine$_1$-type*** receptors. In *Ex-vivo* and *in-vitro* studies in animals, fenoldopam binds strongly to and has agonist activity on several model systems of these ***dopamine$_1$*** 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.

At least in dogs, all vascular beds are not homogeneously dilated during

fenoldopam infusions. Renal blood flow is increased at substantially lower doses than are necessary to increase iliac or systemic blood flow. The variability in blood flow in the various tissues is not explained, but presumably it is related either to the density of receptors in the vascular beds or the subsequent efficiency in the coupling of binding to the stimulation of adenyl cyclase. The consequence of this inhomogeneity of vascular response is most critical in an emergent hypertensive population, in which some vascular beds before therapy, are only marginally capable of supporting end-organ function. It would, therefore, be important to know if, in this population, a steal phenomena is a direct consequence to fenoldopam vasodilatation, negatively impacting marginally perfused end-organs.

Dopamine receptors occur both centrally and peripherally. In the periphery, dopamine receptors are located in vascular tissue as well as within the kidney. The nomenclature for the several types of dopamine receptors in the periphery was derived independently from that of dopamine receptors within the CNS. The classification within the CNS is as follows. D_1 receptors (D_{1A}, D_{1B} and D_5) are closely linked to and stimulate adenylyl cyclase. D_2 receptors (two-isoforms D_{2short} and D_{2long}) are coupled to and inhibit adenylyl cyclase. D_3 and D_4 receptors are structurally related to D_2 receptors but are not linked to adenylyl cyclase.

Human dopamine receptors of both D1 sub-types (from brain) have been cloned and expressed in 293 cells (human embryonic kidney cells)[1]. Fenoldopam preferentially binds to the cloned D1B receptors with a slightly less than 2-fold preference than to the cloned D1A receptor. Dopamine also preferentially binds to the D1B receptor but with a 5-fold preference for this receptor relative to the D1A receptor. The equilibrium dissociation constants for the binding of fenoldopam to D1A and D1B receptors is approximately 25 nM, concentrations that are approached by constant infusions of approximately 0.4 ug/kg/min (assuming that all fenoldopam is unbound to protein). In this model system, both dopamine and fenoldopam are capable of stimulating intracellular cAMP, with both dopamine and fenoldopam maximally stimulating intracellular cAMP to the same extent.

Although there is suggestive data, it is not entirely clear if the dopamine receptors (including sub-types) in the CNS are equivalent to those in the vasculature and kidney. Since fenoldopam binding studies to dopamine receptors were performed with receptors isolated from the CNS, the generalizability of this binding to renal receptors is suggested but not quite proven[2].

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[1] Tiberi, M.; Caron, M.G. " High Agonist-independent Activity is a Distinguishing Feature of the Dopamine D!B Receptor Subtype" J. Biol. Chem., 1994, 269; 27925-27931.

[2] Northern blot analysis of human or rat kidney failed to demonstrate expression of either cloned D1 subtype from brain (Reviewed in Gingrich, J.A.; Caron, "Recent advances in the Molecular Biology of the Dopamine Receptors Annu. Rev. Neurosci 16: 299-321; 1993). This result would suggest that peripheral and central receptors differ. On the other hand, in the opossum kidney cell (a model of proximal tubular cells) a probe (approximately 400 bp out of a gene

Based mostly on animal studies, DA-$_1$ type receptors (functionally equivalent to CNS receptors D_{1A}, D_{1B} and D_5) within the kidney as localized either by radio-ligand and/or autoradiography to both the renal vasculature (artery and arterioles) as well as within discrete nephron segments (proximal convoluted tubules, proximal straight tubules, medullary thick ascending limb as well as the cortical and inner medullary collecting ducts). DA-$_2$ (functionally equivalent to CNS receptors D_2, D_3 and D_4) type dopamine receptors are also present within the renal vasculature (arteries) as well as within the nephron (proximal tubule and inner medullary collecting duct: this latter site contains a novel D_2-type receptor termed D_{2k}. The function of the D_{2k} receptors are unclear.

The renal effect of dopamine, mediated through the DA-1 and DA-2 receptors, include increase in GFR as well as increases in of sodium, calcium, and phosphate excretion. In order for fenoldopam to recreate dopamine's renal effects, it must not only bind to the DA-1 type receptors (as noted above it binds to D1-type CNS receptors) but must also successfully stimulated the intermediary messengers which mediate the effects of dopamine.

With respect to the actual effect of fenoldopam on renal function, the sponsor was kind enough to tabulate the results of the a large number of small studies that were carried out during the development of this drug. I have appended the sponsor's tabulation with some additional comments as Appendix A.

Overall, the data is inadequate to demonstrates that fenoldopam modifies renal function. None of the studies in which fenoldopam was shown to modify renal function were double-blind, randomized and placebo-controlled. Most studies were open-label, many were baseline controlled and few adequately established stable pre-treatment as well as post-treatment measurements. In the few studies that were placebo controlled, mostly in patients with congestive heart failure, there was no consistent finding that fenoldopam had a beneficial effect on RBF, GFR, urine flow or fractional excretion of sodium. Even if there is a suggestion of an effect of fenoldopam on renal function it is not possible to describe the dose range of this activity. Lastly, in the one large data base, in patients with sponsor defined post-operative hypertension (study C1101), net negative fluid balance i.e. output-input during active infusion (either nifedipine or fenoldopam) was greater on nifedipine than on fenoldopam.

IV. Disposition, Kinetics of Excretion of Fenoldopam

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size of 1400 bp) from the D1A and D1B receptor (isolated from opossum brain?) was able to protect from RNAse digestion, m-RNA sequences derived from either opossum brain or kidney. The conclusion to be drawn is that at least within the studied opossum probe (and by presumption across the whole gene) there was sequence homology between D1A and D1B receptors of brain and a class of receptors found in kidney.

There was nearly complete recovery of a single intravenous 30-minute infusion of tracer ^{14}C-labeled fenoldopam (total dose 3.2-4.2 mg). The percentage of the label was recovered in the urine and feces was 89% and 11%, respectively. Only 4-6% of the dose was isolated as unchanged fenoldopam. The major metabolites detected in urine were the 7-methoxy conjugates (sulfate and glucuronide) (11% of dose), 8-methoxy conjugates (17.4% of dose) and fenoldopam conjugates (17.4% of dose). These products are produced by methylation followed by Phase II conjugation. Approximately, 50% of the excreted urinary radioactivity can be associated with specific metabolites of fenoldopam. Based on incubation with liver slices, microsomal and cytoplasmic fractions, fenoldopam is not a substrate for P450 oxidation[3]. Fenoldopam is substantially (88%) protein bound.

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. In this study, a total of 33 (32 completed) mild-moderate hypertensive subjects, off baseline medications, 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 (one subjects, because of a pharmacy error received an infusion of 0.01 ug/kg/min; one subject because of access problems discontinued early). There were two placebo phases to this study, the first preceding the randomized treatment and the second followed the 48-hour randomized 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.

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. Plasma concentrations of racemic fenoldopam were determined in all subjects. Concentrations of the component optical isomers, R-fenoldopam and S-fenoldopam, as well as the metabolite 7-methoxy fenoldopam, 8-methoxy-fenoldopam were measured in a sub-population of 9 subjects from the two high dose infusion groups.

At the start of the infusion, the concentration of fenoldopam rapidly rises,

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[3] These studies were performed by the FDA's Division of Clinical Pharmacology.

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.

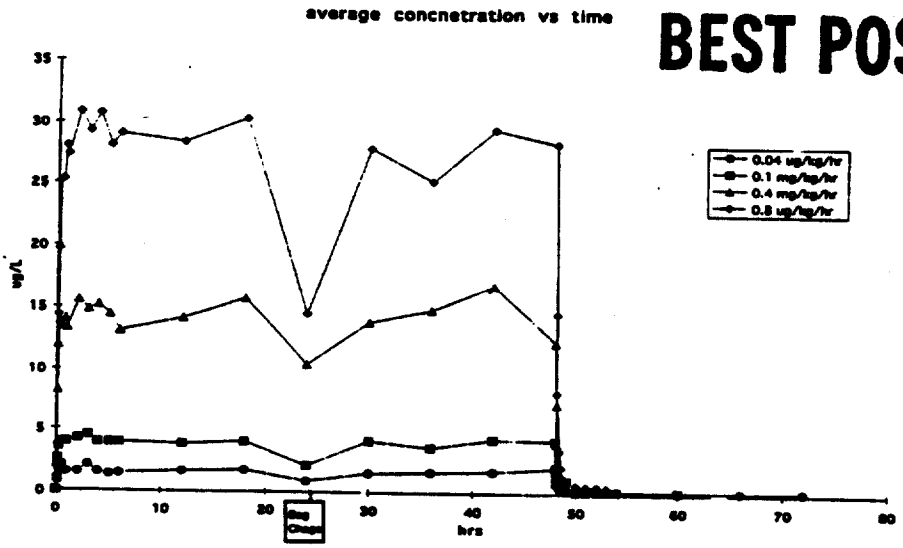

Figure 2. Infusion rate versus steady concentrations.

In study # A-21, normal subjects were treated with 2 hour infusion of fenoldopam. The offset kinetics are described by a bi-exponential decay, with approximately 97% of the AUC accounted for by the first exponential term and approximately 3% by the second exponential term. The terminal half-life was approximately 1 hour. The mean volume of distribution was 500 ml/kg and the mean clearance was 41.5 ml/min/kg.

With respect to the clearance of the individual isomers of fenoldopam, the R-isomer is cleared more rapidly (clearance 3.4 L/min) than the L-isomer (1.9 L/min). Consequently the steady state concentration of the R-isomer is less than that of the L-isomer. The $T_{1/2}$ of the 7-and 8-methoxy fenoldopam (13.2 and 12.5 minutes, respectively) were longer than that of racemic fenoldopam (approximately 5 minutes).

V. Dynamics of Fenoldopam in Mild-Moderate Hypertensives.

Study # 94-05 appears pivotal for defining the dynamics of fenoldopam. The review team has applied two methods of analyses to the data from this study. The first is the analysis performed by Dr. Kun Jin. This analysis was limited to steady

state responses, somewhat arbitrarily defined as and covering the duration of 1-48 hours of active infusion. The alternate analysis was a PK-PD mixed effect model performed by Dr. Grevel, Neurex's consultant, and confirmed and expanded by Dr. El Tahtawy and Dr. Parekh, the biopharmaceutical review team. The PK-PD model incorporates all data including the beginning of the infusion as well as after termination of the infusion. The conclusions derived from the two analysis are generally consistent, though they differ with respect to some specifics. Based on study #94-05, fenoldopam is an antihypertensive, its effects are rapid in onset and are dose related, its dynamic effects, at least for the higher doses, diminish with time, but are still substantial after 48-hours of infusion.

Despite the modest size of this study[4], there is a clear relationship between infusion rate and decrease in supine blood pressures (see Appendix B for each individual's hemodynamic response and Appendix C for the group mean hemodynamic responses). Not surprisingly, heart rate simultaneously increases. All active fenoldopam infusion rates that were studied, demonstrated hypotensive activity that differed from placebo.

The effects of fenoldopam appear to be related to the duration of the infusion. For the two high rates of infusion the trend is towards diminished effect. For the low dose group, the time dependent effect is in the opposite direction. Below is a table that displays the vital signs as modeled for the 1, 24 and 48 hours time points of the infusion. Even at the end of the infusion there is a persistence of blood pressure response that is far from trivial. The effects of all fenoldopam treatment groups tend to converge at or around 48 hours.

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[4]Because of the large number of highly variable data points, several methods which differed between the statistician and the biopharmaceutist were employed to compress the mass of information obtained from this study. With respect to the statistician's analysis, the median value of an individual's measurements of blood pressure and heart rates over a one-hour interval were collapsed to the median value and attributed to the middle of that hour (usually 4 data points/individual/hour, e.g. the median value for the diastolic blood pressures measured at 1:00 am, 1:15 am, 1:30 AM and 1:45 am were considered as the value of the 1:30:am time point). The values at the treatment phase were adjusted by subtracting the corresponding values at the same clock time of the baseline infusion that individual. The adjusted values were then fitted with a linear mixed-effects model (or random-effects model), that included terms for dose, time (to ascertain and quantify tolerance), between-individual random effects and within-individual random errors. The random-effects model was chosen because the measures from the same individual (at different times) could be analyzed. The between individual random effect included random effect and a non-linear (circadian rhythm) random effects. The chosen model was validated by several goodness-of-fit criterion. See Dr. Kun Jin's review for additional information.

Table 1. Calculated Effect at Steady State Based on the Statistical Model for Diastolic and Systolic Blood Pressures and Heart Rate

		1 hours	24 hours	48 hours
Diastolic Blood Pressure (mmHg)	0 ug/Kg/min	-2.46 ± 1.77	-2.46 ± 1.77	-2.46 ± 1.77
	0.04 ug/Kg/min	-8.24± 2.01	-11.13± 1.77	-14.15± 1.92
	0.1 ug/Kg/min	-16.86± 1.77	-16.86± 1.77	-16.86± 1.77
	0.4 ug/Kg/min	-24.05 ± 2.38	-19.87± 2.10	-15.50± 2.29
	0.8 ug/Kg/min	-20.80± 2.18	-17.59± 1.92	-14.25± 2.09
Systolic Blood Pressure (mmHg)	0 ug/Kg/min	-4.76.± 2.78	-4.76 .± 2.78	-4.76 .± 2.78
	0.04 ug/Kg/min	-13.75±3.13	-19.19 ±2.78	-24.86±3.07
	0.1 ug/Kg/min	-25.25± -2.78	-25.25± 2.78	-25.25± 2.78
	0.4 ug/Kg/min	-38.17± 3.71	-28.81±3.30	-19.04± 3.65
	0.8 ug/Kg/min	-31.65± 3.39	-27.34±3.01	-22.841±3.34
Heart Rate (BPM)	0 ug/Kg/min	-0.11±1.38	-0.11±1.38	-0.11±1.38
	0.04 ug/Kg/min	3.79±1.38	3.79±1.38	3.79±1.38
	0.1 ug/Kg/min	8.43± 1.57	5.32± 1.38	2.08± 1.48
	0.4 ug/Kg/min	13.76± 1.86	11.75±1.63	9.65±1.76
	0.8 ug/Kg/min	23.23±1.70	17.77±1.49	12.08±1.61

It should be noted that the result of the time dependent calculations, by assuming linearity, may exaggerate the effect at the extremes of time (1 and 48 hours). Below is displayed the average of the hemodynamic effects (i.e. the mean of the hourly median values,except for placebo which was averaged over the entire duration) during the intervals 1-16 hours, 17-32 hours and 33-48 hours.

Table 2. Average Effect at Steady State Based on Actual Measurements for Three Equal Periods During Active Infusion.

		1-16 hours	17-32 hours	33-48 hours
Diastolic Blood Pressure (mmHg)	0 ug/Kg/min	-1.90 ± 1.94	-1.90 ± 1.94	–1.90 ± 1.94
	0.04 ug/Kg/min	-8.01± 2.35	-11.82± 2.01	-11.80± 2.37
	0.1 ug/Kg/min	-13.71 ± 2.35	-15.90± 2.01	-16.53± 2.37
	0.4 ug/Kg/min	-20.42 ± 2.79	-18.21± 2.38	-14.47± 2.80
	0.8 ug/Kg/min	-20.29± 2.55	-15.69± 2.18	-16.56± 2.56
Systolic Blood Pressure (mmHg)	0 ug/Kg/min	-5.29 .± 3.06	-5.29 .± 3.06	-5.29 .± 3.06
	0.04 ug/Kg/min	-13.54 ± 3.45	-19.60± 3.18	-20..96±3.87
	0.1 ug/Kg/min	-25.13± 3.45	-25.65± 3.18	-26.14± 3.87
	0.4 ug/Kg/min	-31.37± 4.08	-27.18±3.76	-18.10± 4.58
	0.8 ug/Kg/min	-33.18± 3.73	-25.09±3.44	-27.92±4.19

Heart Rate (BPM)	0 ug/Kg/min	1.78±1.38	1.78±1.38	1.78±1.38
	0.04 ug/Kg/min	5.18±2.30	3.71±1.44	4.53±1.63
	0.1 ug/Kg/min	10.22± 2.30	5.15± 1.44	4.51± 1.63
	0.4 ug/Kg/min	14.31± 2.72	11.58±1.71	10.90±1.93
	0.8 ug/Kg/min	25.15± 2.48	15.56±1.56	16.20±1.76

The second analysis method was the PK-PD mixed-effect model. The model was applied only to supine diastolic blood pressure. The data was analyzed as follows. The diastolic blood pressure of the 7 placebo subjects was modeled to a polynomial function (to simulate circadian rhythm). The "drug" effect was defined as the measured blood pressure response at each time point during active infusion (the measured blood pressure[5] - the blood pressure from the equivalent clock time during baseline) with the corresponding value of the placebo profile subsequently subtracted.

The best fit model[6] shown below (as equation 1), is an E_{max} model[7]. A time factor is included that deals with tolerance. This model finds no lag between concentration and onset of dynamic effects (reflected by the lack of additional enhancement of fit in modeling with an "effect compartment"):

$$\text{Effect} = \left[\frac{21 * \text{Concentration}}{(6.31 + \text{Concentration})} + \frac{2.66 * \text{Concentration}}{(0.13 + \text{Concentration})} \right] \times \frac{(\text{Weight})}{75} * (\text{EXP}(-0.0065 * \text{Time}) \quad \text{(equation 1)}$$

where Concentration is in units of ng/ml; Weight in Kg; Time in hours and the constants are defined with reference to the same units.

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[5]Because of the large number of pharmacodynamic measurements and the disparity between pharmacokinetic and pharmacodynamic measurments, the data was compressed as follows:
For the first 30 minutes of the infusion and the first 30 minutes off infusion all values were used.
The average of the measurements of the interval periods 30-45 minutes and 45-60 minutes was attributed to the median time of that interval.
From 1-6 hours the average over 30 minutes were assigned to the median time of that interval
Thereafter, averages over 3 hours were assigned to the median time of that interval.

[6] The initial fit of this data was to a linear model, with the biopharmaceutist rejecting Emax, Hill equation, and Effect-Compartment models which did not improve the fit to the pharmacokinetics-pharmacodynamic data. The best linear model was:

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

This model contains a time dependent factor to account for tolerance.

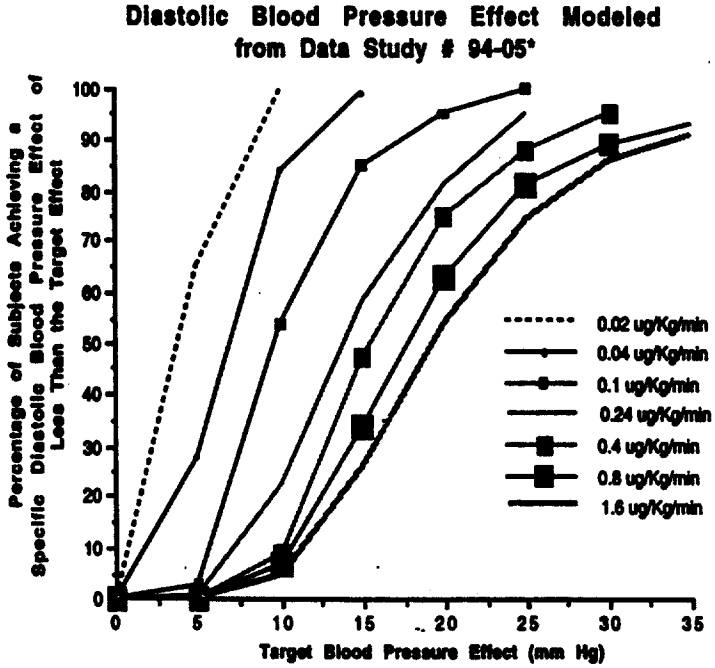
This model, however, fails the credibility test. Absent any concentration of fenoldopam, there would be an anticipated drop of blood pressure of 9 mm Hg!

[7] This equation for this model is what would be observed for a system characterized by two operational classes of receptors, one a high capacity low affinity receptor.and the other a high affinity-low capacity receptor

Based on this model, the predicted decrease in diastolic blood pressure after 2 hours (for a 70 Kg man) would be 23 mm Hg and after 24 hours, 20 mm Hg. The time term which describes tolerance has a half-life of approximately 102 hours.

It is also possible to estimate the percentage of the population who do not achieve a pre-specified response at the various infusion rates of fenoldopam (shown below as Figure 2). To derive these curves the subject was presumed to be a 90 Kg man, with blood pressure readings made at approximately 1 hour. The effects for 100 individuals were simulated based on the population PK-PD parameters. The curves with symbols represent infusion that were studied in study #94-05, other doses were modeled and are shown in Figure 2 without symbols. As an example, the curves indicate that 28% , 84% and 99% of those receiving 0.04 ug/Kg/min would have less than or equal to a 5 and 10 and 15 mm Hg drop in diastolic blood pressure, respectively. At this infusion rate, most will have at least 5 mm Hg, few will have greater than a 10 mm and almost none would have 15 mm Hg drops in DBP. At an infusion rate of 0.1 ug/Kg/min 3 %, 54%, 85% and 95% of patients will have DBP decreases of less than or equal to 5, 10, 15 and 20 mm Hg, respectively. At this infusion rate few subjects would have less than 5 or greater than 20 mm Hg. The full time-course of each infusion rate, as modeled, including some estimate of population variability, are shown as Appendix D (see Dr. El Tahtawy's review for more details).

Figure 2.



VI. Clinical Indications.

VI a. Use in Mild-Moderate Hypertensives Who are Unable to Receive Oral Medication.

Study #94-05 is sufficient to define the specifics of the concentration-effect relationship of fenoldopam in mild-moderate hypertensive. This study unequivocally establishes that fenoldopam is an intravenously active anti-hypertensive. The study allows a set of instructions to be written for the use of fenoldopam in this population.

Based on PK-PD analysis, as performed by Drs. Grevel and El Tahtawy, there is a rapid decrease in diastolic blood pressure with onset of infusion. No lag time between rise in concentration and onset of effect could be detected. No "effect-compartment" could be modeled that had concentrations that differed from the central compartment.

Both the PK-PD modeling, as well as the statistical analysis, indicate that the steady state effect of fenoldopam on blood pressure, at least initially, is monotonically dependent on the infusion rate. The effect at steady state is sufficiently stable so that during 48-hours of infusion, adequate response remains to distinguish active infusion from placebo. Dosing instructions for the initiating dose, the appropriate interval to allow before dosing changes should be considered, as well as the maximal infusion rates can be defined from the kinetic as well as dynamic data from study #94-05 (see section on Dosing).

Upon discontinuation of drug there is a rapid decline in serum concentrations of fenoldopam with a corresponding rapid decline in diastolic blood pressure. There was no evidence of rebound upon discontinuation of medication.

An infusion of 0.04 ug/kg/min should result in an average initial diastolic blood pressure decrease of approximately 7 mm Hg, with higher infusion rates having greater effects. There is a diminution of maximal effect as a function of duration of infusion, for the higher infusion rates. The effect of time on the lower infusion rates is either to increasing effect or at least a stable effect. For the high dose infusions, the time to develop tolerance is long, relative to the 48 hour constant infusions (Dr. El Tahtawy's estimate is a T1/2 for developing tolerance of approximately 102 hours) so that substantial anti-hypertensive effect remains at the end of 48 hours of infusion.

VI b. Hypertensive Emergencies.

As noted above, we do not feel that fenoldopam should be approved for the

use in controlling blood pressure in patients with hypertensive emergencies. The original five studies were reviewed in the submission of 12 December 1988. A tabular description of the studies are shown below as Table 4. These studies were inadequate in supporting this indication for the following reasons:

Table 4- Description of Studies Enrolling Severe hypertensives From the Original NDA.

Protocol #	Design	No Treated	No Evaluable	No. (#) Successes	Titration Duration mean (hr)	Maintenance Duration (hr)Total Infusion Duration mean (hr)
Controlled Studies						
B-74	OL PC, MC; DBP> 120 mm Hg	53 27 F; 26 NP	49 27 F, 22 NP	22 (82%)F; 21 (95%)NP	1.4 F; 1.4 NP	1.5 F 1.1 NP47
Uncontrolled						
B63	OL MC, DBP> 120 mm Hg	51	34	32(94%)	1.3	1.9
B67	OL MC, DBP> 120 mm Hg	42	36	28 (78%)	1.5	1.0
B85	OL MC, DBP> 120 mm Hg	34	31	27 (87%)	3.0	7.6
B69	OL MC, DBP> 120 mm Hg	28	25	22(88%)	1.0	1.0

- All trials were open-labeled or positive controlled with concurrent therapies allowed till shortly before fenoldopam infusion. Consequently, any drug effect that was observed in these studies was confounded by the onset of any hypotensive effects of drugs taken shortly before the start of the infusion.

- None of the studies were able to define the relationship between dose and/or serum concentration and blood pressure or heart rate response in the targeted population. Consequently, dosing instructions such as the initial infusion rate, infusion rate changes, as well as how long to wait between such changes could only be derived in broad strokes from the empirical data base.

- Few of those enrolled in the clinical studies were convincingly emergent hypertensives, that is subjects with ongoing end-organ dysfunction, such as intracranial bleeding, grade III-IV Keith-Wagner retinopathy, congestive heart failure of proteinuria etc. Consequently, safety from the studied population could not necessarily be extrapolated to the proposed treatment population.

The sponsor did not submit any new studies in support of this indication. The sponsor did, however, reanalyze the data from the already completed and reviewed studies. Although neither of these analyses have been verified by this Division, they will be briefly described below. The first analysis, dated 10 February 1992, examined the pre-infusion blood pressure measurements of the original studies, with the intent of demonstrating that baseline vital signs were sufficiently

stable before the start of the infusions. Any rapid decreases or inflection of the blood pressure measurements with the start of the fenoldopam infusion must, therefore, be attributed to drug.

Based on a cohort of 297 fenoldopam and 119 nitroprusside subjects who had at least two baseline blood pressure measurements prior to the beginning of the infusion of active drugs, the slope of blood pressure versus time prior to the infusion was not distinguishable from zero (with confidence intervals for the median change of -0.042 to 0.035 mm Hg/min for fenoldopam and -0.011 to 0.0045 mm Hg/min for nitroprusside)[8]. Among these subjects, the median time of observation before infusion was 33 minutes. Among the small cohort of (n=16) of fenoldopam subject who receive no anti-hypertensive therapy within 24 hours of the infusion, the median slope was also not distinguishable from zero (confidence intervals were greater because of the small size of this cohort).

The second re-analysis was the effect of blood pressure response in those subjects whom the sponsor considered as having hypertensive emergencies. The original sponsor ( ) collated all such subjects from among those enrolled in the studies listed in Table 4. Subjects with hypertensive emergencies are severely hypertensive, with compromise to sensitive end-organs. End-organ compromise can take the form of either hypertensive encephalopathy, CVA (TIA, cerebral infarction, intracerebral hemorrhage), myocardial ischemia, acute pulmonary edema, hypertensive nephropathy or hypertensive retinopathy (Grade III or IV Keith Wagner Fundoscopic changes).

identified a total of 143 subjects with hypertensive emergencies, with 38 of these subjects originating from study D1101. The vast majority (76%) of those ascertained as hypertensive emergencies, were defined by the presence of hypertensive retinopathy. The defining condition for hypertensive emergencies, however, was not further described for each study. Based on a simplistic calculation, approximately 29 subjects from study D1101 should have had hypertensive retinopathy. However, I could only count 8 such subjects with symptoms suggestive of hypertensive retinopathy (with descriptors such as severe hypertensive retinopathy, cotton wool spots, flame hemorrhage, Grade III Keith Wagner eye grounds). Furthermore, these descriptors may reflect past as oppose to presenting ophthalmologic findings. In summary, I could not verify that those who were counted as emergent hypertensives, were truly as listed.

In summary, although the first re-analysis is suggestive that fenoldopam is an antihypertensive medication for those with severe hypertension (study #94-05 would confirm that fenoldopam is an anti-hypertensive drug), the safety and

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[8]So over a 60 minute period the blood pressure change would be between -2.4 to +2.1 mm Hg for fenoldopam and between -0.7 to +0.3 mm Hg for nitroprusside.

efficacy in an emergent hypertensive population is not supported by the submitted data base.

VI c. Use in post-operative Hypertension.

Two pilot studies (study A 50 and D1102) and one large single blind, positive controlled (nifedipine) study (study C1101) were submitted in support of the use of fenoldopam to rapidly drop blood pressures post-surgery. Blood pressure was decreased in the fenoldopam group, and the decrease was apparently more rapid in the fenoldopam treated group than in the positive nifedipine control group. There were, however, problems in the study's design (it was open labeled) and in its implementation (the randomization was not adequately protected, several unplanned interim analyses were performed and the study size changed or the study terminated based on these unplanned analyses). Although there is general agreement within the literature that post-operative hypertension is bad, there is no data to suggest that altering post-operative hypertension routinely results in clinical benefit. In none of the studies on the use of fenoldopam in post-operative hypertension was any clinical benefit established. Bleeding episodes were numerically (though not statistically) increased in the fenoldopam, relative to the positive control, nifedipine (5 versus 1) treated patients.

VII. Dose and Dose Range.

Based on study #94-05, an infusion rate of 0.04 ug/kg/min results in supine diastolic blood pressure decreases of approximately 7 mm Hg. This infusion rate is the lowest rate studied in this population. Based on empirical data, no instructions can be written for a more gradual lowering of the blood pressure, however, based on simulated data from the PK-PD model, infusion rates of 0.02 ug/kg/min might be a reasonable starting dose.

In the empirical data base in severe hypertensives (see Table 3), the starting dose ranged from 0.1-0.2 ug/kg/min in hypertensives, to 0.8 ug/kg/min in post-operative hypertension. Although the 0.8 ug/kg/min infusion dose was well tolerated in the post-operative study, similar or greater initial infusion rates in studies #94-07 and #94-05 in mild-moderate hypertensives led to substantial and possibly excessive blood pressure decreases. Table 2 and 3 indicates the anticipated blood pressure decrease as a function of the infusion rate.

Table 5. Dosing regimens employed in Clinical studies.

Study	No patients	# Centers	Initial dose (ug/kg/min) unless otherwise stated	Dose increases (ug/kg/min) unless otherwise stated	Interval between Dose Changes	Maximum dose
A14	26	2	0.1	0.1	10/30*	1.5
A52	22	6	0.1	0.1	30	

B63	51	7	0.1	0.2	10/20+	1.5
B67	42	5	0,1	0.2	20	1.5
B69	28	3	0.2	0.2	20	1.5
B74	27 Fenol/26 Nitropru	7	0.1 Fenol/ 0.5 Nitropru	0.2 Fenol/ 1.0 Nitropru	15	1.5 for Fenol; 8.0 for nitropru
B85	34	11	0.1	0.1	20	1.5
D1101	90 Fenol/93Nitropru	24	0.1Fenol/ 0.5 Nitropru	0.2 Fenol/ 1.0 Nitropru	10	1.6 for Fenol/ 8.0 for Nitropru
C1101-post operative HBP	62 Fenol/64 Nifedip	8	0.8 Fenol / 1 mg/hr Nifedipine	0.2 ug/kg/min Fenol/ 1-step to 1.25 mg/kg /hr Nifedipine	10 minutes	1.6 for Fenol/ 1.25 mg/hr for nifedipine

* Protocol was amended after 7 patients were enrolled; the titration interval was changed from 10 to 30 minutes
+ Protocol changed after 23 patients were enrolled. The titration interval was changed from 10 to 20 minutes .
Fenol=Fenoldopam; Nitropru=Sodium nitroprusside; Nifedip=Nifedipine (intravenously)

Based on study # 94-05, the kinetic half-life of fenoldopam of approximately 5 minutes. This half-life coupled with what appears to be a tight relationship between concentration change and blood pressure response, indicates that the steady state effect of a given infusion would be reached in approximately 20-25 minutes. The magnitude of the infusion rate changes should, therefore, be predicated on the initial response and the goal blood pressure drop (see Tables 2 and 3). The empirical data base predicated changes in titration rates of between 10-30 minutes.

The maximal dose studied #94-05 was 0.8 ug/kg/min. In the small number of subjects in study #95-07 who received initial doses greater than 0.8 ug/kg/min, there was excessive decrease in supine diastolic blood pressure, associated with excessive tachycardia. Doses as high as 1.6 ug/kg/min have been used in the empiric data base, but only as a culmination of a dose-titration regimen usually starting at 0.1 ug/kg/min.

Dose reductions result in substantial and rapid reversal of the blood pressure and heart rate response of fenoldopam (see Appendix C).

VIII. Safety.

There are two discrete data bases that define the safety of intravenous fenoldopam. The first was reviewed by Dr. B. Freedman on 9 November 1990, the second was the data base collected by Neurex Pharmaceutical and was included in this resubmission. There is actually a third data base, that of patients who received fenoldopam as one of several oral fenoldopam formulations. The oral route, however, is no longer actively being pursued because of diminished anti-hypertensive effectiveness with time. Based on total fenoldopam, this drug as an

oral formulation, is poorly bioavailable (approximately 5%). The contribution of the individual enantiomers of fenoldopam (i.e. active and inactive) to the total fenoldopam concentration after oral administration has not been characterized. Based on the limited fenoldopam exposure after oral formulation, as well as the uncertain composition and activity of the corresponding total fenoldopam blood levels, I've not further tabulated the safety of these formulations. The oral safety was reviewed by Dr. B. Freedman along with the original submission (see Dr. B. Freedman's review of 9 November 1990).

The data base reviewed by Dr Freedman for the intravenous formulations was collected and collated by and included those events captured by the original NDA as well as events which occurred through 13 June 1990. That safety review includes the safety results of study D1101 and A52. The efficacy results of these two studies were not included in the original NDA. Dr. Freedman's safety review is summarized below but the original CRFs have not been retrieved and re-reviewed.

A total of 802 subjects/patients were treated with intravenous fenoldopam. Of these subjects[9], 320 were severly hypertnsive and 64 were mildy hypertensive subjects. An additional 214 subjects were treated with intravenous fenoldopam for conditions other than hypertension, including renal failure, cirrhosis and congestive heart failure.

The cumulative doses of fenoldopam that was given intravenously to severe hypertensive patients ranged between 0.25 to 104.4 mg, with the duration of infusions ranging from 2-46 hours. The median duration of exposure to fenoldopam was approximately 7 hours. The median dose for treatment was approximately 0.1 ug/kg/min. The maximum dose of fenoldopam in the different studies ranged from 0.1 to > 1.5 ug/kg/min. The vast majority (76%) of those in the severe hypertensive data base had maximal doses of between 0.1-0.69 ug/kg/min. The mean duration of the maximum infusion was between 1-2 hours. Concurrent antihypertensive therapies, however, were often administered after only short exposure to fenoldopam alone.

The demographics of those 320 subjects with severe hypertension were: mean age of 49.4 years (range 17-80), gender male (56%), caucasian (48%) black (50%).

Among the 802 subjects who received intravenous fenoldopam one subjects (with CHF) died during therapy due to ventricular fibrillation. Ten additional subjects died within 30 days of completing therapy. One hypertensive patient died of

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[9] There were 8 studies that treated severe hypertensives with fenoldopam.

A14(n=26) A52 (n=22) B63 (n=51) B67 (n=42) B69 (n=28)
B74 (n=27) B85 (n=34) D1101 (n=90)

an aortic dissection. This death occurred 8 days post-infusion.

Of the 802 subjects (both hypertensive and non-hypertensive) treated with intravenous fenoldopam a total of 42 subjects (5.2%) discontinued due to adverse events. Among the 384 hypertensive subjects (severe and mild), 28 (7.3%) discontinued due to adverse events. The most frequent causes of adverse events were cardiovascular in nature (5% of those enrolled) and included events such as hypotension, decreased blood pressure, abnormal ECG, dizziness and flushing.

Among the studies that were submitted there were two nitroprusside controlled studies (D1101 and B-74). The adverse event profile is tabulated below:

Table 6. ADRs in Positive Nitroprusside Controlled Studies.

	Study B 74		Study D1101		
Event	Fenoldopam n=27	Nitroprusside n=26	Fenoldopam n=90	Nitroprusside n=93	
Hypotension/Decreased BP	2	5	8	10	
Flushing	5	5	5	4	
ECG abnormal	2	—	—	—	
Nausea/vomiting	6	4	14	14	
Headache	3	4	15	15	
Dizziness	2	—	2	5	
Hypokalemia (<3.0)	1	2	7	3	

The second data base contains the results for those studies submitted by Neurex and are reviewed in this submission. There were a total of 27 pharmacodynamic and efficacy studies[10] that cover a wide range of indications and patient populations. The populations including those with post-operative hypertension, severe hypertension, CHF and renal failure. Patients received fenoldopam at doses ranging from 0.01 ug/kg/min to 2 ug/kg/min. Infusions were relatively short in duration ranging from less than 4 hours to 48 hours.

In this data base, a total of 424 subjects were exposed to fenoldopam and 125 to comparators (these were not necessarily independent patients, since some subjects were enrolled into cross-over studies). The various comparator treatments were nifedipine, 64 subjects; placebo, 49 patients; nitroprusside, 10 patients and dopamine 2 subjects.

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[10]Studies :# 95-5, #94-7; #C1101; #A50; #A52; #B89; #B1101; #D1102; #A-54; #A-49; #B1105; #A9902; #B-87; #B-1206; #B-1207; #-1208; #B-1214; # A-44; #A-45; #B-1401; #B-1403; #B-1407; #B-1901; #B-1904; #B-1404; #239; #A-9903

There was one subject treated with fenoldopam that died during the infusion. This subject, enrolled in study B1904, died from events related to the rejection of cardiac transplant. An additional 12 subjects that died after but within 30 days of the infusion. The vast majority of those who died shortly after infusion died of their baseline medical conditions. One subject with severe hypertension at baseline died 8 days after therapy, from a presumed aortic dissection. The other 11 deaths were a result, either of baseline conditions or from complications of these conditions. The baseline conditions were: 2 subjects with CHF; 1 with renal failure; 4 with sepsis; 3 who were respirator dependent (1 subject died of renal failure) and 1 cardiac transplant. These subjects died 1-23 days following the end of the study infusion.

Among those subjects included in the recent safety update (inthe Neurex data base, a total of 28 fenoldopam, six nifedipine and 3 placebo treated patients discontinued or dropped out for adverse events (excluding death).

Twelve of the fenoldopam subjects and all the nifedipine subjects who discontinued were enrolled in a study of fenoldopam or nifedipine to control post-operative hypertension (Study C1101). Tachycardia (n=5) and rebleeding (with or without hypotension, n= 4) were the most common adverse event for discontinuing fenoldopam during this study. Other subjects discontinued for AV-block; and hypotension and tachyrhythmia.

Among the other 15 dropouts for adverse events while on fenoldopam, ten of these discontinued due to cardiovascular adverse events [decreased blood pressure (n=3); and one each of bradycardia; hypertension; tachycardia; myocardial ischemia; intracranial hemorrhage, worsening CHF; and palpitations]; 2 for gastrointestinal events (nausea and vomiting; and for diarrhea with restlessness and blurred vision) one with an unspecified lung disorder and one with a hematoma and 1 for confusion and agitation.

Among the nifedipine patients, the most frequent adverse events which lead to discontinuation were tachycardia with or without hypotension (n=4). Rebleeding occurred in only one nifedipine patient. One of those with hypotension, had a myocardial infarction but presented with hypotension in conjunction with AV block. One additional subject had an unspecified arrhythmia associated with low cardiac output. Both the low output and arrhythmia resolved. The three placebo patients (protocol B87) discontinued for agitation and insomnia; general pain, dyspnea and nervousness; and heart failure and dyspnea.

Not surprisingly, vital signs were most frequently changed during the course of fenoldopam therapy. The vital sign changes usually represent over-exuberant pharmacological response, that is hypotension or an excess of the homeostatic counter-regulation i.e. tachycardia-usually defined as a heart rate >120 BPM. The median heart rate increase among mild-moderate hypertensives in study 94-05 treated with 0.8 ug/kg/min was 23 BPM.

With respect to laboratory measurements, the major consistent finding was an increase in the frequency of hypokalemia (defined as a $K^+ < 3.0$). In the comparative nipride studies, however, the frequency of fenoldopam and nitroprusside subjects with hypokalemia was similar.

With respect to ECGs, the two nitroprusside controlled data bases in severe hypertensives are tabulated below. In both studies, QTc increased during or at the end of fenoldopam infusion. In the larger of the two data bases, the increase in QTc on fenoldopam does not materially differ from that observed with nitroprusside. The ECGs are not easily accessible to review (they belong to SmithKline Beecham and have not been retrieved by Neurex). Since fenoldopam will be given only for short term treatment in a controlled environment, the possible prolongation of QTc would require monitoring and this should be included within labeling. There will also be additional ECG data from the emergent hypertensive subjects that has not yet been submitted to this Division. The ECG data from this study will be incorporated into any labeling.

Table 7. QTc Changes While on Fenoldopam. Mean ± SEM

	Fenoldopam		Nitroprusside	
	Baseline	Change On Therapy	Baseline	Change On Therapy
Study B74	454.6 ± 7.2 (n=25)	11.5 ± 4.1 (n=26)	454.2 ± 6.5 (n=26)	-2.6 ± 8.1 (n=26)
Study D1101	437.1 ± 6.4 (n=83)	9.5 ± 4.3 (n=68)	439.4 ± 7.7 (n=88)	9.6 ± 10.5 (n=67)

VIII a. Intra-ocular Pressures.

Corlopam® clearly increases intra-ocular pressure (IOP). In subjects with normal intra-ocular pressure at baseline, fenoldopam increases IOP measurements in a dose and time dependent manner (study #9903). Onset of effect is rapid. By the first measurement of IOP during the infusion (20 minutes after the start of the infusion), steady state effects are evident. At a dose of 1 ug/kg/min the IOP increased by approximately 6 mm Hg. Offset of effect seems somewhat slower with a half life of decline in IOP of approximately 20 minutes (the onset half-life was obviously much quicker since steady state effects were seen by 20 minutes). Caution should, therefore, be exercised in the use of fenoldopam in subjects with increased IOP

VIIIb. Teratology.

Teratology studies were performed in both rabbits and rats. In all studies, the animals were orally and not intravenously dosed with fenoldopam. Given the low oral bioavailability of fenoldopam coupled with the rapid clearance of this drug,

systemic exposure during pregnancy in these studies is likely minimal. Although oral studies are standard even for drugs that are to be administered intravenously, the labeling should caveat any conclusions of non-effect with the uncertainty of the relevance of the oral studies to the proposed route of administration.

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APPENDIX A

Hypertensive Patients

Protocol	Subjects	Design/Dose	Sponsor's Analysis	Sponsor's Comments	Additional Comments
A-25/US	Systemic and renal hemodynamics, urine prostaglandins 10 healthy M 10 M with essential HBP	SIngle- blind, placebo-controlled, cross-over/ 0.1 ug/kg/min	•RPF increased in normals (21-26%) and in hypertensives (14.6-18.2%) •GFR increased in HTN patients but not in normals (162 ± 21 cc/min versus 122 ± 13 placebo). •Na, K excretion increase in HTN patients. •U. Volume increased in HTN patients (541 ± 86 cc/3 hour CORLOPAM® versus 262 ± 47 placebo. •Plasma renin variable. •Aldosterone increased in HTN patients and decreased in NL •BP no change in healthy controls, decreased by 4-8% in HTN with CORLOPAM® •No BP change with placebo	Diet 80 meq Na and 80 meq K for 4-7 days prior to infusion.	•No prospective statistical tests are defined, particularly for pooling the cross-over portions of the study •Apparent difference in effect of CORLOPAM® and PBO with respect to GFR, and electrolyte excretion with respect to HTN versus normals is not explained
White et al.; Archives Int Med. 1989; 149: 870-874	•11 patients with hypertensive urgency (168/124 to 252/135 and assorted renal disease •6 CORLOPAM® 5 Nipride •(this is a subset of 11 patients if 49 enrolled in B74/US protocol, in whom urinary clearance information was collected) •Means baseline CrCl approx. 69 cc/min in CORLOPAM® group and 78 cc/min in hypertension treatment, renal and endocrine function.	Open-label (Nipride) CORLOPAM® 0.1 ug/kg/min	•BP reduction with CORLOPAM® 35/26 mm Hg ; similar to nipride. •CrCl not different, but trend to increase with CORLOPAM® and decrease with NIPRIDE (p=0.10) •Urea clearance increased with CORLOPAM® (88%) compared with Nipride •FeNa, FeK, FeCa increased with CORLOPAM® compared to Nipride. •Urine Flow increased compared with Nipride •Plasma renin aldosterone without change	Many of these patients had documented reno-vascular disease	Data must be considered in the light of open-label nature of study. Contrast results with Study L-42 where effect of RPF, GFR was unchanged and excretion of electrolytes went in opposite direction.
A-14/SPA	Hypertension treatment, renal and endocrine function	26 patients with refractory HTN (DBP >115) or untreated essential HTN (DBP >120) 0.05-1.5 ug/Kg/min	•RPF increased •GFR increased 80-130 cc/min •FeNa increased •FEK increased •Filtration Fraction decreased 0.3 to 0.2 No change in plasma renin, aldosterone,prolactin •Norepinephrine increased	Natruresis, Kaliuresis beginning within first hour of infusion. Dose relationship not evaluable with study design •FF Fenol as different afferent arteriolar dilation occurred in these patients who likely had a high A II level (renin mediated HTN). FF at outset was supernormal.	•This is a baseline controlled, open-labeled study. It is unclear if fluid intake was restricted.

otocol	Subjects	Design/Dose	Sponsor's Analysis	Sponsor's Comments	Additional Comments
L-36/US	Dose ranging mild to mod HTN, open-labeled, uncontrolled 9 M, 12 F	Open-label, no controls for renal effects, Placebo-controlled for cardiac effects, hormone level/ 0.025-1.5 ug/kg/min	•RBF increased by 42% in 60-min from 483 + 161 to 685 + 228 ml/min compared with baseline measurements at 30 and 60 minutes prior to infusion of drug •GFR increased by 47% (not significant). •Urine NA, CL, Ca, Mg excretion increased. •Urine Volume increased by 57.6% compared with baseline (pre-infusion) from 383 ± 26 to 604 ± 77 ml/30 minutes •NE increased by 80% over baseline (pre-infusion) from 398 + 63 to 718 +124 pg/ml (normal range < 600 pg/ml) •Plasma renin increased by 57% over baseline (pre-infusion) from 0.51 = 0.21 to 0.8 + 0.25 ng/ml/hr (normal range 0.5-1.6 ng/ml/hr) Aldosterone decreased by 18.3%	•Renal function measured in patients who got 20 ml/Kg H2O load	This is an open label baseline controlled study. There is no data to suggest that a stable baseline has been established.
L-36 substudy Murphy et al.; Circulation 776, 6 1312-1318; 1987	Hypertension dose-response, renal hemodynamics with and without water load 17 patients with essential HTN (this substudy consisted of 17/21 patients from L-36.	Placebo-controlled open-label 0.025-0.5 ug/Kg/min •study 1 (dose response) N=17 essential HTN •study 2 (renal function (n=10F N=6 M PLC essential HTN •Study 3 no water loading	Study 1: Linear dose-response of SBP and DBP with onset of action at 0.25 ug/kg/min study 2. GFR increased 6 ml/min CORLOPAM® versus decreased by 6 ml/min PLC •Study 2 : GFR increased 6 ml/min CORLOPAM® versus decreased by 6 ml/min PLC RPF increased by 42% with CORLOPAM® versus stable with PLC RVR decreased by 35% with CORLOPAM® FE Na, Ca, Mg, uric acid and Pi increased with CORLOPAM®, no change in control group Plasma renin increased by 50% I CORLOPAM® group. Aldosterone no change NE increased in both groups more in CORLOPAM® group Study 3: BP reduction from 146/98 to 132/75 within 15-min UNA and K increased U Volume no change	The result of this substudy parallel those of L-36; however, the response to placebo is additionally provided.	The placebo control was not part of a randomized study but appears to be a study done separate from the treatment.
L-42/US	Effect of DBP reduction on renal function and NE 13 mild-moderate HTN	Single-blind, cross-over, positive control (nipride) 0.05-1.5 ug/Kg/min	RPF, GFR unchanged in either group Urine NA excretion, Fe NA decreased with nipride more than with CORLOPAM® plasma renin increased (153%-228%) versus Nipiride 103-66%) Aldosterone increased 50-80% in both groups		Note: effects of RPF, GFR are different than study A-25 above.

Summary of Renal Effects of Corlopam® in Normal Subjects

Protocol	Subjects	Design /Dose	Sponsor's Analysis	Sponsor's Comments	Additional Comments
A-25/US	Systemic and renal hemodynamics, urine prosta-glandins 10 healthy M 10 M with essential HBP	Single-blind, placebo-controlled, cross-over/ 0.1 ug/kg/min	•RPF increased in normals (21-26%) and in hypertensives (14.6-18.2%) •GFR increased in HTN patients but not in normals (162 ± 21 cc/min versus 122 ± 13 placebo). •Na, K excretion increase in HTN patients. •U. Volume increased in HTN patients (541 ± 86 cc/3 hour CORLOPAM® versus 262 ± 47 placebo. •Plasma renin variable. •Aldosterone increased in HTN patients and decreased in NL •BP no change in healthy controls, decreased by 4-8% in HTN with CORLOPAM® •No BP change with placebo	Diet 80 meq Na and 80 meq K for 4-7 days prior to infusion.	•No prospective statistical tests are defined, particularly for pooling the cross-over portions of the study •Apparent difference in effect of CORLOPAM® and PBO with respect to GFR, and electrolyte excretion with respect to HTN versus normals is not explained.
A-28 US	Effect protein feeding N=2	Double-blind, uncon-trolled crossover 0.05 ug/kg/min	RPF increased 37-75% GFR variable Fe NA increased Filtration fraction decreased 24-42% Na clearance 75-107% versus 14-31%		Under-powered to find anything
31/US	Renal function 12 healthy M 23-33 y/o	Single-blind, placebo-controlled, cross-over 0.05 ug/kg/min	RPF no change GFR no change Fe NA increased 65-112% versus 11-40% for placebo Na clearance 75-107% versus 14-31%	Diet Na 150 meq K 60 meq 20 ml/Kg H2O at onset.	Effect seems to wane at 24 hours both for FeNA and Na clearance.
A-39 US	Effects of Na balance on natruresis 31 healthy M 21-34 y (7 withdraw pre-inf)	Single-blind, cross-over, placebo-controlled, randomized	Renal plasma flow increased, somewhat more in the High Na+ diet group Urine vol increase Na+ clearance increased 110 versus 13%) GFR variable Li had no effect	16 received Li, 8 received no Li High or Low Na diet	This study was not reviewed either by Dr. Friedman or by Dr. Rodin or myself
A49 HOL	Dose versus renal hemodynamics, metoclopramide effect 7M 3F 18-56 y/o	Open-label, uncon-trolled, 0.05-0.5 ug/kg/min	RPF increased in dose-dependent manner (max 36%) •GFR no change •PRA and aldo increased. :less plasma renin rise with metoclopramide •metoclopramide no effect of CORLOPAM® effect on RPF or GFR but did increased DBP.		This study was not reviewed either by Dr. Friedman or by Dr. Rodin or myself

34 US	Dose versus systemic and renal hemodynamics 22 healthy M; 22-31 y/o	Open-label Uncon-trolled 0.025-1.5	RPF increased in dose-dependent manner (max 60%) GFR decreased at 0.1 ug/kg/min dose Urinary Volume increased Na excretion increased Onset of renal effect in 30 minute Metoclopramide caused no change in BP		These were several substudies that included infusions of 1/2 hour (n=7) and a second part in which subjects received any of 4 different regimens. •Baseline stability is questionable. Subjects received a water load of 20 cc/kg •Despite a large number of doses there did not appear to be a credible dose response
L-58/US	Hepatic and renal blood flow 6 healthy M 18-33 y	Double-blind, cross-over, placebo-controlled/ 0.1 ug/kg/min	RPF increased by (48%) GFR not change FeNa increased to 158 % versus 70%		No statistical analysic plan is provided
61/US	Renal function, PRA, angiotensin, aldo, cortisol 11 healthy M 18-33 y	Double-blind, cross-over, placebo-controlled/ 0.05 ug/kg/min	RPF increased 10-23% GFR slightly decreased Na excretion 239% versus 122% Osm clearance increased 120 versus > 10%-PRA, aldo, prolactin, cortisol no change	Na 150 meq K 60 meq diet 20 ml/kg load.	Value represents single time point out of 3 hours. Other values show no consistant effect of fenoldopam

Summary of the Renal Effects of CORLOPAM® in Patients with Congestive Heart Failure

Protocol	Subjects	Design /Dose	Sponsor's Analysis	Sponsor's Comments	Additional Comments
B72/US	Systemic and renal hemodynamics in CHF 25 M 10 F NYHA III to IV	Open 0.1-1.5 ug/kg/min			This study was not reviewed in any FDA review
B1206 /US	Systemic and renal hemodynamics in CHF 8 M 3 F NYHA III-IV	Double-blind, positive, cross-over (Nipride) dose to increase cardiac output by 25%	•RPF decreased in both groups • GFR no change in either group •Na excretion slightly increased (17.9% in CORLOPAM® versus -44% nipride) •U flow decreased in both groups		The renal dynamic portion of this study was not submitted or reviewed by the FDA.

1207/US	Systemic and renal hemodynamics in CHF 8 M NYHA III-IV	Double-blind, placebo-controlled	•RPF no change • GFR no change •Na excretion no change •U volume no change •Cardiac output increased in treatment group from 4.0 ± 0.42 to 5.46 ± 0.49 L/min but was unchanged in PLC group		The renal dynamic portion of this study was not submitted or reviewed by the FDA.
B-1208 /Belgium	Systemic and renal hemodynamics in CHF 6 M 2 F NYHA III-IV	Double-blind, positive-control, cross-over (nipride) dose to increase cardiac output by 25%	RPF no change GFR no change Na excretion no change U volume no change		
B-1214/US	Systemic and renal hemodynamics in CHF 9 NYHA III-IV	Open-label, dose to increase cardiac output by 25%	RPF increased 306 to 397 ml/min/1.73 M GFR no change Na excretion decreased 171 to 147 uEq/min Urine flow decreased 9.3 to 5.0 cc/min		The renal dynamic portion of this study was not submitted or reviewed by the FDA.

Patients With Other Disorders

Protocol	Subjects	Design /Dose	Sponsor's Analysis	Sponsor's Comments	Additional Comments
35 US	CAPD clearances 8 CAPD patients	Double-blind, placebo-control, randomized	Ultrafiltration no change No change in dialysate to plasma ratios		Not Reviewed
A-45/Hol	Chronic Renal Failure iv and oral 4 M 8 F with chronic renal insufficiency	0.05 or 0.1 ug/kg/min	RPF increased Na excretion increased GFR no change FF no Change U volume no change		
B81/US	Prevention of dye ATN in CRI 25 patients with renal insufficiency undergoing cardiac cath	Single-blind, placebo-controlled, randomized		Goal of 60 patients not reached because of lack of effect in the first 25. Incidence of ARF was too low	study not reviewed
B-1404	Renal Function on PEEP 33 intubated patients	mechanical ventilation with 25% decrease in urine output with initiation of PEEP 0.1-1.3 ug/kg/min	CrCl increased by 4 hours Na excretion increased by 20%		Study not reviewed (was a statistical plan submitted?)

-34/FB	Hepatic and renal hemodynamics in cirrhotics with ascites 2M 3 F alcoholic cirrhosis and ascites	open, uncon-trolled/ 0.1 ug/kg/min for 1 hour	GFR no change RPF no change Urine Volume decreased Na excretion decreased No change in BP or cardiac index		
L-51/US	Renal hemodynamics in cirrhotics 8 M 1 F	open, placebo-controlled/ 0.1-0,2 ug/kg/min	RPF no change GFR no change Na, K, H2O osmolar clearance change plasma NE consistently higher on CORLOPAM® Clearance of CORLOPAM® unchanged in cirrhotics		
A-91101 /BEI	idiopathic edema N=1	Uncon-trolled open-labeled 0.5-1.6 ug/kg/min	urine flow decreased Na excretion without change		

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APPENDIX B

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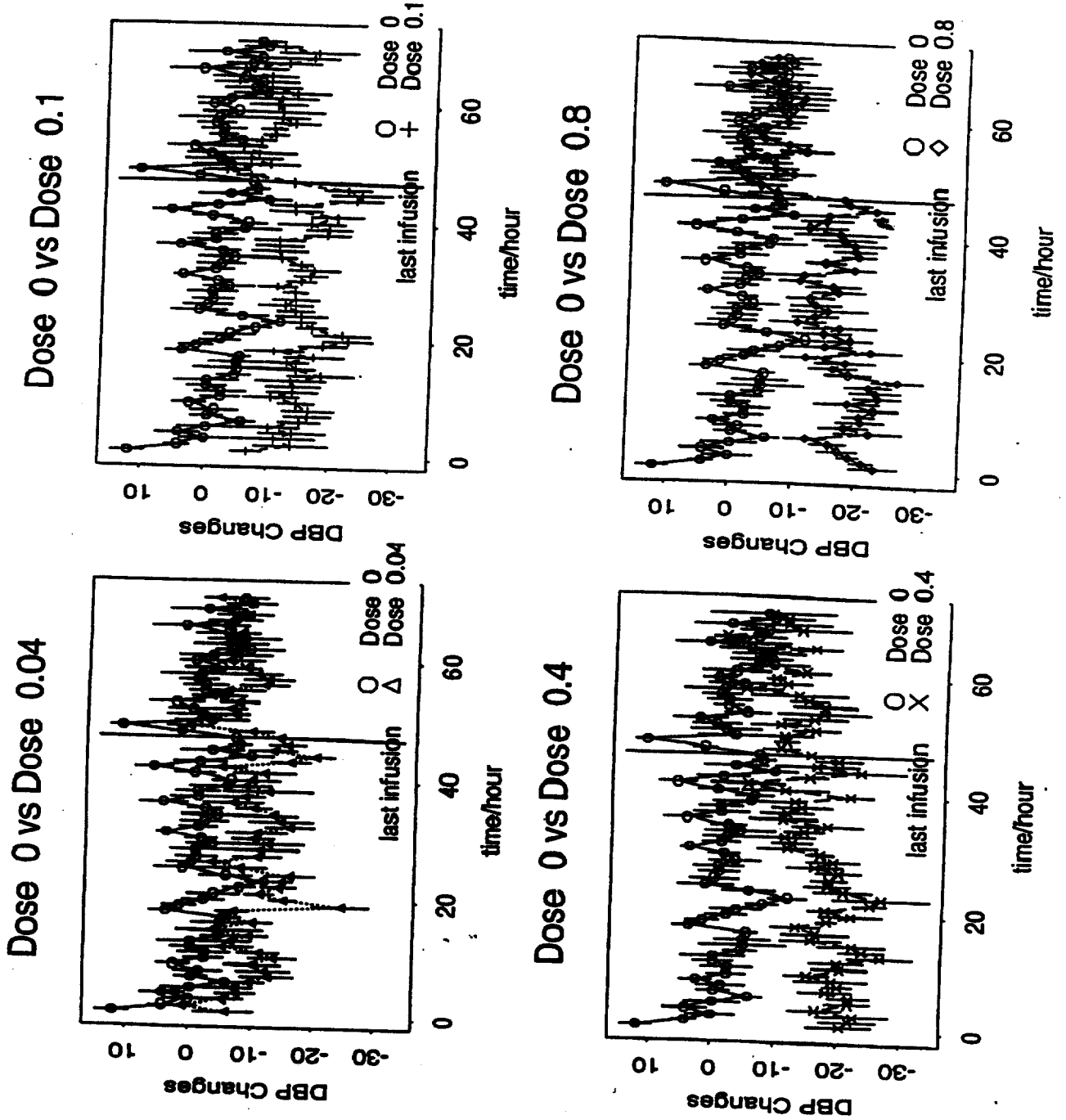
APPENDIX C


Dose 0 vs Dose 0.1
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Dose 0 vs Dose 0.04
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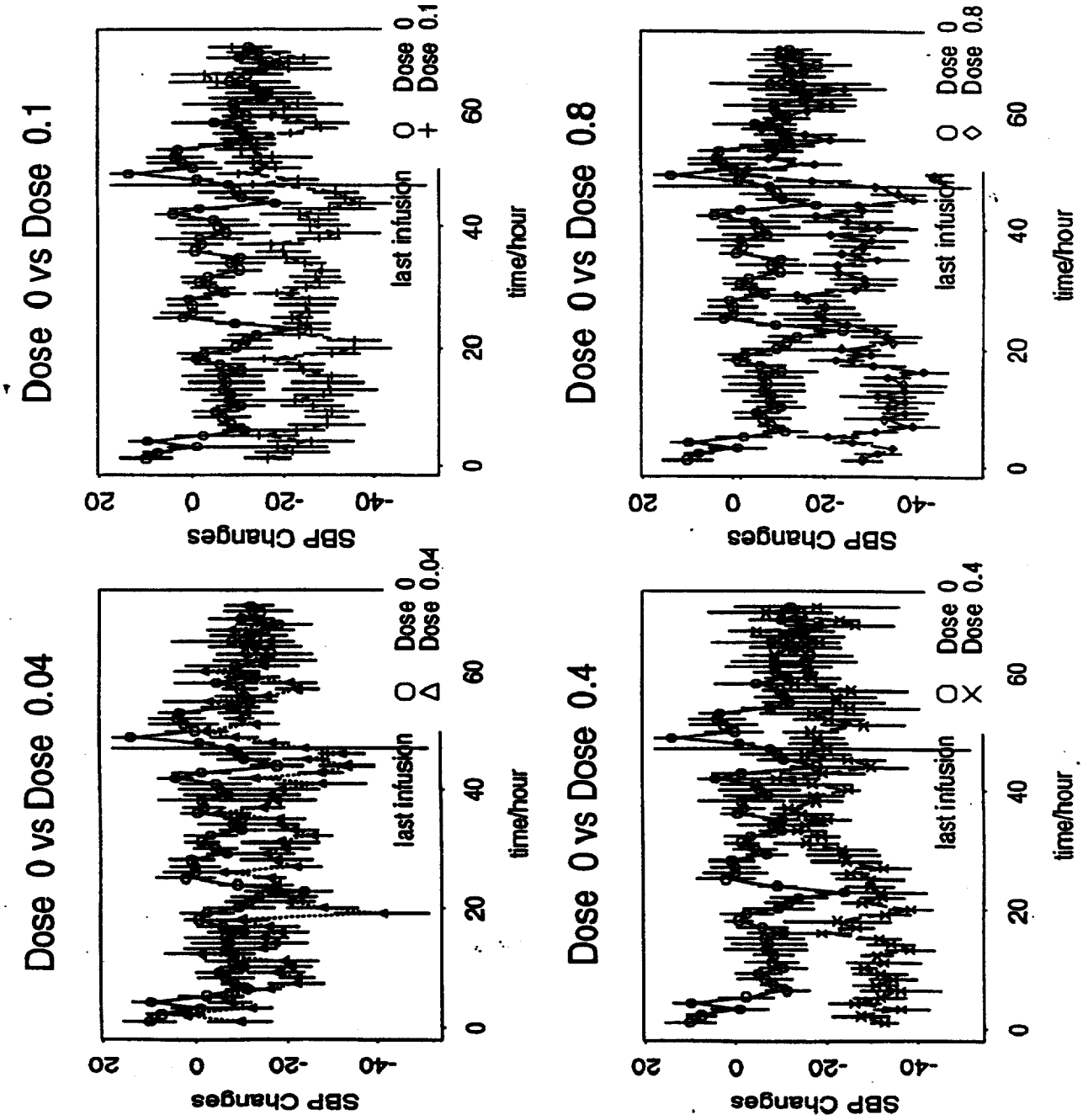
DBP Changes
time/hour
last infusion
Dose 0
Dose 0.1
Dose 0.8
Dose 0.04
Dose 0.4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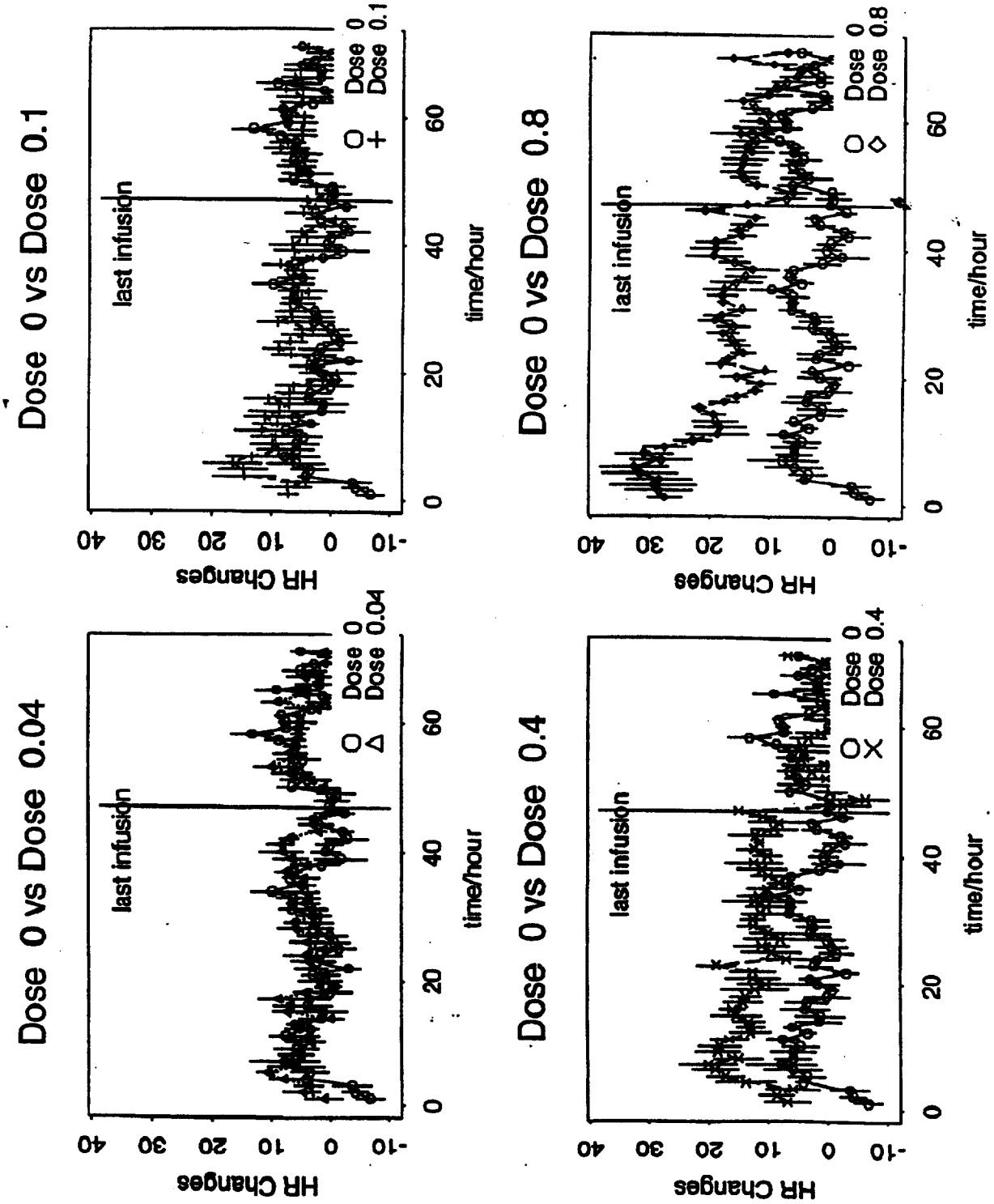
Dose 0 vs Dose 0.8
Dose 0 vs Dose 0.04
Dose 0 vs Dose 0.4
SBP Changes
time/hour
last infusion
Dose 0
Dose 0.1
Dose 0.8
Dose 0.04
Dose 0.4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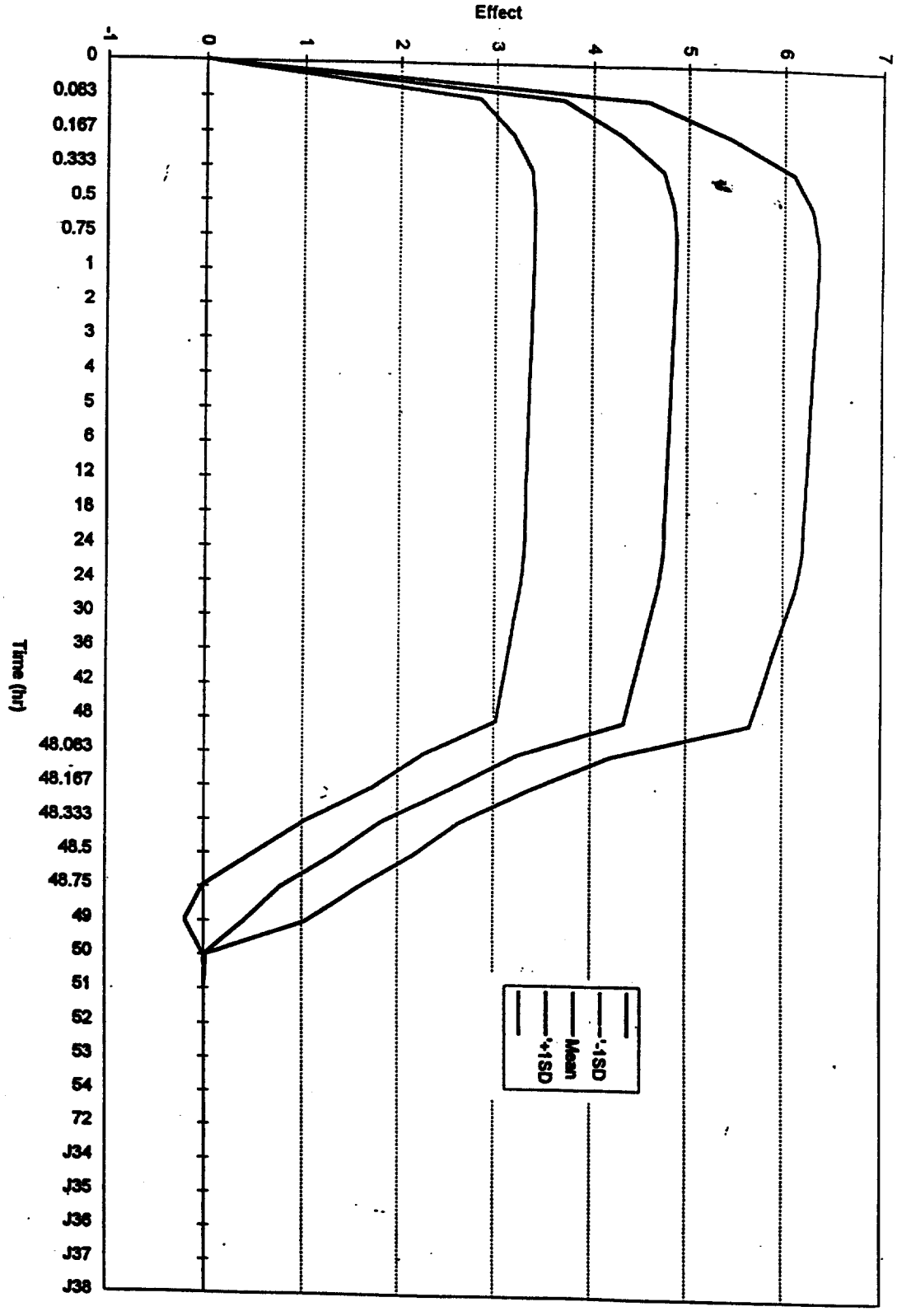
Dose 0 vs Dose 0.8
Dose 0 vs Dose 0.04
Dose 0 vs Dose 0.4
last infusion
HR Changes
time/hour
Dose 0
Dose 0.1
Dose 0.8
Dose 0.04
Dose 0.4

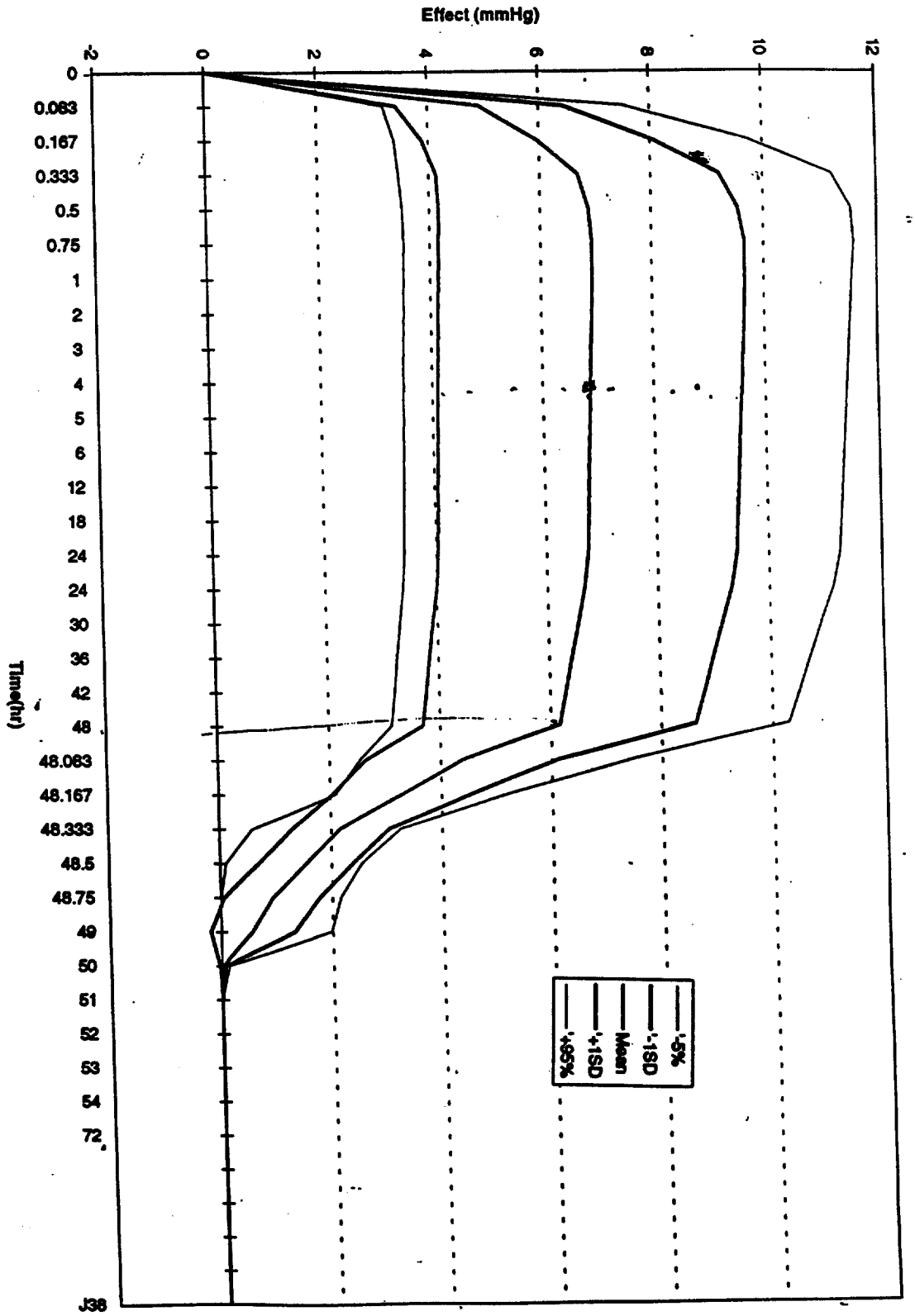
APPENDIX D

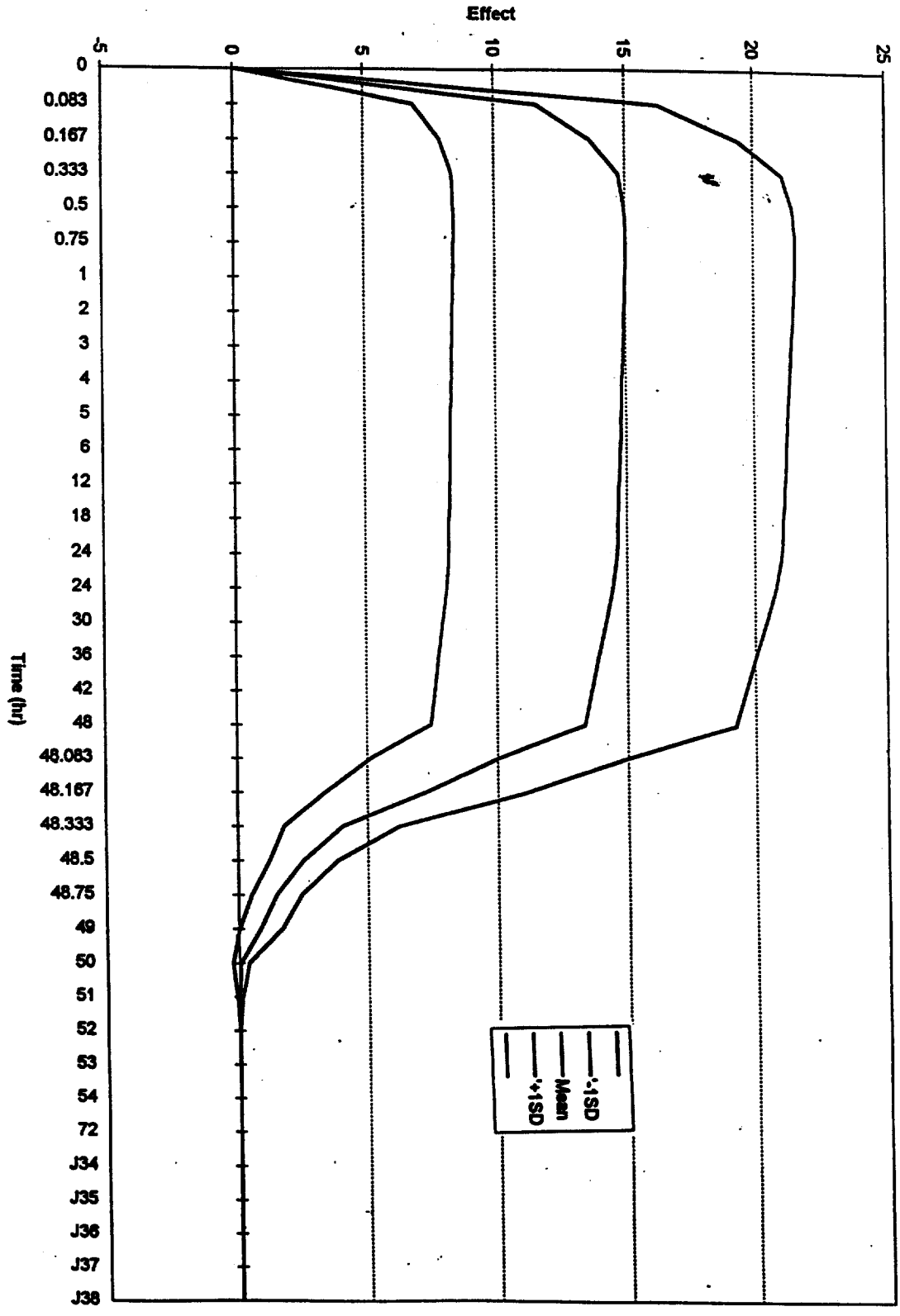
Cumulative Distribution of Effect (Reduction in DBP), Simulated for 100 Patients/Dose									
Dose ug/kg/min	Average Effect	Effect							
		<5	<10	<15	<20	<25	<30	<40	<45
0.02	5	65 %	100 %						
0.04	6	28 %	84 %	99 %					
0.1	11	3 %	54 %	85 %	95 %				
0.24	15	1 %	22 %	58 %	81 %	95 %			
0.4	17	0 %	9 %	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 %



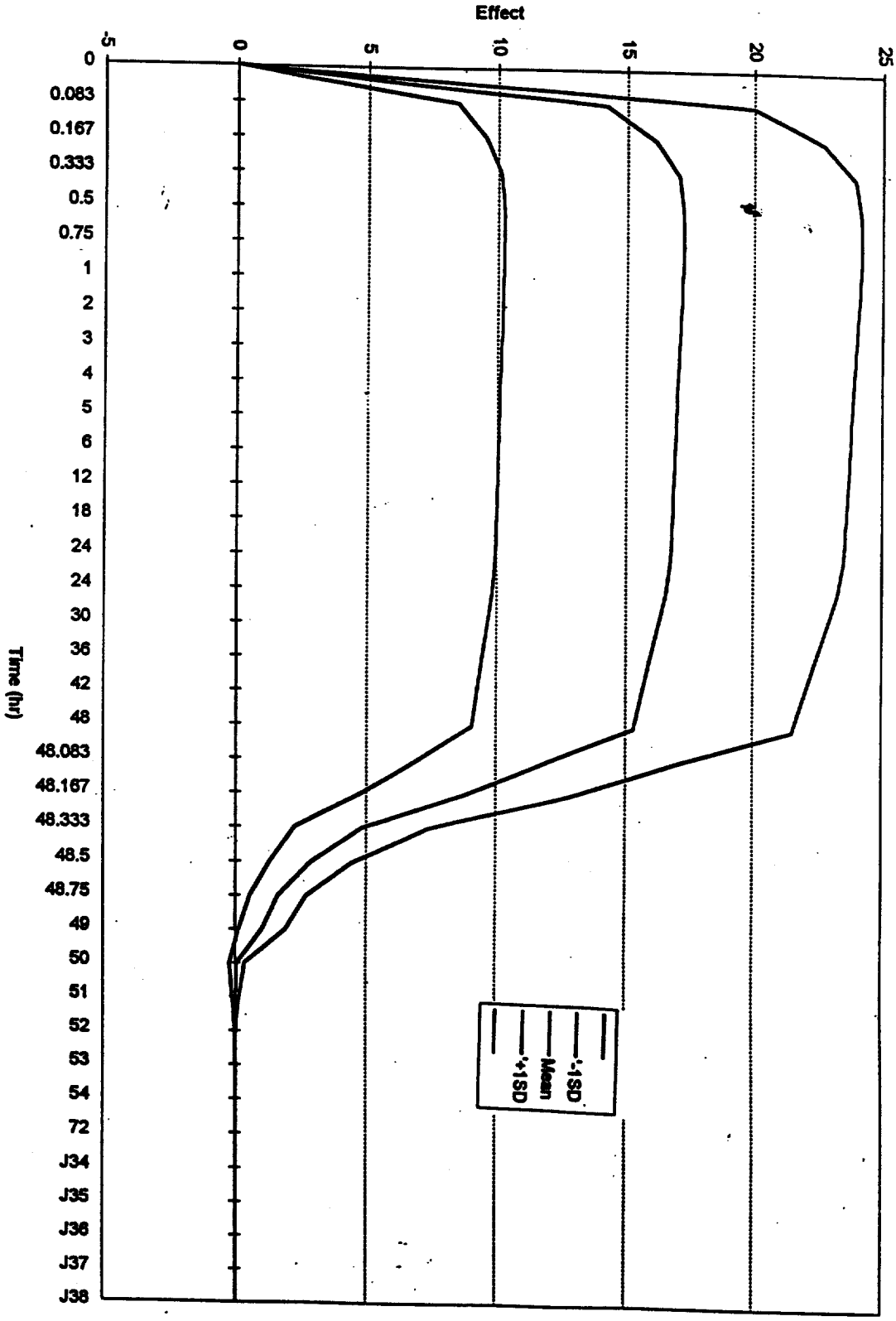
Predicted Diastolic Blood Pressure Effect for 0.02 ug/kg/min

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

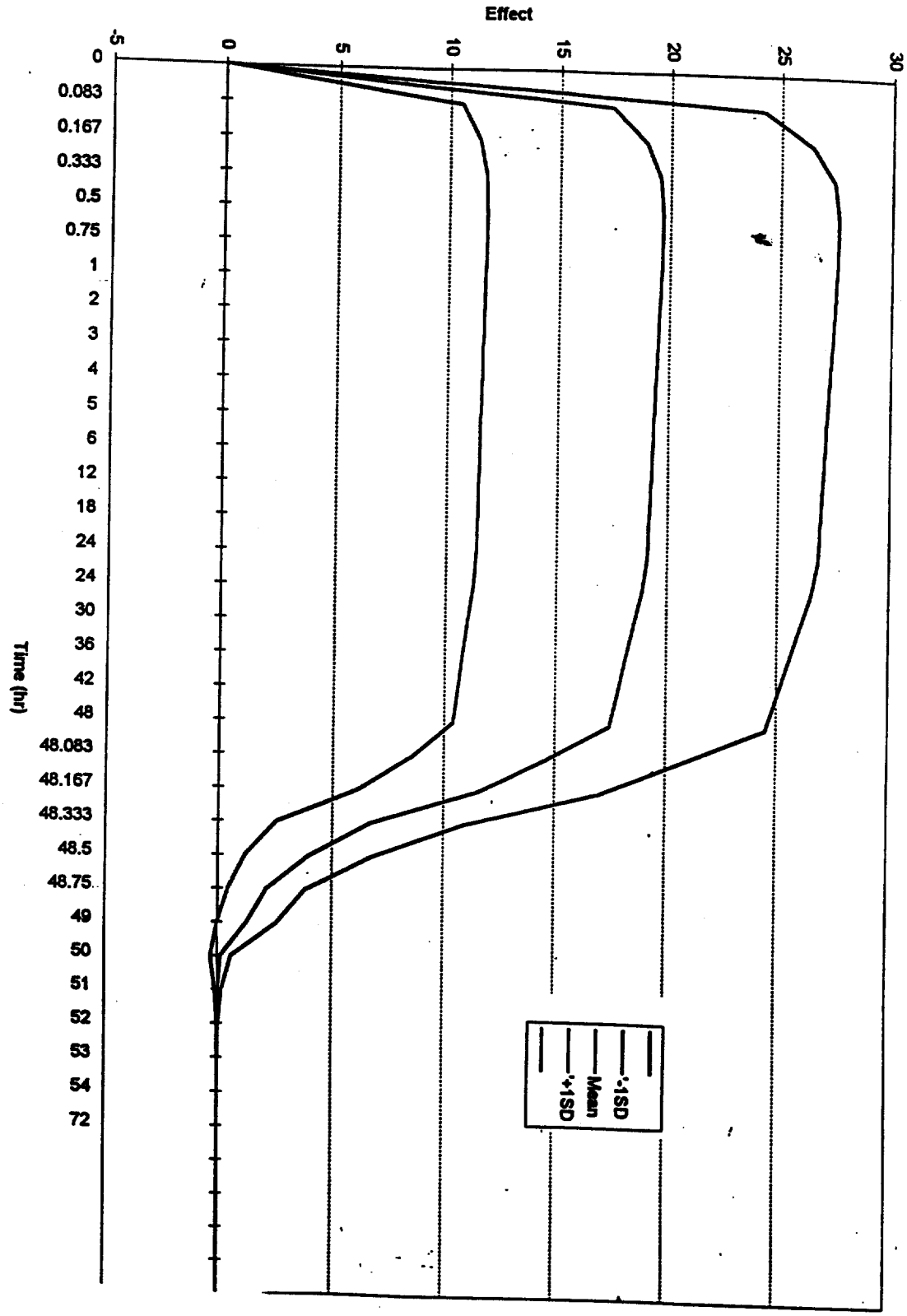




Predicted Diastolic Blood Pressure Effect for 0.24 ug/kg/min

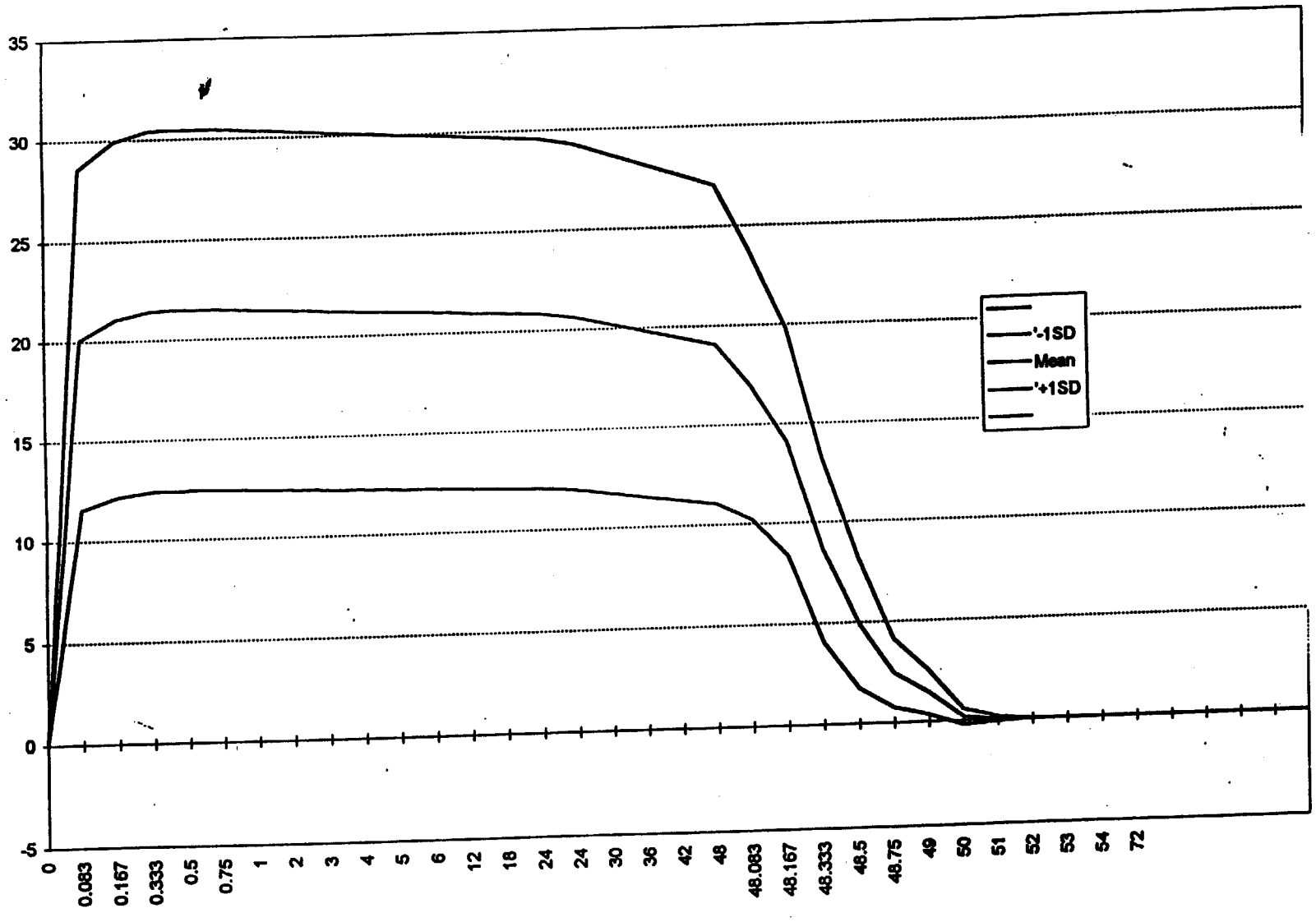


Predicted Diastolic Blood Pressure Effect for 0.4 ug/kg/min



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

Predicted Diastolic Blood Pressure Effect for 1.6 ug/kg/min



Z No.

JUL 22 1997

Summary Review Study #94-006- Fenoldopam Mesylate in Hypertensive Crises

Abraham Karkowsky M.D. Ph.D. HFD-110 7/24/97

CC: NDA 19-922
Division File
HFD-710 Kjin; HFD-860 Aparekh, AEl-Tahtawy

This document summarizes the amendment submitted by Neurex on May 5, 1997 for use of fenoldopam mesylate (Corlopam®) in the treatment of hypertensive crises. Study #94-006 is the pivotal study in support of this indication and the results of this study made up the entirety of this amendment. In addition to study # 94-006, two nitroprusside controlled and 7-open label studies, previously submitted and reviewed, constitute the data base for the use of fenoldopam in the treatment of severely hypertensive subjects. The design of the studies are summarized in Table 1, the titrations schemes are summarized as table 2. Only study # 94-006, however, prospectively enrolled or tried to enroll subjects with ongoing end-organ compromise in conjunction with severely raised diastolic blood pressure.

Table 1- Description of Studies Enrolling Severe hypertensives From the Original NDA.

Proto-col #	Design	No Treated	No Evaluable	No. (#) Successes (per sponsor)	Titration Duration mean (hr)	Maintenance Duration (hr)Tota Infusion Duration mean (hr)
D1101	OL, PC, MC, DBP> 120 mm Hg	183 90 F; 93 NP	153 75 F; 78 NP	70(93%) F 69 (88%) NP	1::26 F 1:28 NP	Mean Duration approximately 9.2 hours
B-74	OL PC, MC; DBP> 120 mm Hg	53 27 F; 26 NP	49 27 F, 22 NP	22 (82%)F; 21 (95%)NP	1.4 F; 1.4 NP	1.5 F ; 1.1 NP Mean duration 4.7 hours
B63	OL MC, DBP> 120 mm Hg	51	34	32(94%)	1.3	1.9 Mean duration 5.0 hours
B67	OL MC, DBP> 120 mm Hg	42	36	28 (78%)	1.5	1.0 Mean duration 10 hours
B85	OL MC, DBP> 120 mm Hg	34	31	27 (87%)	3.0	7.6 Mean duration 13.8 hours
B69	OL MC, DBP> 120 mm Hg	28	25	22(88%)	1.0	1.0 Mean duration 3.1 hours
B89	OL, two-Centered DBP > 120	16	16	13 (81%)	?	?
A-52	OL, MC, DBP> 120	22	21	20 (95%)	?	?
B1101	)L, single Center, SBP> 200; DBP > 120	12 (only 3 had (DBP > 120 mm Hg)	12	12 (100%)	?	?

OL=Open Labeled; PC- Positive Controlled; MC= Multicenter, F=fenoldopam; NP= Nitroprusside; DBP=Diastolic Blood Pressure. ? Data not found in study report.

Table 2. Dosing regimens employed in Clinical studies.

Study	No patients	# Centers	Initial dose (ug/kg/min) unless otherwise stated	Dose increases (ug/kg/min) unless otherwise stated	Interval between Dose Changes (min)	Maximum (ug/kg/min)
D1101	90 Fenol/93 Nitropru	24	0.1 Fenol/ 0.5 Nitropru	0.2 Fenol/ 1.0 Nitropru	10	1.6 for Fenol/ 8.0 for Nitropru

B74	27 Fenol/26 Nitropru	7	0.1 Fenol/ 0.5 Nitropru	0.2 Fenol/ 1.0 Nitropru	15	1.5 for Fenol; 8.0 for nitropru
Uncontrolled						
B63	51	7	0.1	0.2	10/20+	1.5
B67	42	5	0,1	0.2	20	1.5
B85	34	11	0.1	0.1	20	1.5
B69	28	3	0.2	0.2	20	1.5
B89	16	2	0.1	0.1	>20 min	2.0
A52	22	6	0.1	0.1	> 30 min	1.5
B1101	12	1	0.2	?	?	?

* Protocol was amended after 7 patients were enrolled; the titration interval was changed from 10 to 30 minutes
+ Protocol changed after 23 patients were enrolled. The titration interval was changed from 10 to 20 minutes .
Fenol=Fenoldopam; Nitropru=Sodium nitroprusside; Nifedip=Nifedipine (intravenously)

It is clearly difficult to perform a study in a volatile hypertensive population such as in protocol # 94-006. These subjects are only infrequently found, are usually medically unstable and they must also be evaluated and treated in an expeditious manner. Despite the inherent difficulties in performing these studies it is nevertheless, important that study #94-006 be critically analyzed.

Despite the prospective requirement, that subjects enrolled into study be both severely hypertensive (DBP > 120 mm Hg) as well as have evidence that end organs were compromised, or alternatively to have a supine diastolic blood pressure of > 140 mm Hg, independent of any end organ compromise, there were many subjects who were enrolled in study # 94-006 that did not convincingly fit either of these sets of entry requirements.

The sponsor notes that there were 10 subjects who had supine diastolic blood pressures below 120 mm Hg at baseline (see Table 14 within this review). A more careful review, limiting the measurements that define baseline to those performed within 1 hour of infusion, suggest that there are 20 subjects whose blood pressure may have been below the pre-specified 120 mm Hg (there are 22 subjects listed in the review Table 8, however, patient #008/001 and #008/009 listed within that table were listed there because they had only one or two measurements of blood pressure within the hour prior to infusion, not the three as proposed by the protocol. These measurements however, were > 120 mm Hg).

Among those subjects who were enrolled because their supine diastolic blood pressure was > 140 mm Hg with no end-organ dysfunction, only four of the eight subjects so defined by the sponsor's assessment of baseline, satisfied this criteria.

It is unclear how many such subjects in study # 94-006, truly had on-going end-organ dysfunction. Clearly, some of those enrolled had end-organ dysfunction,

as judged by objective findings such as papilloedema, elevations of creatinine and BUN or hematuria (with no previous history of renal dysfunction), and/or acute onset of pulmonary edema, or an ischemic pattern on ECG (with no previous history of cardiac dysfunction).

Other subjects had evidence of end-organ damage but these subjects had a previous history of compromise of these end organs. For example several subjects BUN and creatinines values that were abnormal at enrollment, however, they had a history of abnormal renal function tests. Others had evidence of shortness of breath or angina but had histories of these disorders in the past. Others had headaches which were not further described as to their onset, progressiveness or severity. Whether these subjects had hypertensive emergencies or hypertensive urgencies (severe hypertension absent progressive end-organ dysfunction) in not clear.

It is impossible to know exactly how many of the subjects that were enrolled had hypertensive emergencies. The sponsor in a submission dated 21 May 1997 listed 37 subjects with what they claim was objective evidence of hypertensive crises. Other subjects with no objective end-organ findings, nevertheless, probably had hypertensive emergencies. It is likely that the true number of such emergencies among those enrolled within this study was somewhere between 40-60 subjects[1] This number is only crucial in assessing whether there is an adequate safety data base to approve this drug for use in this population. Among the 313 subjects with severe hypertension enrolled in the other controlled and uncontrolled studies, there are likely to be additional subjects (but the number is not known) who fit the definition of hypertensive emergencies.

There is no doubt that fenoldopam decreases blood pressure in a severely hypertensive (whether these are urgent or emergent) population and that this blood pressure decrease (both diastolic and systolic) is both substantial and occurs in a dose-related manner. At 4 hours the decrease in SDBP ranged from -11.5 for the 0.01 ug/kg/min dose group to -29.1 mm Hg for the 0.3 ug/kg/min. There are similar decreases for supine systolic blood pressures (-14.4 for the 0.01 ug/kg/ infusion to -37.3 mm Hg for the 0.3 ug/kg/infusion) and reciprocal increases in heart rate (-2.2

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[1]There were 94 subjects that were enrolled and received medication, 22 did not have convincing evidence of DBP > 120 mm Hg, however 2 or 3 of these , nevertheless, had objective evidence of end organ dysfunction. Subtracting off 19 This leaves 75 subjects. There were an additional 4 subjects who were enrolled as having DBP > 140 and no end organ dysfunction whose blood pressure at baseline was actually < 140 mm Hg. This leaves 71 subjects.

There were 19 subjects whose only manifestation was neurological -most had headaches listed. Of these, eight were already included among those whose blood pressure was not convincingly above 120 mm Hg. There were in addition 2-3 such subjects who had manifestations more complex than headache. So that this leaves an additional 8 subjects whose BP was > 120 with simple headaches as the end organ involved . Subtracting these subjects leaves 63 subjects.

There were 12 subjects with baseline ECG evidence of ischemia, however, despite adequate blood pressure control only one subject's ECG was read as improved. It is therefore, unclear how many of these truly had marginal coronary artery function as a consequence of high blood pressure at baseline. Subtracting these subjects leaves approximately 52 subjects who might have true hypertensive emergencies.

for the 0.01 ug/kg/min infusion to + 10.6 BPM for the 0.3 ug/kg/min infusion rate)

Table 3. Study 94-006 Effect of Fenoldopam Infusion at 4 hours (sponsor's Analysis)

Effect at 4 hours Change from Baseline	Infusion Rate ug/kg/min			
	0.01	0.03	0.1	0.3
Supine Diastolic Blood Pressure (mm Hg)	-11.5	-18.4	-20.7	-29.1
Supine Systolic Blood Pressure (mm Hg)	-14.4	-20.1	-22.6	-37.3
Heart Rate (BPM)	-2.2	-0.1	+4.4	+10.9

Curiously, the time course for the decrease in blood pressure in this population markedly differs from that seen in mild-moderate hypertensives (see Figures 7and 8 for SDBP and Figures 9 and 10 for SSBP as well as individual subject in Figure 13) and compare this with the data in Appendix C of the review dated May 1, 1997 (reproduced here also as Appendix C).

In the severe hypertensives, over the first four hours where titration upward and concurrent therapies were infrequent, there was a steady decline in blood pressure measurements. Even up to between 8-12 hours after the start of the infusion, when few subjects received concurrent therapies, blood pressure measurements continue to decline.

Dose and Dosing Instructions:

All doses that were studied reduce diastolic blood pressure. At one hour after the start of the infusion, the blood pressure decreased in the lowest and highest infusion rates of - 6.6 and -22.3 mm Hg, respectively (see Review Table 16). At four hours, the corresponding decreases from baseline were somewhere between -9.7 to -12.9 for the low dose and -25.5 to -27.6 for the high dose (depending how the four hour time point is defined I.e. The single time point versus a timeaverage between hours 3-4). The price paid for the greater reduction in diastolic blood pressure at the higher doses is a substantial increase in heart rate, -0.8 and +15.3 BPM at 1 hour for the 0.01 and 0.3 ug/kg/min dose, respectively.

Since there were no irreversible poor outcomes at any of the studied doses, the starting dose would appear to be a matter of balancing off the need for rapid blood pressure response to increase in heart rate.

How frequently should the titration be increased when there appears to be inadequate blood pressure response? The way drug was administered in this protocol, up-titration or doubling the infusion rate could be considered at hourly intervals. Dr. Grevel, Neurex's consult, estimated a terminal $T_{1/2}$ of 12 minutes for the decrease in fenoldopam concentrations in a single compartment model in this severely hypertensive population. Therefore, waiting 3 -4 half-lives would require a

dosing change of between 36-48 minutes.

Dynamic considerations of when to change dose are slightly more tricky. Superimposed on the acute drug effect is a slow gradual decline in blood pressure. Because of the absence of a placebo treatment, it is unclear if this additional drop in blood pressures is a drug related phenomenon or a drug- independent but time-dependent phenomena. Any dosing instructions should acknowledge that there would likely be a slow continuous additional decrease in blood pressure over several hours.

With respect to safety:

•There were no deaths, myocardial infarctions or strokes in the population that was studied. One subject however, had a subarachnoid bleed 8 days after completing the fenoldopam infusion.

•Compromised end-organs could not be convincingly shown to improve or deteriorate with treatment or with lowering of blood pressure.

•Six subjects had substantial increases in BUN/creatinine at follow-up when compared to entry measurements.

•Potassium levels decrease during the initial six hour of infusion decrease and these changes appear to be independent of any diuretic use.

•Group mean QTc changes were modest and not distinguishable from baseline. One subject, however, had a QTc at 12 hours of 605 $msec^{-1/2}$ (in the 0.03 ug/kg/min dose), baseline was 470 $msec^{-1/2}$. One subject also receiving 0.03 ug/kg/min infusion had QTc measured at 12, 18 and 24 hours of 533, 557 and 561 $msec^{-1/2}$, respectively. Baseline QTc was 469 $msec^{-1/2}$. QTc measurements are, however, dependent on plasma K+ concentrations that appear to decrease during treatment with fenoldopam. Whether the few subjects with QTc changes reflect direct drug effect or reflect the ionic milieu of the heart cannot be treased out from this study.

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Study Number: #94-006

Title of Study: A Phase III Multicenter, Randomized, Double-Blind (With respect to Dose) Evaluation of Intravenous Fenoldopam in Patients with Hypertensive Emergency.

Investigator and Sites:

Table 4: List of investigators

Site # 001 James Tumlin, MD Emory University Hospital ; Atlanta, GA	Site #002 James Pool (replaced by Roberto Mangoo-Karim), MD Baylor College of Medicine Houston, TX	Site # 003 Vardaman Buckalew, MD Bowman Grey School of Medicine Winston-Salem , NC	Site # 004 Michael Culpepper Univesity of Southern Alabama; Mobile, AL
Site # 005 Samuel Spitalewitz Brookdale Hospital Medical Center Brooklyn, NY	Site # 006 C Venkata Ram, MD St. Paul Medical Center Dallas, TX	Site # 007 Karl L Yang University of Louisville Louisville, KY	Site # 008 C Venkata Ram, MD University of Texas South-Western Medical Center Dallas, TX
Site # 009 John David Whalen, MD Louisiana State University Medical Center New Orleans, LA	Site # 010 Lala M Dunbar, MD, PhD, Louisiana State University Medical Center New Orleans, LA	Site # 011 Edward A Panacek Davis Medical Center Sacramento, CA	Site #012 Bruce Hamilton, MD Baltimore VA Nedical Center Baltimore, MD
Site # 014 Francisco M. Gonzalez, MD Renal Dynamics Inc New Orleans, LA	Site # 015 Carol A. Terregino, MD Cooper Hospital/University Medical Center Camden, NJ	Site # 016 Vito Campese, MD LAC & USC medical Center Los Angeles, CA	Site # 017 Suzanne Oparil, MD University of Alabama-Birmingham Birmingham, AL
Site # 018 Elamin Elamin, MD Southern Illinois School of Medicien Springfield, IL	Site # 019 Joseph J. Calabro Newark Beth Istrael Medical Center Newark, NJ	Site # 020 Alexander MM Shepard University of Texas Helath Science Center at San Antonio San Antonio, TX	Site # 021 Daniel Kett Jackson Memorial Hospital Miami, FL
Site # 022 Edward D. Fredrickson, MD Piedmont Hospital Atlanta, GA			

Study Design: This was ostensibly a double-blind, dose (infusion rate)-response, multicentered study in subjects with emergent hypertension.

Formulation: A single batch of fenoldopam Lot no. U-93078 was used for this study. Fenoldopam was supplied as 10 ml vials containing approximately [sic] 10 mg/ml. The formulation was reconstituted with 5% dextrose solution at the study site, so that all subjects would receive an infusion rate of 0.5 ml/min.

Blinding: The sponsor claims the study was blinded for the initial four hours of the

infusion. For subjects that are doing well, the investigator would remain blinded for the duration of the study (24 hours). After the first hour, the investigator could, in a blinded manner, increase the rate of infusion twice, at one hour intervals, based on progression or symptoms or inadequate blood pressure response.

[Comment: This reviewer could make the argument that this study should be considered as unblinded. There was a person on site who was unblinded to the medication (the pharmacist who formulated the single concentration of fenoldopam to conform to the randomized dose). In addition, although the investigator was ostensibly blinded for the first 4 hours, it is unclear when the investigator committed the vital signs to paper. It is possible that the vital sign data was recorded after the blind was broken.]

Dates of Study: The original protocol was submitted on 7 July 1995 (serial sequence #189). There was four revisions which were submitted on: 25 October 1995 (serial sequence #197), 12 January 1996 (serial sequence # 203), 2 February 1996 (serial sequence #204) and 23 August 1996 (serial sequence # 215).

The first subject was enrolled on 1 November 1995 (subject # 004/001). The last subject completed the study on 15 January 1997.

The primary endpoint, as stated in the final protocol, was defined in the 25 October 1995 revision and ante-dated enrollment of subjects within the study.

Inclusion Criteria:

The protocol proposes to enroll sufficient subjects that there will be a total of 80 completers. The subjects were to be greater than 18 years old of either sex, If female of child-bearing potential, a negative bedside pregnancy test was required. All potential enrolles are to have hypertensive emergencies, that is, a supine diastolic blood pressure of $\geq$ 120 mm Hg with evidence of acute end-organ dysfunction, defined as follows:

a. Cardiovascular: •Chest pain •Shortness of breath •Pulmonary edema •ECG evidence of ischemia.

b.Renal: •Oliguria •Elevated BUN and/or creatinine •Hematuria •Hemolysis

c.Neurological (excluding acute stroke) •Headache •Confusion •Seizures •Impending stroke (TIA)

d. Ocular: •Papilledema •Grade III-IV retinopathy (Keith-Wagener) •Acute Changes in Vision

[comment: There does not appear to be a requirement that these symptoms be progressive, severe or rapid in onset. Thus, subjects with elevated DBP with a simple headache could by the protocol's

definition be considered as hypertensive emergency but not apparently by the criteria of Calhoun and Oparil (Calhoun and Oparil, N Engl J of Med. 1990 323(17) 1177-83). Similarly subjects with stable chronic renal failure and elevated DBP would fulfill the protocol's admission criteria but would not suggest an acute decompensation of renal function.]

Subjects with supine diastolic blood pressure of ≥ 140 mm Hg, even in the absence of end-organ compromise, would be eligible for enrollment.

Specifically excluded were : •Pregnant or lactating women • Patients who use alcohol or illegal drugs •Patients with malignant ventricular arrhythmias •Patients with pheochromocytoma •Patients requiring dialysis (hemo- or peritoneal-) • Patients receiving immunosuppressive therapy (subjects on physiological doses of steroids are allowed) •Patients who use dopamine antagonists (e.g. phenothiazine or metoclopramide) within 12 -hour of presentation. •Patients who are hypersensitive to fenoldopam or sodium metabisulfite. •Patients with a serum creatinine > 5 mg/dL. •Patients with severe hepatic disease. •Patients with acute stroke. •Previous exposure to fenoldopam in previous studies. • Patients with a history of glaucoma. •Patients who took hypertensive medication within 1 hour of enrolling. If, however, the blood pressures remain elevated and are stable or rising thirty minutes after receiving the hypertensive medication, the subject is eligible for enrollment.

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Randomization: The randomization assignment was provided by a central site. At each study center there was a designated pharmacist who was in direct communication with the central randomization facility. Once a patient was deemed eligible, the pharmacist contacted the central facility as to the randomized dosing rate. Should this patient not complete 4 hours of infusion a substitute subject (receiving the exact same dose but not necessarily at the same site) would be recruited.

[Comment: hardly a way to guarantee blinding. Both the sponsor and a person at each site was unblinded to treatment.]

Dosing: Eligible subjects were randomly allocated to receive initial infusions of placebo or fenoldopam at doses of 0.01, 0.03, 0.1 and 0.3 ug/kg/min. The randomized infusion was to remain constant for the first hour, and if the response was adequate, for a total of 24-hours. After the first, until the fourth hour, if clinically indicated, based on blood pressure control or worsening signs or symptoms related to hypertensive crises, the investigator would be permitted to increase the infusion rate twice, at intervals of no less than one hour, while still remaining blinded to randomized treatment. After the first four hours, and earlier if compelling clinical considerations dictate, the blind could be broken and the infusion continued in an open-label fashion. The infusion rate could either be increased or decreased for insufficient response or excessive response, respectively.

Concomitant medications: Antihypertensive medications were precluded during the study with the exception that patients with acute congestive heart failure could receive parenteral furosemide, as two doses separated by one hour; anginal sufferers could receive topical nitrates during the screening period. In additional to antihypertensive medications, non-steroidal anti-inflammatory drugs, tricyclic antidepressants, MAO inhibitors as well as morphine were precluded.

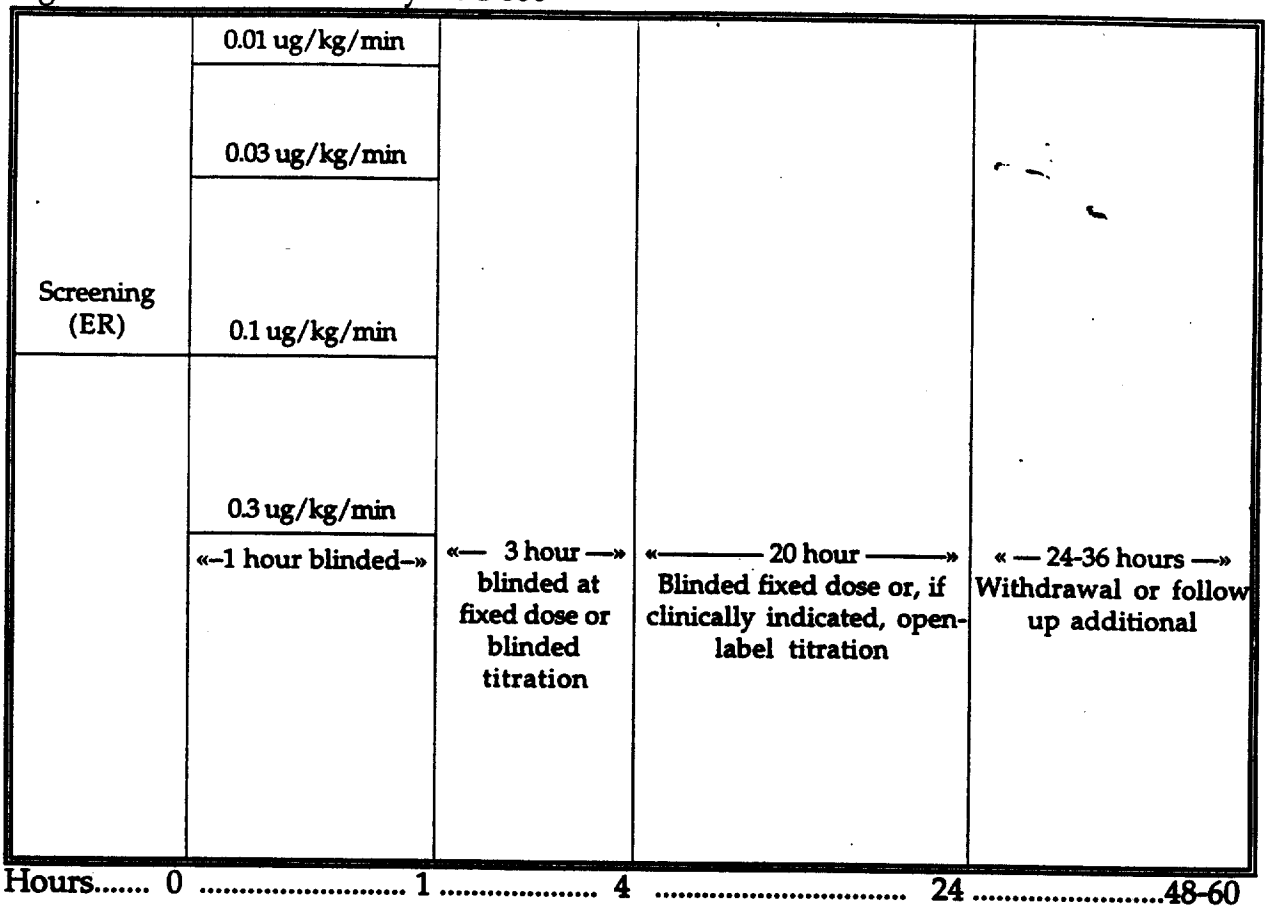
Vital sign measurements: In order to establish eligibility, three measurements of supine diastolic blood pressures taken within one hour, at approximately 5-10 minute intervals, were to be $\geq$ 120 mm Hg. Blood pressure could be measured by any of several different methods including sphygmomanometry, automated blood pressure cuff, arterial line with pressure transducer, but the method was to remain constant throughout the study. After enrollment **(note because of the complicated randomization process there was likely to be some time between the establishment of eligibility and the randomization allocation)**, vital signs were to be measured at 15 minute intervals.

Pharmacokinetic sampling: Blood samples, to measure plasma concentration of racemic fenoldopam and its metabolites, were to be collected at baseline and 30 and 60 minutes and 4 hours following the start of the infusion. Should there be an allowed up-titiration, additional blood for pharmacokinetic measurements were to be drawn 30 minutes after each up-titration. A single sample was to be drawn between 8-20 hours of the infusion and one just prior to the end of the 24-hour infusion. After withdrawal, additional blood samples were to be collected at 15, 30 and 60 minutes and between 8-20 hours and 24 hours after termination of the infusion.

The schematics of the proposed protocol are as shown below (Figure 1):

The initial screening period in the emergency room was to validate the subjects entry criteria (and validate blood pressure measurements), collect baseline information including history, physical exam, informed consent and also collect laboratory assessments including chest X-ray, baseline ECG, chemistry, hematology and urinanalysis. The subject was then randomized to receive one of the four "blinded" infusion rates of fenoldopam. This rate was to be maintained constant for the initial hour. Between one and four hours into the infusion, the rate could be increased twice in a blinded fashion. After four hours, if clinically necessary, the investigator could be unblinided as to treatment. The infusion was to continue for a total of 24 hours with titration changes at no more frequent intervals of 1 hour. During the last 6 hours of the infusion, if clinically indicated, the investigator could administer alternative anti-hypertensive medications.

Figure 1: Schematic of study # 94-006



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Other Procedures: Cardiovascular exams, serum electrolytes and 12-lead ECG (with 2-minute rhythm strip) were to be performed every 6 hours during the infusion. Blood pressure and heart rate were to be measured every 15 minutes during the trial using an automated system (such as Critikon DINAMAP), manual sphygmomanometry, or intra-arterial line, but the method was to be kept constant during the entire study. Urine samples were collected at 12-hour intervals. Adverse events were noted as they occurred. 24-36 hours after completion of the infusion, the subject was to receive a complete physical exam (including a cardiovascular evaluation), vital signs, 12-lead ECG with rhythm strip , CBC, SMA21 and urinanalysis and query of adverse events.

Timing of Procedures: During the screening procedure in the ER the subject was to sign the informed consent, have a medical history taken, receive a physical exam, chest X-ray and baseline ECGs, have baseline vital signs recorded and blood samples collected for laboratory measurements. The various procedures and their timing during the infusion are shown below (Table 5).

Table 5: Schedule of Events an Procedures During Study #94-006

Schedule of Study Events and Procedures				
Procedure	Screening Period-in ER	Infusion Period (4-hour Constant Dose)	Remaining 20 hour infusion	Follow Up Period 24-36 hours post-infusion
Informed Consent	√			
Medical History	√			
PE and Funduscopic exam	√	Cardiovascular + Fundoscopic examinations Q 6 hours		√
Vital Signs	At least 3 times for baseline	Q 1/4 hour during infusion		√
12-Lead ECG	√	Q 6 hours		√
Chest X-Ray	√			√
Laboratory	CBC Chemistries and urine analysis	Electrolytes, BUN , creatinine and complete U/A Q 6 hours		CBC Chemistries and urine analysis
Baseline Urine Samples	√			
Pharmacokinetic Blood Samples	√	1/2, 1 and 4 hours after infusion started and 30 min after any dose change during hours 1-4 and one sample between 8-20 hours. after infusion ends: 1/4, 1/2 and 1 hour		a single value between 8-20 hours and one at 24 hours.
Pharmacokinetic Urine Samples	√	Q 12 hours		√
Infusion		Constant infusion may be titrated twice in blinded manner. Blind can be broken if necessary	Constant infusion may be titrated open label.	
Symptom Assessment	√			
ADR assessment		√	√	

Statistical Issues: The protocol's stipulated primary end point was the supine diastolic blood pressure effect at the end of the initial four hours of infusion, comparing the lowest dose (0.01 ug/kg/min) to the highest dose (0.3 ug/kg/min) infusion groups. The endpoint was to be characterized by a regression on dose, using baseline BP as a covariate. Since there was the possibility of titration of dose during the 1-4 hour time frames the stable effect would be considered one hour after the last titration (my interpretation is that if a titration change was made at 3 1/2 hours into the infusion, the

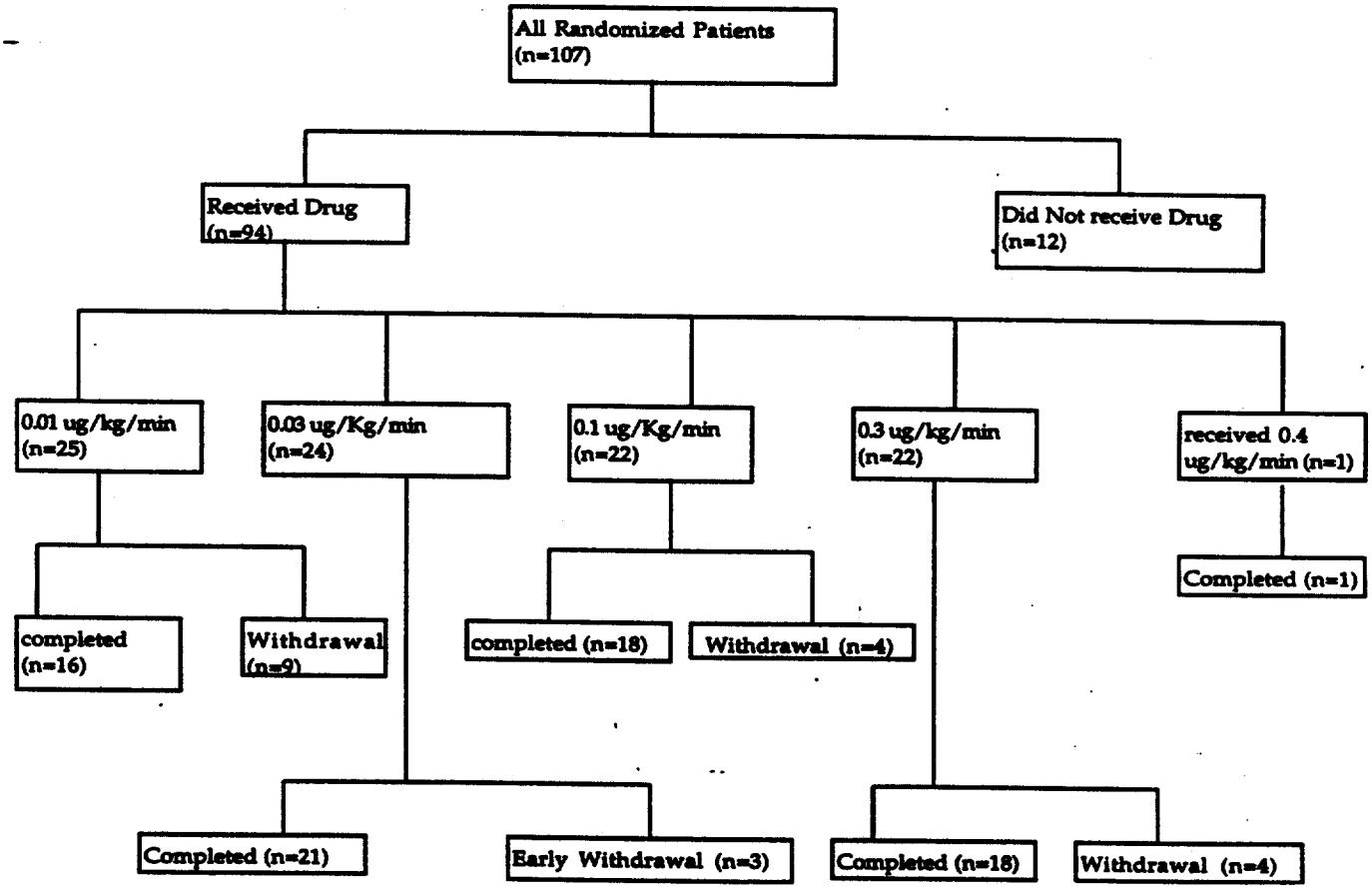
stable effect would be at 4 1/2 hours).

A secondary analysis is directed towards the estimating the 24-hour effect of supine diastolic and systolic blood pressure at the current dose. Additional analyses would involve the characterization of a dose-response curve for each of the 4-hour and 24-hour periods with the cumulative average dose (rather than the current dose).

Results:

Patient Accounting: A total of 107 patients were randomized. Of these, 13 subjects did not receive any infusion of fenoldopam. 94 subjects therefore received some dose of fenoldopam; 25 in the 0.01 ug/kg/min dose group; 24 in the 0.03 ug/kg/min dose group; 22 in the 0.1 ug/kg/min doe group and 22 in the 0.3 ug/kg/min dose group. One subject, randomized to the 0.3 ug/kg/min dose group actually received 0.4 ug/kg/min and was included in 0.3 ug/kg/min group for all analyses. The flow sheet for patients is shown below (Figure 2).

Figure 2- Patient Accounting



The reason enrolled subjects did not receive drug were as follows (data derived from Table F-20 of sponsor vol 20.6 p 181):

- Patient did not exhibit 3 supine diastolic blood pressure of ≤ 120 mm Hg (n=8)[2]
- Concurrent bowel obstruction (n=1);
- No venous access (n=1);
- History of glaucoma (n=1);
- Subject with creatinine > 5.0 (n=1);
- Did not meet some (unstated) eligibility criteria (n=1).

Replacement of missing patients: A copy of a memo dated 2 May 1997 (well after the Neurex submitted this supplement), from Michael D. Thorn, Ph.D. to John Sneed and Jere D. Fellmann, Ph.D, outlined a deviation to the protocol with respect to the stipulated replacement of subjects who discontinued before 4 hours of infusion. Such subjects were to be replaced in a timely manner. The above memo indicated that these patients were not replaced until after enrollment was completed.

[Comment: If no analyses were done prior to the replacement of subjects and I have no reason to believe that analyses were done, then this deviation should not bias any conclusions.]

Demographics:

The demographics of those enrolled are tabulated in Table 6:

Table 6: Demographics of Patients Enrolled into Study 94-006.

	44.8(9.9) n=13	44.2 (11.0) n=25	44.5 (7.7) n=24	43.7 (9.3) n=22	47.4 (13.8) n=23
	87.6 (23.8) n=7	81.3 (21.1) n=25	93.8 (21.9) n=24	83.6 (24.7) n=21	81.7 (20.5) n=23
	168.6 (14.1) n=6	169 (10.6) n=21	177.6 (8.7) n=18	174.3 (9.8) n=19	173 (9.2) n=21
	4/9	12/13	16/8	13/9	14/9
	2/11/0	6/19/0	6/16/2	3/19/0	3/19/1

The group as a whole is young, with an average age of approximately 45 years. Of those enrolled, nearly 80% were African-American, approximately 20 % Caucasian and approximately 3 % Hispanic.

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[2]One such subject excluded #017/001 appears eligible, based on blood pressure criteria, but was excluded. Four such subjects no data was supplied. Three such subjects had data submitted and had blood pressure below 120 mmHg.

Baseline medication:

According to the sponsor, 43/94(46%) of those enrolled took no antihypertensive medication at baseline. Among those enrolled, the median number of medications taken was one per subject. The distribution of number of antihypertensive medications is shown below (Table 7):

Table 7. Number of Baseline Medications in Study #94-006.

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	9	12	8	14	43
[illegible]	6	4	6	2	18
[illegible]	7	8	8	7	30
[illegible]	3	0	0	0	3
[illegible]	25	24	22	23	94

With respect to the nature of the medications, 59% were on calcium channel blockers, 55% were on centrally acting alpha agonists, 43% were on diuretics, 39% were on angiotensin converting enzyme inhibitors, 27% were on beta-blockers, 22% were on direct vasodilator, 4% were on nitrates and 4% were on other drugs.

[Comment: There appears to be a high fraction of patients who were on centrally acting alpha$_2$ adrenergic agonists, most commonly clonidine, either as an oral medication or as a patch (derived from Table F-17 vol 20.6 pages 85-95). In some cases it seems that medication was only given between short term, in others long term in other cases the duration of use was not stated.]

Validation of Entry Criteria:

Were the entry criteria for enrollment satisfied?

With respect to the entry blood pressure criteria, page 10 of the protocol states:

> **" Vital signs including at least three supine diastolic blood pressures (SDBP), paired with heart rate measurements, will be obtained to establish a baseline during screening. These are to be obtained at 5-10 minute intervals during the a period not to exceed one hour prior to initiation of the infusion. The patient must exhibit 3 consecutive supine diastolic readings of ≥ 120 mmHg for enrollment in the study"**

In reporting the results of eligibility the sponsor changed the criteria for analysis to any 3 measurements (not necessarily consecutive) of supine diastolic blood pressure of 120 mm Hg or greater.

Of those who received drug (n=94). based on the data from sponsor's Table F-19 vol 20.6 p 126-175; and Table F-21 Vol 20.7 p 002-270), seventy-two of those enrolled were severely hypertensive by the stated criteria. The other 22 subjects were hypertensive but deviated from the protocol stipulated requirement. Many of these deviations were minor. Several were major with supine diastolic blood pressures at the start of the infusion of < 105 mm Hg. The subjects who deviated are tabualted below (Table 8).

Table 8: .Subjects Whose Blood Pressure Deviated from Protocol Stipulated Values

Pt # 001/001 dose= 0.03	SDBP ranged between 113-125 mm Hg in the hour before infusion	Pt # 010/018* dose =0.01	Supine diastolic blood pressure during 1 hour prior to study was 101 mm Hg.
Pt# 001/006 dose= 0.01	SDBP 1 hour before study ranged from 119-125 mm Hg	Pt # 010/021 dose =0.3	Last blood pressure measurement prior to the start of infusion 117 mm Hg
pt#001/017 dose=0.01	Baseline values of 127.7 were derived from measurements > 1 hour before infusion. Last measurement at baseline 117 mm Hg.	Pt# 011/001 dose =0.01	Last value before start of infusion was 118 mm Hg. Other measurements during the 1 hour period before infusion ranged between 121-140 average 126
Pt# 002/002* dose 0.1	Average values 109.5. With baseline measurements done 4.5 hours before infusion	Pt # 011/002* dose 0	Blood pressure one hour prior to infusion was 105 mm Hg. Average over hour prior to infusion was 114 mm Hg
Pt# 002/001 dose 0.1	Baseline blood pressure was 111.3 mm Hg, more than 2 hours prior to infusion. The last measurement SDBP was 100 mm Hg	Pt # 011/003 dose 0.01	Last measurement prior to infusion 113 mm Hg. Measurements ranged from 105-140 mm Hg.
Pt# 002/003 dose 0.1	Baseline blood pressures of 117.6 was derived from measurements done 6 hours before infusion. Last measurement before infusion, however, was 142 mm Hg.	Pt # 011/004 dose 0.01	Baseline measurements were done 2.5 -1.5 hours before the infusion. The last measurement was 118 mm Hg. (Sponsor estimated mean baseline as 129 mm Hg.)
Pt# 002/005 dose 0.1	SDBP measurements within the last hour 108-122 with average 117 mm Hg	Pt # 011/005 dose 0.01	Last measurement prior to the infusion was 103 mm Hg. Mean as estimated by sponsor was 120 mm Hg.
Pt# 002/006 dose 0.01	At time 0 of infusion,SDBP was 112 mm Hg. Other baseline values were collected 5.5 hours before the infusion.	Pt # 011/006 dose 0.01	Did not have consistently severe elevations in DBP . Measurements were generally in the 100-115 mm Hg range. Last measurement 112 mm Hg. Sponsor estimated average as 113 mm Hg
Pt# 002/007 dose 0.01	Last measurement before the infusion was 112 mm Hg. Average over last hour 119 mm Hg.	Pt # 011/007 dose 0.01	Blood pressure before randomization was 78 mm Hg. Blood pressure in the hour before the infusion averaged 85 mm Hg Sponsor estimated average blood pressure as 107 mm Hg.
Pt# 002/008 dose 0.01	Baseline measurements done 2.5 hours prior to infusion . Average was 124.3 mm Hg, last measurement at infusion was 120 mm Hg	Pt # 011/008 dose 0.01	Last measurement prior to infusion was 119 mm Hg. Sponsor estimated average value as 141 mmHg
Pt# 002/009 dose 0.01	Only two values within hour prior to infusion average of 121 mm Hg. Estimate of baseline blood pressure was 137 mm Hg	Pt # 011/009 dose 0.01	Last measurement prior to infusion was 114 mm Hg. Sponsor estimated average as 114 mm Hg
* Subjects most divergent from protocol criteria			

[comment: There are clearly subjects among those randomized that should not have received drug. For example, subject #018/002 had a last blood pressure measurement of 78 mm Hg. Other subjects that did not fit the enrollment criteria deviated only slightly. I've listed the ones that I thought were the most divergent with an asterisk (*). The most divergent individuals were scattered among all dose groups and in all likelihood add noise and do not bias the study results as to the relative magnitude of blood pressure response to the various fenoldopam infusion rates. Since most of the divergent subjects had measurements which were used to define baseline, that were collected several hours before infusion sometimes till the

beginning of the infusion I've asked the sponsor to define baseline as those values collected within one hour of study infusion.)

End Organ Damage. In addition to elevated blood pressure, subjects were to have manifestations of end-organ dysfunction or at least have a supine diastolic blood pressure of > 140 mm Hg. The end organ damage could involve any one of several systems including: cardiovascular (i.e shortness of breath, pulmonary edema, ECG evidence of ischemia); renal (oliguria, elevated BUN and creatinine, hematuria, hemolysis); neurological (headache, confusion, seizures or impending stroke); or ocular (papilledema, grade II-IV retinopathy, acute visual changes). Several organ systems could be simultaneously involved.

The specifics of the end organ involvement as per sponsor are as shown below (Table 9)(data extracted from sponsor's Table F-4 vol 20.3 p 61-78):

Table 9. Sponsor's Classification of Patients as to End Organ Involved.

Neurological only : n=19 001/010, 001/017 003/001, 003/002, 004/005,006/002, 006/003, 007/003, 008/002, 010/002, 010/011, 010/015, 010/019,011/002, 011/004 , 017/004, 017/006, 017/009, 017/010	Ophthalmologic only : n=0	Renal only n=6 001/002, 001/003, 001/005, 001/006. 001/008, 018/001	Cardiovascular only n=12 002/002, 002/004, 004/002, 009/002, 010/005, 010/008, 010/012, 010/014, 010/018, 012/003, 013/001, 020/001
Neurological and ophthalmologic n=7 001/001, 006/001, 008/008, 008/009, 011/001, 017/011, 018/002	Neurological and Renal n=12 001/007, 001/012, 001/015, 001/018, 002/003, 003/005, 008/005, 010/020, 017/008, 018/003, 019/001, 021/001	Neurological and cardiovascular n=12 001/014, 003/003, 004/001, 004/006, 007/001, 008/003, 010/003, 010/004, 010/016, 010/021, 017/002, 022/001	Ophthalmologic and Renal n=2 001/009, 015/001
Renal and cardiovascular n=2 001/013, 010/010	Cardiovascular and Renal n=0	Neurological/renal /ophthalmological n=4 001/016, 005/001, 010/001, 021/002	Neurological/renal/cardiovascular n=1 016/003
Neurological/ophthalmological /cardiovascular n=7 007/002, 008/001, 009/001, 010/009, 010/013, 010/017, 011/003	Ophthalmological/renal /cardiovascular n=1 005/006	Ophthalmological/ renal/ cardiovascular/neurological n=1 016/002	No end organ damage but DBP of ≥ 140 mm Hg n=8 004/003, 004/004, 008/004, 008/006, 010/006, 012/002, 017/005, 017/007

[comment: Objective verification that supports the nature and the specifics of the end organ systems involvement is difficult to come by. In particular, nearly all subjects with neurological symptoms alone were described as having headache (only one subject had as a description an impending stroke; one other subject had concurrent confusion). Since headache is common and since end-organ involvement suggests some intensification or progression of routine headaches, it is unclear if such subjects really had hypertensive emergencies. Renal signs and symptoms was often confounded by pre-existing kidney disease. Consequently, it becomes difficult to determine if the creatinine at baseline represents hypertensive decompensation or status quo for that subject. I'm incredulous how oliguria was determined. Cardiovascular symptoms was often confounded by pre-existing angina or congestive heart failure. Ophthalmologic symptoms, particularly papilledema was one of the more concrete symptoms observed.

With respect to those who had no end organ damage but had blood pressure measurements of greater than 140 m Hg, only 4 of the 8 patients listed had such blood pressures. The others had average blood pressure measurements between 122 and 139 mm Hg.

A critique as to whether subjects were in emergent crisis is shown as appendix B.]

In an amendment dated 21 May 1997, the sponsor submitted a group of 37 subjects that they felt had objective data to suggest hypertensive crisis. There is substantial agreement between my assessment and that of the sponsor. I've asked the sponsor to review the first 10 subject in the first study center with headaches, paying particular attention to descriptions of headache such as "severe", "progressive" etc.

Dose:

Per protocol, the randomized dose was to be maintained constant for the first hour of the study, but the infusion rate could be increased, in a blinded fashion, during the subsequent three hours of the study. After the four hour time point, the investigator could titrate the infusion as necessary. One subject randomized to the 0.3 ug/kg/min infusion regimen, received 0.4 ug/kg/min. This subject was included in the 0.3 ug/kg/min infusion rate for all analyses. A graph of the doses received versus the randomized group is shown as Figure 3 .

Figure 3. Average Dose Versus Time.

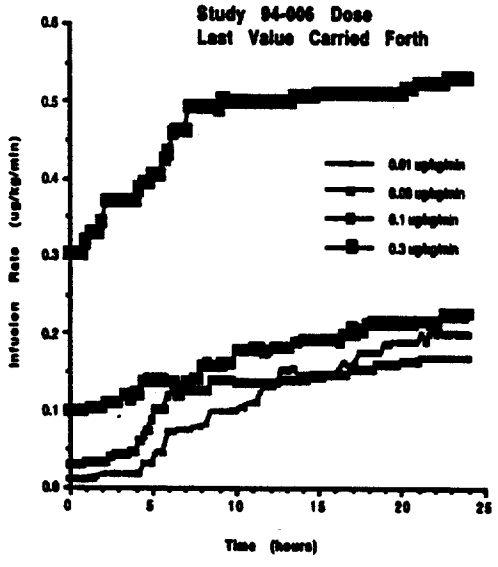
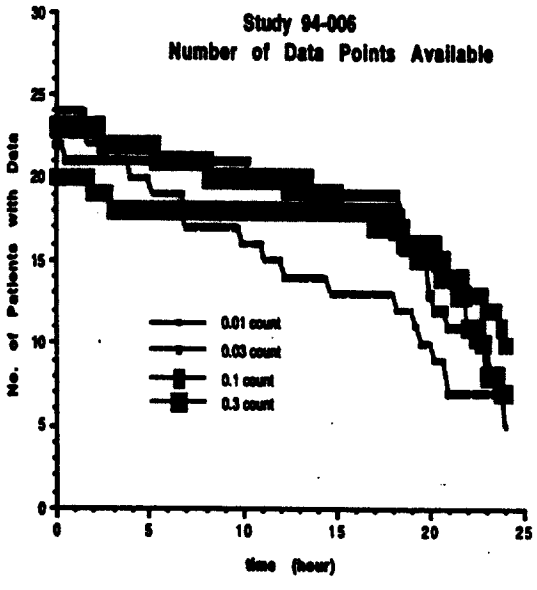


Figure 4. # of Patients With Dose Values Available.



[Comment: In the analysis of average dose, if the subject discontinued, the last infusion rate was carried forth to the end of the measurements, similar to the analysis performed with blood pressures measurements. I have done several additional analyses, including excluding subjects when they received concurrent therapies which might alter blood pressures. These graphs did not differ substantially from the one displayed.]

As can be seen, the infusion rate during the initial four hours, that defines the primary end point drug effect, remain relatively constant and closely correspond to the randomized dose (see Table 10). The number of subjects with non-imputed data over this time frame, corresponds to nearly all the enrolled subjects. Over the 4 hour primary observation period the number of subjects who discontinued did not differ substantially among groups.

The mean dose at the 1 and 4 hour time point for those who continued on infusions is as shown below (Table 10):

Table 10: Average Infusion ± SD at 1 and 4 Hours of Infusion Versus Randomized Dose(Last Dose Not Carried Forth Upon Discontinuation)

	0.011 ± 0.003 (n=25)	0.035 ± 0.011 (n=24)	0.1 ±0.00 (n=22)	0.32 ± 0.21 (n=23)
	0.017 ± 0.015 (n=23)	0.047 ± 0.031 (n=24)	0.125 ± 0.07(n=20)	0.37± 0.32 (n=22)

Kinetics:

Quality of the data:

Kinetic sampling for this study (study #94-006) was far more parsimonious than that of study (#94-05; the pivotal study in the previous review). Blood samples, to measure plasma concentration of racemic fenoldopam and its metabolites, were collected at baseline and 30 and 60 minutes and 4 hours following the start of the infusion and 30 minutes after any titration change. A single sample was drawn somewhere between 8-20 hours of the infusion, and one sample just prior to the end of the 24-hour infusion. After withdrawal, additional blood samples were collected at 15, 30 and 60 minutes and between 8-20 hours and 24 hours after termination of the infusion.

There were a total 93 of the 94 subjects who had records available. Data points consisted of 257 records of dosing and 725 concentrations measurements. There were, however, a large number of unanticipated variant concentrations. The sponsor attributed excessively high individual samples measurements to sampling of blood from the same arm as the infusion. Low values were attributed to improper handling

of samples.

Appendix A contains some, but by no means all of the more variable concentration of racemic fenoldopam versus infusion rate.

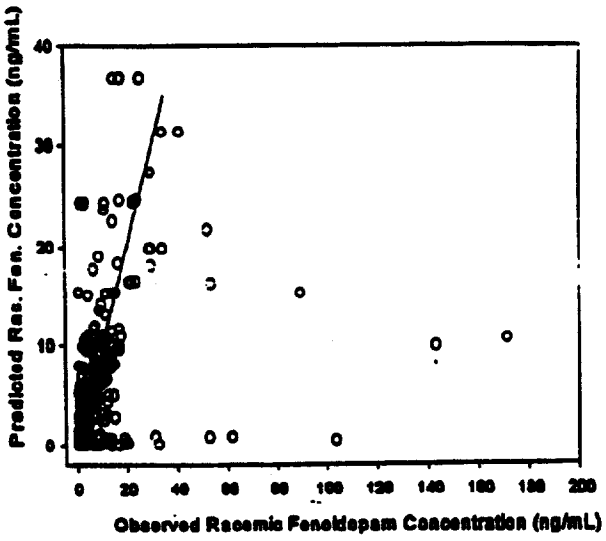
Kinetic Results:

Despite these aberrant kinetic measurements, [redacted] Neurex's consultant, was able to analyze this data. The kinetic data was best fit by a one-compartment model, with the Volume of Distribution estimated as 56 L (95% confidence intervals of 31.3-81.3 L). For a 70 Kg subject, this reflects a volume 800 ml/kg with a range of 413-1,116 ml/Kg. These estimates of Volume of Distribution were not that dissimilar for the volumes calculated for the mild-moderate hypertensives of 500 ml/kg. The half life was calculated at 12 minutes (95% confidence intervals of 8.1-20 minutes). The half-life was somewhat greater the approximately 5 minute half-life estimated from study #94-05. The kinetic constants were not influenced by weight, gender, race, gender, baseline blood pressures.

[Comment: The Division has yet to confirm [redacted] analysis but the description of the process by which the kinetic model was constructed appears appropriate. The conclusions are likely to be confirmed by the Division's review.]

Below is Figure 5, taken from I [redacted] review (Sponsor's Figure 1; Vol 20.2 p 26). The predicted versus observed fenoldopam concentrations (one value of > 3000 ng/ml was excluded). In general, the values were distributed around the line of identity, however, the variability was extremely large.

Figure 5. Observed versus Predicted PK measurements as per modeling



The measured concentration of fenoldopam over time is displayed as Table 11. No data was supplied on the fenoldopam metabolites.

Table 11 .The effect of duration of infusion on serum racemic fenoldopam concentrations

Mean Plasma Fenoldopam in ng/ml, by Randomized Dose (Sponsor's Table 8-3) v 20.1 p 65				
	Infusion Rate (ug/Kg/min)(no SDs Were Supplied)			
	0.56	0.71	2.96	8.15
	1.06	0.93	3.26	7.40
	0.49	3.02	3.71	9.89

Vital Sign effects:

Comment on data: Blood pressure and heart rate were collected at five minute intervals to establish eligibility and at 15 minute intervals during the infusion. For analysis, subjects were assessed within the randomized dose. As noted above, one subject, assigned to the 0.3 ug/kg/min infusion rate actually received 0.4 ug/kg/min but was nevertheless included in the 0.3 ug/kg/min infusion group.

Concomitant medications during the initial 4 hours of infusion and for the hour preceding the infusion were infrequent. Three subjects received diuretics during the initial 4 hours of infusion, one subject received diuretic at the time of start of infusion, 4 subjects had concomitant medications on the day of infusion with no time stated (Table 12).

Table 12 .Concomitant medications received or possibly received during the first four hours of infusion

Patient #	Dose	Drug	Time during Infusion
001/005	0.1	furosemide	2 hours 50 minutes
001/006	0.01	Clonidine patch	Time not stated
001/016	0.01	Nipride	Fenoldopam only give 1.5 hours
010/012	0.01	Furosemide	1 hour 45 minutes
010/020	0.03	Furosemide given	Time not stated
013/001	0.1	Lasix given	Time not stated
017/002	0.03	furosemide	21 minutes
020/001	0.03	Lasix	Start of infusion

The sponsor applied the following rules in performing their analysis:

- Missing data were left missing, there was no interpolation of missing values.
- Patients withdrawn prior to 4 hours of infusion were replaced, those

withdrawn prior to 24 hours were analyzed. The specifics of those withdrawn prior to 4 hours are shown below (Table 13).

Table 13. Subjects withdrawn prior to 4 hours of infusion.

Pt#	Dose	Time Discontinued	Comments
001/016	0.01→0.04	1 hour 30 min	This subject is also included in Table 12 above for those who were administered concurrent therapies. The last measurements the hour before discontinuation ranged form -5.6-18.6 mm Hg despite increase in infusion rate to 0.04 ug/kg/min.
008/004	0.3	2 hours	BP decrease ranged from -9.3 to -26.4 mm Hg- creatinine at baseline was outside protocol-specified range
010/001	0.01 →0.02	2 hours and 30 minutes	BP decrease during the last hour ranged form -6.4 to -8.4, protocol violation creatinine and BUN were outside pre-specified range
013/001	0.1	2 hours 45 minutes	BP decrease during the last hour ranged form -10.3 to -17.3; sudden onset headache with exacerbation of shortness of breath.
017/009	0.1	1 hour 45 minutes	BP decrease during the last hour ranged form -28.3 to -48.3 mm Hg. Discontinued due to excessive effect.

• One subject #016/001 received 20 hours of medication but no data appears to be available, the subject was re-randomized as #016/002 and received 0.01 ug/kg/min.

• Subjects were included in the efficacy analysis even if the baseline blood pressure was below 120 mm Hg or if they did not have sustained blood pressure elevations > 120 mm Hg during the baseline period. The distribution of sponsor defined baseline blood pressures are shown below. Of those who the sponsor calculated baseline, there were a total of 11 subjects whose baseline blood pressure was less than 120 mm Hg. Two of these had baseline measurements of below 110 mm Hg. The distribution of subject's baseline measurements are shown above in Figure 6. The randomization number and the randomized dose are also shown (Table 14).

Figure 6. Baseline Distribution of Blood Pressures

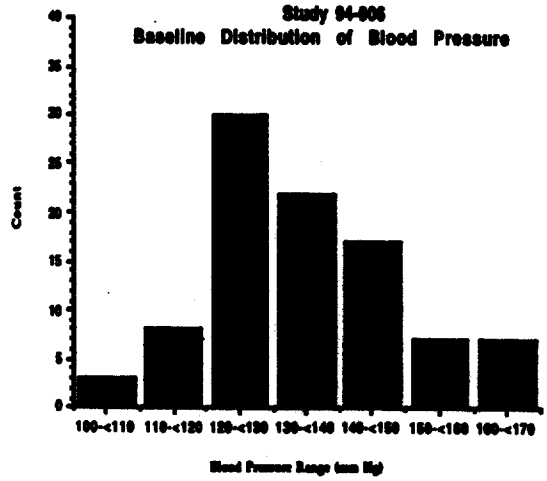


Table 14. Subjects and Dose of Subjects with DBP < 120 mm Hg at Baseline

Diastolic Blood Pressure 100-<110 mm Hg	Dose	Diastolic Blood Pressure 110-<120 mm Hg	Dose
002/002	0.1	001/001	0.03
018/002	0.3	003/001	0.3
		003/002	0.1
		003/003	0.03
		004/005	0.3
		010/018	0.01
		011/003	0.1
		018/001	0.01

- Subjects were included even if the index measurement of baseline blood pressure was remote from the start of the infusion.
- The study cite with the unblinded pharmacist (a total of six subjects were enrolled from site #4.)

[comment: Presumably those who withdrew prior to 4 hour infusions were not analyzed, those who received concomitant medications seem to have been included within the analysis.]

A graphical display based on the sponsor's analyses for supine diastolic blood pressure is shown as Figures 7 and 8. Figure 7 graphically displays the first 4 hours of infusion. Figure 8 displays the whole 24-hour time course. There is a decrease in supine diastolic blood pressure (from sponsor's defined baseline) during the index 4-

Figure 7. DBP Hours 0-4

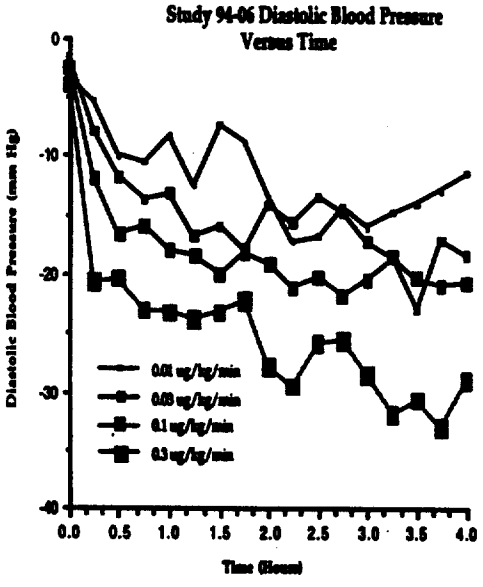
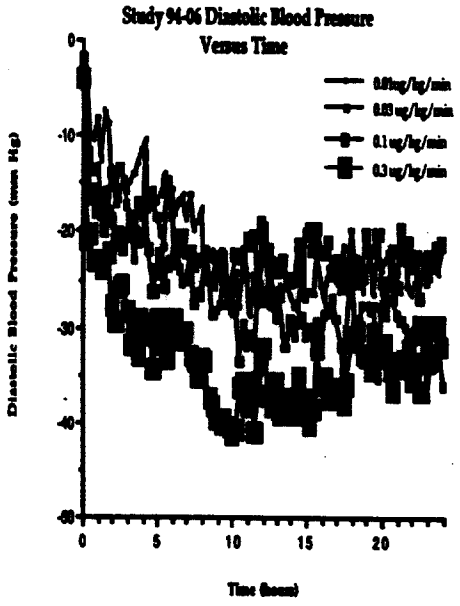


Figure 8. DBP during 24 hours



hours of the infusion. The diastolic blood pressure however, continues to decline over the next several hours. Some of this decline is likely related to up-titration of fenoldopam, some due to the administration of concurrent therapies (however, over the first 12 hours of infusion, few subjects received concurrent therapies, thereafter the frequency of concurrent therapies increase) and some of the blood pressure decrease may be due to drug- unrelated but time-dependent effects. Similar effects for systolic blood pressure Figures 9 and 10. Reciprocal increases in heart rate are displayed in Figure 11 and 12.

Figure 9 .SBP hours 0-4

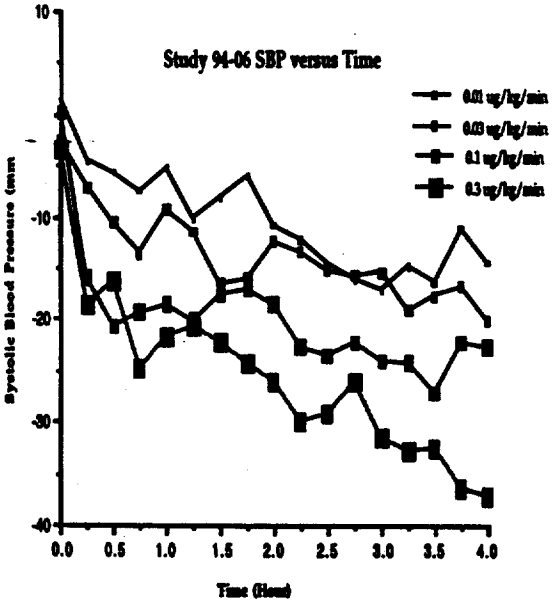


Figure 10. SBP 24 hours

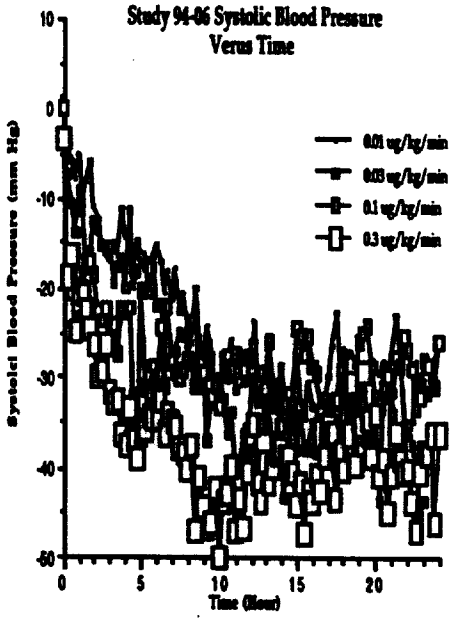


Figure 11 Heart Rate 0-4 hours

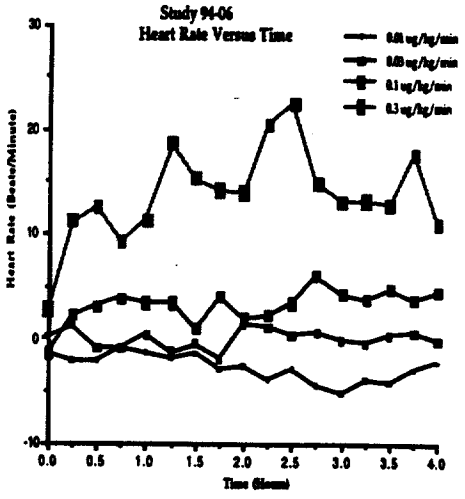
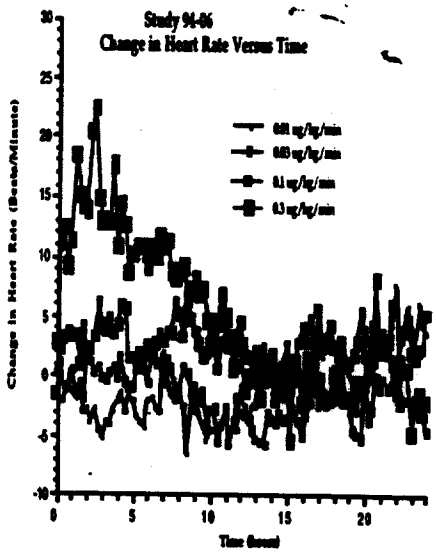


Figure 12. Heart Rate 0-24 hours



The baseline blood pressures as well as the decrease in supine diastolic blood pressure for the individual doses is at the four and 24 hour time points as per sponsor is tabulated below (Table 15):

Table 15. Sponsor's calculated Effects.

	135.6	135.3	133.4	135.6	NS
	-11.5	-18.4[a]	-20.7[b]	-29.1[c]	0.002
	-21.2	-36.1[b]	-21.1	-31.8	NS

* overall comparison; relative to low dose .a 0.1< p < 0.05 b. 0.05<p <0.01 c. P < 0.01

At 4 hours, the primary end-point stipulated by the protocol, there is a highly significant drop in DBP in the higher infusion rate group than in the low rate group. At 24-hours the drops in blood pressure and the increases in heart rate of all the treatment groups tend to converge, with only the 0.03 ug/kg/ minute infusion rate differing from the low dose infusion rate. As noted above, the convergence is likely to be a synthesis of up-titration, concomitant medications and time-dependent effects.

In addition to the above single time point analyses, which defines the blood pressure effect, measured at a single time point, the sponsor also performed a repeated measures analyses that utilizes all recorded values during the initial 4 hours of infusion. The results of these analyses were also highly statistically significant.

FDA analyses:

Dr. Kun Jin, the Agency's statistician, did several analyses to ascertain the robustness of the above conclusions. These analyses looked at blood pressure responses from baseline, in which baseline was limited to measurements taken within one hour before the start of the fenoldopam infusion. Five subjects had no such measurements available and were excluded from further analyses. These five subjects were distributed among the four studies groups (# 010/017 of the 0.01 dose; #003/003 and #012/002 of the 0.03 dose; #003/002 of the 0.1 dose; and 003/001 of the 0.3 dose). Subjects who had baseline values available but discontinued early were analyzed as a last-value carried forth method.

Three analyses were done, the first was the effect of drug in those with valid baseline measurements limited to the single 4 hour time point. This analysis corresponds to the pre-specified analysis but with the definition of baseline limited to 1 hour prior to the start of the infusion. The second analysis was to obtain a better estimate of the drug effect by taking the median vital signs for each individual for the interval hour spanning the 3-4 hour of infusion, then averaged for all subjects within the infusion group[3]. For those who discontinued early, the median of the

Table 16: Supplemental FDA analyses.

						P-value by ANOVA*
1-Hour Time point. Effect With Last Value Carried Forth	DBP	-6.6 _ 2.7	-12.7 ± 2.9	-16.1 ± 2.4	-22.3 ± 3.8	<0.0005
	SBP	-4.7 ± 2.6	-8.2 ± 3.5	-20.3 ± 4.5	-21.6 ± 4.6	<0.001
	HR	-0.8 ± 3.0	-0.2 ± 1.33	2.8 ± 1.2	15.3 ± 2.4	<0.00001
4 hour time point single measurement. Last value carried forth	DBP	-9.7 ± 2.3	-17.4 ± 3.0	-20.3 ± 3.3	-25.5 ± 2.4	0.001
	SBP	-13.5 ± 4.0	-16.9 ± 4.9	-21.3 ± 4.9	-33.4 ± 4.2	0.01
	HR	-0.14 ± 3.7	0.45 ± 2.3	4.3 ± 2.02	18 ± 4.9	<0.001

[3]Thus if a subject had measurements of 99, 93, 107, 100 and 113 mm Hg during the 3-4 hour period the value recorded for this subject would be 100 mm Hg.

4 hour time point median of last hour Averaged Over dose group	DBP	-12.9 ± 3.6	-16.7 ± 2.4	-20.1 ± 2.7	-27.6 ± 2.3	<0.0005
	SBP	-13.7 ± 3.0	-13.7 ± 4.2	-21.7 ± 4.0	-30.2 ± 3.6	<0.005
	HR	-1.9 ± 3.6	0.6 ± 1.8	3.3 ± 1.6	14.3 ± 2.9	<0.0005

* The P-values are essentially unchanged if baseline is used as a covariate.

values measured over the last hour of infusion was carried forth. A last analysis was the effect of drug limited to the one-hour time point. The results of these supplemental analyses support the sponsor's contention that fenoldopam mesylate is active in decreasing blood pressure in a dose dependent manner. Heart rate reciprocally increases (See Table 16 for the results).

Pharmacokinetic-Pharmacodynamic modeling:

The relationship between the kinetics and dynamics from this study was modeled by with the use of NONMEM. report is very clear as to how the data was used as well as the details of the model building procedure. With respect to the data entered into the model, excluded all measurements after the subject received either diuretics or anti-hypertensive medications (very reasonable for the measurement of drug effects).

The relationship between pharmacokinetics and pharmacodynamics was best fit by an E_{max} model[4]. The estimated half-maximal concentration of 3.08 ng/ml (equivalent to an infusion of somewhere between 0.03 and 0.1 ug/kg/min). There is a rapid initial blood pressure response in concert with the rise in plasma concentrations, and a slower progressive drop in blood pressures over the next several hours. The half-life of this slower decrease in blood pressure was on the order of 7.3 hours. The magnitude of this additional drop is substantial (consider the blood pressure drop from approximately 45 minute to 12 hours on Figures 7 and 8 for diastolic blood pressure and Figures 9 and 10 for systolic blood pressure.

The model also predicted a diminishment of blood pressure response (tolerance) with time that has a half-life of between 12.9 (awake hours) and 14.5 hours (sleep hours). submits the fit of one subject and this subjects profile is reproduced below (Figure 13)

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[4]The equation derived by was:

Drug Effect = (Baseline BP) (Onset) (Offset) (concentration/C50 + concentration).

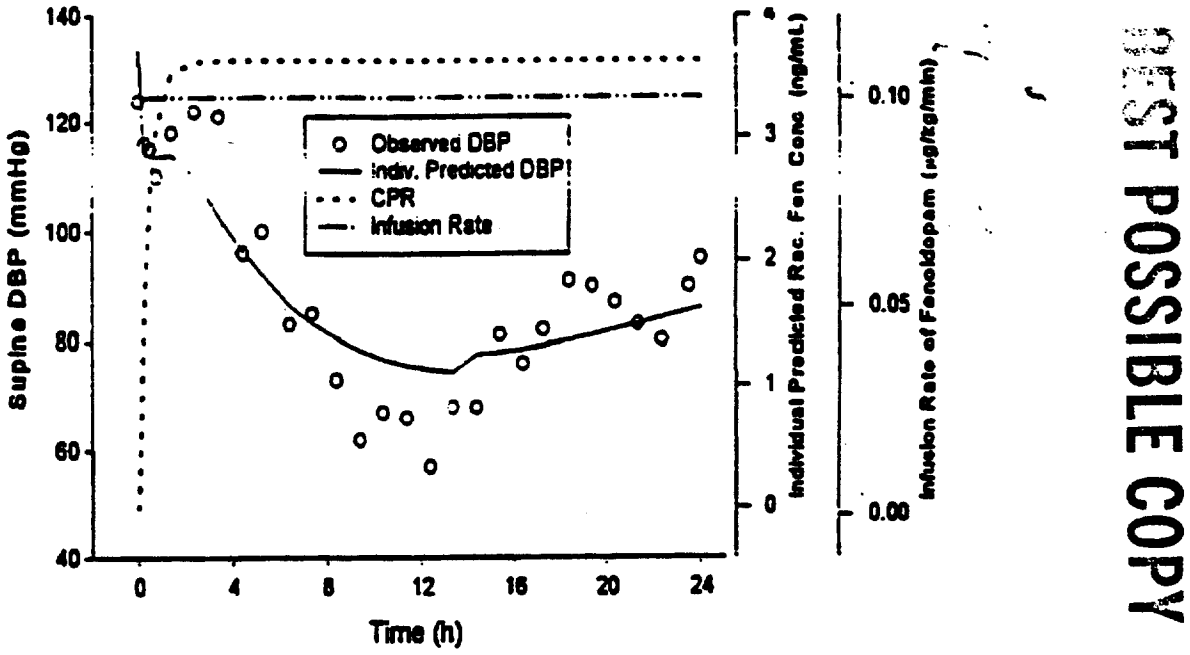
Baseline Blood Pressure = 117 mm Hg for Caucasians and 130 mm Hg for Others.

Onset= [1- EXP (-0.0955 * Time)]

Offset= EXP ($-K_{offset}$ *Time); with K_{offset} = 0.0537 while awake and K_{offset}=0.0479 while asleep.

C50 is the concentration of fenoldopam resulting in half maximal effect.

Figure 13. PK-PD Correlation of a Single Subject



[comment:This subject had a fairly constant infusion of fenoldopam at 0.1 ug/kg/min. Stable concentrations of drug were apparently maintained throughout the infusion period. The diastolic blood pressure, dropped modestly during the first hour (approximately 10 mm Hg) but over the next 11 hours had an additional decrease of 30 mm Hg that is unrelated to any manipulation of drug infusion or concurrent therapies.]

[Comment: Dr. El Tahtawy is in the process of modeling these data. We have no doubt that the model as proposed by adequately fits the data. The concern we have is that model with a second and slower diminution of blood pressure, despite steady infusions rates and steady drug concentrations, seems somewhat at odds with the experience in mild to moderate hypertensives (derived from study 94-05). If this secondary decline in blood pressure is real, it would suggest that there is a second or "effect" compartment that determines the decrease in blood pressure. Any dosing instructions in hypertensive emergencies would have to consider this compartment in defining the infusion rate changes and the intervals between these changes.

It is our impression, however, that the slower decrease in either diastolic blood pressure after kinetic steady state has been reached may be an effect that is independent of drugs. The additional decrease represents those factors that would normally be corrected for if a placebo-controlled group was included. Absent the placebo group, however, it is still possible to decide if this additional fall in blood pressure is dependent on drug dose or concentration or merely reflects some time effect. If this effect was drug related then the magnitude of this effect should be more prominent in the group receiving the higher infusion rates. If it were merely a time dependent effect the magnitude of this effect should be the same across all dosing groups.

Based on the results in Table 16 , the additional decrease in blood pressure in comparing the 1 to 4 hour time points is approximately 3-5 mm Hg, and is the same in all the dose groups (which span a dosing rang of 30). The additional drops are therefore likely to be disease and time dependent effects, unrelated to drug infusion regimen.]

Concurrent Medications:

The classes of antihypertensive medication given to subjects either during infusion or post infusion are shown below (Table 17):

Table 17. List of Medications Given During or After Infusion.

Number of Patients who Were Given Antihypertensive Medications During and Following Fenoldopam Infusion:		
Class of Drugs:	During Infusion	Following Infusion
Calcium Channel Blockers (Total); Dihydropyridines Verapamil Diltiazem	39 35 1 3	25 21 4 0
Diuretics	21	20
ACE-Inhibitors	18	20
Beta-Blockers	5	16
Direct Vasodilators	4	2
Centrally Acting Alpha Adrenergic Agoisnsts	9	8
Nitrates	2	2

[Comment: One patients #001/006 treated with enarlapril as well as nifedipine and minoxidil developed orthostasis and acute renal failure (see below under SAFETY). One other patient #010/017 treated with benazapril developed orthostasis. There might be some signal here about the concurrent use of ACE-inhibitors after fenoldopam. But at t his stage it is insufficiently defined for labeling.]

Safety:

Exposure: A total of 94 of the 107 randomized subjects received at a randomized dose ranging from 0.01 to 0.3 ug/kg/min. Of these 94 subjects, 74 (69%) received fenoldopam for the full 24 hours of the proposed infusion. The outcome of all those who received medication is shown below as Table 18:

Table 18. Outcome For Those Randomized Based on Dose.

	25	24	22	23	94

[redacted]	16	21	18	19	74
[redacted]	2d	0	2e	0	4
[redacted]	2	3	2	2	9
[redacted]	1	1c	0	0	2
[redacted]	1	0	0	0	1
[redacted]	1	0	0	1	2
[redacted]	2f	0	0	1g	3

* Includes 1 subject receiving 0.4 ug/kg/min infusion rates.
a All these subjects were sequentially enrolled from study site 010.
b. Baseline creatinine related :in one subject> 10, in the other > 5.4
c. Subject discontinued also for DBP < 120 and thus double counted
d. One discontinued for Headache, one discontinued for SOB; chest pain.
e. One D/C for HA and SOB; one for excessive BP drop
f One discontinued at 22:15 hrs -no reason given
g. Erratic Blood pressures oscillating 50mm Hg Over 2 hours despite constant infusion rates

[Comment: A large number of sequentially enrolled subjects from study site # 10 were discontinued as the sponsor claims for "blood pressure < 120 mm Hg (patients #010 /012 through #010-021). These subjects in general had baseline blood pressure measurements that were reasonable for enrollment. The reason for discontinuation is, therefore, unclear. Dr. Kun Jin has reanalyze the data without study site # 10 and excluding this study site did not materially change the results.]

Deaths: There were no deaths in this study.

Dropouts/Discontinuations/ Rescue Medications:

There were 4 patients who discontinued due to adverse events their CRFs were submitted and reviewed (my review) .

Patient #005/001 was a 45 year old African-American male who presented with hypertension (189/123 mm Hg), papilledema, headache and increased BUN/ creatinine (22/1.8). He was started on fenoldopam at a rate of 0.01 ug/kg/min. His diastolic blood pressure remained elevated (ranged form 107-145 mm Hg) and he complained of blurred vision and right eye pressure. He was titrated upward to 0.03, 0.1, 0.3, 0.45 And 0.6 ug/Kg/Min. After 1:15 hours on 0.6 ug/kg/min infusion rate, the record ends, stating subject was complaining of headache. 2:45 hours later the subject was again hypertensive and treated with nitroprusside (no record seen in CRF supporting the administration of nitroprusside). Four days after infusion the BUN/Cr increased to 22/2.4.

Patient #013/001 was a 36 year old African-American male with a history of chronic renal disease (elevated BUN/Cr as well as chronic anemia) who came to the ER with complaint of SOB. The enrollment blood pressure was 246/169, his original chest X-

ray was consistent with congestive heart failure. He was randomized to 0.1 ug/kg/min. At 2:45 hours the infusion was discontinued because of headache, shortness of breath and diaphoresis. At some point he received nitroprusside and nitroglycerine via drip. He also received Procardia, intravenous labetolol and lasix. (Despite the abnormal baseline creatinine > 5.0 the subject was enrolled).

Patient #016/002: was a 29 year old caucasian male with a history of chronic renal failure. He was enrolled with chest pain and ECG evidence of lateral ischemia. Exudates were observed in the right eye grounds. The enrollment blood pressure was 178/121. After some initial response to drug (DBP decreased to 84-105 mm Hg) the blood pressure then rose. At 3:30 hours of infusion the DBP was 133 mm Hg and the rate of infusion was doubled. The infusion was stopped at 21: 30 hours because of chest pain, severe headaches, vomiting and nightmares.

Patient #017/009: This was a 49 year old Caucasian male who was enrolled with a blood pressure of 196/128. The diastolic blood pressure at the start of infusion was 103 mm Hg. The subject was randomized to 0.1 ug/kg/min infusion. The infusion was discontinued at 1:45 minutes when blood pressure dropped to 82 mm Hg. Diastolic blood pressure 45 minutes later hovered around 100-105 mm Hg.

Serious Adverse Events (Case reports not submitted and summaries based on sponsor's descriptions):

Patient 003/001: was a 32 year old African-American female patient who had an acute subarachnoid hemorrhage secondary to a cerebral aneurism eight days after completing the fenoldopam infusion. She was enrolled with headaches and a variable blood pressure of 97-138 mm Hg and received 0.3 ug/kg/min. She completed the study and was discharged on oral labetolol 100 mg Q 12 hours. She was re-hospitalized 8 days later because of severe retro-orbital headaches. A CT scan showed a subarachnoid bleed. The aneurism was successfully clipped.

Patient 001/006: Was a 55 year old caucasian male who developed orthostatic hypotension and acute renal failure 16.4 hours after the infusion of fenoldopam was completed. The subject was randomly assigned to the 0.01 ug/kg/min dose that was increased sequentially to 0.02 and 0.03 ug/kg/min. When a new infusion bag of fenoldopam was hung, somewhere around 12-13 hours of the infusion the sponsor claims that an error occurred and the subject received an infusion rate of 0.9 ug/kg/min (30 times the previous infusion dose). One hour prior to the end of the infusion the subject received a 10 mg dose of enalapril. Additional medication including minoxidil and nifedipine were administered (dose not stated) and a nitroglycerine patch placed. A single 40 mg dose of furosemide was administered intravenously because of evidence of congestive heart failure; oxybutynin was administered for bladder spasm. Approximately 15 hours after the infusion was completed, the supine blood pressure was recorded as 99/52 with a standing blood

pressure of 80 by palpation. The serum creatinine increased to 4.1 mg/ml (sic probably mg/dL) from the baseline measurement of 1.3 mg/dl, urinary sodium was undetectable and the urinary sediment was described as "bland". The subject was presumed to have acute renal failure due to pre-renal azotemia. The subject was treated with normal saline with return of renal function to baseline.

Patient 010/017: This was a 33 year old female with a history of congestive heart failure and syncope. She was treated with fenoldopam at a dose of 0.01 ug/kg/min., the infusion was, however stopped after 7:45 hours. She was restarted on her baseline medications including furosemide, benazapril (30 mg) and KCl. Upon leaving the hospital she had a near syncopal episode.

Patient 015/001: A 51-year old male with a history of cigarette smoking was noted to have a right supraclavicular mass, subsequently diagnosed as a poorly differentiated carcinoma.

Adverse Events:

The number of subjects with ADRs as well as specific COSTART term is listed below.

Table 19 .Subjects with Adverse Events.

COSTART Body System	COSTART Adverse Event Term	0.01	0.03	0.1	0.3
Total Infused		25	24	22	23
Any ADR		14	13	11	11
Body General	Headache	5	3	4	3
	Injection Site Reaction	1	3		1
	Abdominal Pain	2			
	Back Pain	1			1
Cardiovascular	Hypotension			2	
	Postural Hypotension	2			
	T-wave Inverted	2	2		
Digestive	Nausea	3		3	3
	Vomiting	2		2	2
Metabolic and Nutritional	Increased Creatinine		2		
	Hypokalemia	2	2		1

Nervous	Dizziness	1		2	
	Insomnia	2			
Respiratory	Dyspnea			1	1
	Epistaxis		1	1	
Skin and Appendages	Sweating			1	
Urogenital	UTI	2		1	

Severe Events: Based on sponsor's Table F-22 (vol 20.8 p. 002-015) seven subjects had nine adverse events that were classified severe. The events for the five subjects: **Patients: # 003/001; #010/017; #013/001; # 015/001 #016/002** were described above.

With respect to the two other subjects, **Patient # 017/002** , randomized to the 0.03 ug/kg/min infusion group was noted to have severe T-waves flipped. The data listing indicates that this subject required treatment and hospitalization with no specifics given. **Patient # 002/004,** treated with 0.01 ug/kg/min and increased to 1 ug/kg/min had severe hypotension (at a dose of 0.7 ug/kg/min) requiring treatment and hospitalization.

A total of 22 subjects had 39 events classified as moderate in severity. These are listed below (Table 20). There are several cases of decreased blood pressure or orthostasis, several cases of headache as well as several cases of gastrointestinal distress.

Table 20. Subjects with Adverse Events Listed as Moderate

Orthostatic hypotension	0.01	0.03	Required Hospitalization	Nausea	0.3	1.0	
ARF		0.03	Required Hospitalization	Emesis		1.0	
Inc Serum Creatinine	0.03	0.06		Diapho-resis	0.3	0.6	Dose Reduced
Inverted T-Waves	0.01	0.01		Nausea		0.6	Dose Reduced
Vomiting	0.1	0.2		Hypoten-sive Response	0.1	0.05	Dose Reduced
HA		0.2		Blurred Vision		0.05	Dose Reduced

002/004	HA	0.01	0.01	
	Hot Sensation		1.0	
	Nausea		0.6	
	Vomiting		0.6	
001/004	Nausea	0.01	0.01	Treatment Required
	UTI		0.01	Treatment Required
003/004	heartburn	0..01	0.01	Treatment Required
004/004	constipation	0.3	0.05	Meds Given
	back pain		0.05	Meds Given
005/004	HA	0.01	0.01	Patient D/C'd
006/004	Sinus bradycardia	0.3	0.3	None
007/004	Nausea	0.1	0.1	Treatment Required
	HA		0.1	Other Meds
008/004	HA	0.03	0.03	
	Sleep Apnea	0.3	0.3	

016/002	Night-mares	0.01	0.02	
	Abd. Cramps		0.02	
017/002	nausea	0.3	0.3	
	Epigas-tric Pressure		0.3	
	SOB		0.3	
018/002	Back Pain	0.01	0.8	
	Abd Discom-fort		0.01	
	Abd pain		0.01	
	Vomiting		0.04	
019/002	Rapid Dec in BP	0.1	0.1	D/C'ds from study
020/002	Hyper-glycemia	0.01	0.04	Other Meds
	Hypoka-lemia		0.04	other Meds
021/002	Left Flank Pain	0.03	0.03	Maalox Given

Change in status of compromised end organs:

Does treatment of a profoundly hypertensive population with fenoldopam lead to benefit or harm? The sponsor makes no claim for a clinical benefit for the use of fenoldopam in the treatment of such hypertensive patients. There is on the other hand, no evidence for irreversible negative outcomes. No subjects had myocardial infarctions or stroke. Several subjects, however, developed retinal hemorrhages noted only after starting the infusion. One subject with ischemia on baseline ECG had exacerbation of ischemia but another subject had improvement of ischemia noted on baseline ECG. Most other patients with ischemia at baseline ECG, had no change in these ECGs even after blood pressure was decreased.

Vital Signs:

Vital signs were to a large extent reviewed as part of the clinical efficacy measurements.

Laboratory Abnormalities

Creatinine/BUN:

A large number of subjects had baseline abnormalities in renal function, either as a consequence of baseline renal insufficiency or due to the hypertensive episode. In sponsor's Table 9-3 (Vol 20.2 p 88) a total of 26 subjects had abnormal BUN/creatinine at baseline.

The sponsor describes six subjects with excessive increases in creatinine and BUN.

Patient # 001/006 is described above under Serious Adverse Events .

Patient # 001/018, a 49 year old African American had an initial BUN/Cr of 45/3.8 and had relatively stable BUN/Cr during the study infusion (maximum dose 0.5 ug/kg/min). He received 210 mg XL nifedipine and 1200 mg labetalol after the infusion. Approximately 11 hours after the infusion he had a hypotensive episode with a BUN/Cr increasing to 48/4.6. He received a 500 ml bolus of normal saline. Unfortunately, no further measurements of renal function are supplied.

Patient # 001/015 , a 47 year old African American with chronic renal insufficiency and dilated cardiomyopathy presented with an initial BUN/creatinine of 21/3.8. Initial dose was 0.03 ug/kg/min which was increased to 0.06 ug/kg/min. His BUN and creatinine rose during the infusion times from 19/3.7, 18/3.7, 19/4.0 and 22/4.4 at 6, 12, 18 and 25 hours of the infusion. Post infusion BUN/Creatinine was 26/4.8. No follow labs were available. The subjects received a single 800 mg dose of ibuprophen at approximately 16 hours of t he infusion.

Patient # 001/008, a 32 year old Hispanic male had an initial creatinine of 1.4 mg/dL. He was randomized to 0.03 ug/kg/min and was upward titrated to 0.4 ug/kg/min. His BUN/Cr was stable during infusion but the follow up BUN/Cr was 50/2.7

Patient # 005/001 is described above.

Patient # 011/001, a 47 year old African American female was enrolled with an initial BUN/Cr of 13/1.5. She was originally randomized to receive 0.01 ug/kg/min but the dose was upwardly titrated to 0.6 ug/kg/min (the dosing table states 0.06 ug/kg/min so one of these is off). The Follow up BUN/Cr was 20/1.9.

Potassium:

Hypokalemia was relatively common within the data base. The data base, however, was confounded both by the concomitant administration of loop diuretics (that would lower serum K+) as well as by parenteral and/or oral supplementation with K+ salts.

Below is a tabulation (Table 21) as per sponsor of the means of the changes in serum K+ at four different time points. At 6 hours there appears to be a consistent drop in serum K+. Serum K+ levels below 3.0 were not uncommon. Since few subjects received diuretics during the initial 6 hours the drop in K+ is likely due either to drug or profound hypertension.

Table 21 .Serum K+ (meq/L) mean (SE)

	3.7 (0.1)	4.0 (0.2)	3.9 (0.2)	3.7 (0.1)
	3.5 (0.1)	3.6 (0.1)	3.6 (0.1)	3.4 (0.1)
	3.6 (0.1)	3.8 (0.1)	3.8 (0.1)	3.5 (0.1)
	3.9 (0.1)	3.8 (0.1)	3.9 (0.1)	3.6 (0.1)
	3.9 (0.1)	3.9 (0.1)	3.9 (0.1)	3.7 (0.1)
	3.9 (0.1)	4.0 (0.1)	4.2 (0.1)	4.1 (0.1)

Hematology:

As per sponsor 21/94 subjects who enrolled were anemic at baseline (HGB< 11.5g/dL) . The group mean average decline in Hgb was a small (< 1 g/dL). The sponsor attributed this drop to phlebotomy, it is likely that some component also reflect hydration status.

ECGs:

Subjects had ECGs done at baseline and at 6, 12, 18 and 24 hours during the infusion and at follow up. The ECGs were machine-interpreted and were also read by a single cardiologist (Dr. Galen Wagner, Duke University). According to the sponsor, the ECGs were read in an blinded manner. Dr. Wagner only analyzed the ECGs for morphological changes, intervals were only collated from the machine-read measurements.

Morphological interpretation by Dr. Wagner often differed from the machine analyzed interpretation. Dr. Wagners readings are incorporated as sponsor's Table 13.6

(vol 20.2 p125-129). This reviewer attached most weight to Dr. Wagner's assessment.

Baseline ECGs were available for 101 patients, and at least one treatment measurement was available for 90 subjects Fifty-three subjects had their ECGs read as LVH with ST-T wave abnormalities and an additional 30 patients had LVH with other findings. LVH was therefore present in 83/101 patients (82%). Previous myocardial infarctions were identified in 17 patients. Changes consistent with ischemia were reported in 10 patients. Four subjects and PVCs, two patients had left anterior fascicular block and one patient had a first degree AV block. Two patients had atrial fibrillation at baseline.

No patient developed a new MI as a consequence of the study. Among those with baseline ischemia eight of the 10 had no change in their ECG readings despite substantial decreases in blood pressure. One subject, #008/005, randomized to 0.01 ug/kg/min infusion had improvement in ischemia, a different subject #016/002 also randomized to 0.01 ug/kg/min infusion developed worsening of ischemia.

Based on the machine generated readings, there was no statistically significant change in QTc intervals over the course of the study. One subject, randomized to the 0.03 ug/kg/min infusion rate had a QTc reading at 12 hours of 605 msec, the same subject had readings at 6 and 18 hours of 488 and 522 msec-1/2. The baseline measurement was 470 msec-1/2, the follow up QTc was 391 msec-1/2. One subject also receiving 0.03 ug/kg/min infusion had QTc measured at 12, 18 and 24 hours of 533, 557 and 561 msec$^{-1/2}$, respectively. Baseline QTc was 469 msec$^{-1/2}$.

Table 22. Change in QTc over time versus dose

	5.3 (4.7)	3.8 (5.0)	-7.1 (5.9)	8.6 (8.3)
	6.9 (6.0)	14 (8.7)	1.3 (4.4)	-2.1 (7.8)
	8.8 (3.7)	5.7(8.1)	-3.1 (4.4)	-3.3 (9.2)
	1.7 (3.1)	5.4 (8.2)	-2.6 (5.3)	-6.2 (5.6)

Any interpretation of the QTc intervals need to be interpreted in the context of K+ concentration changes that occur as a consequence of the hypertensive emergency.

Appendix A

Some Peculiar PK Profiles.

Redacted 1

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APPENDIX B

Assessment of End-Organ Involvement

Patient #	System involved	Description √-Denotes sponsor defined malignant HB	Agree
001/001 √	Neuro-HA	———	OK
	Opth-papilledema	Bilateral Papilledema	
001/002	Renal-Incr BUN, Cr	Hx of Nephrosclerosis; BUN/creatnine was 23/2.0, no previous creatnine stated.	?
001/003 √	Renal-Hematuria	Dip negative for blood; Cr =1.4	no
001/005 √	Renal-Hematuria	Screening microscopic for blood not done- Subjesquent evaluations had both RBC and WBCs; initial dip positive for RBCs; Hx Diabetees M.	possible
001/006 √	Renal-incr BUN /Cr; hematuria	Hx mild renal insufficiency; Creatnine baselin e= 1.3 ; Urine 10-15 RBC/ HPF;	OK
001/007 √	Neuro-HA	———	OK
	Renal incr BUN/Cr; hematuria	Small hypoechoic kidneys noted on ECHO (why done?)years before enrollment. BUN/Cr 42/3.0- no previous values stated. Positive Blood in U/A.	
001/008	Renal incr BUN/CR	Hx mild renal insufficiency Cr =1.4. Baseline BUN/Cr 22/1.4. U/A not impresssive	no
001/009 √	Opthal-Papilledema	Bilateral papilledema	OK
	Renal-Hematuria	Dip positive for blood; But only 2-3 RBC/HPF in microscopic, BUN/Cr 17/1.2	
001/010	Neuro-HA	———	?
001/012 √	Neuro-HA	———	Not convinc-ing
	Renal Hematuria	Dip 2-3 RBC/HPF; dip blood positive	
001/013 √	Cardio-SOB	History CHF; crackles noted 2/3 lung field- Old or new?	possible
	Renal Incr BUN/Cr-hematuria	No hx renal disease noted; BUN /Cr =25/1.6; microscopic 2-5 RBC/HPF; dip postiive	
001/014	Cardio-SOB	Hx asthma; P/E has expiratory wheezess. CXR-L vent hypertrophy	?
	Neuro-HA	———	
001/015	Neuro-HA	———	
	Renal- Incr BUN/Cr	Hx chronic renal insufficiency: 21/3.8 (unusual ratio, past Creanine not stated).	
001/016 √	Neuro-HA	———	OK
	Opth-papilledema	Papilledema OS	
	Renal Incr BUN/Cr	BUN /Cr 32/3.8 -no hx of renal disease stated	
001/017	Neruo-HA	———	?
001/018	Neuro-HA	Hx headaches	OK
	Renal-Incr BUN/Cr	BUN/Cr 45/3.8 No Hx renal disease	
002/002 √	Cardio-ECG evidence of Ischemia-SOB	Hx progressive chest pain inverted T waves in INF, ANF (sic); DOE intermittant SOB; LAFB with anterior ST elevation -+ 1 Pedal Edema on exam.	?

002/003	Neuro-HA	Hx intermittant headache	OK
	Renal incr Bun,Cr	BUN /Cr ; 20/2.4- No hx of previous renal disease	
002/004 √	Cardio-Chest Pain ECG evidence of ischemia	Hx chest pain syndrome with normal evaluation. Baseline ECG- LVH with inferolateral ischemia.	OK
003/001	Neuro-HA	Hx occipital tumor	?
003/002	Neuro-HA	Hx metastatic tumor to CNS	?
003/003	Cardio-SOB	Hx enlarged heart- normal cardiopulmonary exam at baseline- normal CXR at baseline	?
	Neuro-HA	———	
003/005	Neuro-HA	———	?
	Renal Incr BUN/Cr	Chronic history renal failure BUN/Cr: 42/3.2- no previous values stated. Urine trace blood.	
003/006 √	Cardio-Chest pain, SOB	Hx SOB after 2 months- MI 1995, Old MI, LVH wirh ST-T wave abnormality - normal baseline exam	?
	Opth-Acute Visual Change	Hx right eye with shattered retina.	
	Renal-Incr BUN/Cr; oligouria	Hx: Damaged kidney. Baseline BUN/Cr= 34/3.2; Urine sediment c/w chronic glomerulonephritis	
004/001	Cardio-SOB	Baseline cardiovascular exam normal ; Baseline CXR- normal	?
	Neuro-HA	———	
004/002	Cardio-SOB	Hx CHF 1994- Exam : Bilateral basilar rales, enlarged liver 4+ edema, CXR- unchaned from previous exam., persistant cardiomegaly, vascular congestion , bilateral pulmonary edema, left lung effusion Occular exam has blurred disc margin plus hemorrhages	? Old CV OK for occular
004/003	DBP > 140 mm Hg	Last blood pressures prior to infusion 120-130 -	no
004/004	BP > 140 mm Hg	Blood pressure hour before infusion generally between 120-130 single high reading of 157 mm Hg when arterial line placed.	no
004/005	Neuro-Confusion	No specifics given	?
004/006	Cardio-Chest Pain	Smokes 2 PPD. Has Fracture (R) shoulder, occassional heartburtn- Lateral ST-segment depression.	OK
	Neuro-HA	———	
005/001 √	Neuro-HA	———	OK
	Opthal-acute Visual Changes, Papiledema	Positive history papilledema. Papilledema OS	
	Renal Incr BUN/Cr	No Hx renal disease.BUN/Cr= 22/1.8	
006/001	Neuro-HA	———	?
	Opthal-Acute Changes in Vision	Discs normal	

006/002	Neuro-HA	-------	?
006/003	Neuro-HA	-------	?
007/001 √	Cardio-Chest Pain; SOB	HX of CHF: CAD; ECG+LVH with ST elevations -no change after therapy. Cardiopulmonary exam normal- CXR marginally enlarged with some encephalization of blood flow	Sound old ?
	Neuro-HA	-------	
007/002	Cardio-SOB	Hx asthma- CXR normal; Cardiopulmonary exam: normal , However occular exam shows papilldema	OK
	Neuro-HA	-------	OK
	Opthal-Papilledema	Papilledema, blurred discs margins.	
007/003	Neuro-HA	-------	?
008/001 √	Cardio-Chest Pain	No hx of heart disease- ECG , showed evidence of old inferior MI, with LVH and ST-T wave abnormalities. normal cardiopulmonary exam	OK
	Neuro-HA	-------	
	Opthal-Papilledema	Blurred disc margin with papilledema	
008/002	Neuro-HA	Hx CVA 4/96	?
008/003 √	Cardio-ECG evidence of Isch,mia	HX: Dilated Cardiomyopathy and asthma. mECG -LVH with ST-T wave abnormaility (no evidence of ischemia) Cardiopulmonary exam WNL. Central line in atriaum (why central line?)	?
	Neuro-Confusion	S/P CVA	
008/004 √	DBP > 140 mm Hg	Patient did have DBP > 140 mm Hg Occular exam at baseline shows papilledema	OK
008/005	Neuro-HA	-------	OK
	Renal Incr BUN/Cr	Baseline BUN/Cr =32/2.1. Urine benign	
008/006 √	DBP > 140 mm Hg	Last measurment before infusion 130 mm Hg- Overall 1-hour average approxiamtely 140 mm Hg	marginal
008/008 √	Neuro-HA	Hx CVA 1995	?
	Opthal-Papilledemaa	Blurred disc margin only 1 eye only at screening	
008/009 √	Neuro-HA	-------	OK
	Opthal-Papilledema	Blurred disc margin-hemorrhagic later in therapy	
009/001 √	Cardio-Chest Pain	ECG: Old MI no change upon therapy	OK
	Neuro-HA	Hx head ache 3 times/week	
	Opthal- Grade III-IV Retinopathy, Papilledema	Blurred disc margin but macula described as normal	
009/002	CV-SOB	HX : SOB and DOE- Physical exam- Diffuse PMI- II/VI SEM- S3-S4 Gallop; CXR within normal limits	?

010/001 √	Neuro-HA	———	OK
	Opthal-Papilledema	Blurred disc margin (R) eye (l) normal rest of opthalmologic exam WNL	
	Renal Incr BUN /Cr	Hx renal insufficiency Cr 2.4 on 12/95. BUN/Cr on adminssiot 114/10.1	
010/002	Neuro-HA	———	?
010/003	CV-SOB	Hx of cardiac enlargement , stable angina Baselin ecardiovascualr exam normal	?
	Neuro-HA	———	
010/004 √	Cardio-ECG evidence of ischemia	Hx cardiomegaly and angin ECG at baseline LVH with ST-T wave abnormalities CXR: Enlarged cardiac silhouette . Opthalmologic exam blurred dosc margin, hemorrhagic background	OK
	Neuro-HA	———	
010/005 √	Cardio ECG evidence of ischemia	Hx: Angiogram done 1995 ECG: LVH with widespread ischemia which minimal changes during therapy except low atrial rhythm at 18 and 24 hours. Exam: Grade II/VI SEM LLSB unchanged during infusion CXR: Global enlargement of cardiac silhouette -Chamber enlargement vs. Pericard,al Effusion. Minimal Pulm. Vascular congestion Tortuous aorta Opthamologic exam has exudates on background	? Old disease with no response to infusion . BP only modestly altered by infusion OK on opthalmologic.
010/006	Criteria # 5	BP < 140 mm Hg	No
010/008	Cardio-SOB; Chest Pain	Hx atrial fibrillation, CHF, and cardiomegaly Cardiovascular exam: C/W AF CXR: cardiomegaly, and CHF with early pulmonary edema	? HBP related or past
010/009	Cardio-SOB	Hx heart murmur Cardiovascular Exam: normal CXR-Heart silhouette top normal in size. No edema noted.	?
	Neuro-HA	———	
	Opthao-Acute Visual Change	Hx blurred vision in past	
010/010 √	Cardio-SOB	Bypass 1/95 Hx MI Cardiopulmonary Exam: S3 gallop II/VI SEM bilateral rales CXR: Cardiomegaly pulmonary edema findings c/w CHF ECG VPBs, old IWMI, Anterapical ST elevation with VPBs and APBs during infsuion otherwise no changes	OK
	Renal - Incr BUN/Cr	Hx renal insufficiency BUN/Cr at screening 55/4.5- no previou values goven	
010/011	Neuro-HA	———	?
010/012 √	Cardio-pulm edema; SOB	Hx congestive heart failure ECG: Heart rhythm irregular PVCs Tachycarida, IVD(sic ? JVD)) to 15 cm , rales in basese therefore >in (L) base CXR: 1) Cardiomegaly 2) Mod R-Side Pleur; EFN 3) Mix intrstital &Predomin Airspce Opacity R Lowr Lobe c/w pneumon 4) Prominee R Hilum. Repeat Exam Recom After TX & Resolutn R side Pneumon & EFN Eval Poss Mass Lesion	? Sounds old disease
010/013	Neuro-HA	———	
	Opthal-Acute Vis Changes	Normal opthalmologic exam	

010/014	Cardio-Chest Pain, SOB	Hx only hypertenison noted has URI with cough ECG LVH with anterior ST-elevations Cardiovascualr exam Increase expiratory phase CXR: Moderate enlargement of cardiac silhouette either due to cardiomegaly or pericardial effusion Opthalmologic with exudates	Based on CXR possible. OK on opthal
010/015	Neuro-HA	———	?
		Opthalmologic has exudates	OK on opthalmol
010/016	Cardio-Chest Pain	Hx cardiomyopathy, CHF, heart murmur ECG-LVH with anterior ST segment elevations Cardiovascular Exam: normal	OK based on ECG
	Neuro-HA	———	
010/017 √	Cardio-SOB	Hx cardiomegaly/ pulmonary edema Exam: Cardiomegaly bibasilar crackles CXR: enlarged cardiac silhouette eithe due to pericardial effusion or cardiomegasly interstitial opacities maybe due to interstitial pulm edema...	OK
	Neuro-HA	———	
	Opthal-Papilledema	Papilledema L eye	
010/018	Cardio-Chest Pain; SOB	Hx cardiomegaly: ECG: Old inferior wall MI Cardiovascualr exam: cardiomegaly bradycardia CXR: cardiomegaly with LV dilitation and changes suggestive of pulmonary blood flow	? BP on enrollmen 101 mm Hg
010/019	Neuro-HA	———	
010/020 √	Neuro-HA	———	?
	Renal-Hematuria	Hx: IDDM Screening 2-5 RBC/HPF; Urinanalysis consistant with nephrotic syncrome	
010/021 √	Cardio-ECG evidence of ischemia; SOB	Hx; ECG changes old ECG: LVH with ST-T wave abnormalities. Cardiovascualr exam: normal CXR: normal	?
	Neuro-Confusion. HA	Hx alcoohol abuse, bipolar personality	
011/001 √	Neuro-Confusion, HA	Nothing on history	based on opthalmol ogic possible
	Opthal-Papilledema	Blurred disc margin bilaterally	
011/002	Neuro-HA	———	
011/003	Cardio-Chest Pain; SOB	Hx sever bronchitis: Cardiovascular Exam: Bibasilar crackles: CXR: Diffuse interstitial prominance unchanged form previous film	Old versus ,BP effect?
	Neuro-HA	———	
	Opth-Acute Visual CHanges	Discs normal no exudates	
011/004 √	Neuro-HA-Impending Stroke	Past Hx mul;tiple CVAs; MI 1976, Agina 1976 (L) sides paresthesiss	OK but there is clearly a past hx of same events

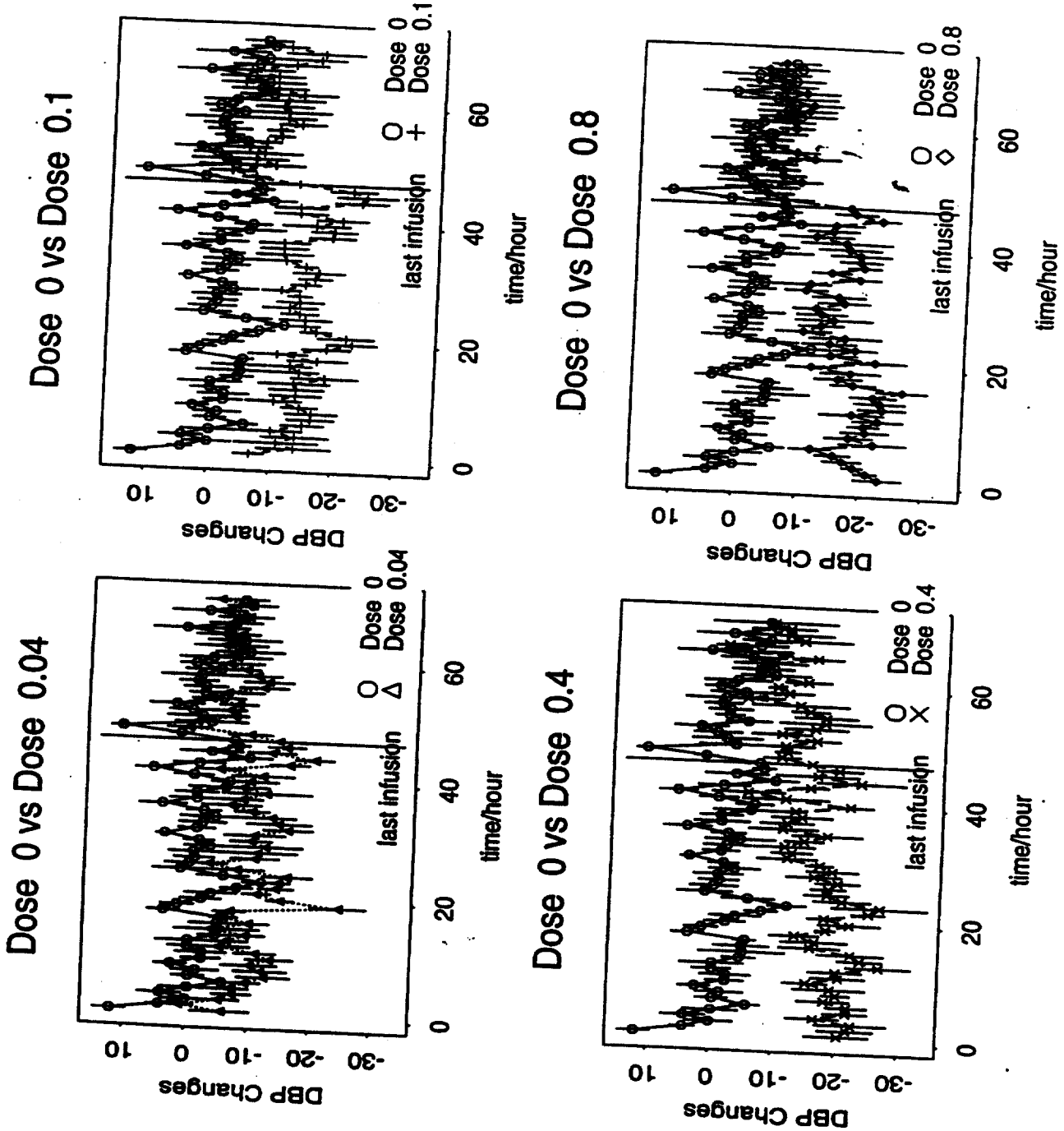
012/002	DBP> 140 mm Hg	Only value within 1 hour of infusion was) hour time point - DBP was 124 mm Hg	no
012/003	Cardio-Chest Pain; SOB	HX; no history of disease listed ECG- Old inferio posterior MI; Inferior ST depression which resolves at 6 hours	OK
013/001	Cardio-Chest pain; SOB	No Hx of cardiovascualr disease: LVH with ST-T wave changes (no change with treatmetn). Cardiovascular exam: Describes inferior ischemia on monitor, CXR: Heart enlarged vascualr marking prominant bases underexposed and possiblity of infitrate cannot be ruled out.	OK
015/001 √	Opthal-III-IV retinopathy; papilledema	Blurred disc margins with hemorrhagic exudates	OK
	Renal Incr BUN/Cr	No Hx renal disease stated. Baseline BUN/Cr 62/4.4	
016/002 √	Cardio-Chest Pain; ECG evidence if ischemia	Hx: LVH with Chest pain LVH with lateral ischemia- gets worse with infusion	OK
	Neuro-HA	———	
	Opthal-III-IV retinopathy	Exudates seen	
	Renal-Incr BUN/Cr	Hx renal insufficiency: Baseline BUN/Cr 48/3.7	
016/003 √	Cardio-ECG evidence of Ischemia	ECG at baseline: LVH with ST-T wave abnormalities no change with infusion Cardiovascular exam: normal CXR: normal	?
	Neuro-HA	———	
	Renal- Incr BUN/ Cr	Baseline 26/1.3 -no previous measuments give. 0-1 RBC/HPF	
017/002	Cardio-Chest Pain; SOB	HX: Hx of heart failure exertional dyspnea ECG:LVH with ST-T wave changes - transient T-wave changes with ifnsuion Cardiovascular exam: S3 gallop with rales bilaterally, II/VI SEM at apex-improved with infsuion Exudates seen on opthalmologic exam	OK
	Neuro-HA	———	
017/004	Neuro-HA	———	?
017/005	DBP > 140 mm Hg	OK Exudates seen on opthalmologic exam	OK
017/006	Neuro-HA	———	?
017/007	DBP> 140 mm Hg	OK	OK
017/008	Neuro-HA	———	
	Renal-Incr BUN/Cr	Baseline BUN /creatinine = 14/1.4	possible but no other Cr measurments
017/009	Neuro-HA	———	?
017-010	Neuro-HA	———	?
017/011	Neuro-HA	———	
	Opthal-Acute Visual Changes	Hx blurred vision No disc abnormality	?

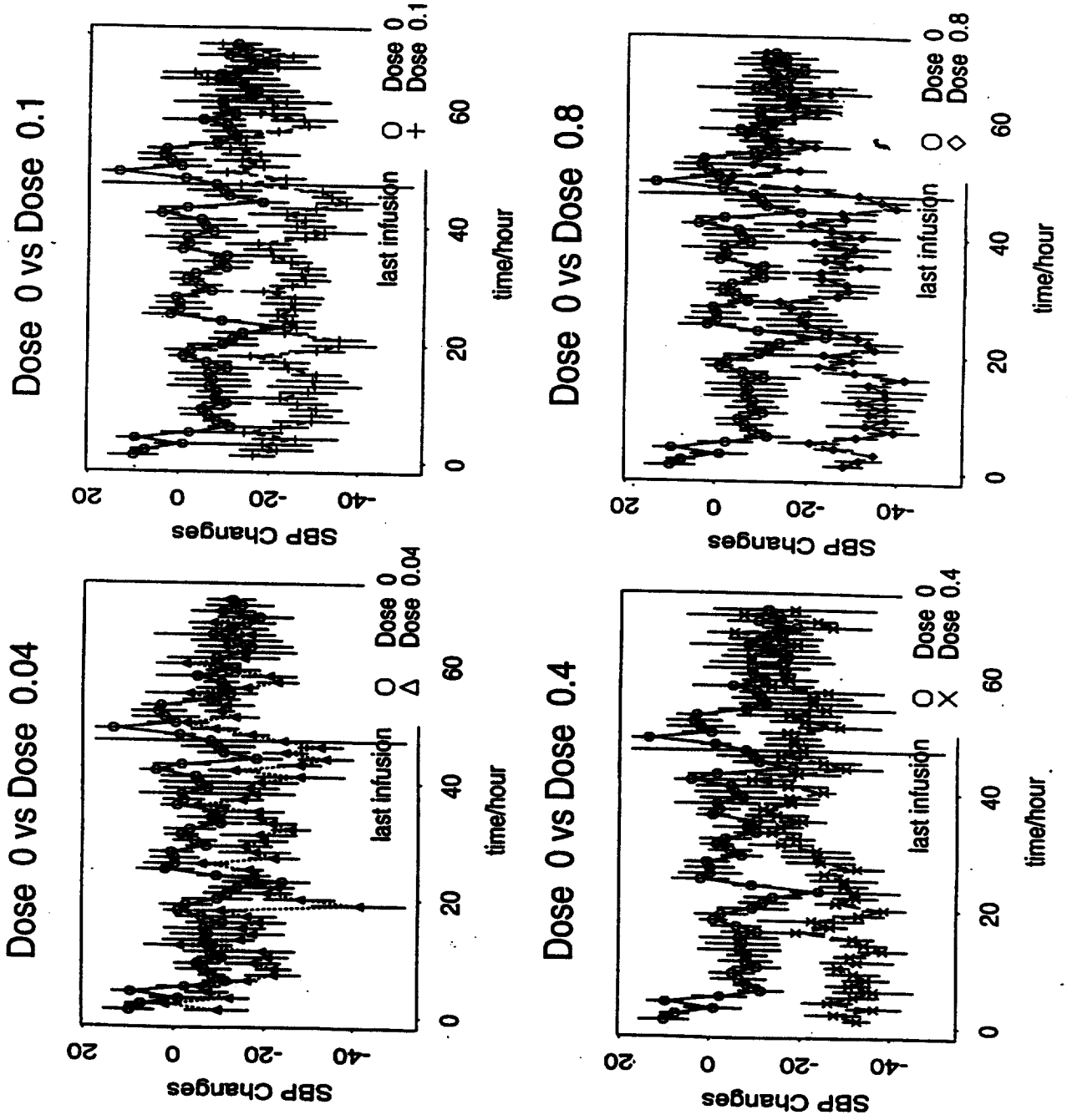
018/001	Renal-Incr BUN/Cr; Oligouria	Hx increase creanine secondary to DM- value not given baseline BUN/Cr=23/2.2 Opthalmologic Exudates noted	? Old
018/002	Nuero-HA	———	OK based on Opthal
	Opthal-Acute Visual Changes	Hx catraracts bilaterally- Exam : no disc abnormality	
018-003 √	Neuro-HA	———	old or newhemat uria?
	Renal-Hematuria	Hx hematuria: sediment 54 RBC/HPF Urinanalysis: protein blood positive	
019/001 √	Neurol-HA	———	old renal disease ?
	Renal Incr BUN/Cr; oligouria	Hx chronic renal failure last value not given Baseline BUN/Cr= 41/3.7	
020/001	Cardio-Chest Pain; SOB	Hx: Orthopnea since 5-96 LVH with ST segment depression and T-wave inversion, no change with infusion Cardiovascular exam: 3rd heart sound CXR: Gross cardiomegaly with early changes of CHF	Clearly in CHF but old or BP related?
021/001 √	Neuro-HA	———	Old or new ? Bas,d on Opthal
	Renal-Incr BUN/Cr; Oligouria	Hx hematuria sediment 10-25 RBC/HPF Opthalmologic with blurred disc margin	
021/002	Neuro-HA	———	OK
	Opthal-Acute Visual Change	Hx papilledema	
	Renal Incr BUN/Cr	No hx renal disease Bun/Cr at baseline 12/1.9	

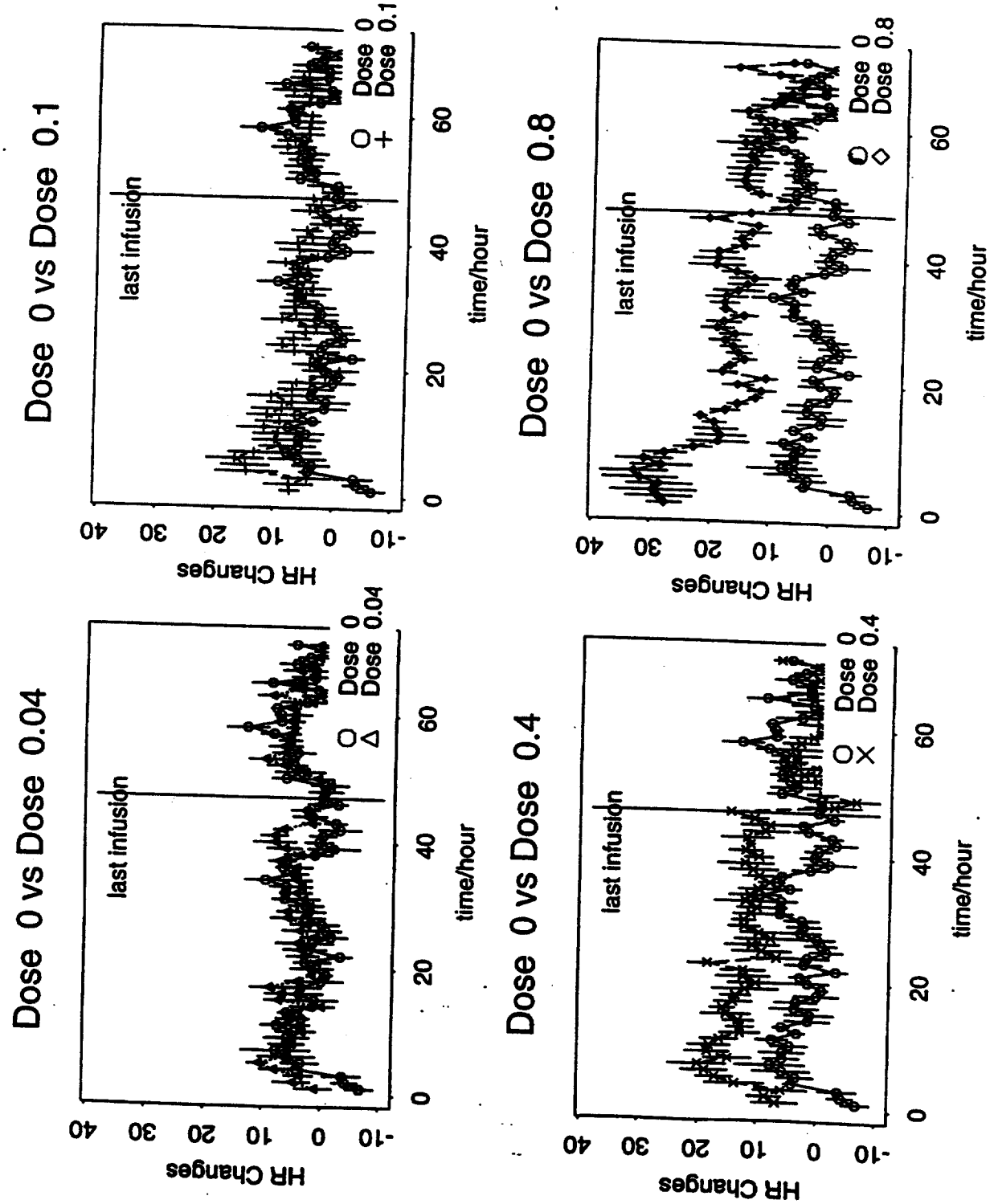
APPEARS THIS WAY
ON ORIGINAL

Appendix C

Time Curves For Mild -Moderate Hypertensives Study # 94-05


Dose 0 vs Dose 0.1
Dose 0
Dose 0.1
last infusion
time/hour
DBP Changes
Dose 0 vs Dose 0.8
Dose 0
Dose 0.8
last infusion
time/hour
DBP Changes
Dose 0 vs Dose 0.04
Dose 0
Dose 0.04
last infusion
time/hour
DBP Changes
Dose 0 vs Dose 0.4
Dose 0
Dose 0.4
last infusion
time/hour
DBP Changes


Dose 0 vs Dose 0.1
Dose 0
Dose 0.1
last infusion
time/hour
SBP Changes
Dose 0 vs Dose 0.8
Dose 0
Dose 0.8
last infusion
time/hour
SBP Changes
Dose 0 vs Dose 0.04
Dose 0
Dose 0.04
last infusion
time/hour
SBP Changes
Dose 0 vs Dose 0.4
Dose 0
Dose 0.4
last infusion
time/hour
SBP Changes


Dose 0 vs Dose 0.1
Dose 0 vs Dose 0.8
Dose 0 vs Dose 0.04
Dose 0 vs Dose 0.4
last infusion
HR Changes
time/hour
Dose 0
Dose 0.1
Dose 0.8
Dose 0.04
Dose 0.4