RESULTS (study # 94-7).

Pre-treatment variables.

Demographic and pre-treatment characteristics of subjects are shown below. There were imbalances in the distribution of race, gender, and pre-treatment BP, as shown in the following table.

Demographic and Pre-treatment characteristics of subjects in study 94-7:

	Fenoldopam (µg/kg/min)			
	0.4	*0.6*	*0.8*	*1.6*
sample size	1	2	3	2
Age mean (yr)	48	47	48	46
Black (%)	0	100	33	100
Caucasian (%)	100	0	67	0
Male (%)	100	0	67	100
Female (%)	0	100	33	0
Mean qualifying DBP (mm Hg)	115	106	107	100

[source: modification of tables on pgs 7 & 45, vol 27]

Subject disposition.

The pertinent aspects of subject disposition were as follows:

- 8 subjects were enrolled and received fenoldopam[16].

- 2 subjects (004 and 003) dropped out (after approximately 0.75 and 2 hours on drug, respectively) because of hypotension and hypotension with bradycardia, respectively.

- 6 subjects were completers.

There was one reported misdosing wherein subject 009 received 0.8 µg/kg/min fenoldopam instead of a 0.4 µg/kg/min dose.

[16]an additional subject (#5) received a randomization number, but was noted not to qualify.

Datasets on which submitted analyses were based

The submitted descriptive statistics were based on a "per dose received" dataset of all randomized patients, including the misdosed and noncompleting subjects, and excluding missing data points.

Exposure to drugs: Deviation between Actual and Prespecified:

Although most of the low-flow demands made of the pump did not exceed its rated capacity, for the pump to have achieved the intended dose rate of 0.6 µg/kg/min in subject 8 (a 71 kg individual) would have required an infusion flow rate (0.43 mL/min) somewhat smaller than the lowest rate (0.5 mL/min) said to be reliably achieved by the pump. On this basis, this subject presumably received a higher than intended rate of drug delivery.

Hemodynamic effects:

One of three subjects who received 0.8 µg/kg/min fenoldopam experienced a marked reduction from baseline SBP of about 60 mmHg by 30 minutes after initiation of infusion. Some 15 minutes later her BPs were 70/47 mmHg with an associated HR of 38 bpm. Similarly, one of two subjects who received the 1.6 µg/kg/min dose experienced severe hypotension (71/47 mmHg) after about two hours of drug exposure[17]. In both cases hypotension reportedly resolved rapidly after discontinuation of the infusion.

The greatest SBP lowering effect was noted in the 0.8 µg/kg/min and 1.6 µg/kg/min groups. In some subjects the steady-state SBP effect was noted to lag behind steady-state plasma concentration. For example, the changes from pre-treatment SBP for subject 2 were -12 and -102 mmHg at the 1 and 2 hours after initiation of a µg/kg/min infusion, respectively.

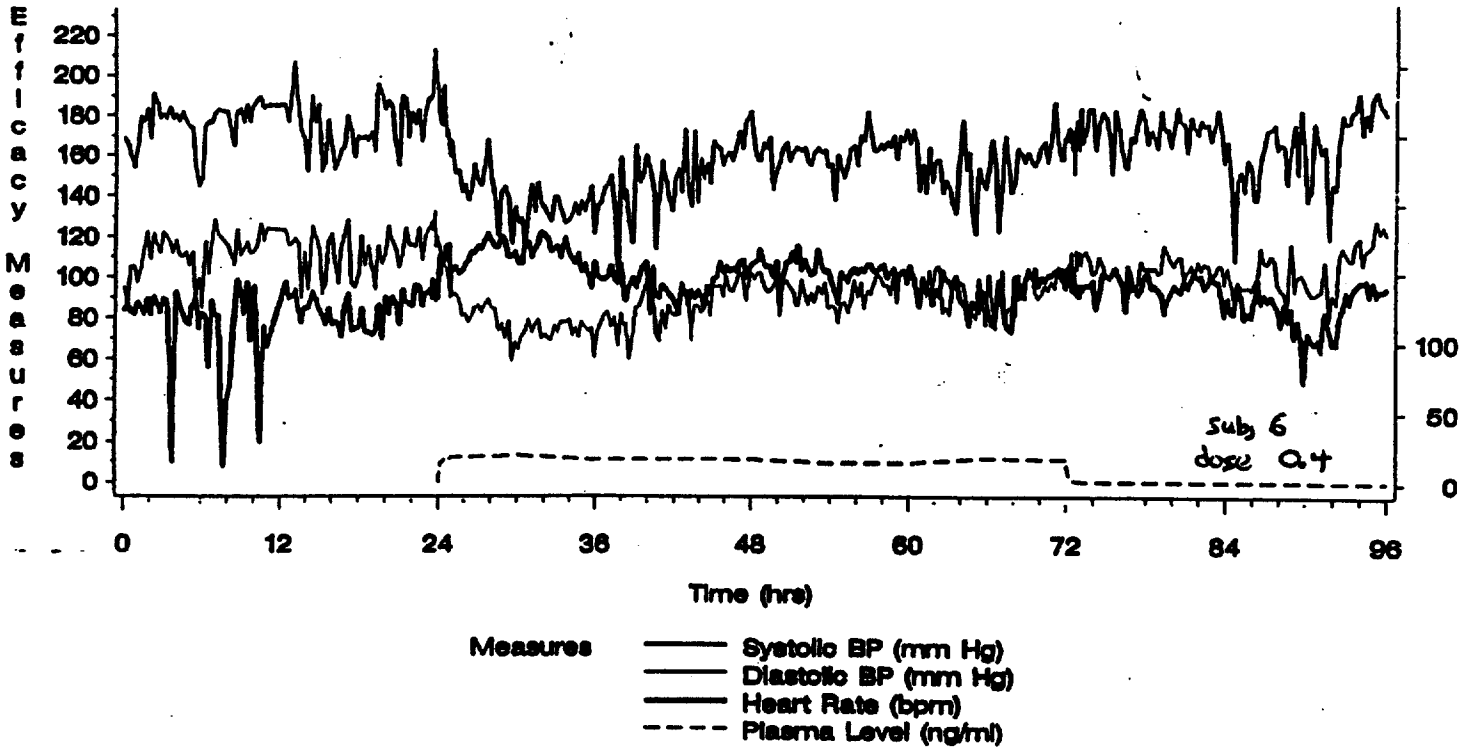
During the two day fenoldopam infusion the range of reported changes from pre-treatment DBP was -2 to -55 mmHg for the one patient in the 0.4 µg/kg/min group, 0 to -49 mmHg for the 0.6 µg/kg/min group (n=2), -10 to -68 mmHg for the 0.8 µg/kg/min group (n=3), and -8 to -47 mmHg for the two patients in the 1.6 µg/kg/min group.

See the following tables for individual subject responses in this study.

[17]see below for further discussion of these cases of hypotension, under Safety outcomes.

Table: 12

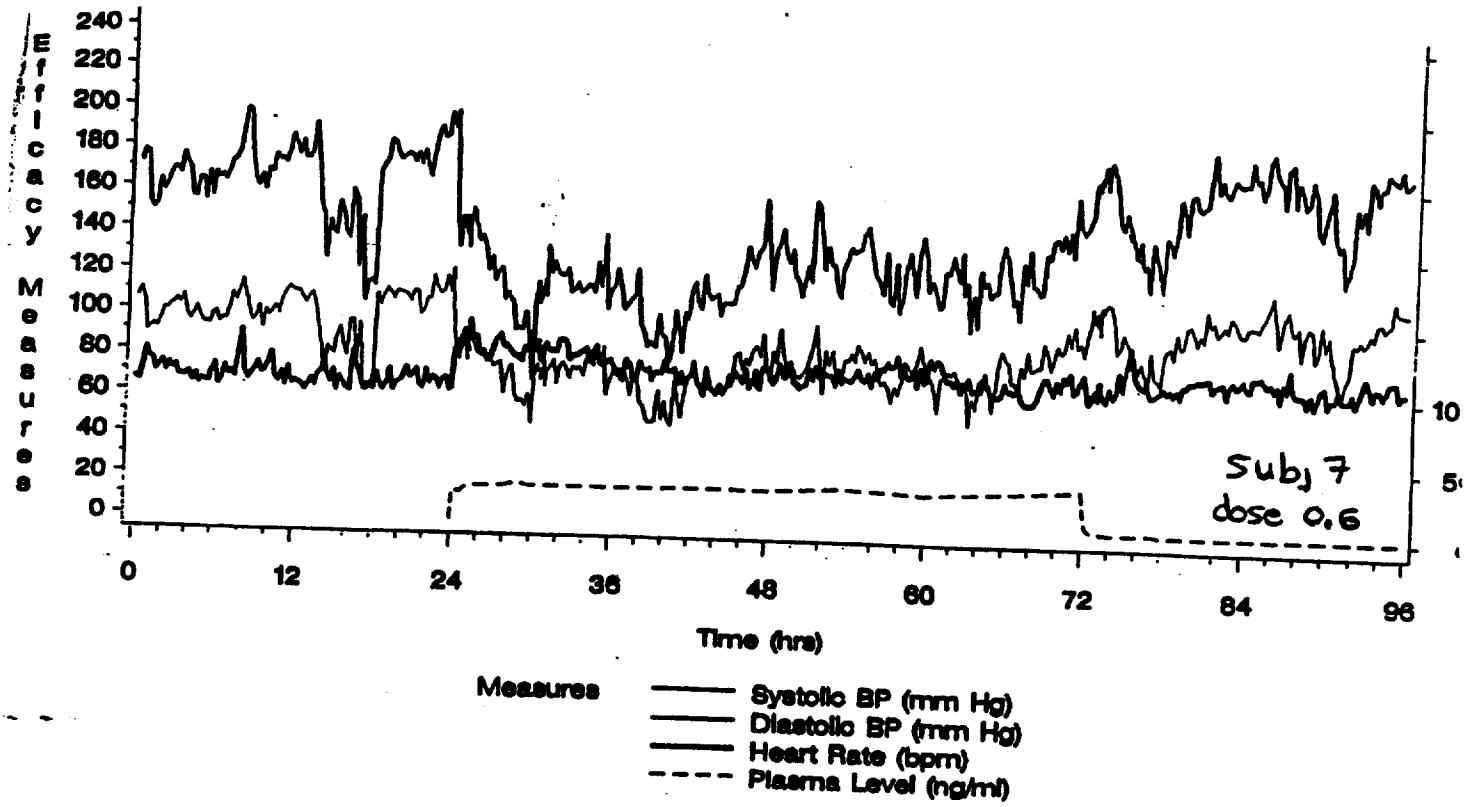
Hemodynamics and Plasma drug levels prior to and after
0.4 µg/kg/min fenoldopam infusion (n=1; study 94-7)

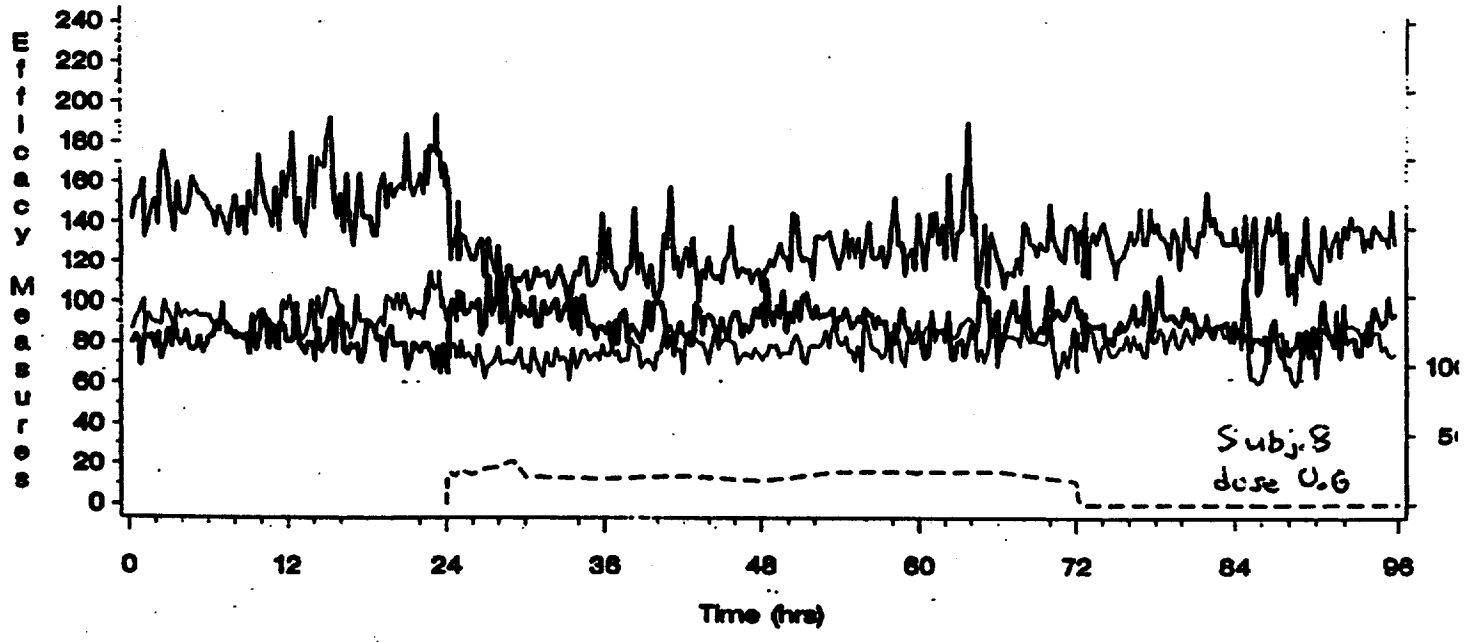


[source: photocopy of figure on page 56, vol 27]

Table: 13

Hemodynamics and Plasma drug levels prior to and after
0.6 µg/kg/min fenoldopam infusion (n=2; study 94-7)

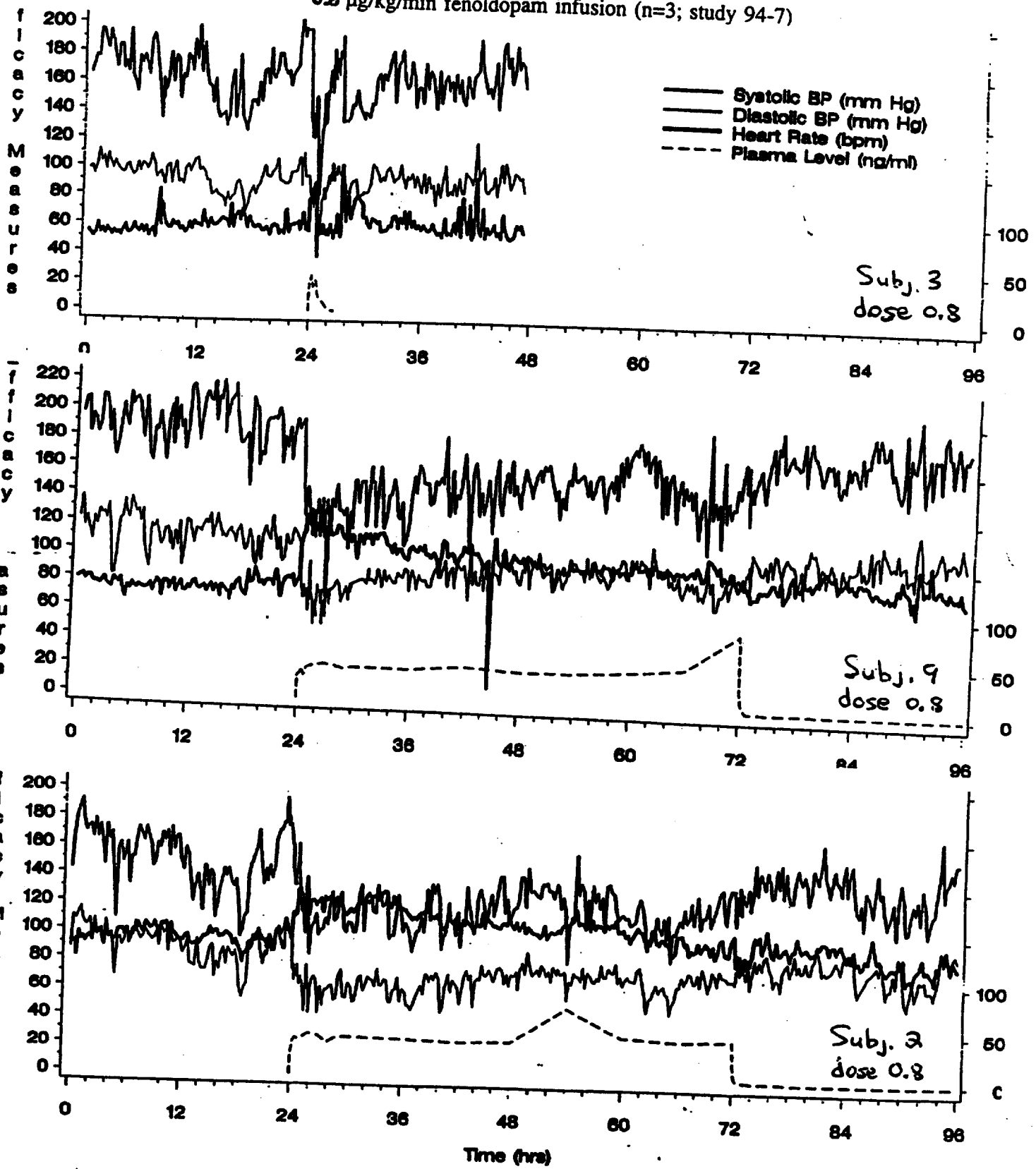




[source: photocopy of figures on page 57-8, vol 27]

Table: 14

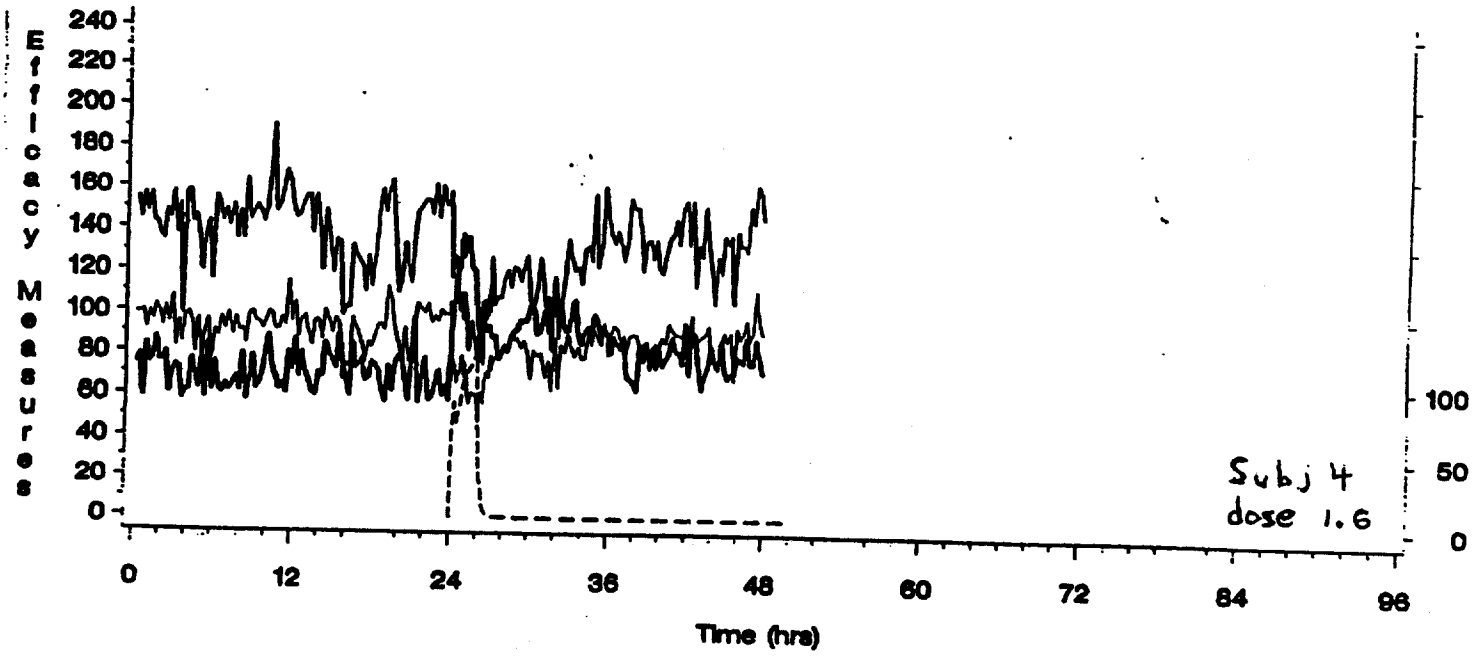
Hemodynamics and Plasma drug levels prior to and after 0.8 µg/kg/min fenoldopam infusion (n=3; study 94-7)

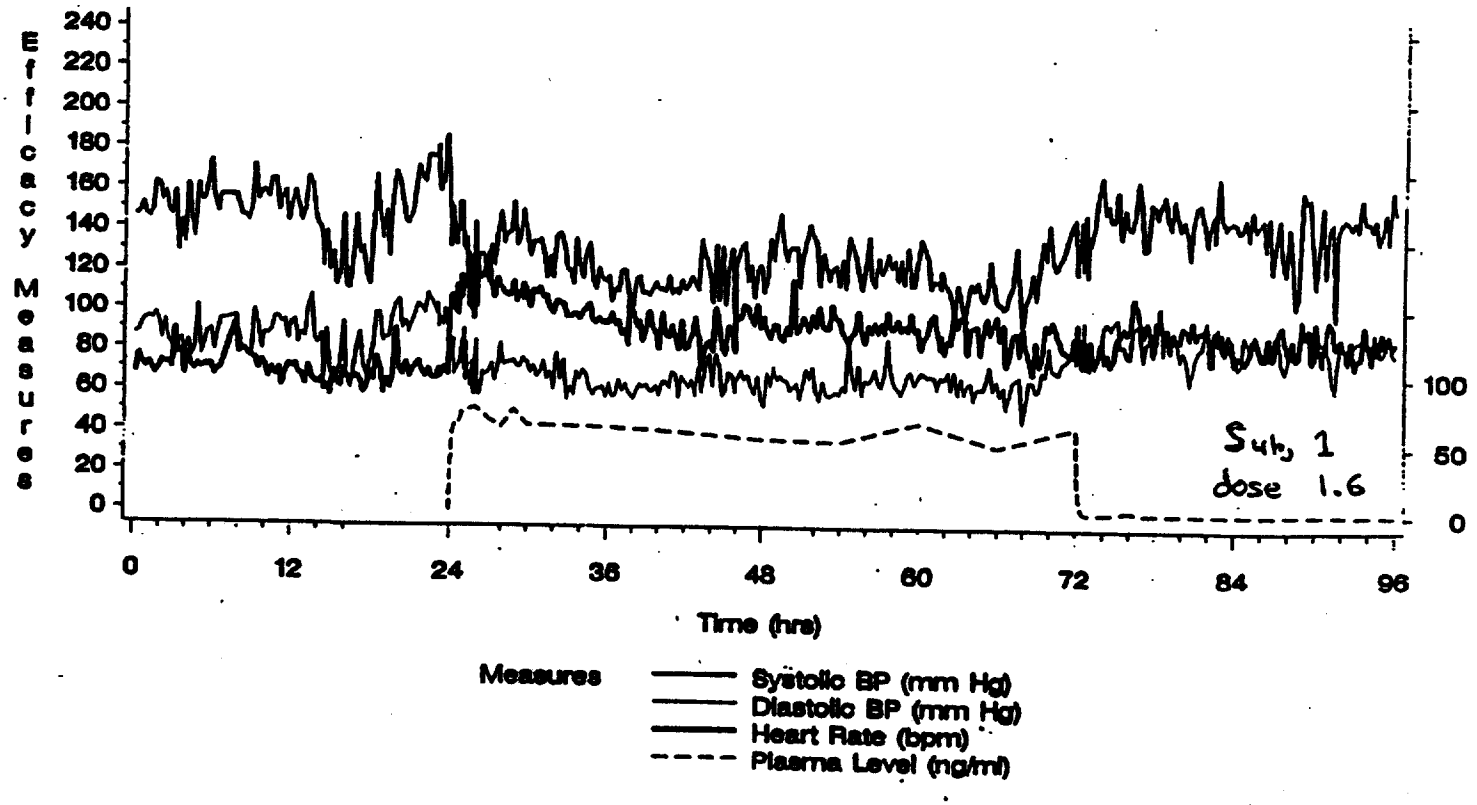


[source: photocopy of figures on page 53-4 and 59, vol 27]

Table: 15

Hemodynamics and Plasma drug levels prior to and after
1.6 µg/kg/min fenoldopam infusion (n=2; study 94-7)





[source: photocopy of figures on page 52 and 55, vol.27]

Response in demographic subgroups

As discussed in greater detail below, both occurences of marked hypotensive responses were in black subjects. Although the number of observations is too few to implicate any conclusive drug-race interaction, this raises the question of whether antihypertensive responses may be disproportionately high in black subjects. No formal subgroup analyses were submitted, given the small size of this study.

SAFETY OUTCOMES •

There were reportedly no deaths in study 94-7, but there were 2 AE-related dropouts. These AE-related dropouts were as follows:

Subject 3 (one of three subjects who received 0.8 µg/kg/min fenoldopam) was a 44 year old black female who experienced a marked reduction from baseline SBP of about 60 mmHg by 30 minutes after initiation of infusion. This subject was discontinued some 15 minutes later due to severe hypotension (70/47 mmHg) with associated bradycardia (HR of 38 bpm). These AEs reportedly resolved rapidly after discontinuation of the infusion, and required no pharmacologic intervention during 24 hours of monitoring.

Subject 4 (one of two subjects who received 1.6 µg/kg/min fenoldopam) was was a 53 year old black male who discontinued due to severe hypotension (71/47 mmHg) after about two hours of drug exposure. This AE reportedly resolved after discontinuation of the infusion.

The most frequently reported AEs among subjects treated with fenoldopam were headache (87.5%) [resolving with analgesia in each case], nausea (50%), diaphoresis (62.5%), flushing (37.5%), hypotension (25%; both cases resulting in dropouts), vomiting (25%), dry heaves (25%), and indigestion (25%).

Headache (responding to analgesia) and nausea/vomiting (not requiring treatment) were reported as severe in one subject each, but each completed the study.

One subject (#7) with a low pre-treatment hemoglobin level experienced a further decrease in hemoglobin which was reported as mild and treated with iron supplementation. Two subjects had pre-existing conditions (gastroesophageal disease causing atypical chest pain, and constipation, respectively) which were reported as AEs, and resolved with treatment.

Several other AE were reported in one subject each (the sponsor did not clarify whether these were all treatment-emergent): palpitations, tachycardia, "dizziness" [not defined], light sensitivity, abdominal fullness, abdominal pain, gastric pain, constipation, stomach discomfort, watery eyes, warm forehead, feeling hot, lightheadedness, feeling of floating, feeling edgy, increased respiration, low back pain, abnormal taste in mouth, and toe cramps.

EKG findings:

Two subjects developed clinically nonserious treatment-emergent changes in EKGs (left axis deviation and/or sinus tachycardia), and a third developed vaguely described treatment-emergent EKG "abnormalities" which were reportedly felt to be nonsignificant by the investigator.

Laboratory findings:

New onset thrombocytopenia was reported in one subject (#004) in the 1.6 µg/kg/min dose group. This subject received a 2 hour exposure limited by the development of hypotension. Two days later there was a decrease in platelet count (from 133,000 to 80,000/mm^3) was observed. There was reportedly no clinical evidence of hemorrhagic sequelae. No thrombocytopenia was evident immediately prior to re-exposure of this subject to fenoldopam 6 months later,[18] and the subsequent 0.8 µg/kg/min fenoldopam infusion was not this time associated with any decrease in platelet count.

COMMENTS (study # 94-7).

a. This small unblinded study provides little to the understanding of this drug provided by study 94-5, with the exception of a suggestive signal of undesirably large antihypertensive effect in some patients exposed to fenoldopam doses of 0.8 or 1.6 µg/kg/min.

b. Both cases of dropouts involved hypotensive responses in black subjects. Although raising interest in whether antihypertensive responses are disproportionately high in black subjects, the number of observations here is too few to implicate any conclusive drug-race interaction.

APPEARS THIS WAY
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ON ORIGINAL

[18]during the subject's participation in study 94-5.

3 Miscellaneous Safety Data

In addition to the newly submitted safety data presented above, the sponsor summarized (in brief form) adverse event experiences from the followin miscellaneous studies:

3.1 Safety in Healthy subjects and Essential Hypertensives

3.1.1 Study A-49 :

Design Summary

As described above in greater detail, this baseline placebo-controlled, open-label, drug-drug interaction study nonrandomly assigned 10 healthy subjects (after a single pre-treatment infusion of placebo) to receive (on separate days) 4 hour iv infusions of fenoldopam (given to each subject as ascending 0.05, 0.10, 0.25, and 0.50 µg/kg/min doses, in the absence and presence of 10 mg/hr iv metoclopramide). The objectives were to assess safety, renal function, and plasma levels of renin and aldosterone.

Safety Outcomes[19] •

There were reportedly no deaths in study A-49[20]. The AE reported during co-exposure to both fenoldopam and metoclopramide were: restlessness/diarrhea/blurred vision (n=1), and restlessness (n=1). The infusions were stopped in both cases and the patients were said to have resolved.

3.1.2 Study A-54 :

Design Summary

This placebo-controlled, single-blind, 4-way crossover study randomized 12 healthy male subjects to crossover between 3 hour iv infusions of placebo, fenoldopam monotherapy (0.10 µg/kg/min), prazosin pre-treatment followed by fenoldopam, and indomethacin pre-treatment followed by fenoldopam. Each treatment period was separated by an interstudy drug-free day. The objectives were to assess safety, and the influence of prostaglandin synthesis inhibition and α1-adrenergic receptor blockade on fenoldopam-mediated changes in urinary excretion, peripheral hemodynamics, and PAH-estimated renal blood flow.

Safety Outcomes •

Reportedly there were no deaths or AE-related dropouts in study A-54. The treatment-emergent AE were: headache (n= 2, each occurring during fenoldopam treatment), and lightheadedness (n= 1). Their severity was described as nonserious, and each AE was said to have resolved.

3.1.3 Study B-1105 :

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[19]See section ?# above for discussion of pharmacodynamic results of this study.

[20]as per addendum submission dated 11/26/96.

Design Summary

This concurrent placebo-controlled, double-blind crossover study randomized 28 subjects (normotensives and hypertensives on a fixed 300 mEq/d sodium diet) to crossover between continuous 3 hour iv infusions of placebo and fenoldopam, with the two randomized periods occurring on consecutive days. Fenoldopam was started at a rate of 0.001 µg/kg/min for the first 30 minutes, and uptitrated at 30 minutes intervals to 0.005, 0.01, 0.05, 0.10, and finally 0.20 µg/kg/min. The objectives were to assess safety, and renal effects [not specified], and to whether hypertensive patient responses were a function of the degree of salt-sensitivity of their hypertension[21].

Safety Outcomes

The interpretability of the reported summary results of study B-1105 is limited by the fact that hypertensive and normotensive subjects were pooled, and the AE were described without mention of the treatment period in which they began.

The mean subject age was approximately 36 years. Among fenoldopam-exposed subjects, reportedly there were no deaths during the trial or within 30 days of its completion. There were 2 AE-related dropouts: one was for palpitations and the other was attributed to nausea and vomiting.

The other reported treatment-emergent AE, and the number of subjects manifesting these during an unspecified treatment period(s) were: digestive system complaints (n= 7), elevated BP (n= 2), peripheral vascular disease (n= 1), headache (n= 4), abdominopelvic pain (n= 1), elevated liver function tests (n= 1), and an unspecified upper respiratory disorder (n= 1). Neither the duration nor severity of the dropout-unrelated AEs was described.

3.1.4 Ongoing study 94-6

This, the only ongoing study, is an investigation of hypertensive emergencies. There have been no deaths thusfar reported, but two AE-related dropouts, and two serious AE in completers have been observed [as of the data cutoff of 10/1/96].

Subject 10-1 dropped out with an elevated serum creatinine (to 10.7). Few details have thusfar been provided other than that creatinine levels were also elevated prior to treatment.

Subject 13-1 dropped out, apparently in association with back spasms.

In subject 1-6, after co-administration of fenoldopam and enalapril orthostatic hypotension developed (supine BPs of 99/52 mm Hg supine, and standing BPs of 80/palpable) with associated acute renal insufficiency (serum creatinine rising from 1.4 to 4.1 mg/dL). These adverse phenomena were said to have resolved with infusion of saline.
In subject 2-4 orthostatic hypotension developed the day after multiple oral antihypertensive agents were restarted upon discontinuation of the fenoldopam infusion. This event reportedly resolved with infusion of iv fluids.

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[21] salt-sensitivity was characterized by observing for aldosterone responses to angiotensin II infusion after completion of the randomized crossover.

3.2 Safety in Congestive Heart Failure patients

3.2.1 Study B-1206 :

Design Summary

This positive-controlled, double-blind, crossover study randomized 15 subjects (patients with NYHA class III-IV CHF) to crossover between iv infusions of fenoldopam (maximum dose rate of 2.5 µg/kg/min) or an unspecified dose of sodium nitroprusside titrated to achieve a 25% increase from pre-treatment level of an unspecified cardiac performance index (presumably CO). The two periods were executed on consecutive days, and each was comprised of 1.75 hours of up-titration, 3 hours of maintenance, and 0.5 hour of down-titration. The objectives were to assess safety, central hemodynamics (including cardiac output (CO), pulmonary capillary wedge pressure (PCWP), pulmonary artery pressure (PAP)), peripheral hemodynamics (BP, HR), and renal effects (including GFR, ERPF, FF, urine volume and flow rate, and electrolyte excretion).

Safety Outcomes •

The mean age of subjects in study B-1206 was approximately 52 years. Among fenoldopam-exposed subjects, reportedly there was one death (a 71 year old male who succumbed of worsened CHF 20 days after completing the study), and one AE-related dropout (for worsening CHF), and three treatment-emergent AE occurring during or within 24 after initiation of fenoldopam (as follows): worsening CHF (n= 1), ventricular tachycardia (n= 1), and ventricular tachycardia/gastritis (n= 1). Neither the duration nor severity of the dropout-unrelated AEs was described.

3.2.2 Study B-1207 :

Design Summary

This placebo-controlled, double-blind, crossover study randomized 9 subjects (patients with NYHA class III-IV CHF) to crossover between iv infusions of placebo or fenoldopam (maximum dose rate of 2.5 µg/kg/min) titrated to achieve a 25% increase from pre-treatment CO. The two periods were executed on consecutive days, and each was comprised of 3.5 hours of up-titration, 3 hours of maintenance, and 1 hour of down-titration. The objectives were to assess safety, central hemodynamics (including CO, PCWP, PAP), peripheral hemodynamics (BP, HR), and renal effects (including GFR, ERPF, FF, urine volume and flow rate, and electrolyte excretion).

Safety Outcomes •

In study B-1207 the mean subject age was approximately 63 years. Reportedly there were no deaths or AE-related dropouts, but there were several treatment-emergent AE (as follows): angina (n=1), oliguria (n=1), and dyspnea (n=1). The duration of these AEs was not described.

3.2.3 Study B-1208 :

Design Summary

This positive-controlled, double-blind crossover study randomized 10 subjects (patients with NYHA class III-IV CHF) to crossover between iv infusions of sodium nitroprusside (maximum dose rate not specified) and fenoldopam (maximum dose rate of 2.5 µg/kg/min) titrated to achieve a 25%

increase from pre-treatment CO. The two periods were executed on consecutive days and each was comprised of 3.5 hours of up-titration, 3 hours of maintenance, and 1 hour of down-titration. The objectives were to assess safety, central hemodynamics (CO, PCWP, PAP), peripheral hemodynamics (BP, HR), and renal effects (GFR, ERPF, FF, urine and electrolyte excretion).

Safety Outcomes •

In study B-1208 the mean subject age was approximately 54 years. Among fenoldopam-exposed subjects, reportedly there was 1 dropout of a 43 yr old male who discontinued with a "lung disorder" [not defined], and died 5 days later on the basis of ischemic and valvular cardiomyopathy which was investigator-attributed to be unrelated to fenoldopam exposure. No other deaths were described.

It was reported that during or 24 hours subsequent to fenoldopam treatment[22] one subject experienced ventricular extrasystoles, tachycardia, and an undefined "liver disorder"; another subject manifested a conduction disorder, and and an undefined "lung disorder". Neither the severity nor duration of the dropout-unrelated AEs was described.

During or 24 hours subsequent to nitroprusside treatment reportedly one subject experienced ventricular extrasystoles, and another subject manifested a flushing and supraventricular tachycardia (severity and durations not described).

3.2.4 Study B-1214

Design Summary

As described above, this uncontrolled, open-label study nonrandomly assigned 9 subjects (NYHA class III-IV CHF patients with left ventricular ejection fraction (LVEF) < 40%) to receive an iv fenoldopam infusion starting at 0.1 µg/kg/min and uptitrated until a 25% increase from pre-treatment CO or a dose rate of 2.5 mcg/kg/min was achieved, with maintenance of the highest achieved dose rate for up to 6 hours. The objectives were to assess safety, and central, peripheral and renal hemodynamics.

Safety Outcomes •

In study B-1214 there were reportedly no deaths or dropouts among fenoldopam-exposed subjects[23]. The adverse events attributed to fenoldopam by investigators were vomiting, mild chest pressure for 15 minutes, premature ventricular and atrial contractions for 50 minutes, mild tachycardia for 4 hours, and decreased serum sodium. Each of these AE was said to have resolved upon doseage reduction or discontinuation. Reportedly there were no clinically important treatment-emergent abnormalities of laboratory indices (hematology and clinical chemistry).

The sponsor's abbreviated report of the pharmacodynamic results of this study is reviewed in section 1 above.

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[22]a less vague description of timing was not provided.

[23]as per the addendum submission dated 11/26/96.

3.3 Safety in patients with, or at risk of, renal dysfunction

3.3.1 Study A-44

Design Summary

As described above, this was an uncontrolled, open-label study in which 27 27 subjects (chronic renal failure patients with edema despite loop diuretic treatment) were nonrandomly assigned to receive 6-24 hour iv fenoldopam infusions (titrated from 0.025 to 0.100 µg/kg/min) subsequent to a 24 hour washout of any previous antihypertensive medications.

Refer to section 1 above for a discussion of pharmacodynamic data from this study.

Safety Outcomes

In study A-44 there was reportedly one death of a 66 year old male who experienced worsening renal failure in the setting of bacterial pneumonia 23 days after fenoldopam exposure. There were no AE-related dropouts; two subjects experienced diarrhea in association with fenoldopam exposure.

3.3.2 Study A-45

Design Summary

As described in detail above, this was an uncontrolled, open-label study which nonrandomly assigned 12 subjects (chronic renal failure patients with GFR of 20-60 ml/min) to receive a 2 hour iv fenoldopam infusion on day 1 (given as 0.05 µg/kg/min in the first five patients, and as 1 µg/kg/min in the rest), 150-300 mg/d of oral fenoldopam on days 2-11, and another iv fenoldopam infusion (at the same dose given on day 1) on day 12 starting 4.5 hours after the oral dose. Refer to section 1 above for a discussion of pharmacodynamic data from this study.

Safety Outcomes

Among fenoldopam-exposed subjects in study A-45 there reportedly were no deaths or AE-related dropouts. Reportedly no subject experienced what was considered by investigators to be a serious AE, and no clinically important changes were observed in EKG tracings.

Treatment-emergent reductions in hematocrit (Hct) occurred in 7 of 12 of these chronic renal failure patients. Three of these cases (subjects 2, 9, and 10) involved only minimal changes of 1-3 percentage points in subjects with low or or low-normal Hct at the pre-treatment baseline. The other 4 cases (see the table below[24]) involved 8-9 percentage point reductions from pre-treatment Hct, and were associated with low hemoglobin values, and either low or normal erythrocyte counts.

[24]the table's caption contains description of the lab's normal range for these parameters.

Table: 16

Subjects with treatment-emergent hematocrit reductions of >3 percentage points in Study A-45:

Subject	Day 12 Hct (%)	Treatment-emergent change in Hct at day 12 (# percentage points)	Day 12 Hemoglobin (mmol/L)	Day 12 RBC (10^{12}/L)	Comment
3	0.37	-8	7.5	normal	--
4	0.27	-8	5.4	3.0	low baseline Hct (0.35)
5	0.33	-9	6.5	normal	--
6	0.32	-9	6.3	3.5	--

[source: pg 147 of vol 56, and pg 1 of addendum dated 12/5/96]

The laboratory's lower limits of normal for hematocrit, hemoglobin, and RBCs was 40-50%, 8.0 mmol/L, and 4.0 x 10^{12}/L, respectively.

The role of fenoldopam in these anemia cases is unclear, given the absence of a control, and the absence of drug rechallenge. A potentially contributory confounder is the underlying defect in red blood cell formation to be reasonably expected in these chronic renal failure patients, a presumed defect which was to some extent challenged by the 300 mL of blood withdrawn via phlebotomy in each subject.

Reportedly no clinically important changes were observed in non-hematology laboratory parameters.

3.3.3 **Study B-1401**

Design Summary

This positive-controlled, single-blind, parallel-group study randomized 4 subjects (patients with oliguric acute renal failure) to receive continuous 12 hour iv infusions of fenoldopam (at 0.20 µg/kg/min, with down-titration to half that rate if SBP fell to <80 mm Hg), or dopamine (at 2.0 µg/kg/min, with down-titration to half that rate if SBP rose to >115 mm Hg). The objectives were to assess safety, and renal effects (urine and sodium excretion).

Safety Outcomes

In study B-1401 the range of subject ages was 40-73 years. Among the 2 fenoldopam-exposed subjects no deaths were described, but there was one AE-related dropout (because of hypotension of unspecified duration].

3.3.4 **Study B-1404**

Design Summary

As described above, this uncontrolled, open-label study nonrandomly assigned 34 subjects (patients with PEEP-induced reduction in urine output of 25%) to receive a 4 hour iv infusion of fenoldopam (given for 2 hours at 0.1 µg/kg/min and uptitrated as tolerated to 0.2 µg/kg/min for 2 additional hours). The objectives were to assess safety, and changes from pre-drug renal and ventilatory function.

See section 1 above for discussion of the pharmacodynamic outcome data from this study.

Safety Outcomes

In study B-1404, among fenoldopam-exposed subjects there were reportedly 3 deaths: one (in an 83 year old female) attributed to myocardial infarction 3 days after fenoldopam infusion, one (in a 75 year old female) attributed to cardiovascular failure and severe pneumonia occurring 5 days after the study, and one (in a 52 year old male) attributed to cardiovascular failure occurring 10 days after the end of the study.

One subject experienced a serious erythematous toxicodermic allergy reported 6 hours after the end of infusion. This subject did not need to be further hospitalized and reportedly recovered completely.

One subject developed a low hematocrit (value of 19%) which was physician-evaluated for its clinical significance and determined to be a laboratory error. Another subject had elevated SGOT levels (to 59 U/L), but in the context of wide fluctuations both within and outside of typical laboratory normal ranges.

3.3.5 **Study B-1407**

Design Summary

This placebo-controlled, double-blind, parallel-group study randomized 4 subjects (patients with 25% fall in urine output during prestudy observation, in the setting of sepsis) to receive 6-9 hour iv infusions of placebo or fenoldopam (starting at 0.1 µg/kg/min, with up-titration to the highest tolerated dose up to a maximum of 0.2 µg/kg/min). An escape design provided for patients with continuing drops in urine output to be crossed-over to the opposite regimen or switched to dopamine. The objectives were to assess safety, renal effects (GFR, urine and sodium excretion), peripheral hemodynamics, arterial blood gases, and venous lactate.

Safety Outcomes

In study B-1407 a seriously ill group of patients actually all died within days or weeks of the study's completion, and yet only one (subject 3) was ever exposed to fenoldopam [there were error in medication packaging which limited the exposure]. This subject was a male of unspecified age whose death, occurring four days after the study's end, was investigator-attributed to bronchopneumonia following a myocardial infarction. During the study this patient experienced a mean arterial pressure which was characterized as "low" and requiring of a reduction in the dose of randomized therapy (although it is unclear whether fenoldopam or placebo was being administered

at the time of this AE), as well as a degree of oliguria which required the use of dopamine escape therapy.

3.3.6 Study B-1403 ;

Design Summary

This concurrent placebo-controlled, single-blind parallel-group study randomized 8 subjects (amphotericin B-treated patients with serious fungal infections) to receive a maximum of 14 days of 9 hour/d iv infusions of placebo (in the form of 5% dextrose in water, the vehicle for fenoldopam infusions) or fenoldopam (given beginning 1 hr before amphotericin B, stopping 4 hours after amphotericin, and titrated as tolerated from 0.2 to 0.6 µg/kg/min). Randomized infusions started one hour before each daily administration of amphotericin B, and continued 4 hours beyond each antifungal infusion. The objectives were to assess safety, and the effect of fenoldopam on amphotericin B-mediated nephrotoxicity (as estimated by measures of GFR, serum creatinine and blood urea nitrogen).

Safety Outcomes •

In study B-1403 the mean subject age was approximately 54 years. Among fenoldopam-exposed subjects, reportedly there were no deaths or AE-related dropouts, but there were several treatment-emergent AE (as follows): decreased serum potassium (n= 2), increased serum creatinine and BUN (n= 1), headache (n= 1), and rash (n= 1). Neither the duration nor severity of these AE was described.

3.3.7 Study B-1901 ;

Design Summary

This concurrent placebo-controlled, double-blind, parallel-group study randomized 26 subjects (cyclosporine-receiving renal transplant patients) to receive two 24 hour iv infusions of placebo or fenoldopam (given initially at 0.10 µg/kg/min, with up-titrattion to 0.20 µg/kg/min), one under volume depeleted conditions and a second infusion of the same study drug 3 days later under volume expanded conditions. The objectives were to assess safety, and the effect of fenoldopam on cyclosporin-mediated nephrotoxicity (as estimated by measures of GFR, ERPF, renovascular resistance, serum creatinine and blood urea nitrogen).

Safety Outcomes •

In study B-1901 the mean age of subjects was approximately 43 years. Among fenoldopam-exposed subjects, reportedly there were no deaths or AE-related dropouts, but there were several treatment-emergent AE (as follows): headache (n= 7), elevated BP (n= 5), hypotension (n= 1), dyspepsia or diarrhea (n= 5). Neither the duration or severity of these AEs was described.

3.3.8 Study B-1904 ;

Design Summary

This placebo-controlled, double-blind, parallel-group study randomized 16 subjects (cyclosporin-receiving cardiac transplant recipients) to receive a 5 day infusion of placebo or fenoldopam

(starting at 0.05 µg/kg/min, and uptitrated by 0.05 µg/kg/min increments every 10 minutes as tolerated to a maximum dose of 0.20 µg/kg/min). The objectives were to assess safety, and the effect of fenoldopam on cyclosporin-mediated nephrotoxicity (as estimated by measures of serum creatinine clearance, electrolyte and microalbumin excretion, and an unspecified tracer-based metric).

Safety Outcomes

In study B-1904 the mean age of subjects was approximately 40 years. Among 8 fenoldopam-exposed subjects, reportedly there were 2 deaths. One involved a 50 year old male who died of transplant rejection after 2 days on fenoldopam. A 71 year old woman also died of worsening renal function after one day of fenoldopam exposure. In the placebo group there were no deaths reported.

The AE-related dropouts associated with fenoldopam exposure numbered 3, and were for acidosis (n= 1), acute worsening of renal failure (n= 1), and hypotension/ventricular tachycardia (n= 1). By comparison there were 2 AE-related dropouts associated with placebo-treatment; these were for acute worsening of renal failure (n= 1), and for hypotension/worsened renal failure/acidosis (n= 1).

The fenoldopam-associated AE[25] were: cardiac arrest (n= 1), ventricular tachycardia (n= 1) extrasystoles (n= 1), worsening renal failure (n= 2), acidosis (n= 1), and hypotension (n=1). Neither the duration nor severity of the dropout-unrelated AEs was described.

In the placebo group the AE[26] were: worsened renal failure (n= 2), acidosis (n= 1), hypotension (n= 1), embolic pulmonary infarct (n= 1), gastroduodenitis (n= 1), gastrointestinal bleed (n= 1), and muscle spasm (n= 1). The severity and duration of these AE were not described.

Steven Rodin, MD 2/20/97
Medical Officer

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[25]it is not clear in the sponsor's report whether some of these were already accounted for under AE-related dropouts.

[26]ibid.

NDA 19-922

MAR - 7 1997

One of Two Parts of the Clinical Review of Fenoldopam Mesylate (Corlopam®):
(see also Review by Dr. Steve Rodin, M.D. for other part) 3/3/97
Reviewed by Abraham Karkowsky, M.D., HFD-110 March 3, 1997.

HFC

Study Number: C 1101

Volume 51-52

Title of Study : Single Blind Study to Compare the Effects of Intravenous Administration of Fenoldopam versus Nifedipine on Postoperative Hypertension and Postoperative Renal Function in Cardiac Surgery Patients.

Investigator and Sites:

Table 1.

PD Dr. med. Wolfagang Meister SmithKline Beecham Pharma GmgH München	Dr. med Gombotz Univ.-Klinik für Anästheiologie Herzstation Landeskrankenhaus Auenbruggerplatz	Prof. Dr. med. Martin/Dr. med F. Fleischer Institut für Anästheiologie Chirurgie Heidelberg
PD Dr. med. Boldt Abt. für Anästheiologie und operative Intensivmedizin amd Zentrum Chirurgie Giessen	PD Dr. med. Iversen/ Dr. M. L. El Gindi Klinik für Herzchirurgie Klinik für Anästhesie und Intensivmmedizin Mainz	Prof. Dr. med D. Birnbaum Klinik für Herzchirurgie Universität Regensburg Regensburg
PD Dr. med. D. Kling Klinik für Herz-und Gefäßchirurgie Abteilung für Anästheiologie und Intensivmedizin Herz-und Kreislaufzentrum Rotenburg Rotenburg and der Fulda	Prof, Dr, med, Sonntag/ Dr. med Spiegel Institut für Anästheiologie und Intensivmedizin Universitätsklinik Göttingen	Dr. A. Kimmel Kerchkoff-Klinik Bad Nauheim

Study Chronology:
Date of Drafts: 2/28/91; 4/30/91; 5/15/91; 5/23/91; 6/13/91; 6/24/91;
Amendments: (1)- 11/21/91; (2)- 10/12/92;

Date first patient enrolled- not stated
Date last patient enrolled- not stated.

Formulations: The specific formulations of either fenoldopam or nifedipine are not stated.

Study Design: This was a single blind, multi-centered study that was carried out only in foreign centers. This study was not submitted to the IND. Although the patients were blinded, the investigators were aware of the treatments.

Inclusion Criteria: Eligibility required that subjects be of either gender, ≥ 18 years old

who were within 24 hours of cardiac bypass graft surgery and who had post-operative hypertension as defined by the sponsor. This required a mean arterial pressure > 105 mm Hg for at least 5 minutes post-operatively, despite adequate sedation/analgesia. Subjects were to have reasonable cardiac function at baseline (EF ≥ 40% and LVEDP≤ 20 mm Hg) and with no evidence of hypovolemia (PCWP ≥ 8 mm Hg).

Exclusion Criteria: Subjects were excluded if they:

- were pregnant or lactating or could not give informed consent or were medically unstable.
- had cardiovascular disease (uncontrolled ventricular or supraventricular arrhythmias; evidence of ongoing myocardial infarction).
- had other organ dysfunction (elevated transaminase >2.5 times upper limit of normal; carotid artery stenosis or cerebral circulatory disturbances. Patients requiring dialysis or patients with pheochromocytoma or patients with glaucoma or increased intraocular pressure were also excluded.
- were sensitive to any of the potential medications (fenoldopam or similar medications or sulfites).
- had taken medications that could potentially confound the interpretation of the study (e.g. dopamine, dopamine agonists or antagonists, MAO inhibitors, PDE inhibitors). Post operatively, other vascularly active medications including nitroglycerine: NTG, however, could be used up till 10 minutes prior to study medication; use of barbiturates; previous investigational drug use for at least 30 days was reason for exclusion.

Protocol: Informed consent as well as history, physical examination and laboratory assessments were performed on all potential patients. In the operating theater, as part of the routine surgical procedures, each potential subject was instrumented both with a pulmonary as well as an intraarterial catheter.

After entering the ICU, laboratory assessments (CBC + platelets, electrolytes, LFTs, Creatinine, blood gasses) were performed and cardiac hemodynamics (RAP, PAP, PCWP, CO, SV, SVR, PVR, RVSWI and LVSWI) were measured. Urine was collected and the following measured (volume, creatinine, Na^+, and K^+).

Those subjects deemed by the investigator as hypertensive for > 5 minutes as defined by a mean arterial pressure (MAP={[SBP-DBP]/3 + DBP}>105 mm Hg), were enrolled into the study and received one of the two treatments; either fenoldopam at a dose of 0.8 ug/kg/min or nifedipine at a dose of 1.0 mg/hr. The drugs were administered open-label by the clinician. The infusion rate of fenoldopam was dependent on and that of nifedipine independent of the patient's weight[1]. For

[1]The difference in infusion rates are not likely to be significant: The concentration of fenoldopam in the infusate was 400 ug/ml (20 mg in 50 ml). For fenoldopam the rate of infusion for a 50, 60, 70, 80 and 90, kg subject would be 6, 7.2, 8.4, 9.6 and 10.8, respectively. For nifedipine the 5 mg was dissolved into 50 ml of infusate. The initial

fenoldopam the infusion could be titrated upward or downward at 10 minute intervals in increment of 0.2 ug/kg/min. For nifedipine the dose could be increased to a maximum of 1.25 mg/kg as a single step. The dose could also be down-titrated to a minimum dose of 0.63 mg/hr. The intent of the study is to most rapidly lower MAP to between 80-90 mm Hg.

During the course of the infusion, blood pressure and heart rate were measured continuously, but recorded only every 10 minutes or at the time of any adverse event or during premature termination. Hemodynamics were measured at baseline and at 30, 60, 120 and 240 minutes post enrollment. Blood gases were measured at baseline and at every 2 hours and at the termination of the study medication. Urine was collected at 6 hour intervals.

Study medication was terminated (there is no down-titration scheme) once the patient became hemodynamically stable, at the discretion of the investigator. After termination of the infusion, the blood pressure and heart rate were measured and recorded every ten minutes for the first 1/2 hour and then at half hour intervals for the next 6 hours. Hemodynamics and blood gases were measured at three and six hours after the end of the infusion; renal function, as judged by urine volume and electrolyes were measured at 6 hours after completion of the infusion.

Infusion was terminated for drug-induced tachycardia (increase by > 30% or 120 BPM for > 10 minutes); for sustained hypotension (MAP < 70 mm Hg) despite decrease in drug medication; sustained elevated BP (MAP > 115 mm Hg) for more than 30 minutes; or intolerable side effects.

End Points:

Primary efficacy end point- The primary end point was the comparison between treatments of the number of success. A success was defined as a subject whose MAP was reduced to between 80-90 mm Hg or decreased 15 mm Hg within 30 minutes of the start of infusion, with this decrease in MAP must sustained for at least 30 minutes. Those who fail to sustain the drop in blood pressure were considered partial successes.

Secondary end-points included:

-The incidence of rebound hypertension during the 6 hours after the termination of the study or until weaned from the ventilator, whichever occurred earlier.
-Time course for the reduction of MAP.
-Urine output till 6 hours post infusion.
-Sodium excretion till 6 hours post infusion.
-Number of subjects with prolonged increase in MAP > 105 mm Hg who could be controlled by up-titrating of study medication.

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rate of an infusion for nifedipine are 10 cc/hr for any weight subject.]

-Creatinine clearance, sodium and potassium clearance during study medication.
-Need for dialysis and number of dialysis treatments.
-Effect on hemodynamics.
-Pulmonary shunt fraction.

Statistical Issues: The study size as stated in the first amendment (original protocol was not submitted) was predicated on an anticipated response rate of 90% for fenoldopam and 70% for nifedipine, with an alpha of 0.05 and beta of 0.15 and assuming a 20% dropout rate of patients. The number of subjects/group was estimated as 96 patients. The second protocol amendment, after an interim analysis, increased the sample size to 103 subjects per arm.

There was no prospective statement as to the number and timing of any interim analyses.

Patients were randomized in block sizes of eight. It is unclear if the individual investigators were aware of the block sizes. Since the study was unblinded to the investigators, knowledge of the block size would allow a reasonable guess as to the next sequence in the treatment would be.

The was no pre-specified prospective analytic plan.

Results:

Demographics: There were seven study centers. A total of 126 subjects were enrolled into this study, 62 in the fenoldopam and 64 in the nifedipine group. Of these patients, 103 were male and 23 were female. The sponsor included as the per-protocol group, 64 patients; 36 who received fenoldopam and 28 who received nifedipine. The frequency of several baseline medical conditions for those who entered the study are tabulated below:

Table 2 Baseline medical Conditions Study C1101

	Fenoldopam	Nifedipine
Coronary Artery Disease	62	64
Hypertension	42	38
Diabetes	7	13
Gastritis/ulcers	9	14
Obesity	8	7
Gout/Elevated Urate	5	9
Liver abnormality	7	2
Respiratory/COPD	5	2

All subjects had coronary artery disease at baseline. No specifics are given as to the nature (single versus multi-vessel) or duration of the disease. The duration of the surgical procedures was not easily determined.

Of those who entered the study, a total of 42 subjects were discontinued; 19/62 (31%) from the fenoldopam group and 23/64 (37%) from the nifedipine group. The reason for discontinuation are listed below:

Table 3. Reason for Discontinuation

Reason	Fenoldopam	Nifedipine
Insufficient Response	6 (10%)	16 (25%)
Adverse Events	12 (19%)	6 (9%)
Protocol Violations	1(2%)	1 (2%)

The specifics of the adverse events leading to discontinuations are described in greater detail in Appendix A. Most of those who discontinued, did so after the initial blood pressure measurements.

Caveats: Randomization was performed by pulling envelopes which contained the specifics of treatment. Subjects, however, were not always allocated in the proper numerical sequence because some of the envelopes were pulled out of turn. It is impossible from the data to determine if this mis-randomization coupled with the open-label design of the study was harmless or whether it irreparably biased the outcome of the study.

Since several of the study centers routinely used nitroglycerin, such therapy was allowed until 10 minutes prior to the institution of index drug treatment.

Subjects who received greater than the pre-specified dose of nifedipine were included in the analysis except if drug was stopped because of adverse events:

The sponsor performed at least two interim analyses. Neither of these analyses were pre-specified, in fact, the number and timing of any interim analyses were never stated in advance. Furthermore, the size of the study was modified based on these interim analyses. After the first interim analysis the study size was increased. After the second analyses the study was truncated.

Doses: I have put together the doses for each drug during the 1 hour infusion portion for the study. For those whose infusion was stopped I took the last value and carried it to the end of the infusion. The values represent the means $\pm$ SD. For fenoldopam there was an approximately 12% increase in the dose during the infusion period. The SD for the dose increases over time as subjects could have their dose increased or

decreased. For nifedipine the dose also inched upward. Since the flexibility for dosing with nifedipine was limited, the SD at the individual time points was also less than that who received fenoldopam.

Table 4. Doses of Fenoldopam and Nifedipine Study C1101

	10 minutes	20 minutes	30 minutes	40 minutes	50 minutes	60 minutes
Fenoldopam	0.8 ± 0.0	0.84 ± 0.14	0.87 ± 0.27	0.89 ± 0.35	0.89 ± 0.38	0.85 ± 0.44
Nifedipine	1.0 ± 0.2	1.08 ± 0.17	1.15 ± 0.16	1.18 ± 0.15	1.18 ± 0.17	1.16 ± 0.22

Missing Data:

Mean arterial baseline blood pressures were to be greater than 105 mm Hg for at least five minutes. The time course of blood pressure either before or during the baseline period is not tabulated so the stability of the baseline measurements cannot be verified.

Several subjects had data missing for mean arterial pressure during the initial hour of the analysis. No adequate explanation was given.

Table 5- Times in Which Blood Pressure Measurements Were Missing.

Fenoldopam		Nifedipine	
Pt #122	missing 50-60 min	pt # 81	missing 40-60 min
pt # 164	missing 60 min	pt # 121	missing all
pt #165	missing baseline	pt #124	missing 50-60 min
pt #169	missing baseline, 30-60 min	pt #173	missing 50-60 min
pt #210	missing 40-60 min	pt #208	missing 20-60 min
pt #221	missing all	pt #214	missing 40-60 min
pt #224	missing 40 min	pt #222	missing 40-50 min
pt #225	missing 40-50 min		

Of those with missing data, three subjects in the fenoldopam (#122, #165, #221) and none in the nifedipine group were discontinued during the study. Only one of the patients (# 165) discontinued as a consequence of tachycardia during the initial hour of the infusion. Blood pressure during this hour was not inconsistent with that seen in other individuals (148/64 MAP =92) but the patient was tachycardic (HR 120). So it is likely that this subject would not materially alter the group means of blood pressure but would likely increase the heart rate. Assuming a heart rate increase of approximately 50 bpm, for this person, excluding this person would underestimate the heart rate effect by approximately 3/4 BPM.

Per-protocol Analysis:

In the per-protocol analysis, the sponsor excluded a total of 62 subjects, 26

fenoldopam and 36 nifedipine for the following reasons. Subjects could be considered as protocol violators for more than one reason and consequently may be listed more than once:

Table 6. Reason Sponsor Excluded Subjects.

Reason	Fenoldopam	Nifedipine
Mean Arterial Pressure <105 mm Hg	#42, 43,52, 56, 62, 69, 77, 130 , 167, 169,195,,	#44, 48, 49, 50, 51,65, 71,72,75, 80, 121, 244,
Use of Dopamine	# 47, 59, 204	#44, 60, 209,
Use of Nitroglycerin	#53,78, 195, 205, 207, 122, 150, 228.	#51, 66, 248, 121, 202, 203, 206,125, 131, 132, 136, 137, 300,
Randomization	#74, 77, 78, 79, 169	#73, 75, 76, 80, 173, 200 241, 242, 244, 248, 249,
Selection Criteria	#195, 204	# 76
Other Co-medications	#221	#163
Baseline MAP missing	#165, # 221	
Starting Dose		#168, 202, 203, 206, 225

[comment: The intention to treat analysis is clearly confounded by the above protocol violations. There is insufficient information given to assess the seriousness of these violations and how these violations influenced the end-points. Several protocol violations particularly those involving concurrent medications may reflect failure of treatment and consequently the need for additional after load reducers.]

Concurrent therapies:

Subjects enrolled into this study received medications for analgesia, sedation, muscle relation or elevated blood pressure either during or immediately after surgery or during the observation phase of the study. I have tabulated the data from Appendices 6A, 6B, 7A and 7B of the submission below. There appears to be some differences in the use of concurrent therapies. More nifedipine then fenoldopam patients received sedation both before and during the intravenous infusion. Since the need for sedation anteceded the study infusions, the subjects eventually given nifedipine likely differed from those who received fenoldopam.

Table 7. Confounding Medication Study C1101

	NTG < 10 min prior to infusion	Sedation < 30 min prior to infusion	Muscle Relaxant < 30 minutes prior to infusion	Analgesia <30 minutes prior to infusion
Fenoldopam	2/62	11/62	6/62	2/62
Nifedipine	4/64	22/64	10/64	2/64
		0.1 > p >0.05		

	Sedation during infusion	HBP Medication Given during Infusion	Muscle Relaxant During	Pain Medication During Infusion
Fenoldopam	2/62	15/62	4/62	13/62
Nifedipine	4/64	31/64	2/64	13/64
		p <0.01		

Diastolic Blood Pressure:

Table 8 summarizes the diastolic blood pressure for the intent-to-treat groups. The baseline subtracted difference is shown as Figure 1. It should be noted that the baseline blood pressure implies that this diastolic blood pressure represents stable measurements. Assuming that the baseline values are not precipitously changing and that the modest changes in doses only minimally altered the time course of blood pressure change, these curves then describe some description of the time course of fenoldopam or nifedipine on supine diastolic blood pressure. The maximum drop in blood pressure at the dose(s) of fenoldopam was approximately 23 mm Hg. It took approximately 10 minutes to attain approximately 50% of this drop.

Table 8 Supine Diastolic Blood Pressure (Mean ± SD)

Treatment	Baseline	10 minutes	20 minutes	30 minutes	40 minutes	50 minutes	60 minutes
Fenoldopam	88.2 (9.4) n=59	75.9 (12.7) n=61	68.6 (9.0) n=61	66.7 (8.9) n=60	66.5 (9.6) n=58	66.8 (8.2) n=57	65.8 (8.2) n=56
Nifedipine	89.0 (9.0) n=63	84.8 (9.8) n=63	82.0 (10.5) n=62	79.2 (9.8) n=62	78.4 (9.7) n=58	77.1 (10.9) n=56	74.6 (11.9) n=57

Systolic Blood Pressure

Table 9 summarizes the effect of treatment on supine systolic blood pressure and Figure 2 represents the drug effects on supine systolic blood pressure. There is clearly a difference in the effect between the interventions. With respect to nifedipine, there appears to be two phases to the decrease in systolic blood pressure. A rapid decrease over the first 1/2 hour, then a continuous slower decline in pressure over the next hour. For fenoldopam, there appears to be a precipitous drop in blood pressure over a 20 minute period, followed by only a small additional drop in systolic pressure over the next 40 minutes. Somewhat more than 50% of the drop seen at the 1 hour time point is attained within 10 minutes of starting the infusion.

Figure 1 (Mean ± SEM)

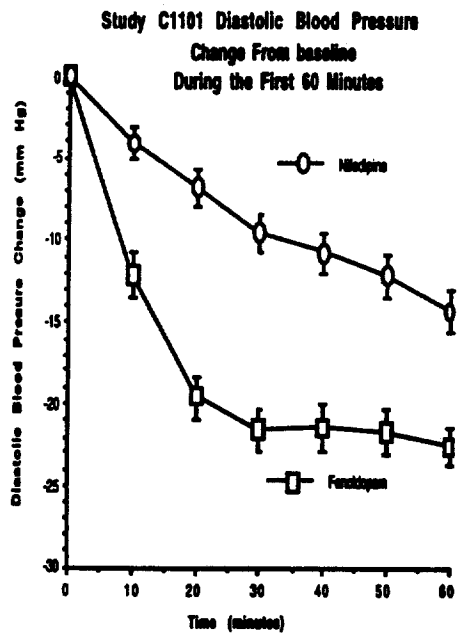


Figure 2 (Mean ± SEM)

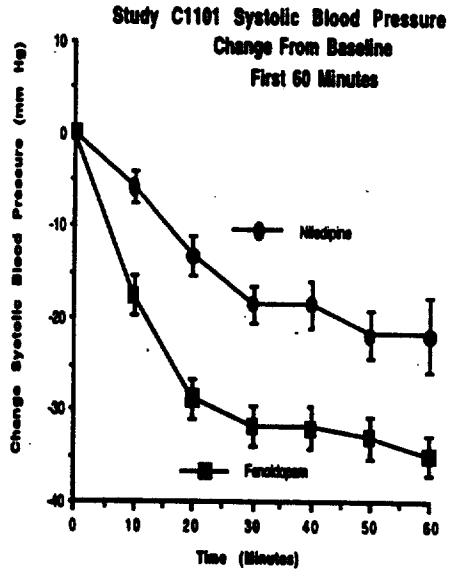


Table 9 - Study C1101 Systolic Blood Pressures (mean+ SD)

Treatment	Baseline	10 minutes	20 minutes	30 minutes	40 minutes	50 minutes	60 minutes
Fenoldopam	165.7(17.7) n=59	148.9 (23.3) n=61	137.8 (21.4) n=61	134.2 (19.0) n=60	134.1 (21.6) n=58	132.8 (20.5) n=57	130.7 (16.0) n=56
Nifedipine	164.7 (17.2) n=63	158.7 (18.9) n=63	151.2 (20.6) n=62	145.9 (19.5) n=62	146.2 (21.3) n=58	143.1 (20.4) n=56	141.3 (21.1) n=57

[comment: Defining the time course of drug effect requires the same assumptions as with diastolic blood pressure, namely that the baseline systolic blood pressures was truly stable and that the small dose changes did not modify the observed blood pressure effect.]

Heart Rate:

The heart rates are tabulated below (Table 10). The baseline subtracted heart rates are also graphically displayed (Figure 3). Coincident with the drop in both systolic and/or diastolic blood pressure is an increase in heart rate. For fenoldopam, the heart rates consistently are greater than those of nifedipine treated subjects. For fenoldopam there was an increase in approximately 9 BPM and for nifedipine

approximately 7 BPM. The time to attain 50% of the 60 minute heart rate is between 10-15 minutes for fenoldopam. The heart rate increase with nifedipine is less steep.

Table 9. Heart Rates Study C1101 (Mean ± SD)

Treatment	Baseline	10 minutes	20 minutes	30 minutes	40 minutes	50 minutes	60 minutes
Fenoldopam	88.6 (15.1) n=59	92.8 (15.1) n=61	95.4 (15.9) n=61	95.7 (15.9) n=60	96.4 (16.5) n=58	96.6 (16) n=57	97.1 (15.1) n=56
Nifedipine	88.3 (15.1) n=63	89.7 (13.8) n=63	91.4 (13.3) n=62	92.1 (14.2) n=62	93.2 (12.4) n=58	93.5 (13.8) n=56	94.8 (14.4) n=57

Figure 3- (Mean ± SEM)

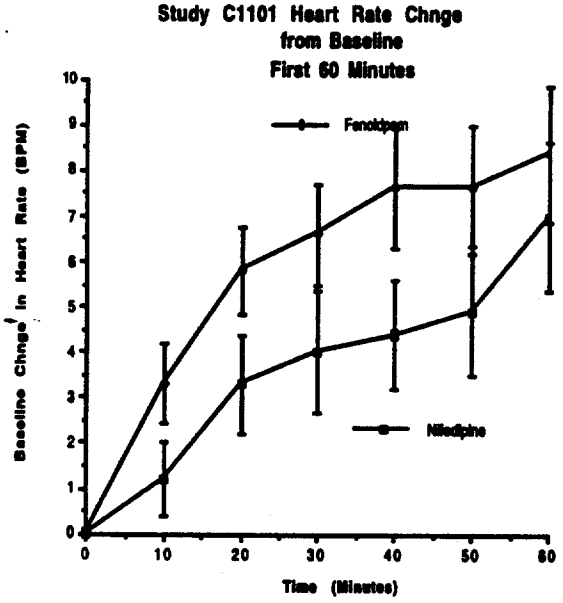
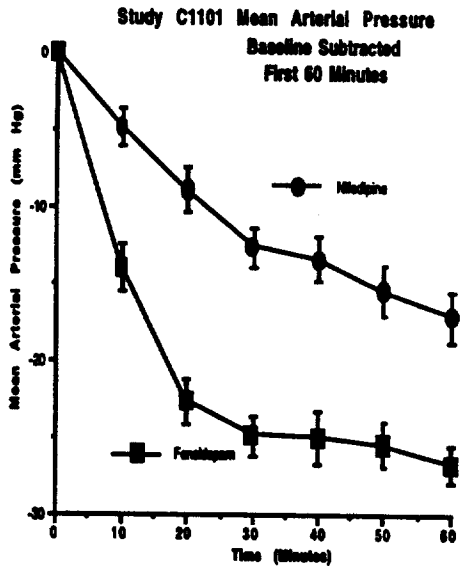


Figure 4 -(Mean ± SEM)



MAP- The primary efficacy end-point of this study as proposed by the sponsor, was a decrease in mean arterial pressure. The mean arterial pressures are shown inTable 10. Since this parameter is a composite of both systolic and diastolic blood pressures, it is not surprising that MAP would have a similar profile to these BPs. For fenoldopam, there appears to be a rapid drop in MAP followed by a small additional drop. Half the effect seen at the end of the hour is attained by approximately 10 minutes. For nifedipine, the effect is much less rapid on onset with blood pressure still dropping at the end of the 60 minute period.

Table 10- Mean Arterial Pressure (Mean ± SD)

Treatment	Baseline	10 minutes	20 minutes	30 minutes	40 minutes	50 minutes	60 minutes
Fenoldopam	114.1 (9.1) n=59	100.2 (14.7) n=61	91.7 (11.7) n=61	89.2 (10.7) n=60	89 (12.2) n=58	88.8 (10.9) n=57	87.4 (9.0) n=56
Nifedipine	114.2 (8.5) n=63	109.5 (10.0) n=63	105.1 (11.5) n=62	101.4 (10.2) n=62	101.0 (10.8) n=58	99.1 (11.4) n=56	96.9 (12.8) n=57

Primary End Point Analysis: Categorical Analysis:

Based on the data supplied in Table 34 (vol. 50 p. 82) of the submission, the categorical analysis comparing fenoldopam and nifedipine are shown below (Table 11). The definition of responders are those subjects whose MAP dropped below 90 mm Hg[2] or had a 15 mm Hg drop in MAP by 30 minutes of infusion that was sustained for at least 30 minutes. Partial responders are those who had the appropriate drops in MAP but did not sustain this drop during the remaining portion of the study. These results are highly significantly different ($P < 0.001$).

Table 11. Study C1101 Responder Analysis

	Responder	Partial Responder	Failure
Nifedipine	16	9	39
Fenoldopam	43	9	11

Kaplan-Meier plots for the time to either a MAP drop to ≤ 90 mm Hg or a 15 mm Hg drop for the intention to treat group indicate that the time to achieve these end points was statistically shorter for the fenoldopam group than for the nifedipine group. ($p < 0.0001$- Sponsor's figure 7, vol 50 p 169, data not shown). In the intent-to-treat group, 53 and 78% of the subjects in the fenoldopam group responded by 10 and 20 minutes respectively. In the nifedipine group, the corresponding responses at 10 and 20 minutes were 13 and 32%.

Per-protocol Analysis:

There was little difference in the results when comparing the intent-to-treat to the per-protocol analysis. In Table 12 I've tabulated the systolic and diastolic blood pressures and heart rates for the 10 and 60 minute time points for both the intent-to-treat and per-protocol.

Table 12-Comparison between per-protocol and intent-to-treat effects.

	Fenoldopam				Nifedipine			
	Intent-To-Treat		Per-Protocol		Intent-To-Treat		Per-Protocol	
	10 min	60 min	10 min	60 min	10 min	60 min	10 min	60 min
Systolic Blood Pressure	-17.6	-34.9	-19.8	-31.3	-6.0	-22.8	-4.5	-17.0
Diastolic Blood Pressure	-12.2	-22.6	-15.2	-22.2	-4.1	-6.8	-3.6	-11.8
Heart Rate	+3.3	+8.4	+5.1	+8.9	+1.2	+7.0	+1.5	6.4

[2] The protocol actually stipulates that the MAP should drop to between 80-90 mm Hg. Many subjects, nearly all in the fenoldopam treatment group had decreases in MAP below 80 (the lowest was recorded at 59 mm Hg). I have, nevertheless, as per sponsor included these subjects in the response group.

Effects after 60 minutes:

Subjects were to be treated with intravenous formulation for a total of a total of at least 6 hours or a maximum of 24 hours, with an additional 6 hours of observation following completion of the infusion. There was substantial attrition of subjects with longer durations of infusion. By 2 hours, only 95 (47 fenoldopam and 48 nifedipine) had data available. By six hours only 61 subjects (31 fenoldopam, 30 nifedipine) had data available. Over time the differences in DBP (for those with values) between nifedipine and fenoldopam appear to be rather small.

Table 13. Diastolic Blood Pressure Measurements after the Efficacy Phase (Mean±SD)

	120 minutes	240 minutes	360 minutes
Fenoldopam	-28.3 (12.4); n=47	-27.9 (9.7); n=34	-29.8 (11.5); n=31
Nifedipine	-21.5 (13.6); n=48	-25.7 (11.7); n=36	-24.1 (10.2); n=30

Hemodynamics:

Invasive hemodynamics were to be performed every 1/2 hour for two hours. The sponsor only submitted Only the intent-to-treat data for systemic vascular resistance. There was substantial attrition in the number of such subjects that had measurements. The SVR decreases substantially with duration of infusion with a somewhat greater decrease with fenoldopam relative to nifedipine. Most, but not all the effect is seen by 30 minutes with fenoldopam.

Table 14- Systemic Vascular Resistance (Mean ± SD) dyn.sec.cm^{-5}

	baseline	30 minutes	60 minutes	120 minutes	240 minutes
Fenoldopam	1832 (544); n=56	1039(392); n=56	1006 (321); n=55	932 (282); n=45	961 (310)n=32
Nifedipine	1788 (554); n=56	1450 (462); n=51	1315(396); n=53	1175 (381); n=41	1048 (266); n=34

Cardiac output was only supplied by the sponsor for the per-protocol group. There appeared to be an substantial increase in the fenoldopam treated group with an increase over baseline at 1 and 2 hours of 33% and 39% , respectively. For nifedipine the corresponding increases were 18% and 33%.

Right atrial pressure was supplied only for the per-protocol subjects. Right atrial pressures for fenoldopam were increased a maximum of 16% at 1 hour and decreased 8% at 2 hours. For nifedipine the right atrial pressure decreased a maximum of 12% at 1/2 hour and increased a maximum of 1% at 2 hours. None of the changes either for fenoldopam or nifedipine for right atrial pressures differed from baseline.

Stroke volume index was also only supplied for the per-protocol population. For fenoldopam there was an increase relative to baseline of between 7-17%. For nifedipine, few subjects had available measurements. The change in SVI was

between 5-16%.

Table 15 - SVI for the Per-Protocol Analysis % Change From Baseline (Mean ± SD)

	30 minutes	60 minutes	120 minutes	240 minutes
Fenoldopam	17% (24%); n=30	17% (26%); n=29	11% (35%); n=22	11% (37%) n=14
Nifedipine	5% (15%); n=19	9% (12%); n=18	16%(26%); n=14	15% (13%); n=11

Renal function: (Data derived from Table 78 and 79 of study). Fluid intake and output for the per-protocol cohort are shown below:

Table 16- Fluid Input and Output (mean ± SD)

	Fluid Intake ml/hr		Fluid Output		Delta Intake-Output	
	Entry to ICU	0-6 hours	Entry to ICU	0-6 hours	Entry to ICU	0-6 hours
Fenoldopam	537 (451) n=28	411.7 (222) n=35	880 (596) n=28	429 (197) n=35	-339 (679) n=28	-17 (17) n=35
Nifedipine	566 (288) n=22	525 (360) n=26	879 (375) n=22	645 (85) n=26	-312 (486) n=22	-120 (273) n=26

If anything, urine output is greater for the nifedipine treated per-protocol group than the fenoldopam group. [comment: Somewhat surprising for what would be expected from a dopamine$_1$ agonist]. This difference may be, in part, rationalized by the apparently lower blood pressure in the fenoldopam group.

Safety:

This was a small study in which subjects received infusion for only a short duration.

Deaths:

There were no deaths in the study.

Dropouts and Discontinuations :

Therapy was discontinued in 19 patients in the fenoldopam group and 23 patients in the nifedipine group. The reasons are already listed in Table ~~4~~ Capsular summaries of the dropouts and discontinuations are reproduced as (Appendix A). These summaries were as written by the sponsor (copied from Appendix I vol 50 p. 194 of the NDA). I have added some comments based on a review of the CRFs.

Table 3 ank 4/4/97

Other Adverse Events: A total of 40 subjects reported one or more adverse events (51 events); 23 in the fenoldopam treated group and 17 in the nifedipine treated group. Most of the events were cardiovascular (hypertension, hypotension or tachycardia). Two subjects, one treated with nifedipine and one with fenoldopam

suffered a myocardial infarction. One additional subject in the nifedipine group (# 143) had a suspected perioperative MI (elevated SGOT, SGPT, CK, CK-MB, LDH and HBDH). Bleeding was more common in the fenoldopam group than in the nifedipine group (5 versus 1).

Table 17. Adverse Events

Event	Fenoldopam	Nifedipine
Tachycardia	#165; #167; # 169; # 140; #141; #148; #152; #159	#206;# 212; #146
Low Blood Pressure	# 9	#57; # 203; #214;
Hypertension	#157;	#144; #145; #147; # 151
Bleeding	# 56; #70; #77, # 122, #148	#155
Decreased Diuresis	#158; #159, #221;	
Low Output State/Hemodynamic Instability	# 122	#160
Shivering	#126; #141	
Myocardial Infarction/possible peri-operative MI	#69;	# 57; #143
Rhythm Disturbances	# 53(AV block); #223 (unstated)	#160(Lown Grade IV)
Elevated Potassium	# 149;	#145; # 146
Miscellaneous	# 42 (esophagitis); # 47 (pneumothorax); # 78 (infection); # 221 (low ph) # 223 (transaminase elevated)	#7 (Bronchoconstriction)

Laboratory: Only group means for laboratory values were submitted, line listings were not. Since these subjects are immediately post-surgery, any changes in values could as well be attributable to the surgical intervention. For example equilibration of hemoglobin and hematocrit to the amount of blood loss during surgery may not be fully appreciated till several hours post-surgery.

Table 18. Lab Values; Mean (SD) (n= 59-61 in the fenoldopam, 60-64 in the nifedipine group)

Parameter	Fenoldopam			Nifedipine		
	ICU	12-hours post	Difference	ICU	12-hours post	Difference
Hgb(g/dL)	11.2 (1.2)	10.9 (1.3)	-0.3	11.4 (1.3)	11.2 (1.1)	-0.2
Hct (%)	33.8 (3.7)	33.2 (3.1)	-0.7	34.5 (4.1)	33.7 (2.9)	-0.8
WBC /nl	12133 (3899)	10866 (2859)	-1267	12041(4817)	10807 (10400)	-1234
Plt/nl	144617(46397)	14300 (42868)	1617	134397 (36199)	141081 (39412)	+6684
Sodium	137.4 (3.0)	140.3 (5.0)	+2.9	137.9 (3.2)	139.5 (5.4)	+1.6
Potassium	4.3 (0.7)	4.4 (0.3)	+0.1	4.4 (0.7)	4.3 (0.4)	-0.1
Creatinine	0.9 (0.2)	1.1 (0.4)	*	0.9 (0.3)	1.0 (0.5)	*

* n=41 in the ICU group both treatments with n=57, 59 respectively in the fenoldopam and nifedipine groups at 12 hours.

Conclusion: This was a comparative study of intravenous nifedipine and fenoldopam in patients who are immediately post-operative from cardiac bypass

surgery. On its surface, the study seems to suggest that intravenous fenoldopam lowers blood pressure to a greater extent and faster than intravenous nifedipine. This study, however, is too flawed (see below) to allow such a conclusion to be drawn.

The study was both open-labeled and also contained irregularities in the manner in which subjects were randomized, in that investigators occasionally took randomization envelopes out of sequence. Concurrent therapies were allowed immediately before and during the 1-hour pivotal infusion period which included volume expanders, sedatives, analgesics and muscle relaxants. Any measurements and/or interventions were done with full knowledge of the treatment that subjects received. Subjects were excluded from analysis again with full knowledge of the treatment that they received. Although continuous readings were done only those at ten minute intervals were placed on the case report form-again with full knowledge of the treatment.

The sponsor did not pre-specify that they will perform any interim analysis. Nevertheless, at least two documented such analyses were done. Not only were the analyses done, but based on the interim analyses the study was modified; once to increase the sample size of the study groups and once to prematurely terminate the study. The concept of an interim analysis in an open-label study is suspicious in itself. I would therefore expect, on an unofficial basis of course, that the study was re-analyzed after every subject completed the study.

The intravenous formulation of nifedipine is a non-approved formulation. Nifedipine is, furthermore, not indicated for the control of blood pressure post-surgery.

Although the literature suggests that it is bad to be hypertensive post-operatively, I could not find convincing data to show that dropping blood pressure and in particularly, dropping it rapidly, is associated with a positive clinical benefit. On the down side, fenoldopam causes a substantial tachycardia, also not particularly desirable post-operatively. It is unclear if any net benefit from the drop in blood pressure is counter-balanced by the adverse outcomes consequent to an increase in heart rate.

With respect to this study, adverse events were more frequent in the fenoldopam group than in the nifedipine group. There was no decrease in bleeding episodes in the fenoldopam versus nifedipine.

Surprisingly, there did not appear a discernable effect on diuresis in those who received fenoldopam. Three fenoldopam versus one nifedipine subjects had decreased diuresis.

Study D1101 Vol 52 pp 1-129

Title of study: A Multinational, Multicenter, Open-Label Comparison of Intravenous Fenoldopam Versus Sodium Nitroprusside in Patient with Severe Hypertension:

Summary: This study was previously reviewed by Dr. Basil Freedman, His review of March 3, 1992 is attached as Appendix B.

APPEARS THIS WAY
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Study : Vol 52 pp 136-206

Title: An Evaluation of the blood Pressure Lowering Effect of Intravenous Fenoldopam in Patients with Hypertensive Emergency:

This document is an overview analysis of the eight open label multicenter clinical trials that enrolled a total of 320 severe (both emergent and non-emergent) hypertensive patients. As far as study organization, all studies included baseline, up-titration, maintenance an follow-up periods. Subjects were enrolled if their supine diastolic blood pressure was between 120 and 170 mm Hg. Descriptive information for each of the studies is summarized in the table below:

Table 1. Description of Studies in Severe Hypertensive.

						Maintenance Phase			
Study	# PTs	# Centers	Initial Dose ug/kg/min	Dose increases ug/kg/min	Dose Changes Interval (Min)	Minimum Duration (Hrs)	Con-stant Rate	Down Titration	Maximum Infusion Duration (hr)
A14	26	2	0.1	0.1	10/30*	3/6	No	No	3/6
A52	22	6	0.1	0.1	30	6	No	No	13
B63	51	7	0.1	0.2	10/20+	4/1	No	No	24
B67	42	5	0.1	0.2	20	1	No	No	24
B69	28	3	0.2	0.2	20	1	No	No	24
B74	27Fen /26Nit	7	0.1Fen/ 0.5 Nit	0.2Fen/ 1.0 Nit	15	1	Yes	Yes	24
B85	34	11	0.1	0.1	20	6	Yes	Yes	48
D1101	90Fen /93Nit	24	0.1Fen/ 0.5 Nit	0.2Fen/ 1.0 Nit	10	0.5	Yes	Yes	24

* 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 . The duration of maintenance was changed from 4 hours to 1 hours.
Fen=Fenoldopam; Nit=Sodium nitroprusside

The protocols were divided into a screening phase, in which subject's eligibility were confirmed and baseline measurements made. The up-titration phase followed the screening phase. During the up-titration phase, the infusion of fenoldopam or positive control was started and increased, as noted in the above table, until the target blood pressure or the stipulated blood pressure decrease was reached. The maintenance phase began once this blood pressure was reached and was continued for the stipulated number of hours. At the completion of the maintenance phase, the titration was either completely stopped or down-titrated before stopping. Subjects were usually followed for at least 48 hours post infusion. Concomitant medications were administered prior to baseline phase. During baseline, up-titration and the early part of maintenance phase the only medication that was allowed was a single dose of furosemide for those with congestive heart failure. During the latter part of maintenance, during down titration and post-

infusion phases all medications were allowed.

Based on a review of the CRFs the sponsor separated out a cohort of patients that they considered as having emergent hypertensive crises. Severe hypertension can be divided into urgent or emergent hypertension[1]. The difference between the two categories is that subjects with emergent hypertension have ongoing compromise to sensitive end-organs. End organ compromise can take the form of either hypertensive encephalopathy, CVA (TIA, cerebral infarction, intracerebral hemorrhage or subarachnoid hemorrhage), myocardial ischemia, acute pulmonary edema, hypertensive nephropathy, or hypertensive retinopathy (Grade III or IV Keith Wagner Fundoscopic Changes).

The number of subjects in each of the above studies and the number with emergent hypertension, as per sponsor, are tabulated below.

Table 2. Number of Subjects Enrolled and Those Considered by the Sponsor as Emergent Hypertensive.

	A14	B63	B67	B69	B74	B85	A52	D1101	Total
Fenoldopam Treated	26	51	42	28	27	34	22	90	320
Emergent	0	12 (24%)	5 (12%)	14 (50%)	5 (19%)	12 (38%)	6 (27%)	38 (42%)	93 (29%)
Nitroprusside Treated					26			93	119
Emergent					6 (23%)			32 (34%)	38 (32%)

There were a total of 93 (29%) of the fenoldopam and 38 (32%) of the nitroprusside treated subjects that were considered by the sponsor as having emergent hypertension. The specific emergent symptoms for the fenoldopam and nitroprusside subjects are shown below. Approximately 40% of the ostensibly emergent subjects were enrolled from study D1101.

Table 3. Symptoms Defining Emergent Hypertension in Uncontrolled and Controlled Studies (Subjects could Have More than One Symptom).

	Retino-pathy	Pulmonary Edema	Nephro-pathy	Encepha-lopathy	CVA	Eclamp-sia	Myocardial Ischemia	Total
Fenoldopam								
All (n=143)	71 (76%)	34 (37%)	20 (22%)	12 (13%)	4 (4 %)	2 (2%)	0	143
Controlled (n=43)	34 (79%)	13 (43%)	9 (21%)	9 (21%)	3 (7%)	1(2%)	0	69
Nitroprusside								
Controlled (n=38)	25 (66%)	11 (29%)	12 (32%)	9 (24%)	2 (5%)	0	1 (3%)	60

Among the symptoms that defined the subjects as emergent, the most common was hypertensive retinopathy.

[Comment: I went through the volumes of study D1101 that were submitted in February, 1992. I could not confirm the number of subjects that the sponsor defined as having emergent retinopathy. The only tabular listing I could find was titled "Number and Percent of Patients with Presenting Conditions Displayed by

Disease Classification"; Appendix 3.0. This tabulation contained a total of 8 subjects who received fenoldopam with descriptors such as severe hypertensive retinopathy, cottonwool spots, flame hemorrhage, Grade III Keith Wagner eye grounds. It is, furthermore, not clear if these indicators of severe hypertension were noted on the baseline exam or were historical information of past examinations. Since 76% of the events that designated a subject as emergent were listed as retinopathy, and since nearly 38 of the emergent subjects were derived from study D1101, it would have been expected that approximately 0.76 x 38 or approximately 29 subjects should have had hypertensive retinopathy in this study. Far more than I could derive from this one table.

I spoke with Ms Bonnie Horner of Neurex on 11/22/96 with my concerns about confirming the incidence of emergent hypertension from this study. She said that the data was put together by the previous sponsor, and that it is not an easy task for Neurex to recreate this data. In addition, there is an ongoing study in patients with emergent hypertensive crisis. So, Neurex will not attempt to recreate the data now, but if this data is needed to support approval for hypertensive crises they will, at that point, try to recreate this data.]

Efficacy -Definition of End Point

The pre-specified protocol criteria for **success** was a decrease in diastolic blood pressure of 40 mm Hg for those with a BP of 150 or greater or a decrease to less than 110 mm Hg for those whose blood pressure was between 120-150 mm Hg. A subject could be considered a **success** if less than the requisite blood pressure drop was realized but the investigator considered further decrease in blood pressure as not necessary. The sponsor considered **partial success** as those whose blood pressure did not decrease the amount specified although further diastolic blood pressure would have been useful. **Failures** were those whose blood pressure did not attain either of the above criteria.

[Comment: The criteria that defines outcome is subjective, particularly as these criteria are applied to treatment successes. The investigator could declare a patient as a treatment success despite the lack of a substantial decrease in blood pressure. Furthermore, the sponsor could arbitrarily define the end of the maintenance phase and could do this at the nadir of blood pressure measurements.]

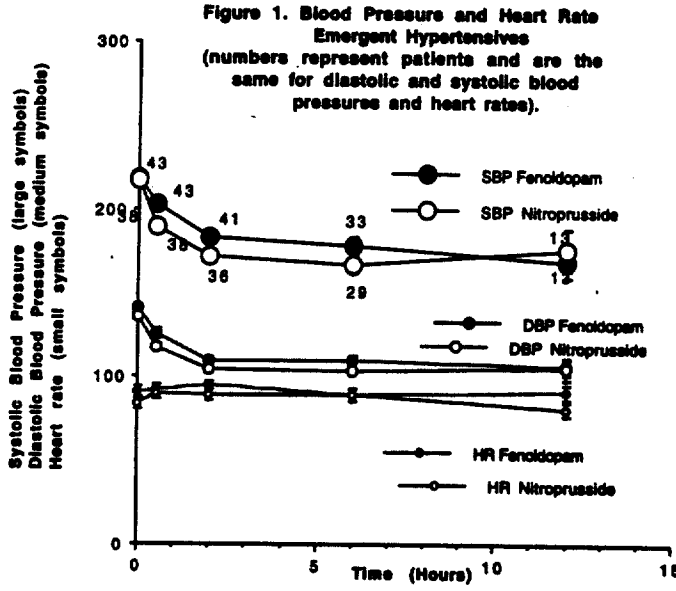
Table 3. Success Rate in Emergent Patients

	Fenoldopam Emergent-total	Fenoldopam Emergent-Controlled Studies	Nitroprusside Emergent-Controlled Studies
Success	80/93 (86%)	33/43 (77%)	31/38 (81%)
Partial Success	5/93 (5%)	4/43 (9%)	3/38 (8%)
Failure	8/93 (9%)	6/43 (14%)	4/38 (11%)

According to the sponsor's assessment, the fenoldopam emergent group had nearly equivalent, though somewhat fewer successes than the fenoldopam group from the controlled clinical trial data base. In the uncontrolled data base, the success rate was approximately 94% (in Table 3, subtract out the controlled group from the total group).

Changes in vital signs for those considered by the sponsor as emergent

hypertensive are shown in Figure 1. There appears to be a rapid decline in blood pressure both for the fenoldopam and nitroprusside groups. Surprisingly, heart rate is not substantially increased. [comment: Both controlled studies pre-specified constant infusions during the maintenance phase.]



Safety:

There were no deaths during the study or within thirty days after terminating infusions.

Ten of the 43 (23.3%) subjects were discontinued from the controlled studies while on fenoldopam.

Among the sponsor-defined emergent patients, 13 of the 93 fenoldopam treated subjects and 10 of the 43 such subjects in controlled studies discontinued prematurely from the infusion. The reason for discontinuation is shown below:

Table 4. Reason for Discontinuation.

Reason For Withdrawal	Fenoldopam Emergent Total (n=93)	Controlled studies Fenoldopam (n=43)	Controlled studies Nitroprusside (n=38)
Clinical Events	8 (8.6%)	6 (14%)	3 (7.9%)
Insufficient Therapeutic Effect	5 (5.4%)	4 (9.3%)	3 (7.9%)
Other	0	0	1 (2.6%)

The sponsor tabulated the clinical events as follows:

Table 5. Specific Adverse Clinical Events Leading to Premature Discontinuation

	Fenoldopam Emergent Total	Fenoldopam Emergent	Nitroprusside Emergent
Hypotension*	5 (5.4%)	3 (7%)	2 (5.3%)
Decreased Blood Pressure	1 (1.1%)	1 (2.3%)	0
Vomiting	1 (1.1%)	1 (2.3%)	0
GI Bleeding	1 (1.1%)	1 (2.3%)	0
Arm Pain	0	0	1 (2.6%)

* Only those subjects as designated by the investigator as hypotensive were included in this category as well as in decreased blood pressure.

[comment: There were a total of 4 subjects in the emergent hypertensive fenoldopam group that apparently had excessive blood pressure drops. It is not clear if these subjects did not respond to a decrease in the infusion rate. The details of these events are not further described].

Clinical Events that occurred on therapy are shown below. The events tabulated by the sponsor include only events which occurred in 3 or more fenoldopam treated subjects.

Table 6. Adverse Events During Treatment

	Emergent Fenoldopam Total n=93	Fenoldopam Emergent-Controlled (n=43)	Nitroprusside Emergent-Controlled (n=38)
Headache	8 98.6%)	3 (7%0	3 (7.9%)
Decreased Potassium	8 (8.6%)	6 (14%)	2 (5.3%)
Hypotension	8 (8.6%)	5 (11.6%)	2 (5.3%)
Decreased Blood Pressure		1 (2.3%)	1 (2.6%)
Ventricular Extrasystole	6 (6.5%)	2 (4.7%)	0
Flushing	5 (5.4%)	1 (2.3)	1 (2.6%)
Limb Cramp	6 (6.5%)	3 (7.0%)	0
Nausea	3 (3.2%)	2 (4.7%)	4 (10.5%)
Vomiting	3 (3.2%)	3 (7.0%)	2 (5.3%)
Anxiety	3 (3.2%)	2 (4.7%)	0
Total patients with Event/Total Patients	51/93 (55%)	26/43 (60%)	18/38 (47%)

In the controlled and uncontrolled fenoldopam cohort, only limb cramps and vomiting were severe. Among those events considered as moderate in severity were headache (n=6), decreased K+ (n=2); hypotension (n=5); ventricular extrasystole (n=4); flushing (n=1); limb cramp (n=2); nausea (n=1); vomiting (n=1) and anxiety (n=2).

In the controlled trials fenoldopam group there was 1 severe event (vomiting). Events classified as moderate were: headache (n=3), decreased K+ (n=4); hypotension (n=4); ventricular extrasystole (n=2); flushing (n=1); limb cramp (n=2); nausea (n=1); vomiting (n=1) and anxiety (n=2).

In the controlled trials there was one severe event in the nitroprusside group (hypotension). Events that were classified as moderate were: headache (n=2); decreased blood pressure (n=1); nausea (n=1).

The vital signs that were reached the sponsor's level of concern during the infusion are tabulated below:

Table 7. Vital Signs of Concern-Emergent Patients.

	All Fenoldopam Emergent Patients	Fenoldopam in Controlled Studies	Nitroprusside Emergent in Controlled Studies
Supine DBP < 60 mm Hg	1 (1%)	1 (2%)	2 (5%)
Supine SBP <100 mm Hg	1 (1%)	1 (2%)	0
Supine Pulse < 60 BPM	4 (4%)	2 (5%)	4 (11%)
Supine Pulse > 120 BPM	12 (14%)	7 (16%)	7 (18%)

[Comment: Given the small data base, there does not appear to be differences between the different treatments in adverse events. It should be noted that the sponsor's defined criteria for tachycardia requires a heart rate of > 120 BPM, not the standard 100 BPM.]

Laboratory assessments were performed at baseline during therapy and shortly after (1-2 days) and long after (3-10 days) completing the infusion. Collection of samples for the 3-20 day period was less reliable with only approximately 30% of entered patients had such evaluations. Consequently, the existence, persistence or absence of laboratory abnormalities after infusion are not accurately known for this data base.

Table 8. Number with Laboratory Abnormalities (%) of those who had values that were abnormal (Derived from Tables 4.16-4.19 vol 52 pp 181-185).

	All Fenoldopam Emergent (n=93)			Fenoldopam Emergent Controlled Studies (n=43)			Nitroprusside Emergent Controlled Studies (n=38)		
	Baseline	On Tx	1-2 days post Tx	Baseline	On Tx	1-2 days post Tx	Baseline	On Tx	1-2 days post Tx
Low HGB	32/93 (34)	10/30?(33)	40/87(46)	12/43 (28)	10/30 (33)	20/41 (49)	9/36(25)	13/31 (42)	12/36 (33)
Low WBC	4/93 (4)	1/30? (3)	7/87 (8)	2/43 (5)	1/30 (3)	3/41 (7)	4/36 (11)	13/31 (13)	12/36 (6)
High WBC	23/93 (25)	9/30?(30)	23/87 (26)	10/43 (23	9/30 (30)	11/41 (27)	7/36 (19)	6/31 (19)	8/36 (422)
Low Platelets	7/91 (8)	2/30?(7)	7/85 (8)	3/43 (7)	2/30 (7)	3/40 (8)	1/34 (3)	1/31 (3)	0/35 (0)
Low Potassium	23/89 (26)	37/83 (45)	25/90 (28)	12/41 (29)	17/35 (49)	9/41 (22)	10/37 (27)	15/36 (42)	8/37 (22)
High Potassium	3/89 (3)	1/83 (1)	7/90 (8)	2/41 (5)	1/35 (3)	4/41 (10)	1/37 (3)	1/36 (3)	0/37 (0)
High BUN	37/91 (41)	28/82 (34)	52/90 (58)	18/43 (56)	13/35 (37)	22/41 (54)	18/37 (49)	16/36 (44)	24/37 (65)
High Creatinine	52/91 (57)	43/81 (53)	64/90 (71)	24/43 (56)	17/35 (49)	26/41 (63)	27/37 (73)	23/36 (64)	29/37 (78)
High SGPT	22/83 (27)	7/26 (27)	17/80 (21)	10/40 (25)	7/26 (27)	9/37 (24)	6/33 (18)	6/30 (20)	7/33 (21)

? Obvious misprint in sponsor's table-values appear to be those of the emergent fenoldopam controlled study group.

The number of subjects with abnormalities were nearly the same when comparing the emergent fenoldopam cohort to the cohort who received fenoldopam in controlled studies. [Comment: Based on the data from Dr. Freedman's safety update review of 11/9/90 there were 20% (62/312) who had hypokalemia as defined above at baseline; 38% (103/273; and 1-2 days post therapy 29% (92/312).]

There was an increase in the number of subjects with hypokalemia (sponsor defined as < 3.0!!). A number of subjects with hypokalemia was also noted in the nitroprusside group. There were also a large fraction of the subjects who had abnormalities in the renal markers, BUN and creatinine. No marked increase in these numbers of subjects occurred during treatment.

Conclusion: This was an retrospective overview of sponsor-defined emergent hypertensive patients culled from the controlled and uncontrolled studies. I could not verify, based on the information that was available, that these subjects were truly emergent hypertensive patients.

Study D1102 IIIA (CPMS #172)

Vol. 53 pp 1-145

Title of Study: A Pilot Study of the Antihypertensive Effect of Corlopam in Post-Operative Hypertension

Investigator and Site: Dr. Michael E. Goldberg
Department of Anesthesiology
Helene Fuld Medical Center
Trenton, NJ

Study Design: This was a double-blind, placebo-controlled, pilot study in post-operative patients with sponsor defined, post-operative hypertension.

The protocol, amendments, appendices and line listings were not supplied by the sponsor. The sponsor amended the protocol twice and the changes are already included in the description of the protocol.

Formulation: Fenoldopam mesylate batch: IPO #88162 lot # X258-8K29) or matching placebo infused in 5% dextrose in water.

Dates: The first subject was enrolled into the study on January 17, 1990 and the last on November 29, 1990.

Protocol:

Subjects were to be of either gender between the ages of 18-70 years with post-operative hypertension defined as a systolic blood pressure >20% above baseline pre-operative measurements. Heart rate at the time of enrollment was to be less than 110 beats/minute. Treatable causes of systolic hypertension such as pain, hypoxia or hypercapnia were to be addressed before enrollment. All enrolled females were to be post-menopausal, surgically sterile or using an adequate contraceptive method.

Subjects were excluded if they were pregnant or lactating, had a recent MI or stoke, or cardiovascular baseline condition [e.g. ventricular couplets or tachycardia; supraventricular tachycardia or AV block (grater than 1st degree)]. Subjects were also excluded if they had significant liver disease or required peritoneal- or hemo- dialysis or used concomitant confounding medications (i.e. dopamine blockers, phenothiazine, metoclopramide or MAO inhibitors) or received, in the recent past, experimental medication. Those who had acetaminophen on the day of the operation were excluded.

Subject's baseline eligibility, with respect to systolic blood pressure, as well as baseline laboratory assessments were performed 6 hours prior to the surgery. After surgery, subjects were defined as hypertensive if the average of 3 values was 20% greater

than the average of the pre-surgical baseline measurements. Subjects were randomized to receive either fenoldopam at a dose of 0.1 ug/kg/min or corresponding placebo, and titrated at 10 minute intervals until systolic blood pressures was no greater than 10% above the pre-surgical value (baseline). The maximum dose was 1.3 ug/kg/min for fenoldopam and 1.5 ug/kg/min for placebo (comment: how could the maximum doses be different if the formulations were blinded?). The infusion rate could be reduced, the infusion terminated or an alternate treatment started, based on the judgment of the investigator. The protocol stipulated several phases to the study: titration, maintenance, offset and follow-up.

During the titration phase, the infusion rate could be increased at increments of 0.2 ug/kg/min or less, at 10 minute intervals, until the target blood pressure was reached. Upon reaching the target systolic blood pressure, subjects entered the maintenance phase for at least four-hours, during which the target blood pressure was maintained. Even dufing this phase, titration, at the discretion of the investigator, was allowed. There was a down titration phase which lasted 1/2 hour in which the infusion rate was halved and finally there was a 24 hour post-infusion observation period.

Pre-medication and medication during anesthesia was standardized (fentanyl, thiopentane, isoflurane, nitrous oxide/oxygen and vecuronium). Subjects were only randomized after extubation. Concomitant medication after surgery was generally prohibited although single doses of meperidine were allowed at doses of 50 mg or less, with one repeat administration 30 minutes later.

Blood pressure could be measured either by Dynamap® or intra-arterial line but the same method was to be used throughout the study. Baseline was defined as the mean of 3 systolic readings that did not differ by more than 10% of the highest systolic reading. Additional readings, if needed were permitted to establish the baseline blood pressure. During the randomization phase, vital signs were measured every 5 minutes for 15 minutes after dosing adjustments and after each 15 minutes with stable infusion rates. ECG was continuously monitored.

In the study report, the sponsor's defined a **primary success**, (comment: I don't know if this was a protocol specified end-point), as an individual with a systolic blood pressure during the observation period that was decreased to at least 10% above the pre-op baseline (pre-hypertensive value) for more than 15 minutes during any time during the infusion. A **primary failure** was defined as an individual who, at no time during the infusion, had their systolic blood pressure at or below the target blood pressure or did not remain at or below this level for more than 15 minutes.

A **secondary success** was defined as those who attained the target blood pressure and no other systolic blood pressure levels exceeded target level for more than 15 minutes (I interpret this endpoint as indicating that subjects could have one and no more than that one reading exceeding the target systolic measurement).

The dose and time to the primary success was also analyzed. For the instances where the investigators did not follow the protocol stipulated titration regimen, in particular, that dose changes were made more frequent than every 10 minutes, the dose at which titration ended was the dose accepted as the end of titration dose.

Subjects concluded protocol upon:

a) completion of all phases of the study
b) death
c) discontinuation due to ADR or insufficient response
d) patient request
e) sponsor discontinued study

Laboratory evaluations as well as 12-lead ECGs were done during the pre-operative screening as well as post-operatively before infusion and one and 24 hours following the completion of the infusion.

The sponsor refers to three amendments (not submitted) that were instituted after the study was started:

Amendment 1:

1) baseline blood pressure mearsurments could be taken 3-5 days prior to the surgery. 2) meperidine for pain control (in excess of the stated 50 mg dose?) could be administered for patient comfort.

Amendment 2:

Inclusion of ASA Physical Status III patients with endarterectomy.

Amendment 3:

Patients with evidence of glaucoma were excluded.

Results:

A total of 17 subjects were enrolled into the study. Nine subjects received fenoldopam and 8 placebo. The demographics Mean ± SEM. are shown in Table 1

Table 1 Demographics of Subjects in Study D1102

Characteristic	Sex	Age	Weight	Race
Fenoldopam (n= 9)	6M/3F	51 ± 4.8	86.6 ±6.7	5 W/3 B/1Hispanic
Placebo (n=8)	7M/1F	47.4 ± 3.6	87.1 ± 7.5	6W/2B

With respect to previous medical history, 2 subjects in the fenoldopam treatment group had a history of coronary artery disease.

The average infusion rate for fenoldopam was 0.6 ug/kg/min (range 0.1-1.3

ug/kg/min); and placebo 1.0 ug/kg/min (range 0.3-1.5 ug/kg/min). Two fenoldopam and no placebo patients were discontinued from the study. Four fenoldopam and three placebo subjects discontinued the infusion before the end of the maintenance phase.

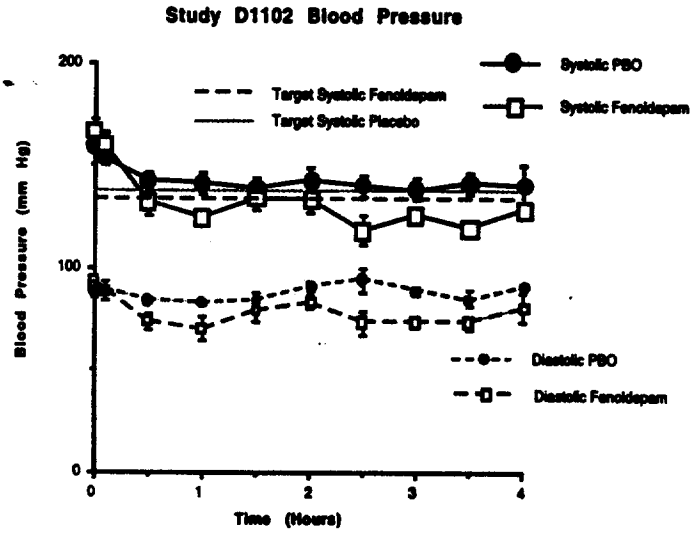
The time to the end of the titration phase was more rapid with the fenoldopam than placebo group (since only responders successfully completed titration the numbers that are listed are the responders). The results are derived from sponsor's Table 16 vol 53 p 83.

Table 2. Success Analysis-Dose and Duration of Infusion.

	Fenoldopam	Placebo
Time to End of Titration (min)	21.9 ± 5.1 (n=8)	40 ± 6.1 (n=4)
Dose at End of Titration (ug/kg/min)	0.33 + 0.10 (n=8)	0.45 + 0.1 (n=4)

Below is a graphical display of the systolic and diastolic blood pressure among those who had measurements (data was derived from sponsor's tables 10 and 11 v 53 p 70-71).

Figure 1



This is not an intent-to-treat analysis. Each point represents between 9 (early time points) to 5 or 6 (2.5 -4 hours) subjects. Based on the above defined end points there were 8/9 primary successes (i.e. titration to 4/8 in the placebo. Secondary successes (i.e. those who maintained this blood pressure) were 6/9 and 3/8 in the fenoldopam and placebo groups, respectively.target endpoint) in the fenoldopam and

The differences between placebo and fenoldopam in the primary end-point was not statistically significant.

Heart rate (mean ± SEM) is shown as Figure 2 (graphed from the data in Sponsor's

Figure 2

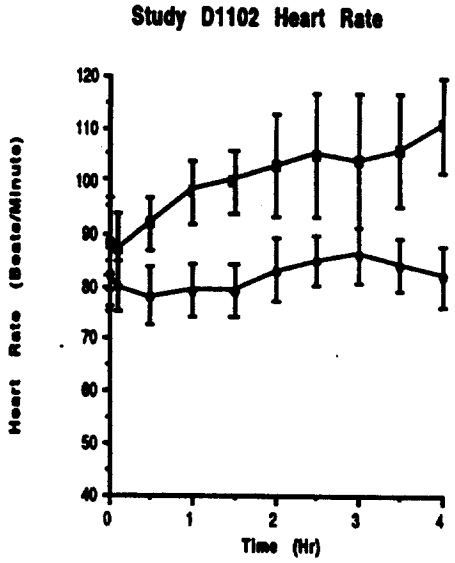


Table 12; vol 53 p 74). Again, this is not an intent-to-treat analysis nor is it a last value carried forth analysis. The heart rate represents the average for those who had measurements at that time. There is an appreciable increase in heart particularly for the fenoldopam treated subjects. There is also a trend to increase in heart rate with time for the placebo treated patients.

Following completion of the infusion (I believe the time represents the time after completing the 1/2 hour down-titration phase), vital signs between fenoldopam and placebo gradually converge, although the slight differences similar to those that were observed during infusion remained at 0.5 hours post-infusion. At this point, the systolic/diastolic BP for the fenoldopam group was 9/9 mm Hg lower than placebo and the heart rate was 17 BPM above placebo.

Table 3. Vital Signs After the Completing the Infusion

Parameter	Drug	0.5 hours post	1 hour post	24 hour post
Systolic BP	Fenoldopam	131 ± 6.7	130 ± 6.7	138 ± 5.1
	Placebo	140 ± 7.7	148 ± 5.6	141 ± 7.1
Diastolic BP	Fenoldopam	79 ± 4.3	90 ± 5.4	87 ± 4.1
	Placebo	88 ± 2.9	88 ± 3.8	85 ± 2.9
Heart Rate	Fenoldopam	101 ± 6.5	90 ± 5.6	88 ± 4.0
	Placebo	84 ± 4.6	85 ± 4.4	85 ± 7.2

Safety.

There were no deaths in the study. Two of the nine fenoldopam and none of the placebo subjects discontinued for adverse events.

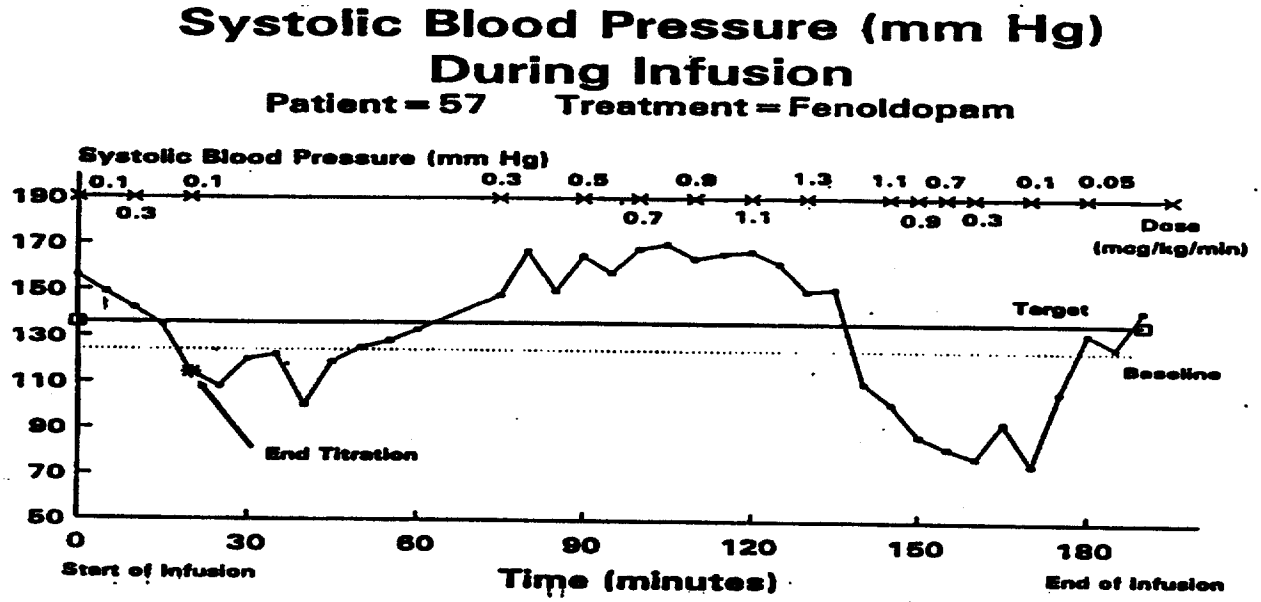
Patient #52 discontinued due to increased diastolic blood pressure (no CRFs are included within this study) systolic blood pressure appeared to hover around 190 mm Hg. The dose of fenoldopam was increased to a maximum of 0.7 ug/kg/min prior to discontinuation. The sponsor claims the patient recovered after 20 minutes.

Patient # 55 was discontinued, according to the sponsor due to a decrease in systolic blood pressure (the graphical display shows a systolic blood pressure of 90 mm Hg, not that different from the systolic BP of other subjects). This subject received a dose of 0.1 ug/kg/min. Recovery was rapid after discontinuation of infusion.

Although not considered a drop-out, subject # 57 illustrates the potential of fenoldopam to over-exuberantly lower blood pressure. The entirety of the blood pressure data is shown as Figure 3. The sponsor did not include line listings for heart rate or diastolic blood pressure. This subject received an initial dose of 0.1 ug/kg/min and was titrated to 0.3 ug/kg/min. Upon attaining the goal blood pressure and to some extent exceeding this BP, the infusion rate was decreased to 0.1 ug/kg/min. Over the next

approximately 50 minutes the SBP gradually rises. Over the next 50 minutes the dose was rapidly up-titrated to 1.3 ug/kg/min. At this point, there was a rapid and profound (nearly 100 mm Hg) drop in systolic blood pressure. This profound drop lasted 20 minutes despite a rapid downtration of dose to 0.05 ug/kg/min. This subject terminated the study at approximately 3 hours- less than the stipulated 4 hour infusion.

Figure 3.



Clinical events were divided as those occurring during the infusion and those which occurred within 2 hours of completing the infusion. For fenoldopam, cardiovascular events occurred in 1 subject (1 event-elevated blood pressure #52) during the infusion and 2 subjects (3 events- 1 hypertension, # 54 and tachycardia # 54; and decreased blood pressure # 55) within 2 hours after the end of the infusion. Digestive events were noted in 2 subjects (2 events-vomiting # 54, # 55) during infusion and 1 patient (1 event- nausea and vomiting # 65) within 2 hours post infusion. Pyrexia occurred in 1 fenoldopam patient within 2 hours of completing the infusion. One placebo patient had 1 episode of vomiting.

Five subjects (#50, # 55, # 57, # 63, # 65) treated with fenoldopam had diastolic blood pressures of <60 mm Hg during the infusion and two (# 55, 63) within 2-hours post-infusion. Two systolic patients had systolic blood pressures < 100 mm Hg (# 55, # 57) during the infusion and two subjects (# 50, #55) within two hours of infusion. Two subjects (# 54 and # 63) had heart rate > 120 BPM during the infusion.

[comment: Some of the cut-off points employed by the sponsor are unusual for the definition of unusual vital signs. Thus the usual cut-off for tachycardia is 100 BPM and not 120 as employed here.]

With respect to laboratory evaluations, three fenoldopam and one placebo subject had elevated glucose measurements during the infusion (maximum 148-151 for fenoldopam and 195 for placebo mg/dL). No abnormalities in ECG intervals were noted.

Conclusion: This was a small placebo-controlled study, comparing titrated doses of fenoldopam to corresponding placebo in post-operative patients with hypertension. Although the data are suggestive of a decrease in both systolic and diastolic blood pressure in comparing fenoldopam to placebo the primary response rate i.e. number of subjects who attained target blood pressures did not differ between the two small groups. Safety issues that are raised are tachycardia, with heart rate increases of more than 30 BPM noted during the 4 hour infusions. One subject # 57 had profound blood pressure changes that were not acutely reversible upon down-titration of fenoldopam.

Study A50

vol 53 p 146-285

Title of Study: A Single-Blind Study to Compare the Effect of Intravenous Infusion of Fenoldopam and Nitroprusside on Post-Operative Hypertension in Patient who Have Undergone Cardiac Surgery.

Investigator and Site: Dr. R. Feneck
Mr. R. Walesby
Department of Cardiothoracic Anaesthesia and Surgery
London Chest Hospital
London, UK

Study Design: The study report consists of two distinct short-term infusion studies that have been joined in this analysis. The first study of 8 subjects, all who received fenoldopam, was a feasibility study. The second study was a single-blinded randomized positive (nitroprusside) controlled study in subjects post-cardiac surgery. There were 10 nitroprusside and 10 fenoldopam patients enrolled into this study.

Protocol, Amendments, Line Listings and CRFs were not submitted with this study.

Formulation: Fenoldopam Mesylate: formula 120 Batch 5A:BPBR #1379 diltued in 5% dextrose- final concentration of 200 ug/ml.
Sodium Nitroprusside (Nipride, Roche) in 5% dextrose in water -final concentration was 500 ug/ml.

Dates: The first patient enrolled into the pilot study on 8 December 1988 and the last completed the study on 26 October 1989.

Protocol: Both the pilot and nitroprusside-controlled study enrolled cardiac surgery patients between the ages of 21-80 years old of either gender, who were within 24-hours of surgery and who had systolic blood pressure readings of > 130 mm Hg and were otherwise stable (with respect to respiratory, fluids and acid base status, urine output and also that sedation and analgesia were adequate). Females who were enrolled, were to be post-menopausal, surgically sterile of using reliable contraceptive methods with a negative pregnancy test prior to entry.

Specifically excluded were pregnant or lactating females, unstable subjects, or those with on-going myocardial infarction or ongoing uncontrolled arrhythmias (either supraventricular or ventricular), known cerebral blood flow disturbances, hypothyroidism or Vitamin B12 deficiency, clinically significant liver disease, need for dialysis (either pre-or post-operatively), or who used contraindicated medications (dopamine blockers, L-amino decarboxylase inhibitors, MAO inhibitors, tricyclic

antidepressants or dopamine agonists or hypotensive agents).

The first eight subjects were enrolled as a dose ranging pilot study and received doses of fenoldopam starting at 0.2 ug/kg/min with upward titration at dose increments of 0.2 ug/kg/min at 10 minute intervals, with a maximum dose of 1.5 ug/kg/min.

For the nitroprusside comparison study, the starting dose of fenoldopam was 1 ug/kg/min with upward or downward titration at the discretion of the investigator. Maximum dose was 1.6 ug/kg/min. In the controlled portion of the study, nitroprusside subjects received a starting dose of 1.0 ug/kg/min with dose increments of 0.4 ug/kg/min at an interval of at least 10 minutes and a maximal dose of 4 ug/kg/min. During either portion of the study and across either infusion regimens, the investigator could exercise discretion to decrease the dose.

All potentially eligible subjects underwent screening before surgery which included physical exam, medical history and informed consent. In preparation for surgery, both a pulmonary artery catheter and an intraarterial line were inserted. ECGs were monitored from 6 hours prior to surgery till after termination of the study with ECG output in the form of both a direct display and hard copy for archival purposes.

In order to enter the study, subjects had to have the average of three systolic blood pressure measurements, performed at 5 minute intervals, less than 30 minutes before the infusion of > 130 mm Hg.

Each subject had two baseline hemodynamic measurements separated by 5 minutes, within 30 minutes of entry into the study. The following parameters were measured or calculated: right atrial pressure (RAP); pulmonary artery pressure (PAP); pulmonary capillary wedge pressure (PCWP); cardiac output (CO); cardiac index (CI); stroke volume (SV); stroke volume index (SVI), systemic vascular resistance (SVR); pulmonary vascular resistance (PVR); and stroke work index (SWI). Shunt fraction[3] was calculated from oxygen saturation data obtained from the Swan-Ganz and the pulse oximeter.

Subjects were titrated by the regimens described above, until their systolic blood pressure was below 130 mm Hg or fell by at least 25 mm Hg, which ever was greater. Once titration was completed, the infusion was continued for a total of three hours, with dose changes, either upward or downward, made at the discretion of the physician. Intraarterial blood pressure measurements and heart rate were measured 5 and 10 minutes after any dosing adjustment. Hemodynamics were measured in duplicate once titration was completed and at 30, 60 and 120 minutes, thereafter.

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[3]Calculated as:

$$\frac{\text{Alveolar } O_2 \text{ Saturation} - \text{Arterial } O_2}{\text{Arterial } O_2 \text{ Saturation} - \text{Mixed Venous } O_2 \text{ Saturation}}$$

Additional antihypertensive medication was permitted at the end of the treatment period. Vital signs were measured at 0.083, 0.17, 0.33, 0.5, 1, 1.5, 2, 3, 4, 8, 12, 16, 20 and 24 hours after the termination of the infusion. Hemodynamics were measured once, 2 hours after the end of the infusion.

The sponsor defined subjects as successes or failures, A **success** was a subject, who within 30 minutes of the end of the infusion, had a reduction in systolic blood pressure to 130 mm Hg or decreased by 25 mm Hg from baseline. A **partial success** was to be reported for a patient who had less than the required blood pressure reduction but in whom further acute blood pressure reduction was considered unsafe. A **failure** was one who required termination of study medication and acute initiation of another antihypertensive treatment.

The sponsor refers to two protocol amendments. The first, included the measurement of pulmonary shunt fraction. The second, deleted the requirement for 2 minute ECG rhythm strips. This second amendment also redefined treatment failure, in that subjects who were discontinued for excessive blood pressure response were nevertheless considered successes (comment-this definition is like the old snide crack"the operation was a success but the patient died"!).

Results: The sponsor combined the results of the pilot with those of the nitroprusside/ fenoldopam controlled study. This reviewer did not have the raw data to dissociate the two separate studies.

A total of 28 subjects were (18 fenoldopam and 10 nitroprusside) were included in the sponsor's analysis. The demographics are summarized below (mean ± SE- adapted from sponsor's table 1 vol 53 p. 206).

Table 1. Demographics of Study A50 (Mean ± SEM)

Characteristic	sex	Age	Weight	Race
Fenoldopam	16 M/2 F	58.6 ± 2.3	80.9 ± 3.0	17 W/ 1 Asian Indian
Nitroprusside	9 m /1 F	61.6 ± 3.0	77.9 ± 2.2	10 W

The baseline conditions, limited to those that were noted for at least 2 subjects in any one group are shown below:

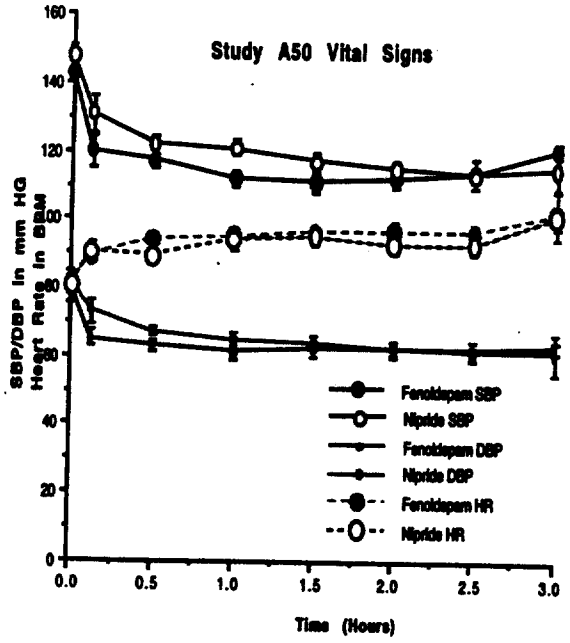
Table 2. Baseline Conditions Study A50

Condition>	Ischemic Heart Disease	MI	HBP	Angina	Surgery	Diabetes Mellitus
Fenoldopam	16 (89%)	6 (33%)	4 (22%)	1 (6%)	13 (72%)	2 (11%)
Nitroprusside	7 (70%)	4 (40%)	2 (20%0	3 (30%)	5 (50%)	0 (0%)

Nearly all the subject had a history of coronary artery disease described either as ischemic heart disease (how defined), angina, or previous MI. Concurrent medication of various nature (not available to this reviewer) were received by all 28 enrolled patients.

All subjects received their infused medication for at least 2 hours. Seven (39%) of the fenoldopam and 6 (60%) of the nitroprusside patients were infused for 2.5 hours or less. The pattern of doses i.e. how doses were titrated for individual subjects could not be teased out from the study. The maximum dose for most fenoldopam patients was between 1-1.5 ug/kg/min (89%). The median fenoldopam dose during for those considered successes at the end of titration and also at the end of the infusion studies was approximately 0.6-0.7 ug/kg/min.

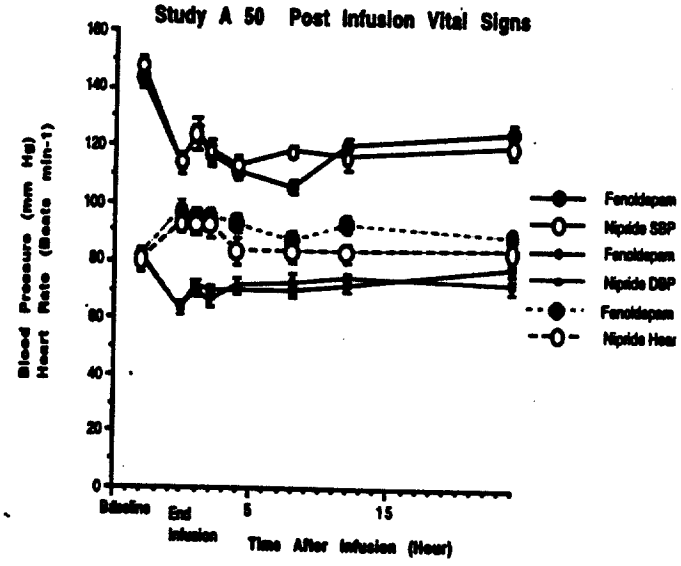
Figure 1



Based on the above definition of success rate there were 13 fenoldopam (72%) and 9 (90%) of the nitroprusside that were considered successes by the sponsor.

The vital signs during the infusion period are shown as Figure 1. Both systolic and diastolic blood pressures during each intervention are decreased with a corresponding increase in heart rate (data graphed from sponsor's Table 10 and 11 vol 53 p 221-221). The magnitude of the blood pressure response during fenoldopam infusion was approximately -30/-20 mm Hg; with a corresponding heart rate increase of approximately 18 BPM.

Figure 2



The vital signs post infusion are shown as Figure 2 (data derived from Tables 15 and 16; vol 53 p 232-233). Blood pressure post-infusion did not return to pre-infusion measurements. Whether this represents the spontaneous or ephemeral nature of post-surgical hypertension or the influence of any concurrent medication (either anti-hypertensive, pain or sedative) is a matter of

speculation. Heart rate for the fenoldopam group remained elevated during the post-infusion periods. The heart rate at the end of infusion was 97 BPM (16 BPM above baseline) and remained anywhere between 6-14 BP, during the 24 hour post infusion period. For nitroprusside the baseline heart rate was 80 BPM, that after infusion was 92 BPM. By 4 hours post-infusion, the heart rate was indistinguishable from baseline measurements.

With respect to hemodynamics, there did not appear to be any effect of fenoldopam on RAP, PAP(D)iastolic), PAP(S)ystolic) or PCWP at the end of titration and at the end of infusion. For nitroprusside, there was a substantial drop in PAPD, PAPS and PCWP at the end of titration with gradual return to baseline during the infusion and post infusion phases.

Cardiac output (and the corresponding derived cardiac index) were increased over baseline at the end of the titration period and remained relatively constant for both treatments during the remainder of the infusion period. At 2 hours post infusion, these parameters remained elevated both for the fenoldopam and nipride groups. In general, the CO and CI are increased to a greater extent with fenoldopam than nipride during the infusion (maximum measurement 46% increase for fenoldopam and 17% for Nipride).

Stroke volume (and the derived stroke volume index) increased for fenoldopam (approximately 22%) and returned to approximate baseline readings 2 hours post-infusion. No consistent changes were noted in the Nipride group.

Stroke work index for fenoldopam decreased modestly during the titration and infusion phases of the study (approximately 6%), and was substantially below baseline (19%) 2 hours post-infusion. For nipride there was a substantial decrease in SWI during the titration and infusion portions of the study as well as 2 hours post infusion (22%).

Table 3. Hemodynamics Study A50

Parameter	Time	Fenoldopam		Nipride	
RAP	Baseline	n= 18	4 ± 0.7	n= 10	4 ± 1.0
	End Titration	n=18	5 ± 0.8	n=10	2 ± 0.5
	0.5 Hr. Post Titration	n=17	5 ± 1.0	n=10	3 ± 0.3
	1.0 HR. Post Titration	n=17	6 ± 1.1	n=10	3 ± 0.5
	2 HR. Post Titration	n=17	5 ± 1.1	n=10	3 ± 0.6
	2 Hr Post Infusion	n=18	6 ± 0.6	n=10	4 ± 0.8
PAPD	Baseline	n=.18	24 ± 1.6	n= 10	24 ± 1.5
	End Titration	n=18	27 ± 1.7	n=10	16 ± 1.1
	0.5 Hr. Post Titration	n=17	26 ± 1.5	n=10	19 ± 1.6
	1.0 HR. Post Titration	n=17	27 ± 1.4	n=10	19 ± 1.4
	2 HR. Post Titration	n=17	27 ± 1.6	n=10	20 ± 1.3
	2 Hr Post Infusion	n=18	24 ± 1.6	n=10	21 ± 1.5
PAPS	Baseline	n= 18	10 ± 1.1	n= 10	10 ± 0.8
	End Titration	n=18	11 ± 1.2	n=10	6 ± 0.7
	0.5 Hr. Post Titration	n=17	11 ± 1.1	n=10	8 ± 0.8
	1.0 HR. Post Titration	n=17	12 ± 1.2	n=10	8 ± 0.9
	2 HR. Post Titration	n=17	12 ± 1.1	n=10	8 ± 0.9
	2 Hr Post Infusion	n=18	11 ± 0.8	n=10	9 ± 1.4

PCWP	Baseline	n= 18	7 ± 0.9	n= 10	8 ± 1.4
	End Titration	n=18	6 ± 0.7	n=10	2 ± 0.6
	0.5 Hr. Post Titration	n=17	6 ± 0.9	n=10	3 ± 0.6
	1.0 HR. Post Titration	n=17	7 ± 1.0	n=10	4 ± 0.4
	2 HR. Post Titration	n=17	7 ± 1.0	n=10	4 ± 0.5
	2 Hr Post Infusion	n=18	6 ± 0.6	n=10	6 ± 1.5
CO	Baseline	n= 17	3.9 ± 0.21	n= 10	3.9± 0.26
	End Titration	n=17	5.4 ± 0.37	n=10	4.2 ± 0.21
	0.5 Hr. Post Titration	n=16	5.6 ± 0.40	n=10	4.5 ± 0.28
	1.0 HR. Post Titration	n=16	5.6 ± 0.35	n=10	4.6 ± 0.25
	2 HR. post Titration	n=16	5.7 ± 0.38	n=10	4.6 ± 0.27
	2 Hr Post Infusion	n=17	4.5 ± 0.20	n=10	4.7 ± 0.34
CI	Baseline	n= 17	2.0 ± 0.09	n= 10	2.1± 0.14
	End Titration	n=17	2.8 ± 0.16	n=10	2.2 ± 0.09
	0.5 Hr. Post Titration	n=16	2.8 ± 0.17	n=10	2.3 ± 0.11
	1.0 HR. Post Titration	n=16	2.8 ± 0.15	n=10	2.4 ± 0.11
	2 HR. post Titration	n=16	2.9 ± 0.16	n=10	2.4 ± 0.13
	2 Hr Post Infusion	n=17	2.3 ± 0.10	n=10	2.5 ± 0.19
SV	Baseline	n= 17	47.9 ± 3.08	n= 10	48.2± 1.56
	End Titration	n=17	57.1 ± 4.08	n=10	46.6 ± 2.12
	0.5 Hr. Post Titration	n=16	57.3 ± 3.88	n=10	48.0 ± 2.15
	1.0 HR. Post Titration	n=16	57.3 ± 3.40	n=10	49.6 ± 1.97
	2 HR. Post Titration	n=16	58.4 ± 3.81	n=10	49.6 ± 2.48
	2 Hr Post Infusion	n=17	46.9 ± 2.17	n=10	50.8 ± 2.47
SVI	Baseline	n= 17	3.9 ± 0.21	n= 10	3.9± 0.26
	End Titration	n=17	5.4 ± 0.37	n=10	4.2 ± 0.21
	0.5 Hr. Post Titration	n=16	5.6 ± 0.40	n=10	4.5 ± 0.28
	1.0 HR. Post Titration	n=16	5.6 ± 0.35	n=10	4.6 ± 0.25
	2 HR. Post Titration	n=16	5.7 ± 0.38	n=10	4.6 ± 0.27
	2 Hr Post Infusion	n=17	4.5 ± 0.20	n=10	4.7 ± 0.34
SWI	Baseline	n= 17	31.6 ± 1.16	n= 10	34.5± 1.37
	End Titration	n=17	29.0 ± 1.36	n=10	26.9 ± 1.18
	0.5 Hr. Post Titration	n=16	28.1 ± 1.22	n=10	27.0 ± 0.45
	1.0 HR. Post Titration	n=16	28.1 ± 1.14	n=10	26.9 ± 0.57
	2 HR. Post Titration	n=16	29.6 ± 1.34	n=10	27.3 ± 1.59
	2 Hr Post Infusion	n=17	25.5 ± 1.16	n=10	28.5 ± 2.24
SVR	Baseline	n= 17	2151 ± 156	n= 10	2183± 182
	End Titration	n=17	1216 ± 103	n=10	1600 ± 106
	0.5 Hr. Post Titration	n=16	1150 ± 106	n=10	1505 ± 129
	1.0 HR. Post Titration	n=16	1124 ± 100	n=10	1379 ± 107
	2 HR. Post Titration	n=16	1139 ± 101	n=10	1366 ± 91
	2 Hr Post Infusion	n=17	1453 ± 95	n=10	1413 ± 119
PVR	Baseline	n= 17	195 ± 15	n= 10	170± 17
	End Titration	n=17	172 ± 18	n=10	153 ± 15
	0.5 Hr. Post Titration	n=16	152 ± 11	n=10	152 ± 20
	1.0 HR. Post Titration	n=16	154 ± 12	n=10	144 ± 21
	2 HR. Post Titration	n=16	155 ± 13	n=10	143 ± 18
	2 Hr Post Infusion	n=17	168 ± 15	n=10	133 ± 17

The pulmonary shunt fraction increased for both nipride and fenoldopam both at the end of titration and 2 hours post-titration, with return to baseline 2 hours post-infusion.

[comment: If you accept the data from the study-despite the lumping together of the pilot and comparative studies, there appears to be differences both in magnitude of effect for Fenoldopam and Nipride on hemodynamics. The data are confounded both by the hemodynamic changes that occur post surgery as well as the use of concurrent therapies].

Safety: There were no deaths, either on therapy or within thirty days of the study. No subject withdrew.

There were three adverse events during the study- two on fenoldopam and one in the nitroprusside group. The three events were bradycardia, one day post-infusion (n=1); hyperglycemia (n=1); on fenoldopam and 1 episode of pulmonary edema 1 day post therapy (n=1) on nitroprusside. All recovered.

During the infusion regimen 16/18 of the fenoldopam and 7/10 of the nifedipine subjects had diastolic blood pressures (at least 1 reading) of < 60 mm Hg. 5/18 of the fenoldopam and 3/10 on the Nipride subjects had DBP < 60 mm Hg during the 2 hour observation period. 4/18 fenoldopam and 3/10 fenoldopam had DBP < 60 mm Hg within 24 hours of the infusion.

Vital signs of concern are shown below:

Table 4. Hemodynamics Study A50

Parameter	Phase During Study	Fenoldopam	Nipride
Low DBP (< 60 mm Hg)	Titration/Infusion	16/18	7/10
	Post Infusion	5/18	3/10
	24-hours	4/18	2/10
Low SBP< 100 mm Hg	Titration/Infusion	10/18	3/10
	Post Infusion	5/18	2/10
	24-hours	6/18	2/10
Pulse < 60	Titration/Infusion	2/18	0/10
	Post Infusion	2/18	0/10
	24-hours	2/18	2/18
Pulse > 120	Titration/infusion	1/18	1/10

[Comment: The usual definition of tachycardia is 100 BPM and not 120 BPM. Since the mean pulse during the infusion phase was > 100 BPM, it is likely that most of the subjects were at least intermittently tachycardic either while on fenoldopam or Nipride.]

Laboratory:

Below are the patients who had laboratory values defined as of concern to the sponsor. Since all subjects were status post-cardiac surgery it is unclear whether the values measured were due to infusion regimen or a consequence of the cardiac surgery.

Table 5. Abnormal Laboratory Values either on Infusion or after Infusion Study A50

	Fenoldopam			Nipride		
Parameter	Patient #	Pre-Tx Value	Greatest or Least Value	Patient #	Pre-Tx Value	Greatest or Least Value
Hemoglobin (g/dl)	#6	10.8	9.5			
Platelets /nl	#4	112,000	91,000	#110	117,000	63,000
	#111	200,000	93,000			
	#120	103,000	93,000			
WBC /nl	#116	12.6	21.0			
BUN(mmol/L)	#109	7.4	14.8	#110	7.8	11.5
				#113	5.3	12.2

ASAT/SGOT (u/l)	#3 #103	23 23	42 68	#106 #115	7.8 5.3	11.5 12.2
Alkaline Phosphatase u/l	#114	ND	341			
CO2 (meq/l)	#6 #116	ND ND	38 19.1			
Potassium (meq/l)	#104	4.6	3.3			
Sodium (meq/L)	#118	134	129			

[comment: Since there was no convincing information to assert the values post-surgery were stable and also in the absence of a better description of the surgery and interventions it is impossible to attribute any laboratory intervention to infusion intervention.]

Conclusion: The sponsor combines the results of a Fenoldopam pilot study with that of a positive controlled-nitroprusside study in the control of blood pressure post-cardiac surgery. It is unclear what component of the blood pressure change represents drug action and what component represents the rapid decrease in blood pressures that occurs after surgery. Even shortly after therapy, with withdrawal of both medications, the blood pressure did not budge. Of course, concurrent medications were allowed. Nevertheless the lack of a sustained time course of drug effect argues that a substantial portion of the decrease in blood pressure is not therapy related.

The invasive hemodynamics seemed to differ between the fenoldopam and nitroprusside groups despite the appearance of nearly equivalent effect on blood pressure. Whether the differences between treatments is an artifact of the combining of two different protocols (the pilot and comparable study) or is real is a matter of conjecture.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY

Study B89

Title of Study: Multicenter Open-Label Trial of Intravenous Fenoldopam in Patient with Severe Hypertension

Investigator and Site:

Dr. Mau Chang
Veterans General Hospital
Cardiology
Taipai, Taiwan

Dr Shou Wong
Queen Elizabeth Hospital
Kowloon, Hong Kong

Date of Study: First subject enrolled on 15 February 1989 and last on 20 February 1990.

Protocol, line Listings of Data and CRFs were not submitted.

Type of Study: This is a two-centered, uncontrolled, open labeled, foreign study in subjects with excessive blood pressure.

Formulation: Fenoldopam Mesylate , Formula 11, Batch 24F, 27F, 28F, and 30F) supplied as 10 ml glass vials.

Protocol: Subjects of either gender, between the age of 21-75 years old, with diastolic blood pressures of between 120-170 mm Hg (average of three readings) were eligible for enrollment. Subjects were excluded if they were pregnant or lactating or had history of uncontrolled or malignant arrhythmias; concurrent medical problems (hematologic, renal status post transplant) or concurrent or recent use of confounding medications (phenothiazine, dopamine antagonists dopamine agonists, experimental medications, immunomodulators including corticosteroids, cyclosporine or azothialprine).

The study consisted of 6 phases these are descriptively defined in the table below (Table 1):

The outcomes of subjects were categorically classified as success, partial success or failure, with the definitions as follows:

Success- A subject who at the end of the 6-hour maintenance period had a reduction in DBP to less than 110 mm Hg, if the baseline value was between the closed intervals of 120-150 mm Hg or if the baseline DBP was > 150 mm Hg a 40 mm Hg drop. A success was also defined for less of the above effect, if based on the judgement of the investigator further reduction was unsafe.

Partial Success- Less of a blood pressure effect than success not limited because of caution of the investigator.

Failure: Within 118 hours of starting infusion, demonstrated an inadequate therapeutic

response that required termination of infusion and initiation of other acute antihypertensive medication, or that required termination due to drug-related adverse events prior to achieving protocol specified blood pressure reduction and 6-hour maintenance infusion.

Table-1 Specifics of Study B89

Stage	Duration	Criteria	Dosing	Concurrent Rxs?
Screening	6-hours prior to infusion	informed consent, history, laboratory test, X-Ray, ECG and PE.	None	Must be discontinued prior to infusion - How much prior?
Baseline	Within 1 hour of infusion	Entry criteria[1]	None	Furosemide allowed 2 doses at 1 hour intervals
Infusion or p-Up-Titration	< 18 hours	If baseline DBP > 120 m Hg then must decrease to 110 mm Hg. If > 150 m Hg must decrease > 40 m Hg. DBP must however must be > 95 mm Hg.	0.1 ug/kg/min, with increases at > 20 min. Maximum change 0.1 ug/kg/min. Maximum Dose 2 ug/kg/min	None
Maintenance	Between 6-24 hours. Blood pressure to be maintained-Criteria for stability of BP not stated.	Not Stated	Could be adjusted up or down at discretion of investigator.	None
Down-Titration	Started less than 36 hours after Titration. Duration between 4-12 hours	None Stated.	Infusion decreased by 25% at 1/2-3 hour intervals	oral antihyperten-sives and or oral or iv diuretics allowed.
Post-titration	48 hours post termination of infusion	None Stated	None	Any

[1] Baseline value defined as the average of 3 measurements done within 1 hour of infusion.

[comments:
1. The fact that subjects were available for screening 6-hours prior to the start of the infusion suggest they were stable hypertensives and were not of the emergent variety.

2. The criteria used by the investigator to limit further decrease in BP and, therefore, declare a subject as a success is unclear.

3. By the above definitions a drop in BP of 5 mm Hg would be considered a partial success.

4. No specific criteria were given to define the length of the infusion and maintenance period. It appears that infusions could be stopped just as a single efficacy measurements achieved the success DBP.]

Baseline labs were collected within 6-hours of initiation of treatment and included

hematology, blood chemistry urine analysis. Baseline physical and fundoscopic exams were also done within 6 hoursof the study. As far as I can tell the table below captures the timing of these safety analysis.

Table 2. Timing of Interventions Study B89 (Mean ± SEM)

	Screening	Baseline	Titration	Maintenance	Down-Titration	Post-Infusion
Hematology	Yes		Q 12 h	Q 12h	Q12h	Q12h
Chemistry	Yes		Daily	Daily	Daily	Daily
Urine Analysis	Yes		Daily	Daily	Daily	Daily
Cardiovascular, PE, fundoscopic and 12-lead ECG	Yes		Once???			Daily x 48 Hours

Results: 16 subjects from two sites were enrolled. All but two subjects were enterred from one of the study sites. The demographics are as shown below:

Table 3. Demographics

Sex	Age	Weight	Race
11M/5F	49.6 ± 3.2	64.4 ± 3.5	16 Asian

Among those enrolled, all had a history of hypertension, 7 had a history of severe hypertensive episodes, 4 had a history of cardiovascular disease and 3 had a history of minor stroke.

The maximum dose that individuals received is not easily found. Based on the data from Table 4, 10/16 subjects had their maximum dose between 0.1-0.39 ug/kg/min. The median successful dose was 0.25 ug/kg/min.

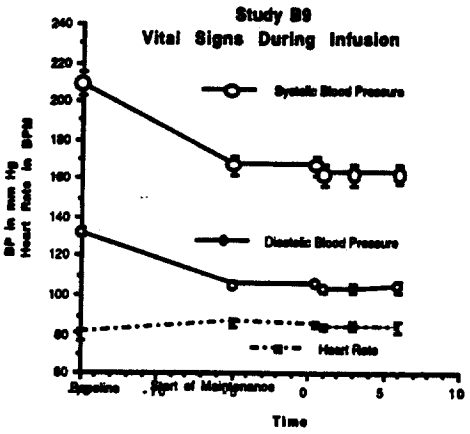
The sponsor sites 13/16 enrolled subjects as successes, 2/16 as partial successes and 1/16 as a treatment failure. The one failure was a subject whose blood pressure was persistently below 90 mm Hg at doses of 0.1 ug/kg/min.

The blood pressure response during the titration phase is not supplied. Both diastolic and systolic blood pressures are decreased from the baseline phase during the maintenance phase. Heart rate is modestly increased (note: the data is derived from sponsors tables 9, 10 and 11 vol 54 pp 66-68. It is unclear why the sponsor limited the data presentation to these time points, since measurements were performed at least every 30 minutes).

For 12/16 subjects, no dosing change was made during the maintenance phase.

[comment: There are clearly several subjects whose diastolic blood pressure are either unstable in that they oscillate substantially. There are several other subjects whose blood pressure continued to decrease upon entering the maintenance phase].

Figure 1.



During the down titration phase (data not shown), the sponsor tabulates data at times 0.5, 1 , 2, 3 and 4 hours. There did not seem to be any lessening of effect during this period of time, with DBP decrease of approximately 32 mm Hg, systolic blood pressures decreased approximately 60 mm Hg. Heart rate did not increase. [Comment: The stability of the bllod pressures during this phase is rather surprising since fenoldopam is being withdrawn at this stage. It is, however possible that the ongoing use of oral medication has kicked in. No data is provided as to concurrent therapies during this period.

During the post-infusion period there was marked stability in blood pressures. Diastolic blood pressure remained approximately 35 and systolic 65 mm Hg below baseline. Heart rate dropped approximately 5 BPM over the 48 hour post-infusion time (Data not shown).

Safety:

No deaths occurred during the infusion phase of the study. One subject, however, died 8 days after the infusion. This subject after discharge, complained of chest pain and then collapsed and died before arrival at the hospital without regaining consciousness . The presumed diagnosis was aortic dissection (there did not appear to be an autopsy). One subject was withdrawn from the study for low blood pressure (88 mm Hg that persisted for 15 minutes). The sponsor claims all the adverse events were mild/moderate in severity.

Table 1.Adverse Events Study B89

	On Therapy	Post Therapy
Cardiovascular	(#1)-Decreased blood pressure (#42) Orthostatic hypotension	(# 31) Supraventricular tachycardia
Gastrointestinal	(# 38) Vomiting (#31) Nausea and Vomiting	
General Body	(#31 and #35) Headache	
Hematological	(# 36) Anemia (# 31, # 34, # 38, # 41 and # 43) Leucocytosis	(# 41) Anemia (# 35) Other (#33) Leukopenia (# 39) Polycythemia (# 41) Thrombocythemia

Metabolic	(# 31, # 40 and # 44) Decreased K+ (# 37 and # ???) Elevated transaminase /LDH (# 39) Alkaline phosphatase (# 37) Azotemia (# 39) Bilirubinemia	(# 35, # 35, # 38 amd # 3 9) Azotemia (# 42 and # 43) Bilirubinemia (# 33) Increased BUN (#2) Decreased K+
Nervous/Sense	(3 31, # 35, # 35 and # 37) Insomnia	(#35 and # 3 6) Anxiety
Genitourinary		(# 31) Urinary casts/WBCs (# 41) Urinary Tract Infection

Abnormal vital signs (per sponsor):

The sponsor claims no patients had low (< 100 mm Hg) systolic or diastolic (< 60 mm Hg) blood pressures . One patient had both a low pulse rate (<60 BPM) and a sponsor defined high pulse rate (> 120 BPM). Four patient were bradycardic post-therapy.

Laboratory: The laboratory values that were abnormal and reached the sponsor's stipulated level of concern, whether these values occurred on therapy or post therapy are tabulated below. Of note, one subject developed hypokalemia, 4 developed acidosis and 3 developed elevated BUN values.

Table 4. Abnormal Laboratory Parameters.

Parameter	Pt #	Pre-Tx	Post Tx
Hgb (g/dl)	#35	13.6	11.7, 11.2
	#36	12,8	11.2, 11.5
K+ (meq/L)	#44	3.8	3.2, 3.3
BUN mg/dL	#33	24	43
	#35	17	32
	#37	20	31

Parameter	Pt #	Pre-Tx	Post Tx
CO_2 (mmol/L)	#2	28	18
	#38	24	19
	#40	22	19
	#43	26	19
Fasting Glucose	#34	88	150
Bilirubin (mg/dL)	#39	1.5	2.0
	#42	1.5	1.7
	#43	1.4	2.0

Discussion:

This was essentially a single-center study (two subjects were enrolled from a Hong Kong study site) in subjects with high blood pressure that were apparently sustaining no on-going end-organ damage. The study was, furthermore, only baseline controlled.

With respect to the end-point there was a large degree of arbitrariness to the determination of success. The duration of each of the phases was arbitrarily long and not prespecified so that the end-point at which efficacy was defined could be declared at a single nadir of blood presssure measurment.

In summary, although this study did not prove that fenoldopam is antihypertensive it is certainly consistent with that capability. Neither the dose range duration of action any effect during fenoldopam treatment cannot be drawn from this study.

Study A 52

Vol 54 pp 128-144

Title of Study: A Multi-center, Open, Uncontrolled Trial of Intravenous Fenoldopam in Patients With Severe Hypertension.

Investigator and Sites:

Table 1. Investigators Study A52		
Prof. Arnaldo Libretti University of Milan Milan, Italy	Prof. Domenico Riva Desio Hospital Desio, Italy	Prof Renato Beretta Legnano Hospita; Legnano, Italy
Prof. Alessandro Salvadea Fondazione Clinica Del Lavoro, Pavia, Italy	Prof. Giuseppe Maschio Borgo Trento Hospital Verona, Italy	Prof Calogero Ospedale degil Infemi Biella, Italy

Study Design: Open-label, Multicenter, European study.

Formulation: Fenoldopam mesylate/Vial batches nos 24 F Lot 1 and 27 F lot 1.

Dates of Study: First subject enrolled 10 October 1988 and last on 22 December 1989.

Protocol, Line Listings , Amendments and CRFs were not included.

Protocol: Subjects of either gender, between 20-70 years old with severe hypertension (DBP between 120-150 mm Hg) measured 30-60 minutes prior to the beginning of the infusion were enrolled into the study. Specifically excluded, were subjects with concurrent cardiovascular disease [CHF-NYHA Class III-IV; malignant ventricular arrhythmias, unstable angina, recent MI and/or CVA (within 3 months)] malignant retinopathy, renal disease or post renal-transplant, use of proscribed medications (phenothiazine, dopamine agonists, catecholamines, recent investigational medications).

All concurrent antihypertensive medications were to be stopped at least 12 hours before the infusion.

The study consists of several stages as outlined below (See Table 1):

The sponsor analyzed the outcomes as a categorical variable, with the possible outcomes categories listed below:

Success- A subject who at the end of the 6-hour maintenance period had a reduction in DBP to less than 110 mm Hg if the baseline value was between the closed intervals of 120-150 mm Hg or if the baseline DBP was > 150 mm Hg had a 40 mm Hg decrease. A success was also defined for less than this effect, if based on the judgement of the

investigator, further reduction was unsafe.

Table 1. Description of Study A52

Stage	Duration	Criteria	Dosing	Concurrent Rxs?
Screening	within 12-hours prior to infusion	informed consent, history, PE including fundoscopic exam. recent therapies, laboratory test, X-Ray(optional) and ECG.	None	Must be discontinued 12-hours prior to infusion -
Infusion or Up-Titration	Less than 7 hours	If baseline[1] DBP > 120 and <150 mm Hg then must decrease to 110 mm Hg. If > 150 m Hg must decrease > 40 m Hg. DBP must however must be > 90 mm Hg during the infusion.	0.1 ug/kg/min, with increases at > 30 min. Maximum change 0.1 ug/kg/min. Maximum Dose 1.5 ug/kg/min	None
Maintenance	Maximum 6 hours	Not Stated	Could be adjusted up or down at discretion of investigator.	None
Post-Treatment	48 hours post termination of infusion	None Stated	None	Could be left without therapy up to 12 hours-at investigator's discretion.
Follow-Up	7-10 days post therapy	Interim History and Exam	None	Yes

[1] Baseline value defined as the average of 3 measurements done within 1 hour of infusion.

Partial Success- Less of a blood pressure effect than success, not limited because of investigator concern.

Failure: Within 7.5 hours of starting infusion demonstrated an inadequate therapeutic response that required termination of infusion and initiation of other acute antihypertensive medication.

Results:

A total or 22 patients were enrolled into the study, 10 males and 12 females. The age ranged from 30-69 years old with a mean(± SE) weight of 74 (± 16) Kg.

As per sponsor, all patients except one reached the goal blood pressures. That one patient was discontinued due to sinus tachycardia.

The dose of fenoldopam during the maintenance infusion ranged from 0.1-0.8 ug/kg/min (Not further broken down in the study report).

Table 2

	Baseline	End Titration	1 Hour	2 Hour	3 Hour	4 Hour	6 Hour	24 Hour	48 Hour
DBP	129± 10	97 ± 7	96±7	96 ±6	96 ± 8	97 ± 8	97 ±10	114 ±14	104 ±12
SBP	219 ±28	165 ±23	162 ±17	158 ±14	156 ± 13	155 ±13	156 ± 15	182 ± 25	170 ±21
Heart Rate	81 ±14	89 ±15	90 ±16	88 ±16	88 ±16	88 ± 15	86 ± 12	77 ± 11	79 ± 13

Safety: One subject discontinued the study because of a transient episode of sinus tachycardia.

One subject discontinued due to asymptomatic episode of inferior myocardial ischemia 6 hours after the beginning of the infusion. This subject also had premature atrial contractions beginning 8 hours after the end of infusion. CPK and LDH were within normal limits.

One subject experienced a transient aphasia with a CT scan that disclosed a small intracranial hemorrhage in the temporal region. This event occurred 2 1/2 hours after the start of the infusion.

Other adverse events were headaches (7 patients) with associated flushing in (4 patients) nausea and vomiting (1 patients) and hypokalemia (2 patients).

Comments; This was a modest sized study in subjects with severe hypertension. The nature of that hypertension cannot further be classified as urgent or emergent in nature. The data is consistent with an effect of fenoldopam in decreasing blood pressure and concomitant increase in heart rate.

There were three adverse events of note 1 subject with sinus tachycardia, 1 subject with cardiac ischemia (on ECG) and one subject with a documented temporal lobe stroke.

APPEARS THIS WAY
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Study B1101

vol 54 pp-145-160

Title of Study: Efficacy and Hemodynamics and Fenoldopam Infusion in Patients with Hypertensive Crisis.

Investigators and Sites: Dr. H. P. Schuster
Städisches Krankenhaus
Hildesheim, Germany

Brief Summary:

A total of 12 subjects (5 M/7F) were studied. These subjects had a mean age of 66 years (range 43-83). The subjects were, moderate-severe hypertensives with 9 subjects having DBP of between 100-119 mm Hg and 3 between 120-140 mm Hg. Systolic blood pressure ranged from 200-245 mm Hg.

The starting infusion dose, as pre-specified was 0.2 ug/kg/min, the dose was increased until the blood pressure decreased to < 170/110. The average maximum dose was 0.41 ug/kg/min. The duration of infusion ranged from 54- 95 minutes. The maximum heart rate during the infusion for each individual is not discernable from the information that was submitted. The average (over several readings) heart rate was over 100 beats/minute, in 3 of the 12 subjects.

Safety: The study report notes no safety events occurred.

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Study # 239

Vol 54 pp. 161-186

Title of Study : Investigation of the Effect of Fenoldopam and Placebo on Intraocular Pressure in Patient with Elevated Intraocular Pressure.

Investigator and Sites: Daniel E. Everitt
Department of Medicine
University of Pennsylvania School of Medicine

The protocol, line listings, amendments and CRFs were not submitted.

Protocol: This was a two-period, crossover study in which subjects of either gender, older than 18 years old, who weighed over 50 Kg and were within 30% of their ideal weight were weaned off intra-ocular medication. Those subjects with subsequent intraocular pressures between 21 and 30 mm Hg were randomized to receive either fenoldopam or placebo. After a seven day washout period, subjects were crossed-over to be receive the alternate treatment. Specifically excluded were those subjects with a history of laser trabeculoplasty or intraocular surgery, a history of significant ocular trauma or infection, the presence of orbital or intracranial pathology, pigment dispersion of pseudo exfoliation syndromes, abnormality of the irido-corneal angle, a cup/disc ration of > 0.7 in either eye, visual defects of more than 15 db outside of reference limits (age matched controls) within 10 ° of fixation, or the use of contact lenses on study day 1 or 2.

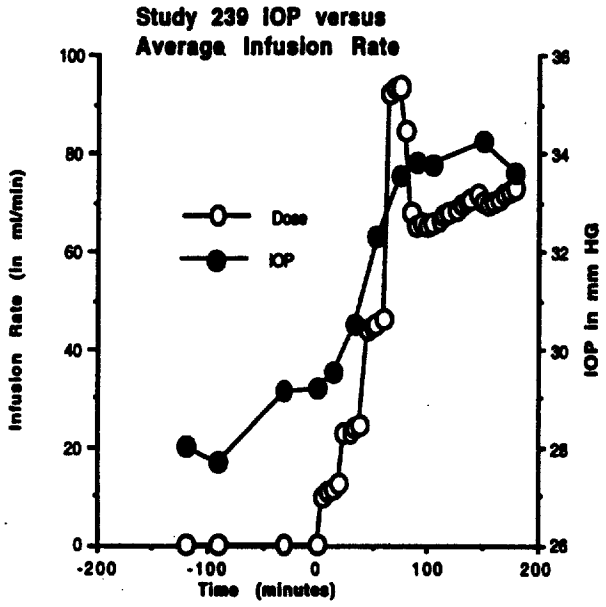
Additional exclusion criteria included pregnancy or lactation confounding medical condition, or recent use of drugs or foods which may effect IOP (use of tobacco, alcohol or caffeine) within 24 hour.

Ocularly active medications were discontinued between 4-21 days prior to establishing eligibility.

Subjects received an infusion of fenoldopam with the initial dose of 0.05 ug/kg/min for 20 minutes which was increased to 0.1, 0.2 and 0.5 ug/kg/min at 20 minute intervals. The highest dose was maintained for 150 minutes. **Supine intraocular pressure measurements** (Eye A) were performed 2 hours prior to the infusion to establish baseline and at 15, 30, 45, 75, 90 , 105, 135, 180 and 210 minutes during infusion as well as 15, 30, 45, 60 and 120 minutes after discontinuing infusion. **Sitting intraocular pressures** were measured in the other eye (Eye B) 1 hour prior to infusion and 2 hours into the infusion. **Fluorophotometry** (Eye B) was performed every 30 minutes for 2 hours prior to the beginning of the infusion and 15, 30, 45, 75, 90, 105, 135, 180 and 210 minute during the infusion. **Computerized automated perimetry** (Eye B) was done 1 hour prior to the infusion and 105 minutes into the infusion. **Blue field exam** (Eye B) were done 90 minutes before and 2 hours after the start of the infusion.

Dose was decreased to the next highest dose or discontinued if the subject developed either a supine heart rate of > 120 BPM, or supine SBP of < 90 mm Hg, or decreased by > 30 mm Hg from the baseline infusion; or supine DBP of < 50 mm Hg or a decrease of > 20 mm Hg or an increase in intra-ocular pressure of > 35 mm Hg.

Results: Thirteen subjects were enrolled into the study. Five subjects prematurely discontinued the study during the fenoldopam infusion phase because their intraocular pressure readings were greater than 35 mm Hg. None of the subjects discontinued during the placebo phase. The rise in intraocular pressure in all subjects did not respond to a decrease in the infusion rate. Below is a graph of average infusion rate versus intra-ocular pressure for the 12 subjects during fenoldopam infusion. Dose decreases as subjects were cut back or discontinued during the infusion. Not all subjects who had increases in IOP above 35 mm Hg had an acute IOP response to decrease in dose. The mean increase in IOP for fenoldopam exceeded those during the placebo infusion by 6.7 mm Hg (this is the sponsor's conclusion the way the data is handled, however, is not entirely satisfactory). No washout datafor IOP versus concentration is supplied.



Conclusion: There is little doubt that fenoldopam increases intra-ocular pressure. In some subjects IOP increases did not immediately respond to decrements or cessation of fenoldopam infusion.

Study A9903

Vol 54 p 187-229

Title of Study: A Double-Masked, Placebo-Controlled Crossover Study of the Effect of Intravenous Fenoldopam on Intraocular Pressure.

Investigators and Site: Jody R. Pitz-Seymour M.D.
Scheie Eye Institute
Presbyterian Medical Center
Philadelphia, PA

Daniel E. Everitt, M.D.
Smith Klein Beecham Clinical Research Unit
Presbyterian Medical Center
Philadelphia, PA

The study site was the Presbyterian Medical center of Philadelphia, Philadelphia, PA.

Formulations: . (fenoldopam mesylate) 100 mg/10 ml (Lot # 881 62). The formulation was reconstituted in 5% Dextrose in water so that the final fenoldopam concentration was either 20 ug/ml or 50 ug/ml.

Protocol, Amendments, and CRFs were not submitted. Some, but not all, of the line listings were included.

Protocol Design: This was a double-blind, four period, balanced, cross-over study. The subjects received 2-hour infusions of placebo and each of three different doses of fenoldopam (0.2, 0.5 and 1.0 ug/kg/min).

[comment; Although the protocol claims double blinding, the amount of fenoldopam differed at each portion of the cross-over phase either as judged by the volume that was infused or the concentration used to formulate the infusion. At the minimum the pharmacist or who ever prepared the infusions was unblinded to the specific infusion.]

Protocol: A total of twelve healthy male subjects between that ages of 18-50 were enrolled. Subjects were excluded if they had any of several ophthalmologic disorders such as: prior intraocular surgery, refractive error of more than 4 diopters of sphere or 2 diopters of cylinder, IOP more than 21 mm Hg with Goldmann applanation tonometry in either eye or a difference of more than 2 mm Hg between the two eyes, history or suspected glaucoma, cup to disc ration exceeding 0.6 in either eye, visual field defect on Goldmann perimetry examination, abnormality of anterior chamber angle, use of topical ophthalmic medications within two weeks of screening or other significant intraocular or orbital pathology.

Subjects were screened 30-days prior to enrollment which included history, physical examination, ophthalmic examination (refraction, perimetry, external and slit lamp examination, gonioscopy, Goldmann visual field examination and dilated fundoscopic exam), ECGs and baseline laboratory evaluations.

Subjects were started on one of the infusions with premature discontinuation

predicated on tachycardia (> 150 BPM [comment-150 BPM????], hypotension (SBP < 80 mm Hg). Dose adjustment was not permitted. IOP measurements were performed with a Perkins hand-held tonometer after local anesthesia. All subsequent IOP measurement were performed on the same eye (randomly assigned and designated Eye A) in the supine position. Five measurements were performed during the pre-infusion period during each phase of the study. The first of these measurements were performed in the sitting position bilaterally and was discarded. The second and third measurements were averaged to define the sitting baseline IOP measurements. The fourth and fifth IOP were performed in EYE A, 15-20 minutes after the subject was reclined and averaged to define the baseline supine IOP.

During the infusion, the IOP was measured at 20, 40, 60, 80, 100 and 120 minutes after the start of the infusion. Sitting IOP measurements were also measure in Eye A at 40, 80 and 120 minutes after the start of the infusion in Eye A. Gonioscopy and tonography were performed in Eye B at 120 minutes.

Subjects remained supine for 1 hour after study medication and remained an additional 2 hours in the Clinical Research Unit during which time vital signs were measured.

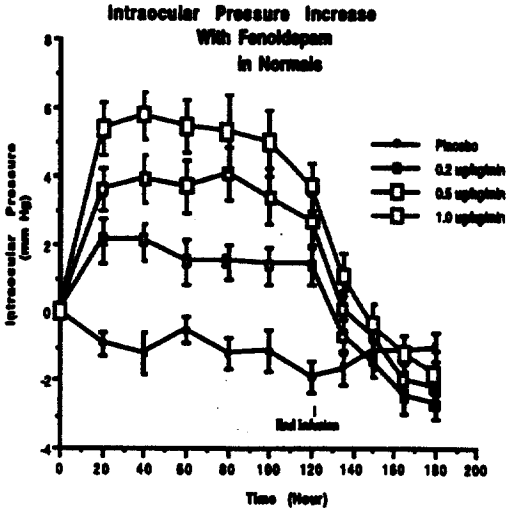
Results: A total of thirteen subjects were enrolled into the study, of which 12 received active medication. One subject discontinued before the infusion because the subject could not tolerate tonometry.

The demographics of those enrolled are shown below (mean ± SD):

Table . Demographics study A 9903.

Age	Body Weight	Height
25 ± 6 (range 20-38)	73.1 6.8 (Range 63.4-86.5)	1.76 ± 0.05 (Range 1.65-1.81)

Figure 1



The change in the intraocular pressure for the 12 evaluable subjects (mean ± SEM) are shown (Figure 1) The mean baseline IOP measurements at the different infusion days ranged from 13.6-14.1 mm Hg. At least for these patients with normal intraocular pressure at baseline, the increases in these pressures on fenoldopam are related to dose of drug, though this effect is not linear. Doubling the rate of infusion from 0.5 to 1.0 ug/kg/min had only a 60% increase in the IOP increase over baseline.

The effect on fenoldopam on IOP was rapid in onset and nearly equally as rapid in the offset. By 30 minutes after the cessation

of the infusion, there were no differences between the IOP changes in the active infusion groups from placebo.

Figure 2

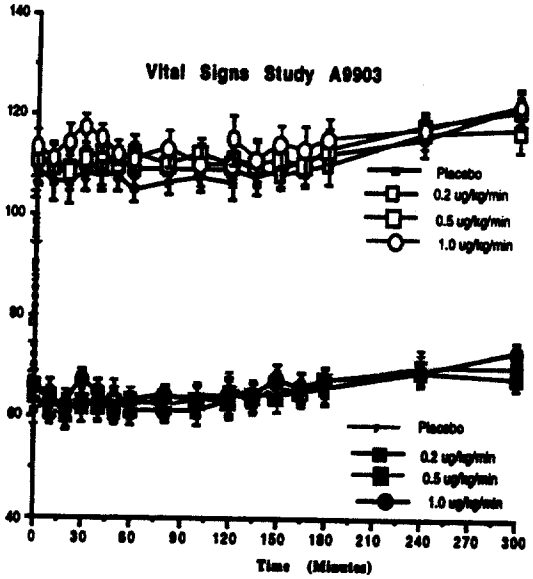
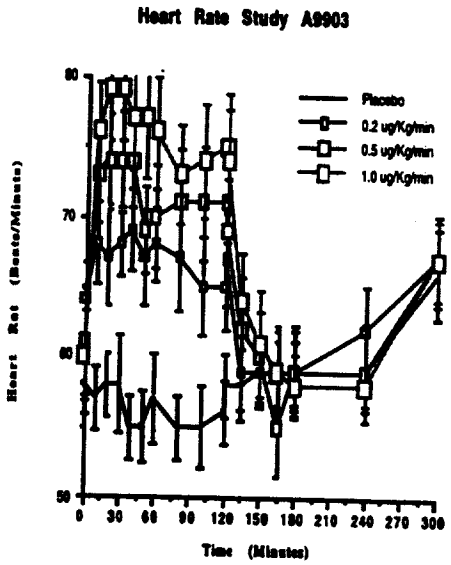


Figure 3



The effect of fenoldopam in sitting IOP were similar to those of the supine IOPs.

The infusion did not substantially modify either supine SBP or DBP. Heart rate, however, increased in a dose related manner and returned to baseline value shortly after the infusion was discontinued.

Safety: There were no deaths or serious adverse events. Five of the 12 subjects had new onset adverse events during infusion. The majority of adverse events were headache (3 patients, 4 events); flushing (1 patients, 2 events), heart racing (1 patient, 1 event), nasal congestion (1 subject 1 event), iv infiltration (1 subject 1 event), swelling antecubital space (1 subject, 1 event).

Conclusion: This was a small cross-over study in subjects with normal intra-ocular pressure at baseline, who received 2 hour infusions of placebo or fenoldopam mesylate at doses of 0.2, 0.5 and 1.0 ug/kg/min. When subjects received any of the doses of fenoldopam intra-ocular pressure increased in a dose dependent manner. By 20 minutes after the start of the fenoldopam infusion (the first measurement on treatment), subjects IOP already peaked. Although IOP increases were dose related they were not dose proportional. At a dose of 0.2, 0.5 and 1.0 ug/kg/min were approximately 2, 4 and 6 mm Hg, respectively. Upon termination of the infusion the half-life of decay in IOP was approximately 20 minutes (longer than the kinetic $T_{1/2}$ of fenoldopam of approximately 6 minutes).

Study 87

Vol. 54 pp. 230-278

Title of Study: Double Blind, Randomized, Placebo-Controlled, Assessment of the Hemodynamic Response to Intravenous Infusion of Fenoldopam for Durations Up to 48 Hours/Congestive Heart Failure, NYHA Class III or IV.

Investigator and Site: Dr. Barry F. Uretsky
Division of Cardiology
Presbyterian University Hospital
Pittsburgh PA

Dates: The study was conducted between 4 October 1988 and 31 August 1989.

Formulation: batch IPO #86131

Protocol, line listings and CRF were not supplied.

Protocol Design: This was a placebo-controlled, randomized, dose-titration study.

The study enrolled male or females subjects between 21-80 years old, with females of child bearing potential required to have adequate prophylaxis to prevent conception. These subjects were to be of NYHA Class III or IV (the duration of CHF is not stated nor is the criteria that this degree of CHF be maintained despite adequate therapy). Subjects were excluded if they were pregnant or lactating, had diseases that impede cardiac outflow (valvular heart disease, constrictive or restrictive CHF, primary pulmonary hypertension), clinically significant arrhythmias, subjects requiring assisted ventilation, recent MI or CVA, hypo-or hyperkalemia (<3.5 or > 5.5) and abnormal LFTS. The following medicines were to be discontinued at least 12 hours prior to the beginning of the infusion vasodilators, captopril, calcium channel blockers, beta-blockers, NSAIDS, MAO inhibitors, dopamine agonsits or antagonists. L-amino decarboxylase and enalapril were to be discontinued 5 days prior to the start of the infusion. Investigational new drugs were to be discontinued for at least 5-half-lives.

Subjects were screened with a history, physical exam ECG, X-Ray, vital signs, neurohumoral profile and laboratory assessments. All subjects were admitted to the intensive care unit and continuous ECG monitoring was begun between 6-12 hours before the insertion of the Swan-Ganz catheter. The Swan-Ganz catheter was inserted two hours before baseline hemodynamics were measured. Baseline values were the mean of two measurements 30 minutes apart , with measurements consisting of right atrial pressure, pulmonary artery pressure, PCWP and cardiac output. Baseline required three measurements in which the cardiac output did not differ by more than 15% over a less than 10 minute period. Two PCWP measurements were to be within 5 mm Hg.

Each subjects was randomized to receive either fenoldopam or placebo at an initial rate of 0.1 ug/kg/min with upward titration in dose levels to a maximum dose of 2.5 ug/kg/min. The allowed dose levels were 0.1; 0.3; 0.5; 0.75; 1.0; 1.25; 1.5; 2.0 and 2.5 ug/kg/min. Dose could be modified at the discretion of the investigator. The dose was increased to raise cardiac output until next increase in dose did not further increase cardiac output (± 5%). The penultimate dose tested was considered the "maximal-effect" dose. This "maximal" dose was then infused for 2 hours. Vital signs and hemodynamics were measured after two hours of the optimal/maximal dose. The salt content (Na^+ of 50 meq/day) and timing of meals was strictly controlled.

Subjects completing the 2-hour infusion had an additional 24-48 hours of infusion at the "maximal" rate. Vital signs were measured hourly for eight hours, then every 4 hours till the end of the infusion. Hemodynamics were measured every 2 hours for the first eight hours of this period, then every 4 hours till the end of maintenance. At the end of the maintenance period, vital signs and hemodynamics were measured 30 and 60 minutes. The continuous ECGs were discontinued 60 minutes after the termination of the infusion.

Laboratory assessments included hematology, blood chemistry, neurohumoral profile and urinanalysis. Blood and urine samples for the above analyses were collected prior to the infusion, the end of the two hour infusion, after 24 hours on the maintenance portion of the study and at the end of the study. A 12-lead ECG was recorded at the end of 24 hours of maintenance infusion and 1 hour at the end of the infusion.

Subjects were observed for 24 hours after the termination of the infusion, independent of the duration of the infusion.

The sponsor terminated the infusion for:

Excessive tachycardia (> 30% above baseline or > 125 BPM)
Hypotension (20% decrease in BP or mean BP < 60 m Hg).
Organ hypoperfusion (confusion, angina or oliguria)
Ventricular or atrial arrhythmias
Other adverse event

If the cardiac output did not increase at least 20% above baseline during the 24 hour maintenance period, patients were dropped from the double-blind portion of the study.

Statistical: No primary end-point was stated.

Results: There were at total of 22 subjects enrolled into the study; 18 male and 4 females. Of these, 14 were assigned to receive fenoldopam and 7 to placebo [comment- this does not appear to be a random allocations of patients]. Twelve fenoldopam and 4 placebo patients completed the study. Demographics are tabulated below:

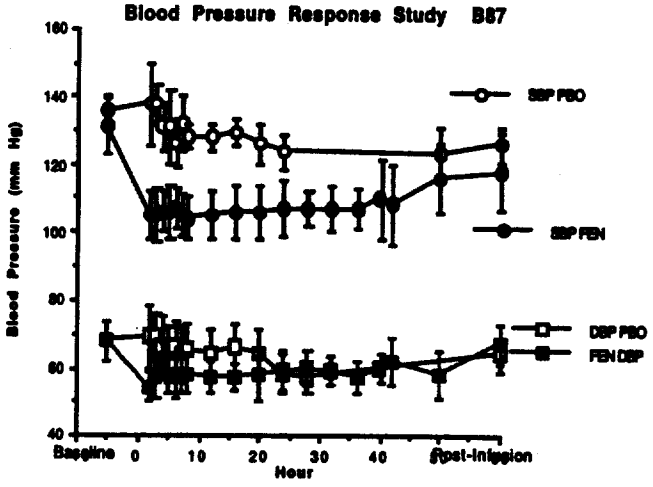
Doses: There is no description of the doses that these subjects received. In particular, there was no information as to when subjects discontinued.

Table 1. Demographics Study B 87

Parameter	AGE[1]	Weight	Gender	Race	NYHA Class	Etiology;
Fenoldopam	59.1 (11.3)	77.81 + 15.7	13 M/1F	13 W/1B	III (6)/IV (8)	CHD =4; CHD + H=1; DC=5; DC + H=2; CHD + DC +H=2
Placebo	7 (8.4)	77.75 + 15	5 M/2F	7 W	III(4)/IV (3)	CHD =2; CHD + H=2; DC=0; DC + H=3; CHD + DC +H=0

[1]Values areMean ± SD; M=Male; F=female; W=Caucasian; B=Black; CHD= Coronary Heart Disease; DC= Dilated Cardiomyopathy; H=Hypertensior

Figure 1



Vital Signs: I've attempted to recreate the blood pressure response in this study (the source of this graph is Sponsor's Figure 2A and 2b vol 54 pp. 265-266). The data in the figure do not include those vital signs that were measured during the titration phase, since the sponsor considered the variability too high. There is an early drop in both systolic and diastolic blood pressures, the curves then gradually converge. Certainly by 20-24 hours there is no difference between the two curves.

Table 2. Diastolic Blood Pressures Study B 87

Mean ± SD	Baseline	4 Hours after Optimal Dose	24 hours after Optimal Dose	1 hour post-infusion
Fenoldopam	83.1 ± 12.5	91.1 ± 17	85.1 ± 13.7	83.9 ± 16.4
Placebo	80.0 ± 6.7	80 ± 8.1	81.2 ± 9.0	81.6 ± 9.5

Only sketchy heart rate data is supplied. There appears to be little or no changes in heart rate for the placebo group. For the fenoldopam group, at 4 hours into the optimal dose infusion, the heart rate increased by 8 BPM. At 24 hours into this infusion, there appears to a diminution of this heart rate increase.

Table 3. Vital Signs which the sponsor defined as of concern.

Parameter	Fenoldopam (n=14)	Placebo (n=7)
SBP < 100 mm Hg	#3, #4, #7, #10, #15, #18, #21, #34	
DBP < 60 mm HG	#1, #3, #4, #5, #7, #9, #10, #14, #15, #16, #18, #21, #34	#6, #8, #12
Heart Rate > 120 BPM	#5, #10.	
Heart rate < 60		#6

Not surprisingly more fenoldopam than placebo subjects had lower blood pressure and increases in heart rate. The definition of tachycardia is not traditional in that it required a value of > 120 BPM.

Hemodynamics: The sponsor did not submit the results of the hemodynamic measurements.

ECG results: The values of the intervals derived from the ECGs are shown below (mean ± SD). Unfortunately, the table does not include all subjects. For the fenoldopam group the numbers represent the mean of between 10-14 subjects, for placebo between 3-7 subjects. Heart rates increased for the fenoldopam during the optimal dose stage of the infusion by approximately 8 BPM. None of the intervals in the small study seem to significantly change.

Table 4. ECG results Mean ± SD

ECG results:	Atrial Rate		Ventricular Rate		PR Interval		QRS Interval		QT interval	
	FEN	PBO	FEN	PBO	FEN	PBO	FEN	PBO	FEN	PBO
Screening	81.9 ± 16	78 ± 10	80.3 ± 14	76.4 ± 9	0.19 ± 0.03	0.19 ±0.03	0.13 ± 0.04	0.15 ±0.05	0.39 ± 0.06	0.43 ± 0.06
Assessment A	88.9 ± 11	80 ± 13	89.5 ± 17	79.6 ± 12	0.18 ±0.02	0.18 ±0.02	0.13 ± 0.04	0.14 ±0.04	0.38 ±0.05	0.41 ±0.05
Assessment B	79.9 ± 12	88.0 ± 9	81.2 ±13.2	88 ± 9	0.18 ±0.02	0.18 ± 0.01	0.14 ± 0.05	0.13 ± 0.03	0.39 ±0.08	0.38 ± 0.04
post Treatment	80.1 ± 13	79.7 ± 5	80.3 ± 12	78 ± 6	0.18 ± 0.020	0.18 ± 0.02	0.13 ± 0.04	0.14 ± 0.04	0.38 ± 0.05	0.41 ± 0.05

Assessment A= "Optimal Dose" infused for 2 hours; Assessment B- 24 hours of optimal or maximal dose; Post infusion: 24 hours after end of infusion

Adverse Events: A total of 27 adverse events were reported in 4/7 placebo and 9/14 fenoldopam treated subjects. Only two events were considered serious; a mental status change in one fenoldopam subject and heart failure in 1 placebo subject.

Below are listed those adverse events that were either considered more than moderate in severity or that reflected some cardiovascular adverse events (aside from headache and flushing).

Table 5. Adverse Events that were Considered Noderate or Greater in Severity

Tx/patient ID	Phase	Description	Severity	Tx/patient ID	Phase	Description	Severity
FEN/00004	< 1 Hr post Tx	Dyspnea	Mild	FEN/00005	Titration < 1 Hr post Tx	AF Dyspnea	Mild Mild
PBO/00006	Baseline	Bradycardia	Mod	FEN/00007	Start Infusion Maintenance post tx >1 but < 24 hours	Dyspnea hypotension Dyspnea	Mild Mild Moderate
FEN/00010	Maintenance	Mental Status Change	Severe	PBO/000012	Baseline Infusion	Dyspnea Heart Failure	Moderate Moderate

Table 9.13: Number and Percentage of Patients in Intravenous Congestive Heart Failure Studies with Test Values of Sponsor-defined Concern or with a Change* from Baseline of Sponsor-defined Concern
(1 of 2)
(Appendix 9.14)

Laboratory Test Combined Data	Baseline (%)	On-therapy (%)	Post-therapy 1-2 days (%)	Post-therapy 3-20 days (%)
Hemoglobin				
<80% lower limit normal	11/107 (10)	14/90 (16)	9/63 (14)	4/22 (18)
>120% upper limit normal	0/107 (0)	0/90 (0)	0/63 (0)	0/22 (0)
-25% change	--	0/88 (0)	1/61 (2)	1/21 (5)
+25% change	--	1/88 (1)	0/61 (0)	0/21 (0)
Total neutrophils				
<1.5 x $10^3/mm^3$	5/83 (6)	1/68 (1)	0/42 (0)	0/4 (0)
-20% change	--	14/65 (22)	9/40 (23)	2/4 (50)
Platelets				
<100 x $10^3/mm^3$	1/103 (1)	5/86 (6)	3/58 (5)	0/19 (0)
-20% change	--	34/82 (41)	18/56 (32)	3/18 (17)
WBC				
<3 x $10^3/mm^3$	1/107 (1)	0/89 (0)	0/63 (0)	0/22 (0)
>20 x $10^3/mm^3$	0/107 (0)	0/89 (0)	0/63 (0)	0/22 (0)
-25% change	--	5/87 (6)	6/61 (10)	4/21 (19)
-25% change	--	26/87 (30)	18/61 (30)	6/21 (29)
Potassium				
<3.0 mEq/L	0/92 (0)	2/88 (2)	0/46 (0)	1/19 (5)
>5.5 mEq/L	2/92 (2)	2/88 (2)	0/46 (0)	0/19 (0)
-25% change	--	8/87 (9)	5/45 (11)	1/19 (5)
+25% change	--	10/87 (11)	1/45 (2)	3/19 (16)
Sodium				
<130 mEq/L	15/93 (16)	15/88 (17)	4/46 (9)	1/19 (5)
>150 mEq/L	0/93 (0)	1/88 (1)	0/46 (0)	0/19 (0)
-10% change	--	0/88 (0)	0/46 (0)	0/19 (0)
+10% change	--	2/88 (2)	0/46 (0)	0/19 (0)
Urea				
>8.3 mmol/L	22/58 (38)	18/42 (43)	17/42 (40)	3/9 (33)
+50% change	--	1/42 (2)	2/42 (5)	2/8 (25)

* Percentages for change from baseline are calculated based on the number of patients with an on- or post-therapy value who also had a baseline value.

Table 9.13: Number and Percentage of Patients in Intravenous Congestive Heart Failure Studies with Test Values of Sponsor-defined Concern or with a Change from Baseline of Sponsor-defined Concern
(2 of 2)
(Appendix 9.14)

Laboratory Test Combined Data	Baseline (%)	On-therapy (%)	-----Post-therapy----- 1-2 days (%)	3-20 days (%)
BUN				
>12.5 mmol/L	15/51 (29)	11/47 (23)	2/16 (13)	2/10 (20)
+50% change	--	1/47 (2)	0/16 (0)	4/10 (40)
Creatinine				
>200% upper limit normal	6/110 (5)	9/89 (10)	1/58 (2)	0/19 (0)
-50% change	--	1/89 (1)	2/58 (3)	1/19 (5)
Alkaline phosphatase				
>200% upper limit normal	10/108 (9)	10/88 (10)	4/56 (7)	1/19 (5)
+100% change§	--	1/87 (1)	0/56 (0)	0/18 (0)
ALAT				
>200% upper limit normal	12/104 (12)	13/89 (15)	5/54 (9)	2/19 (11)
-50% change¶	--	4/84 (5)	4/53 (8)	3/19 (16)
ASAT				
>200% upper limit normal	11/108 (10)	11/88 (13)	6/56 (11)	0/19 (0)
+50% change¶	--	4/87 (5)	5/55 (9)	3/19 (16)
Fasting glucose				
<3.3 mmol/L (59 mg/dL)	1/35 (3)	1/22 (5)	0/27 (0)	0/12 (0)
>7.8 mmol/L (141 mg/dL)	7/35 (20)	9/22 (41)	3/27 (11)	2/12 (17)
-25% change	--	3/15 (20)	6/26 (23)	5/12 (42)
-25% change	--	5/15 (33)	3/26 (12)	2/12 (17)

* Percentages for change from baseline are calculated based on the number of patients with an on- or post-therapy value who also had a baseline value.
§ If Alkaline phosphatase was less than 50 U/L at baseline, the sponsor-defined change from baseline was 200%; if the value was greater than 50 U/L at baseline, the sponsor-defined change from baseline was 100%.
¶ If ALAT/ASAT was less than 25 U/L at baseline, the sponsor-defined change from baseline was 200%; if the value was greater than 50 U/L at baseline, the sponsor-defined change from baseline was 50%.

Table 9.15: Number and Percentage of Patients in Intravenous Studies Other than Hypertension or Congestive Heart Failure with Test Values of Sponsor-defined Concern or with a Change from Baseline of Sponsor-defined Concern
(1 of 2)
(Appendix 9.17)

Laboratory Test Combined Data	Baseline (%)	On-therapy (%)	-----Post-therapy----- 1-2 days (%)	3-20 days (%)
Hemoglobin				
<80% lower limit normal	25/101 (25)	9/50 (18)	14/53 (26)	14/44 (32)
>120% upper limit normal	0/101 (0)	0/50 (0)	0/53 (0)	0/44 (0)
-25% change	--	0/49 (0)	0/53 (0)	0/44 (0)
-25% change	--	2/49 (4)	2/53 (4)	1/44 (2)
Total neutrophils				
<1.5 x $10^3/mm^3$	2/79 (3)	0/34 (0)	2/35 (6)	1/32 (3)
-20% change	--	6/32 (19)	8/31 (26)	9/32 (28)
Platelets				
<100 x $10^3/mm^3$	11/94 (12)	5/49 (10)	10/51 (20)	5/41 (12)
-20% change	--	4/48 (8)	6/50 (12)	4/41 (10)
WBC				
<3 x $10^3/mm^3$	2/99 (2)	0/50 (0)	0/53 (0)	3/42 (7)
>20 x $10^3/mm^3$	1/99 (1)	0/50 (0)	0/53 (0)	0/42 (0)
-25% change	--	5/49 (10)	6/53 (11)	2/42 (5)
-25% change	--	6/49 (12)	9/53 (17)	5/42 (12)
Potassium				
<3.0 mEq/L	0/101 (0)	2/66 (3)	1/69 (1)	0/48 (0)
>5.5 mEq/L	3/101 (3)	1/66 (2)	0/69 (0)	1/48 (2)
-25% change	--	3/65 (5)	7/69 (10)	2/48 (4)
-25% change	--	2/65 (3)	5/69 (7)	4/48 (8)
Sodium				
<130 mEq/L	3/101 (3)	3/67 (4)	5/58 (9)	2/48 (4)
>150 mEq/L	0/101 (0)	0/67 (0)	0/58 (0)	0/48 (0)
-10% change	--	1/66 (2)	0/58 (0)	0/48 (0)
-10% change	--	0/66 (0)	0/58 (0)	0/48 (0)
Urea				
>8.3 mmol/L	24/65 (37)	19/42 (45)	3/31 (10)	9/27 (33)
-50% change	--	0/41 (0)	2/30 (7)	1/26 (4)

• Percentages for change from baseline are calculated based on the number of patients with an on- or post-therapy value who also had a baseline value.

Table 9.15: Number and Percentage of Patients in Intravenous Studies Other than Hypertension or Congestive Heart Failure with Test Values of Sponsor-defined Concern or with a Change from Baseline of Sponsor-defined Concern
(2 of 2)
(Appendix 9.17)

Laboratory Test	Baseline (%)	On-therapy (%)	-----Post-therapy----- 1-2 days (%)	3-20 days (%)
BUN				
>12.5 mmol/L	12/27 (44)	8/23 (35)	8/26 (31)	5/14 (36)
+50% change	--	0/23 (0)	0/26 (0)	4/14 (29)
Creatinine				
>200% upper limit normal	27/101 (27)	15/66 (23)	15/68 (22)	20/49 (41)
+50% change	--	3/65 (5)	5/68 (7)	4/49 (8)
Alkaline phosphatase				
>200% upper limit normal	13/100 (13)	1/52 (2)	8/52 (15)	5/43 (12)
+100% change §	--	0/51 (0)	0/52 (0)	0/43 (0)
ALAT				
>200% upper limit normal	1/63 (2)	1/31 (3)	1/28 (4)	0/27 (0)
+50% change¶	--	1/30 (3)	2/28 (7)	4/27 (15)
ASAT				
>200% upper limit normal	10/93 (11)	7/44 (16)	6/55 (11)	3/38 (8)
+50% change¶	--	2/43 (5)	2/55 (4)	2/38 (5)
Fasting glucose				
<3.3 mmol/L (59 mg/dL)	1/34 (3)	0/23 (0)	0/24 (0)	0/12 (0)
>7.8 mmol/L (141 mg/dL)	2/34 (6)	1/23 (4)	3/24 (13)	0/12 (0)
-25% change	--	1/10 (10)	1/17 (6)	2/9 (22)
+25% change	--	1/10 (10)	2/17 (12)	4/9 (44)

* Percentages for change from baseline are calculated based on the number of patients with an on- or post-therapy value who also had a baseline value.
§ If alkaline phosphatase was less than 50 U/L at baseline, the sponsor-defined change from baseline was 200%; if the value was greater than 50 U/L at baseline, the sponsor-defined change from baseline was 100%.
¶ If ALAT/ASAT was less than 25 U/L at baseline, the sponsor-defined change from baseline was 200%; if the value was greater than 50 U/L at baseline, the sponsor-defined change from baseline was 50%.

Table 11.3
Number and Percentage of Patients with the Most Frequently (≥ 4%) Reported On-therapy Clinical Events in Severe Hypertension Studies by Fenoldopam Infusion Rate at First Onset

(Appendices 11.1 and 11.1A)

Patients Exposed	Total		FENOLDOPAM INFUSION RATES (mcg/kg/min.)											
			< 0.1		0.1-0.2		0.3-<0.6		0.6-<0.7		0.7-<1.0		1.0-1.5		>1.5-<10	
INTERVAL	112		60		112		79		43		28		18		14	
COMBINED	320		107		317		214		119		73		46		14	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Headache																
INTERVAL	17	(15)	1	(2)	8	(7)	4	(5)	-	(-)	1	(4)	2	(11)	1	(7)
COMBINED	39	(12)	3	(3)	16	(5)	9	(4)	3	(3)	2	(3)	5	(11)	1	(7)
Nausea/Vomiting*																
INTERVAL	15	(13)	1	(2)	4	(4)	3	(4)	2	(4)	2	(7)	2	(11)	1	(7)
COMBINED	28	(9)	1	(<1)	7	(2)	3	(<1)	2	(1)	8	(11)	6	(13)	1	(7)
Flushing																
INTERVAL	7	(6)	-	(-)	3	(3)	3	(4)	1	(2)	-	(-)	-	(-)	-	(-)
COMBINED	30	(9)	-	(-)	16	(5)	9	(4)	4	(3)	1	(1)	-	(-)	-	(-)
Decreased K																
INTERVAL	7	(6)	-	(-)	1	(<1)	2	(3)	3	(7)	-	(-)	1	(6)	-	(-)
COMBINED	16	(5)	1	(<1)	2	(<1)	4	(2)	3	(3)	2	(3)	4	(9)	-	(-)
Vent. Extrasys.																
INTERVAL	4	(4)	1	(2)	-	(-)	1	(1)	1	(2)	1	(4)	-	(-)	-	(-)
COMBINED	14	(4)	1	(<1)	6	(2)	4	(2)	1	(<1)	2	(3)	-	(-)	-	(-)
Dizziness																
INTERVAL	4	(4)	-	(-)	2	(2)	1	(1)	-	(-)	-	(-)	-	(-)	1	(7)
COMBINED	13	(4)	-	(-)	7	(2)	5	(2)	-	(-)	-	(-)	-	(-)	1	(7)
Hypotension																
INTERVAL	5	(4)	-	(-)	2	(2)	2	(3)	-	(-)	1	(4)	-	(-)	-	(-)
COMBINED	14	(4)	1	(<1)	5	(2)	5	(2)	1	(<1)	2	(3)	-	(-)	-	(-)

Key: Vent. Extrasys. = Ventricular extrasystoles; K = potassium; dizziness includes giddiness and postural dizziness in one patient at 1.0 - 1.5 rate.

* Nausea, vomiting and nausea with vomiting

PBO/000017	Infusion	Dyspnea	Moderate	FEN/000018	Infusion-Maintenance & Post-Tx	Dyspnea Dyspnea	Mild Mild
FEN/000034	Inf Maintenance	Heart Failure	Moderate	PBO/000036	Start Infusion	HEart Failure & Dyspnea	Severe

Discussion: This is a small study, labeled as double-blind and placebo controlled, in subjects with a history of CHF. Although the study was supposedly randomized (on a 1: 1 basis?) there were twice as many fenoldopam subjects as placebo subjects. The hemodynamics either at baseline or treatment is not described so that it is not clear whether these subjects were symptomatic or at least had hemodynamics suggestive of poorly compensated CHF. It was also impossible to determine whether the degree of CHF at the time of the study was the same in the fenoldopam and placebo group.

It is not clear whether infusions remained constant during the entire infusion and maintenance periods and consequently, whether the effect of fenoldopam was constant. Although blood pressure decreased and heart rate is increased at the start of the maintenance phase there is a clear trend for the pressures to converge as the duration of infusion continues. Certainly by 20-24 hours after the start of the infusion diastolic blood pressure does not differ between fenoldopam and placebo groups.

It is difficult in this small study to conclude that there is or is not any safety problems in the use of fenoldopam in subjects with CHF.

Appendix A

Appendix A

Deaths and Dropouts:

Fenoldopam Patients:

Patient number 53 , a 68 year old male with a history of coronary heart disease, hyperlipidemia, myocardial infarction and percutaneous transluminal coronary angioplasty, discontinued therapy due to atrioventricular block. The time of onset of this event (at the time, the patient's blood pressure was 80/45 mm Hg, the mean arterial pressure was 56 mm Hg and the heart rate was 60 beats/min) was 150 minutes after the start of the infusion of study drug. Infusion of study drug was discontinued at the time of onset of the event. The event was considered to be of moderate severity and not related to study medication. The patient was treated with atropine for bradycardia, and the atrioventricular block resolved within 10 minutes of onset. Fifty minutes after resolution of the event the patient's blood pressure was 170/80 mm Hg and the heart rate was 100 beats/minute.

[comments: Over the course of the first hour the dose of fenoldopam ranged from a high of 0.8 ug/kg/min to a low of 0.25 ug/kg/min. The most proximate vital signs prior to the adverse event was BP 149/69;HR 103.]

Patient number 56, a 62 year old male, discontinued therapy due to rebleeding in the thoracotomy surgical area. The time of onset of this event was 179 minutes after the start of infusion of study drug, at which time the infusion was discontinued. The event was considered to be of moderate severity, not related to study medication , and was reported as a serious event. The patient was treated for bleeding with calcium gluconate, Trayslol (aprotinin), human albumin and transfusions of fresh frozen plasma and erythrocyte concentrates. The bleeding resolved within 7 hours nd 20 minutes of onset. Four hours and 30 minutes after onset of bleeding, the patient's hemoglobin and hematocrit ere 8.6 g.dL and 28.3% respectively.

[comments: Above noted hemoglobin and hematocrit was performed after transfusion of 800 cc of erythrocyte concentrates. Subject required 5 hours of treatment with dopamine for hypotension. MAP was 79 with HR of 100. The dose of fenoldopam at the time of this hypotension was 0.25 ug/kg/min. It is unclear if the drop in blood pressure was a consequence of bleeding and some component of fenoldopam.]

Patient number 77, a 66 year old female, discontinued therapy due to postoperative bleeding. The time of onset of this event was 119 minutes after the start of infusion of study drug, and infusion was discontinued 30 minutes after onset of the event. The event was considered to be of moderate severity, not related to study medication and was reported as a serious adverse event. The patient was treated for postoperative bleeding with a transfusion of fresh frozen plasma. The bleeding resolved within 3 hours of onset. Twelve hours and 30 minutes after resolution of the bleeding, the patient's hemoglobin and hematocrit values were 12.3 g/dL and 36.6% respectively.

[comment: Only a single baseline MAP measurement above 105 mm Hg was documented, other measurements were between 100-86 mm Hg. The dose of fenoldopam during the first hour of therapy was decreased to 0.5 ug/kg/min. The subject was treated with 800 cc of erythrocyte concentrate at the end of the first hour of observation and the subject shortly thereafter received FFP. The subject also received fentanyl at the time of entry and Dormicum (a sedative) also during the first hour of observation. The drop in BP was likely due to a constellation of factors including hypovolemia, and sedation. the site of the bleeding is not stated.

Patient number 122, a 73 year old male, discontinued therapy due to hemodynamic instability/bleeding. The time of onset of this event was 289 minutes after the start of infusion of study drug, at which time infusion was discontinued. At the time of the event the hemodynamic parameter of PRP, PAP, PCWP, CO, SV, SVI, PVR, RVSWI and LVSWI ad fallen approximately 50% from their values one hour earlier. SVR increased at this time by approximately %. The event was considered to be severe possibly related to study medication and was reported as a serious adverse event. The patient underwent further surgery and the bleeding resolved within 1 hour and 25 minutes of

onset. Fourteen hours after resolution of the bleeding, the patient's hemoglobin and hematocrit values were 10.3 g/dL and 32.4%, respectively.

[Comment: Subject likely had ongoing bleeding during the observation time and received 800 cc of autotransfusion during the one-hour observation period. Site of bleeding is not stated.]

Patient number 140, a 49 y ear old male with a history of coronary heart disease, hyperlipidemia, myocardial infarction and arterial hypertension, discontinued therapy due to tachycardia. The time of onset of this event (at which time the patient's blood pressure was 185/97 mm Hg, the mean arterial pressure was 122 mm Hg and the heart rate was 121 beat/min) was 85 minutes after the start of infusion of study drug. Infusion of study drug was discontinued 90 minutes after the onset of the event. The event was considered to be of mild severity and possibly related to study medication. The patient was treated with acebutolol and the tachycardia resolved within 2 hours and 30 minutes of onset. At the time of resolution of the event, the patient's blood pressure was 118/70 mm Hg and the heart rate was 108 beats/min.

[comments: Subject received midazolam after baseline period. Subject's dose ranged from 0.2 to 0.8 ug/kg/min of fenoldopam. Despite the use of midazolam during baseline measurement the subject was included both in the intent-to-treat and per-protocol analysis. This subject also received piritramide (an analgesic) during the 1 hour measurement period]

Patient number 141, a 55 year old male with a history of coronary heart disease and arterial hypertension, discontinued therapy due to tachycardia. The time of onset of this event (at which time the patient's blood pressure was 154/78 mm Hg, the mean arterial pressure was 98 mm Hg and the heart rate was 125 beats/min) was 19 minutes after the start of infusion of study drug. Infusion of study drug was discontinued 10 minutes after onset of the event. The event was considered to be of mild severity and possibly related to study medication. The patient was treated with acebutolol, and the tachycardia resolved within 10 minutes of onset. At the time of resolution of the event, the patient's blood pressure was 96/60 mm Hg, the mean arterial pressure was 70 mm Hg, and the heart rate was 105 beats/min.

[comment: The case report form suggests that fenoldopam was continued and dose even raised during the tachycardic event. Pulse generally hovered between 125-134. midazolam an piritramide were given during the 1 hour observation period. This subject was included both as intent-to-treat and per-protocol data bases.]

Patient number 148, a 50 year old male with a history of coronary heart disease, myocardial infarction and arterial hypertension, discontinued therapy due to bleeding in the area of thoracotomy and tachycardia. The rebleeding began 59 minutes and the tachycardia began 119 minutes after the start of infusion of study drug (at which time the patient's blood pressure was 131/86 mm Hg, the arterial pressure was 105 mm Hg and the heart rate was 131 beats/min). Infusion was discontinued 60 minutes after the onset of tachycardia. The rebleeding was considered to be severe, not related to study medication and was reported as a serious adverse event, while the tachycardia was considered to be moderate in severity and possibly related to study medication. The patient was treated with acebutolol for tachycardia which resolved within 1 hour of onset. At the time of resolution of tachycardia, the patient's blood pressure was 119/89 mm Hg, the mean arterial pressure was 100 mm Hg, and the heart rate was 107 beats/min. The rebleeding was treated with two auto-transfusion and resolved within 5 hours of onset. Eleven hours after resolution of the bleeding, the patient's hemoglobin and hematocrit values were 9.6 g/dl and 28.7%, respectively.

[comments: Dose ranged from 0.8-1.0 ug/kg/min during the initial hour observation but increased to 1.6 ug/kg/hr over the next hour. The subject received an auto-transfusion 1/2 hour after the end of the initial hour of observation. Subject received sedation during the 1 hour observation period. Monitor's note suggests there was pericardial tamponade. Effect on blood pressure likely a mixture of hypovolemia and drug and sedation. The heart rate during the observation period was 120-130 beats/min.]

Patient number 152, a 60 year old male with a history of coronary heart disease and arterial hypertension, discontinued therapy due to tachycardia. The time of onset of this event (at which time the patient's blood pressure was 143/81 mm Hg, the mean arterial pressure was 100 mm Hg and the heart rate was 131 beats/min) was 59 minutes after the start of infusion of study drug. Infusion of study drug was discontinued 30 minutes after onset of event. The event was considered to be of moderate severity and possibly related to study medication. The patient was treated with acebutolol, and the tachycardia resolved within 50 minutes of onset. At the time of resolution of the event,the patient's blood pressure was 121/89 , Hg, the mean arterial pressure was 101 m Hg, and the heart rate was 113 beats/min.

[comment: Subject received sedation during 1-hour observation period (Dormicum). Maximum heart rate was 135 beats/min.]

Patient number 157, a 53 year old male with a history of coronary artery disease, hyperlipoproteinemia and arterial hypertension, discontinue therapy due to persistent hypertension. The time of onset of this event (at which time the patient's blood pressure was 143/83 mm Hg, the mean arterial pressure was 108 mm Hg, and the heart rate was 101 beats/min) was 59 minutes after the start of infusion of study drug. Infusion of study drug was discontinued 60 minutes after onset of event. the event was considered to be of moderate severity and possibly related to study medication. The patient was treated with clonidine and the hypertension resolved within 1 hour and 10 minutes of onset. At the time of resolution of the event the patient's blood pressure was 115/70 mm Hg, the arterial pressure was 87 mm Hg, and the heart rate was 114 beats/min.

[comments: Patient did not receive sedation, Dormicum, till after the initial hour observation period.]

Patient number 165, a 57 year old male with a history of coronary heart disease, discontinued therapy due to continuous tachycardia. The time of onset of this event was 20 minutes after the start of infusion of study drug. Ten minutes after onset of the event the patient's blood pressure was 148/64 mm Hg, the mean arterial pressure was 89 mm Hg, and the heart rate was 120 beats/min. Infusion of study drug was discontinued 90 minutes after onset of the event. The event was considered to be of moderate severity, possibly related to study medication and was reported as a serious adverse event. The patient was treated with nifedipine and urapidil for hypertension, and the tachycardia resolved within 5 minutes of onset. At the time of resolution of the event, the patient's blood pressure was 140/68 mm Hg, the mean arterial pressure was 104 mm Hg, and the heart rate was 104 beats/min/

[comment: No sedation or analgesiawas administered during first hour.]

Patient number 167, a 67 year old female with a history of coronary heart disease and angina pectoris, discontinued therapy due to tachycardia ≥ 120 for 20 minutes. The time of onset of this event (at which time the patient's blood pressure was 149/95 mm Hg, the mean arterial pressure was 117 mm Hg, and the heart rate was 120 beats/min) was 79 minutes after the start of infusion of study drug. Infusion of study drug was discontinued 20 minutes after the event. The event was considered to be of moderate severity and related to study medication. The patient was treated with nifedipine and urapadil for hypertension and tachycardia resolved within 2 hours of onset. At the time of resolution of the event, the patient's blood pressure was 120/80 mm Hg, the mean arterial pressure was 100 mm Hg, and the heart are was 104 beats/min.

[comments: Subjects baseline BP of 151/80 is a MAP of 103 mm Hg as a single qualifying measurement.]

Patient number 221, a 73 year old female with a history of coronary heart disease, posterior myocardial infarction, hyperlipoproteinemia and arterial hypertension discontinued due to decreased diuresis and decreased pH-value of the blood , judged to be metabolic acidosis. The decreased diuresis was first recorded 370 minutes and the decreased pH value of the blood began 439 minutes after the start of infusion of study drug. Study drug infusion was discontinued after 360 minutes. Both events were considered to be of mild severity and not related to study

medication. The patient was treated with furosemide for decreased diuresis which resolved within 1 hour of onset; the decreased pH-value of the blood resolved within 4 hours of onset. Two hours and 15 minutes after the recorded time of onset of the metabolic acidosis, the arterial blood pH was 7.35; at the time of resolution of the event, the arterial blood pH was 7.42.

[comment:- No blood pressure measurements for this subject was available with the exception of the BP upon entry to the ICU, At that time the MAP was 78 mm Hg far too low for enrollment. Subject received Disoprivan for sedation early during the course of her ICU stay. Subject also received large volumes of fluid (1800 cc shortly after arrival at the ICU). There did not appear to be any active bleeding for this patient (no evidence of transfusion). In summary this subject was likely hypotensive at some time and prolonged period of time either independent of or as a result of fenoldopam.]

Patient number 223, a 66 year old male with a history of coronary heart disease and pulmonary hypertension. discontinued therapy due to hypertension secondary to tachyrhythmia. The time of onset of this event (at which time the patient's blood pressure was 102/53 mm Hg, the mean arterial pressure was 76 mm Hg, and the heart rate was 144 beats/min) was 119 minutes after the start of infusion of study drug. Infusion of study drug was discontinued 40 minute after onset of the event. The event was considered to be of mild severity and not related to study medication. The patient was treated with electrolyte and trace elements, etiomidate for cardioversion, and flecainide for the arrhythmia. The arrhythmia resolved within 1 hour and 55 minutes of onset. Fifteen minute after resolution of the event the patient's blood pressure was 107/58 mm Hg, the mean arterial pressure was 79 mm Hg, and the heart rate was 86 beats/min.

[comment: MAP on enrollment 103 insufficient for enrollment. Dose decreased rapidly to 0.4 ug/kg/min. During the ıfusion the heart rate was controlled by external pacing.]

Nifedipine

Patient # 57, a 71 year old male with a history of coronary artery disease and hyperlipidemia, discontinued therapy due to tachycardia, hypotension and intermittent atrioventricular block. The time of onset of these events (at which time the patient's blood pressure was 119/68 mm Hg, the mean arterial pressure was 83 mm Hg, and the heart rate was 94 beats/min) was 269 minutes after the start of infusion of study drug. Infusion of study drug was discontinued at the time of onset of the events. The events were considered to be severe, possibly related to study medication and were reported as serious adverse events. The events resolved within 10 minutes of onset. Twenty minutes after resolution of the events, the patient's blood pressure was 117/68 mm Hg, the mean arterial pressure was 82 mm Hg, and the heart rate was 97 beats/min. In addition to these events, this patient experienced a myocardial infarction that was reported as a serious adverse event. This event, was considered to be severe and not related to study medication, began approximately one and one half days after discontinuation study medication and resolved within 6 days of onset.

[comments: This subject received nitroglycerine till the time of onset of infusion. Thus the baseline blood pressure may have underestimated the true blood pressure. Notwithstanding this subject had a substantial decrease in BP on nifedipine. The dose was dropped to 0.5 mg/hr. The sponsor notes the subject had a myocardial infarction and the implication is that the hypotension and AV block are a consequence of the MI. No documentation of the MI is given. The is no statement as to whether the subject complained of chest pain, whether enzymes were elevated or whether there were ECG changes.)

Patient number 65, a 59 year old male with a history of coronary artery disease, hypercholestolemia and posterior myocardial infarction, discontinued therapy due to increased heart rate. The time of onset of this event (at which ne the patient's blood pressure was 157/88 mm Hg, the mean arterial pressure was 111 mm Hg and the heart rate as 117 beats/min) was 59 minutes after the start of infusion of study drug. Infusion of study drug was discontinued 60

minutes after onset of the event. The event was considered to be of moderate severity and related to study medication. The patient was treated with esmolol for tachycardia, and the event resolved within 7 hours of onset. At the time of resolution of the event, the patient's blood pressure was 100/55 mm Hg, and the heart rate was 97 beats/min.

[comment: This subject did not have a stable baseline, since only a single measurement was included.]

Patient number 145, a 45 year old male with a history of coronary artery disease, myocardial infarction, hypercholesterolemia, and arterial hypertension, discontinued therapy due to persistent hypertension. The event began at the same time as the start of infusion of study drug (at which time the patient's blood pressure 146/100 mm Hg, the arterial pressure was 116 mm Hg and the heart rate was 78 beats/min). Infusion of study drug was discontinued 60 minutes after onset of the event . The event was considered to be of moderate severity and possibly related to study medication. The patient was treated with clonidine, and the event resolved within 1 hour of onset. Ten minuter after the resolution of the event the patient 's blood pressure was 81 mm Hg, and the heart rate was 84 beats/min.

[comment: Midazolam given at 20 minutes into infusion.]

Patient number 147, a 67 year old male with a history of coronary artery disease, myocardial infarction, hyperlipidemia and arterial hypertension, discontinue therapy due to persistent hypertension. The event began at the same time as the start of infusion of study drug (at which time the patient's blood pressure was 164/92 mm Hg, the mean arterial pressure was 113 mm Hg and the heart rate was 99 beats/min), Infusion of study drug was discontinued 60 minutes after onset of the event. The event was considered to be of mild severity and possibly related to study medication. The patient was treated with clonidine, and the event resolved within 1 hour of onset. Ten minutes after resolution of the event, the patient's blood pressure was 121/64 mm Hg , the mean arterial pressure was 81 mm Hg, and the heart rate was 96 beats/min.

[comment: This patient received no listed sedation or pain medication.]

Patient number 151, a 59 year old male with a history of coronary artery disease, arterial hypertension, renal artery stenosis and arterial occlusive disease, discontinued therapy due to persistent arterial hypertension. The event began at the same time as the start of infusion of study drug (at which time the patient's blood pressure was 164/86 mm Hg, the mean arterial pressure was 113 mm Hg, and the heart rate was 82 beats/min). Infusion of study drug was discontinued 90 minutes after onset of the event. The event was considered to be of moderate severity and related to study medication. The patient was treated with clonidine, and the event resolved within 1 hour and 40 minutes of onset. At the time of resolution of the event, the patient's blood pressure was 156/79 mm Hg, the mean arterial pressure was 104 mm Hg, and the heart rate was 95 beats/min.

[comment. Subject received both sedation and analgesia during the 1-hour observation period.]

Patient number 155, a 53 year old male, discontinued therapy due to rebleeding at the thoracotomy surgical area. The time of onset of this event was 19 minutes after the start of infusion of study drug, and the infusion was discontinued 170 minutes after onset of the event. The event was considered to be of moderate severity, not related to study medication and was reported as a serious adverse event. The patient was treated with protamine, fresh frozen plasma, and autotransfusion, and the event resolved within 3 hours of onset. Twelve hours after resolution of the bleeding, the patient's hemoglobin and hematocrit values were 11.4 g/dL and 33.5%, respectively.

Patient number 160, A 58 year old male history of coronary artery disease and myocardial infarction, discontinued therapy due to arrhythmia and low cardiac output syndrome. The arrhythmia began 29 minutes after the start of infusion of study drug (at which time the patient's blood pressure was 116/79 mm Hg, the mean arterial pressure was 90 mm Hg, and the heart rate was 69 beats/min) and the low cardiac output syndrome began 59 minutes (at which

time the cardiac output volume was 3.4 L/min) . Study drug infusion was discontinued 60 minutes after onset of low cardiac output syndrome. The arrhythmia was considered to be of moderate severity, and the low cardiac output syndrome was considered to be of mild severity; both events were noted as possibly related to study medication. The arrhythmia resolved within 1 hour and 30 minutes of onset, and the low cardiac output syndrome resolved within 4 hours of onset. At the time of resolution of the arrhythmias, the patient's blood pressure was 112/72 mm Hg, the mean arterial pressure was 85 mm Hg , and the heart rate was 64 beats/min. At the time of resolution of the low cardiac output syndrome, the patient's cardiac output was 5.0 L/min.

[Comment: Subject received sedation 10 minutes before baseline measurement and during 1-hour observation period.]

Patient number 200, a 61 year old male with a history of anteroseptal myocardial infarction and hypertension, discontinued therapy due to sudden onset of tachycardia and hypotension. The time of onset of this event (at which time the patient's blood pressure was 120/75 mm Hg, and the heart rate was 160 beats/min) was 419 minutes after the start of infusion of study drug. Infusion of study drug was discontinued 10 minutes after onset of the event (at which time the blood pressure was 100/60 mm Hg). The event was considered of moderate severity, possibly related to study medication, and was reported as a serious adverse event. The hypotension was treated with digoxin and pindolol for tachycardia, and the tachycardia and hypotension resolved within 1 hour of onset. Twenty minutes after resolution of the event, the patient's blood pressure was 120/75 mm Hg, the mean arterial pressure was 90 mm Hg and the heart rate was 90 beats/min.

[comment: Received no sedation or analgesia during first hour.]

Patient number 203, a 62 year old male with a history of coronary artery disease, angina pectoris, hyperlipidemia nd hypertension. discontinued therapy due to hypotension. The time of onset of this event (at which time the atient's blood pressure was 78/38 mm Hg, the mean arterial pressure was 55 mm Hg, and the heart rate was 82 beats/min) was 89 minutes after the start of infusion of study drug. Infusion of study drug was discontinued at the time of onset of the event. The event was considered to be severe and possibly related to study medication. The patient was treated with adrenaline, and the event resolved within 10 minutes of onset. At the time of resolution of the event, the patient's blood pressure was 155/62 mm Hg, the arterial pressure was 93 mm Hg, and the heart rate was 85 beats/min.

[comment: Received nitroglycerine till time of study drug.]

APPEARS THIS WAY
ON ORIGINAL