# CENTER FOR DRUG EVALUATION AND RESEARCH

**ADVISORY COMMITTEE: CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE**

**DATE OF MEETING: 06/26/97**

## SLIDES

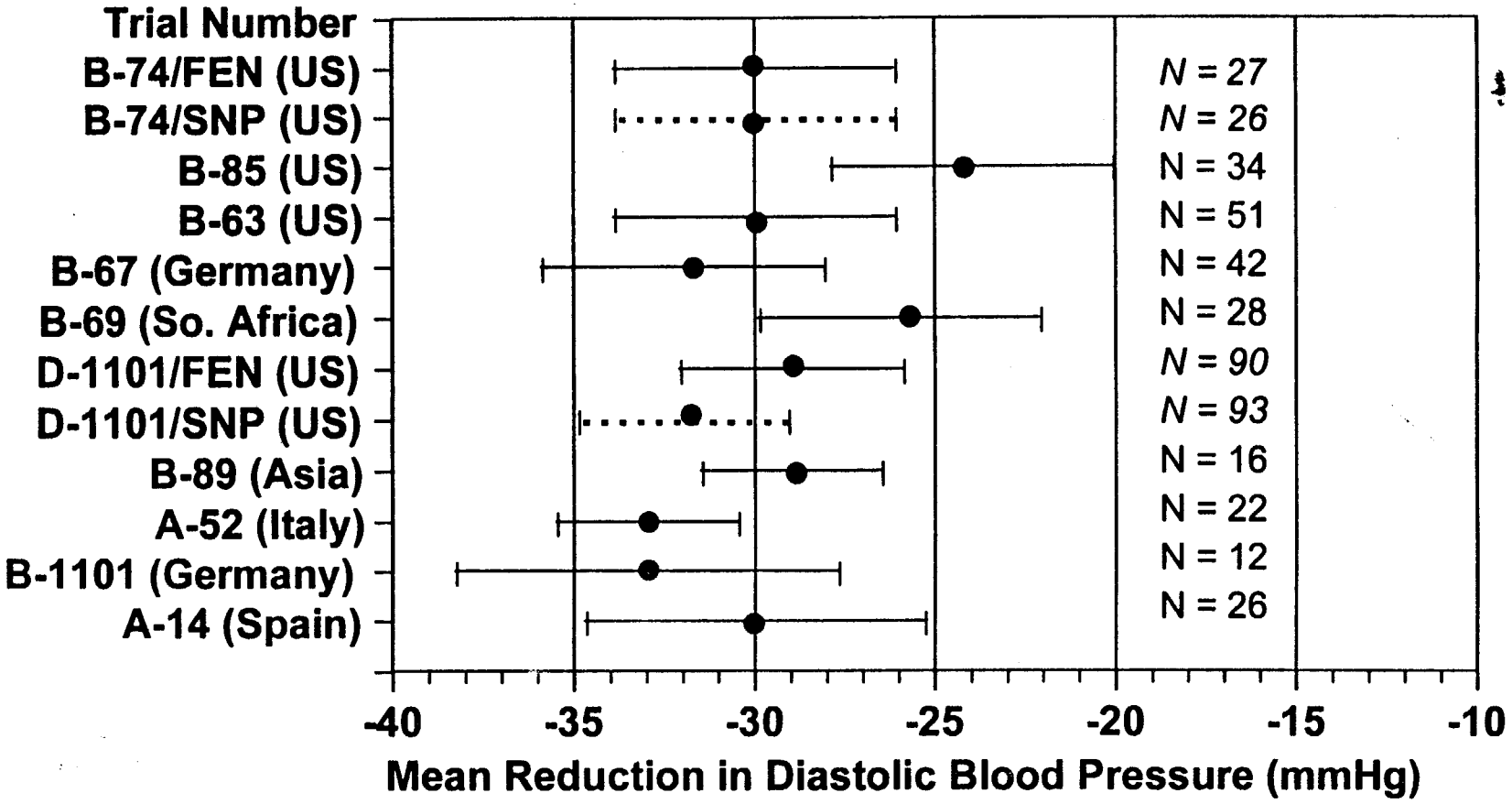
# Fenoldopam History

- Discovered and developed by SKF
- Extensive preclinical and clinical programs
- SKF discontinued development of oral fenoldopam
- SKF continued development of IV fenoldopam
- Broad experience in severe hypertension

NEUREX

# SKF Severe Hypertension Trials

## Overview of SKF Trials in Severe Hypertension*




* 95% confidence intervals

NEUREX

# Neurex Licensed Fenoldopam

- 1988: SKF filed NDA
- 1991: Nonapprovable letter issued
  - Dosing regimen not defined
  - Malignant hypertension population not studied
- Neurex licensed rights to fenoldopam in 1994

NEUREX

# Neurex Trials

- Pharmacokinetic/pharmacodynamic trial
- Malignant hypertension trial
- Renal function trial

NEUREX

# Fenoldopam Profile

- Well-behaved pharmacokinetics
- Dose-response curve well-defined
- Predictable hypotensive effects
- Good safety profile
- Well tolerated
- Maintains/improves renal blood flow

NEUREX

# Label Indications

- Short-term treatment of hypertension when oral therapy is not feasible or possible
- Treatment of severe hypertension with or without acute end-organ damage

NEUREX

# Clinical Pharmacology

Addison Taylor, M.D., Ph.D.

Baylor College of Medicine

NEUREX

# Fenoldopam Clinical Pharmacology
## Pharmacokinetics and Pharmacodynamics

- Dopamine receptor pharmacology - focus on fenoldopam
- PK/PD in previous clinical trials: Unanswered questions
- Blinded fixed-dose, constant 48 hour infusion PK/PD trial

NEUREX

# Fenoldopam Interaction with Catecholamine Receptors

No Duplicat Slide

| | |
|---|---|
| D-1 like receptors<br>D1B<br>D1A | □ vasodilation (coronary, mesenteric, renal), natriuresis, GI motility |
| D-2 like receptors | ≠□ decreased norepinephrine release |
| α-adrenergic receptors | ≠□ vasoconstriction |
| β-adrenergic receptors | ≠□ chronotropy |

# Pharmacokinetics and Pharmacodynamics Unanswered Questions

- PK Questions:
  - PK during prolonged infusions?
    - Time to $C_{ss}$
    - Dose proportionality of $C_{ss}$
    - Time-dependent $\Delta$ in $C_{ss}$
  - PK after stopping infusion?
    - Plasma $t_{1/2}$
    - Clearance

# Pharmacokinetics and Pharmacodynamics Unanswered Questions

- PD Questions:
  - PD during fixed-dose infusion different from PD during titration-to-effect?
  - PK/PD relationship during fixed-dose infusions?
  - Onset, offset, tolerance, rebound?

NEUREX

# Pharmacokinetics and Pharmacodynamics Study Objectives

- PK
  - Plasma fenoldopam (racemate + enantiomers) concentrations during and after 48 hour infusion
  - Time to $C_{ss}$
  - PK parameters after 48 hour infusion

# Pharmacokinetics and Pharmacodynamics Study Objectives

- PD
  - Time to peak effect?
  - Maximum tolerable infusion rate?
  - Persistent hemodynamic effect during prolonged infusion (tolerance)?
  - Hemodynamic response to drug withdrawal after prolonged infusion?
  - Dose-response relationship?

NEUREX

# Pharmacokinetics and Pharmacodynamics Study Design

| Day 0 | Day 1 | Day 2 | Day 3 | Day 4 |
|---|---|---|---|---|
| Admission H&P | Vehicle infusion | Fenoldopam infusion (0, 0.04, 0.1, 0.4, 0.8 μg/kg/min) | Fenoldopam infusion (0, 0.04, 0.1, 0.4, 0.8 μg/kg/min) | Vehicle infusion |
| Entry DBP 95-119 mmHg | | Qual. DBP > 90 mmHg | | Safety lab |
| Safety lab | BP & HR q 15 min | BP & HR q 15 min | BP & HR q 15 min | BP & HR q 15 min |
| | | Fenoldopam PK | Fenoldopam PK | Fenoldopam PK |

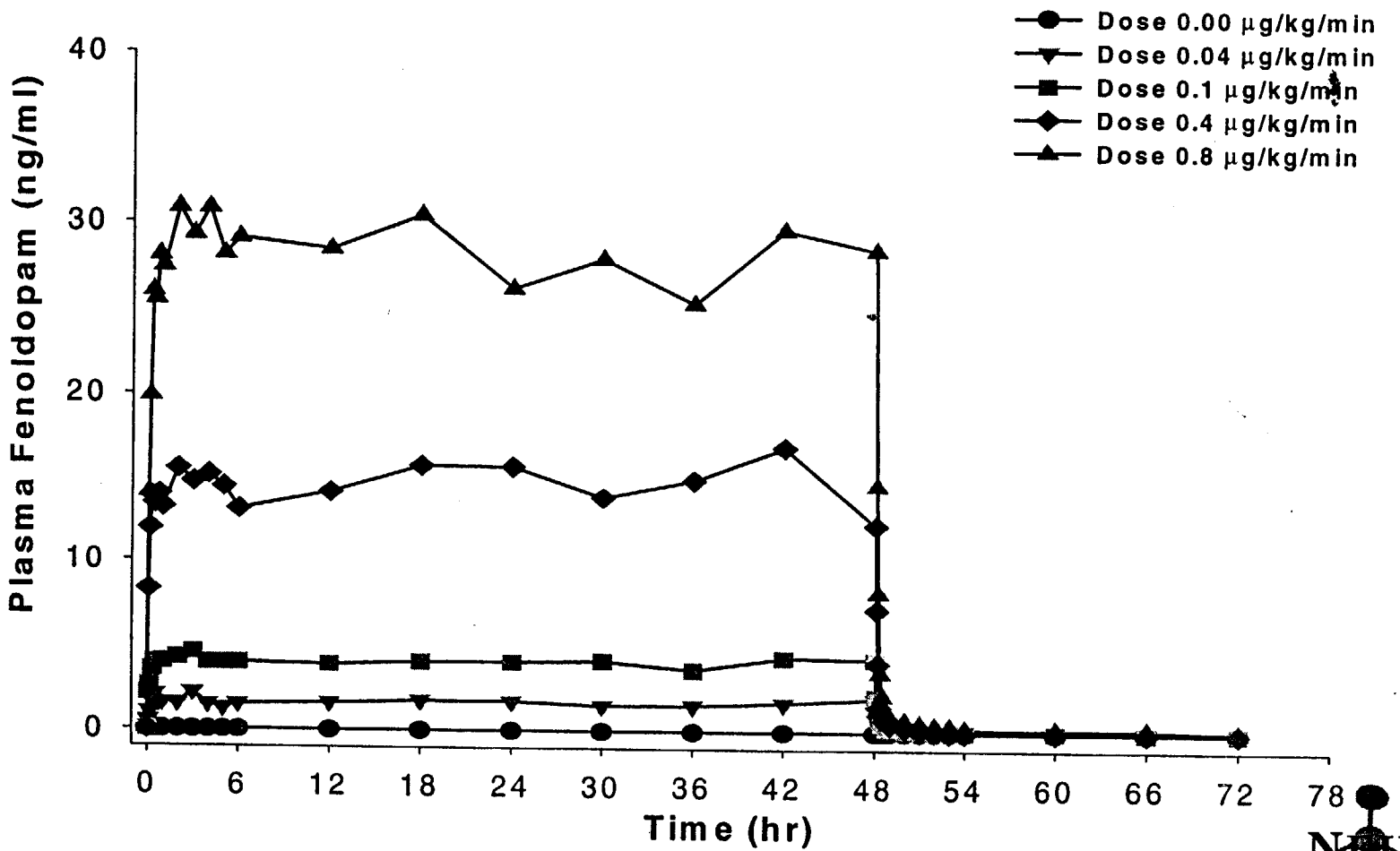
NEUREX

# Pharmacokinetics and Pharmacodynamics
# 94-005 Patient Demographics

| | |
|---|---|
| N | 32 |
| Mean Age | 50.5 |
| Black | 24.3% |
| Caucasian | 60.0% |
| Hispanic/Asian | 15.7% |
| Male | 81.7% |
| Female | 18.2% |
| Mean DBP Screening | 98.8 |

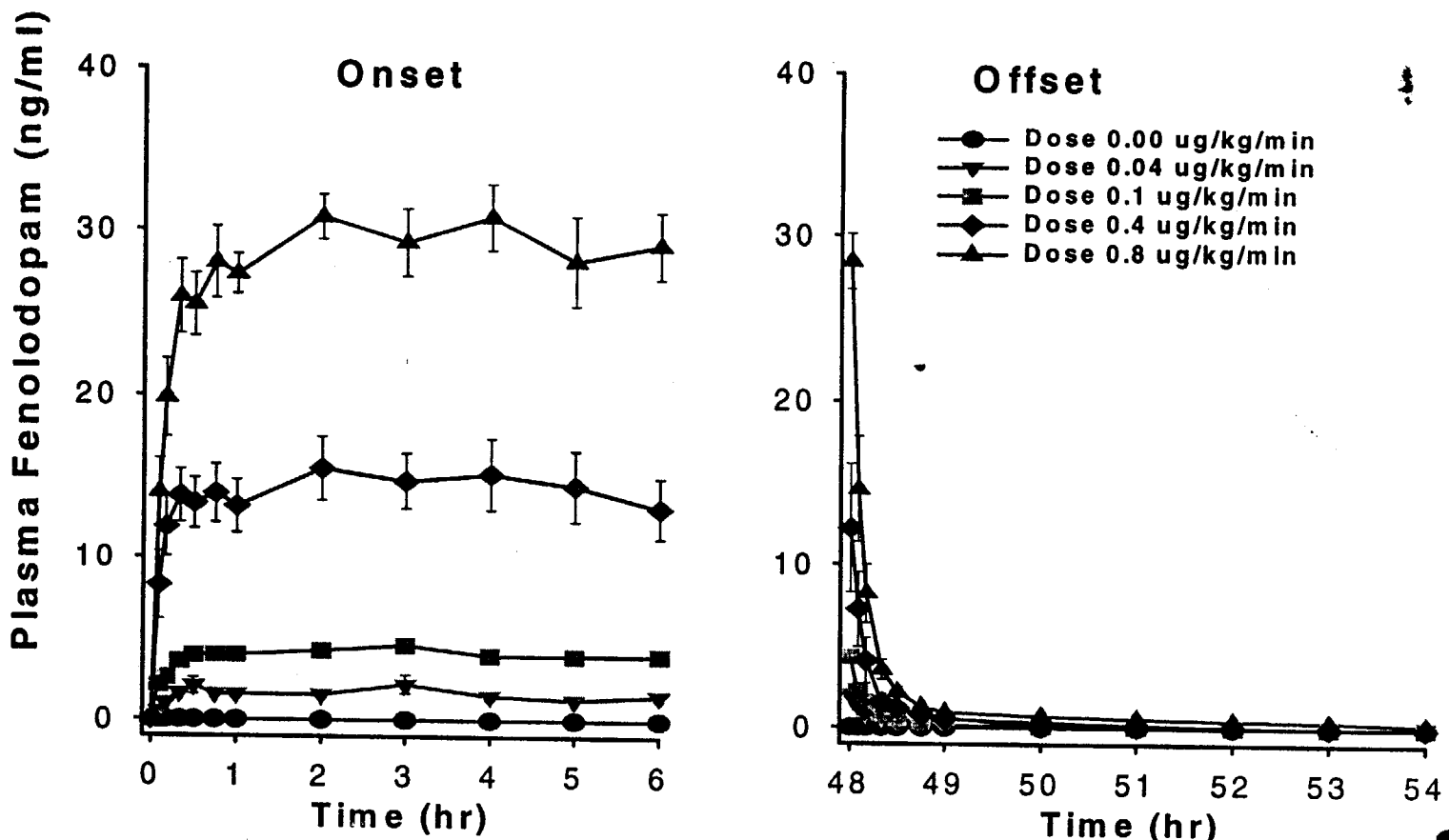
NEUREX

# Pharmacokinetics and Pharmacodynamics Results: Pharmacokinetics




NEUREX

# Pharmacokinetics and Pharmacodynamics Results: Onset and Offset Pharmacokinetics

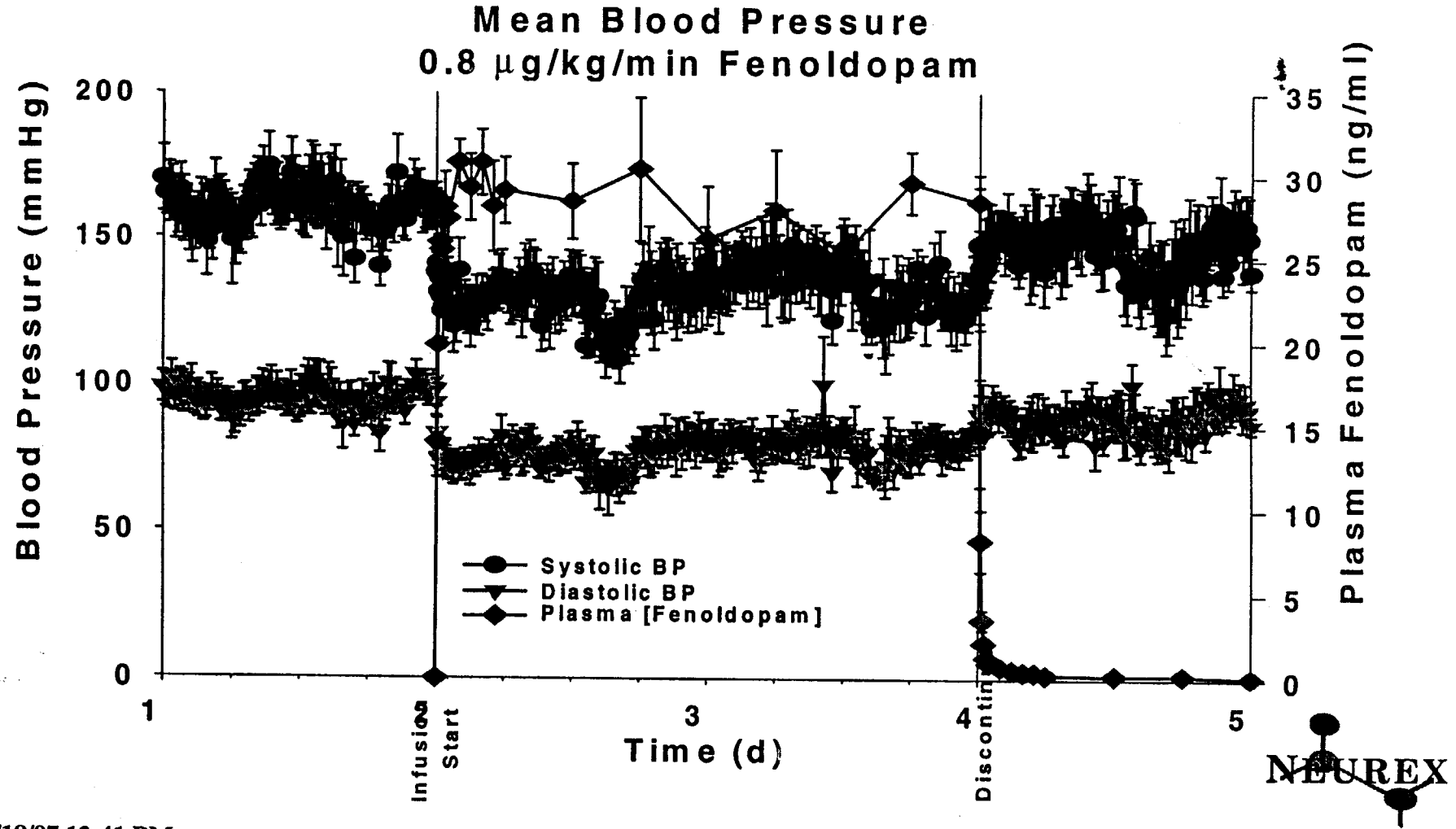



NEUREX

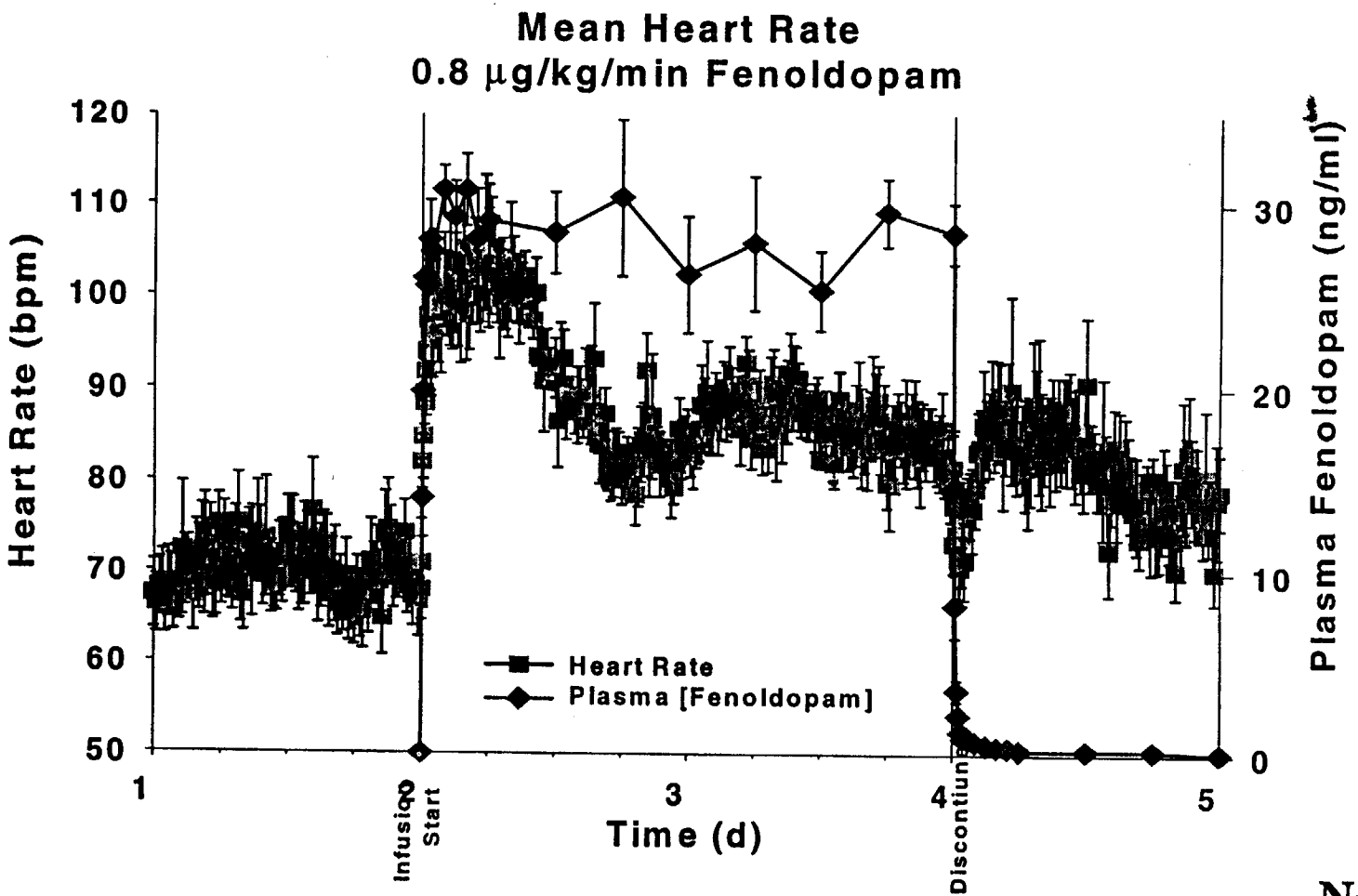
6/18/97 12:40 PM

A04

# Pharmacokinetics and Pharmacodynamics
# Results: Pharmacodynamics



# Pharmacokinetics and Pharmacodynamics
# Results: Pharmacodynamics

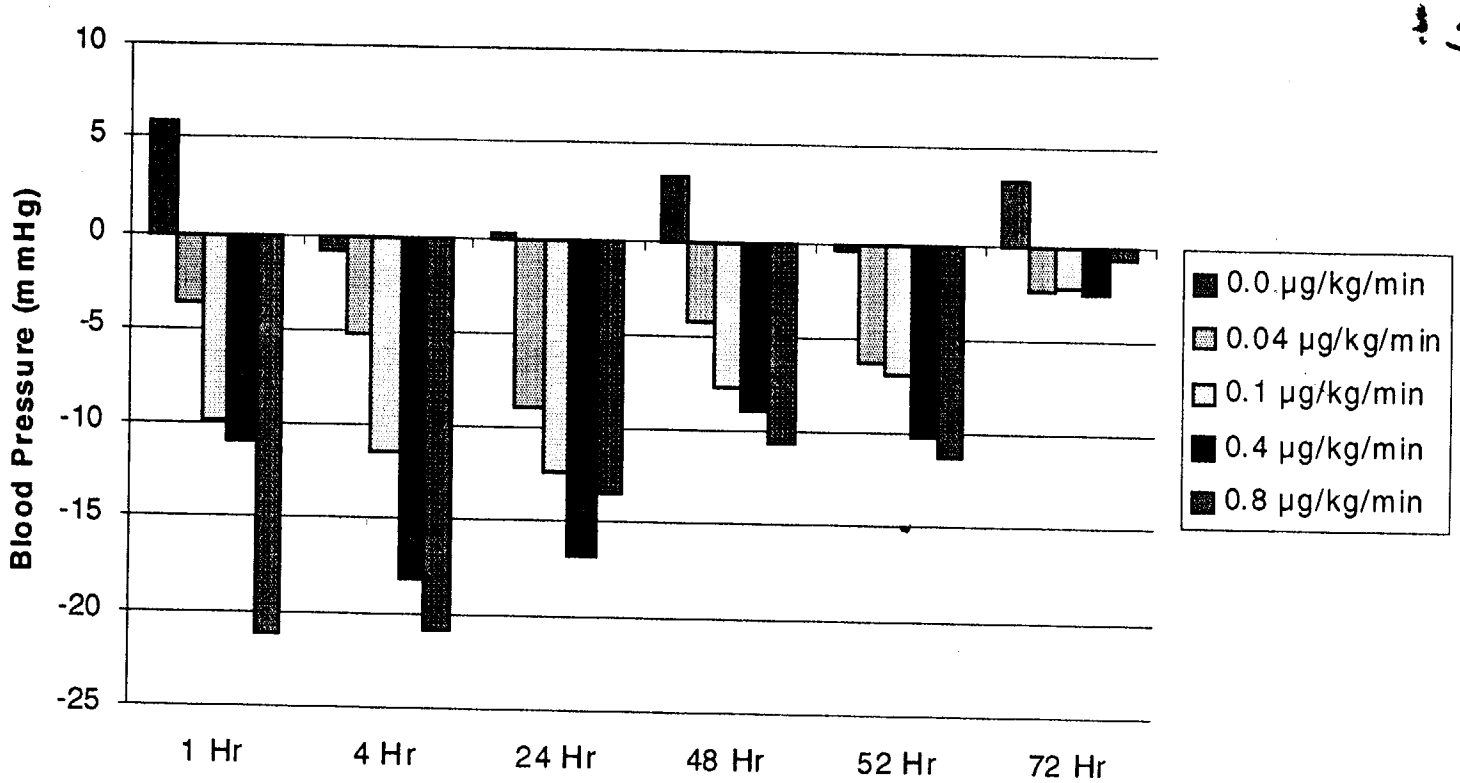



NEUREX

6/18/97 12:43 PM

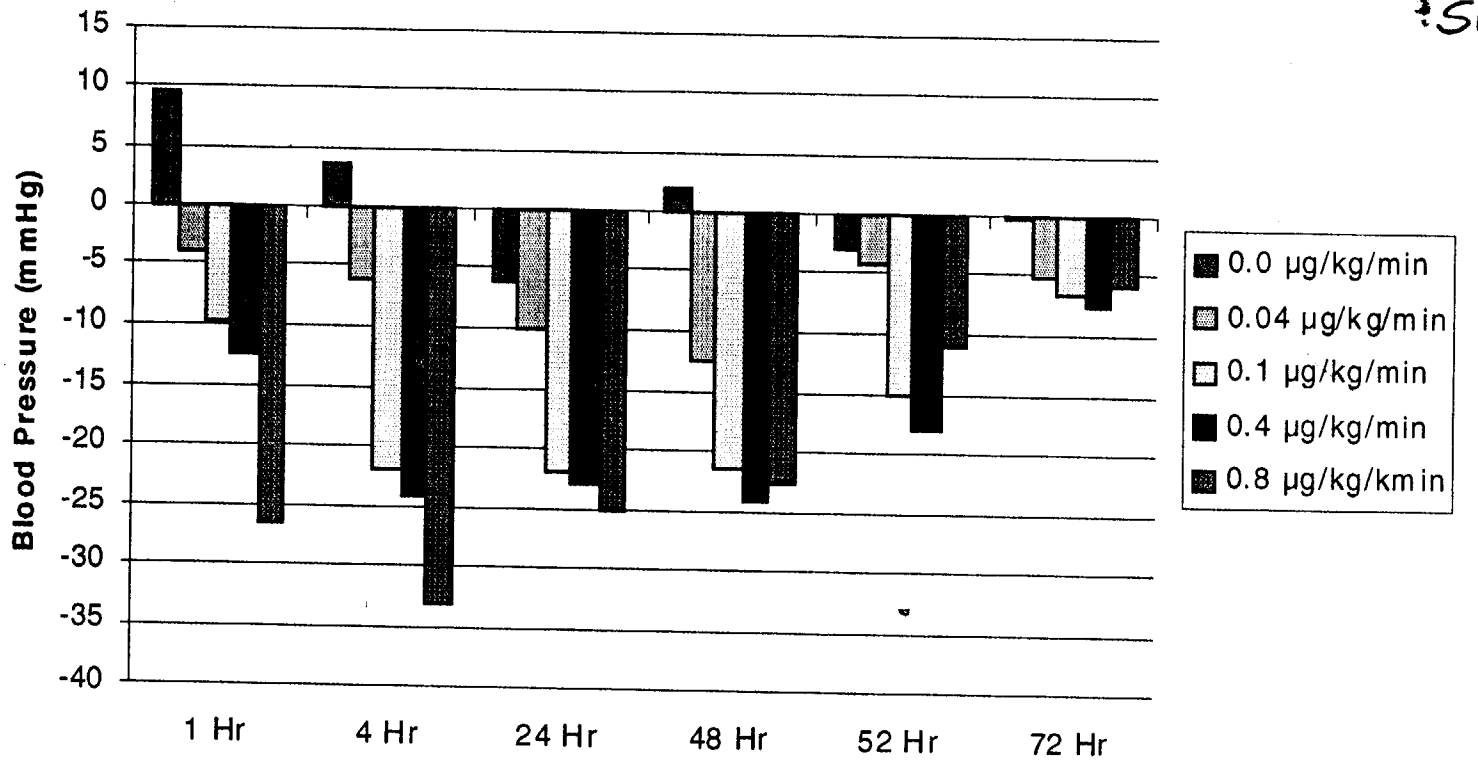
# Mean Change in Diastolic Blood Pressure from Baseline

No Duplicate Slide



# Mean Change in Systolic Blood Pressure from Baseline

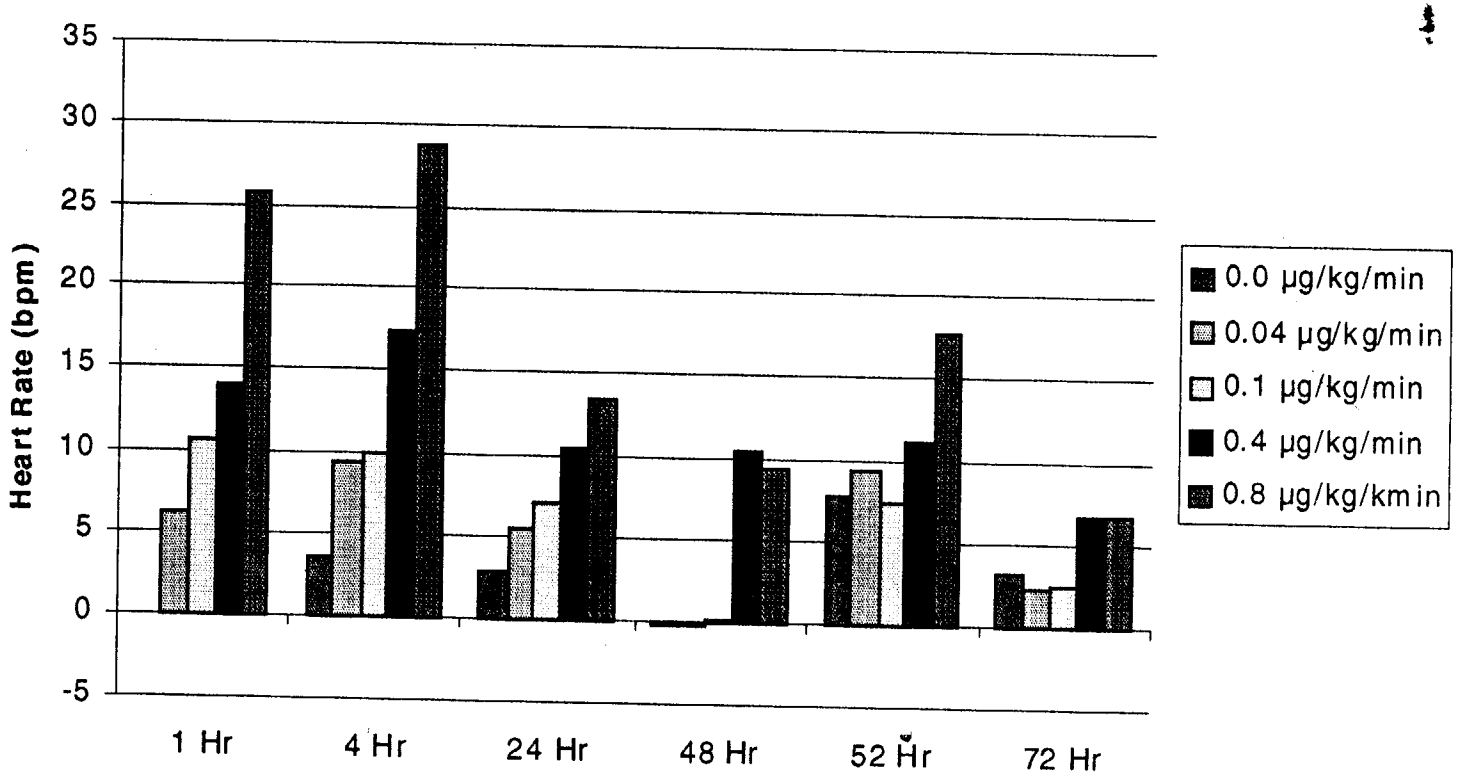
No Duplicate Slide




088

# Mean Change in Heart Rate from Baseline

No Duplicate Slide



# Pharmacokinetics and Pharmacodynamics Conclusions

- PK
  - Short $t_{1/2}$ (~ 5 min)
  - Rapid attainment of Css (~ 30 min)
  - Plasma levels proportional to dose
  - No alteration in PK over 48 hr infusion
  - Rapid elimination upon discontinuation

NEUREX

# Pharmacokinetics and Pharmacodynamics Conclusions

- PD
  - Predictable hemodynamic effect
  - Rapid onset of effect
  - Dose proportionality PD response (SBP, DBP)
  - Gradual tolerance with maintenance of effect
  - No rebound

NEUREX

# Efficacy

David Ellis, M.D., Ph.D.
Neurex Corporation

NEUREX

# Study Design

## Hypertensive Emergency Trial

- Confirmation of pharmacokinetic/pharmacodynamic study findings
- End-organ damage and DBP $\geq$ 120 mmHg
- Double-blind, constant infusion, 4 rates
  - 0.01, 0.03, 0.1, 0.3 μg/kg/min
- 24-hour infusion, transition to PO after 18 hours
- No target BP specified
- Reduction in DBP at 4 hours primary endpoint
- Statistical comparison vs. 0.01 dose group

NEUREX

# Patient Population

- Balanced for demographic parameters
- Age: 45 ± 10.4
- Gender: 55% male
- Race: 78% African American
- Baseline BP: 208 ± 22 / 134 ± 15 mmHg

NEUREX

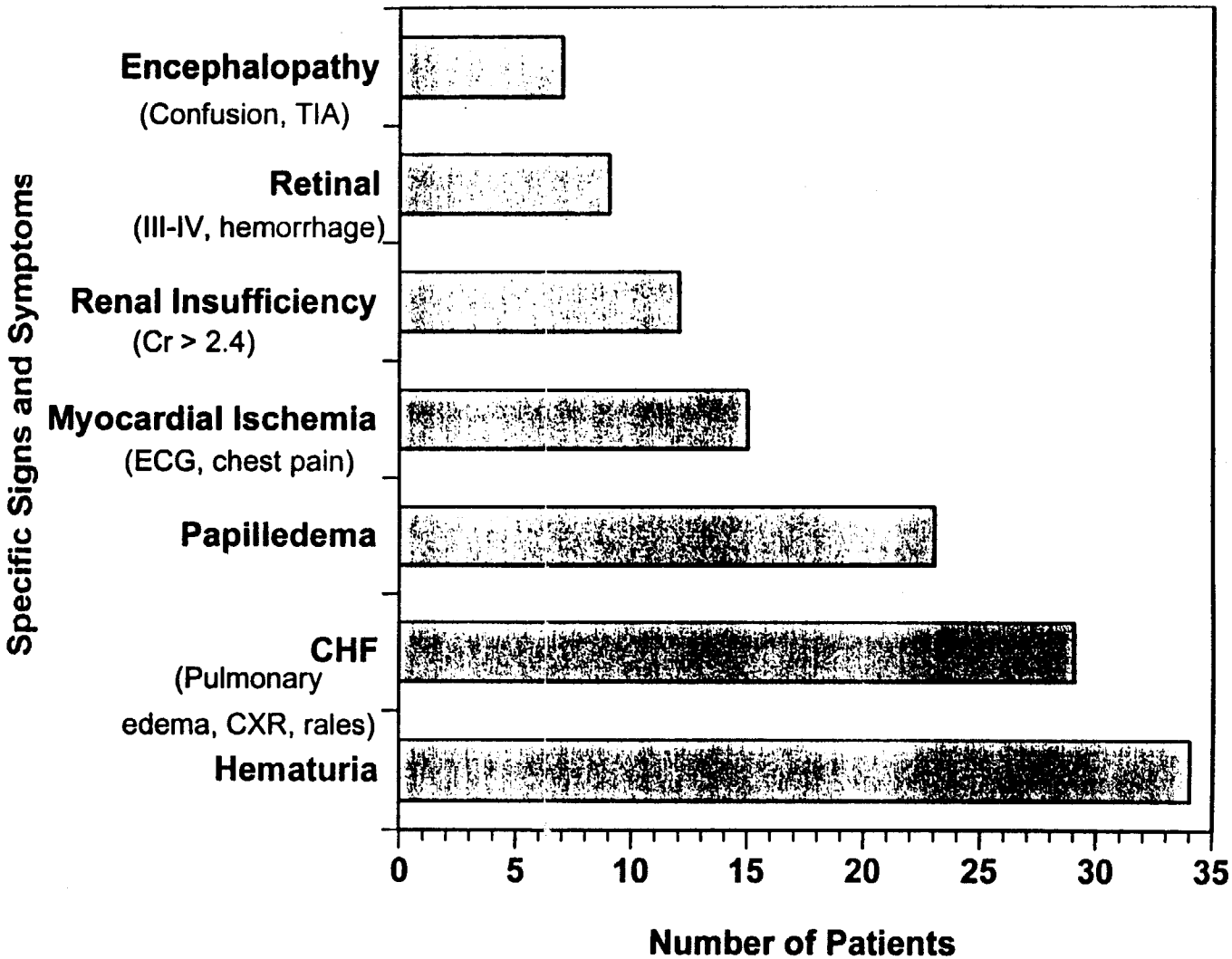
# Protocol-specified End-Organ Damage

- Percent of all randomized patients
  - 65% neurological criteria
  - 39% cardiovascular criteria
  - 35% renal criteria
  - 25% ophthalmological criteria

- 99% of treated patients $\geq$ 1 criteria

NEUREX

# Objective End-Organ Damage
## Malignant Hypertension Trial




NEUREX

# Clinical Features of Population

- 49% off antihypertensives for > 7 days
- 20% had history of drug or alcohol abuse
- 82% had LVH on baseline ECG
- 17% history of heart failure
- 17% old MI on ECG
- 20% had discontinued clonidine in past week

NEUREX

# Patient Disposition (cont.)

- 89 patients treated up to at least 4 hours
  - 15 patients did not complete 24 hours
    - 2 discontinued due to adverse events
    - 11 discontinued due to controlled blood pressure
    - 1 required proscribed medications
    - 1 treatment failure
- 74 patients treated for 24 hours

NEUREX

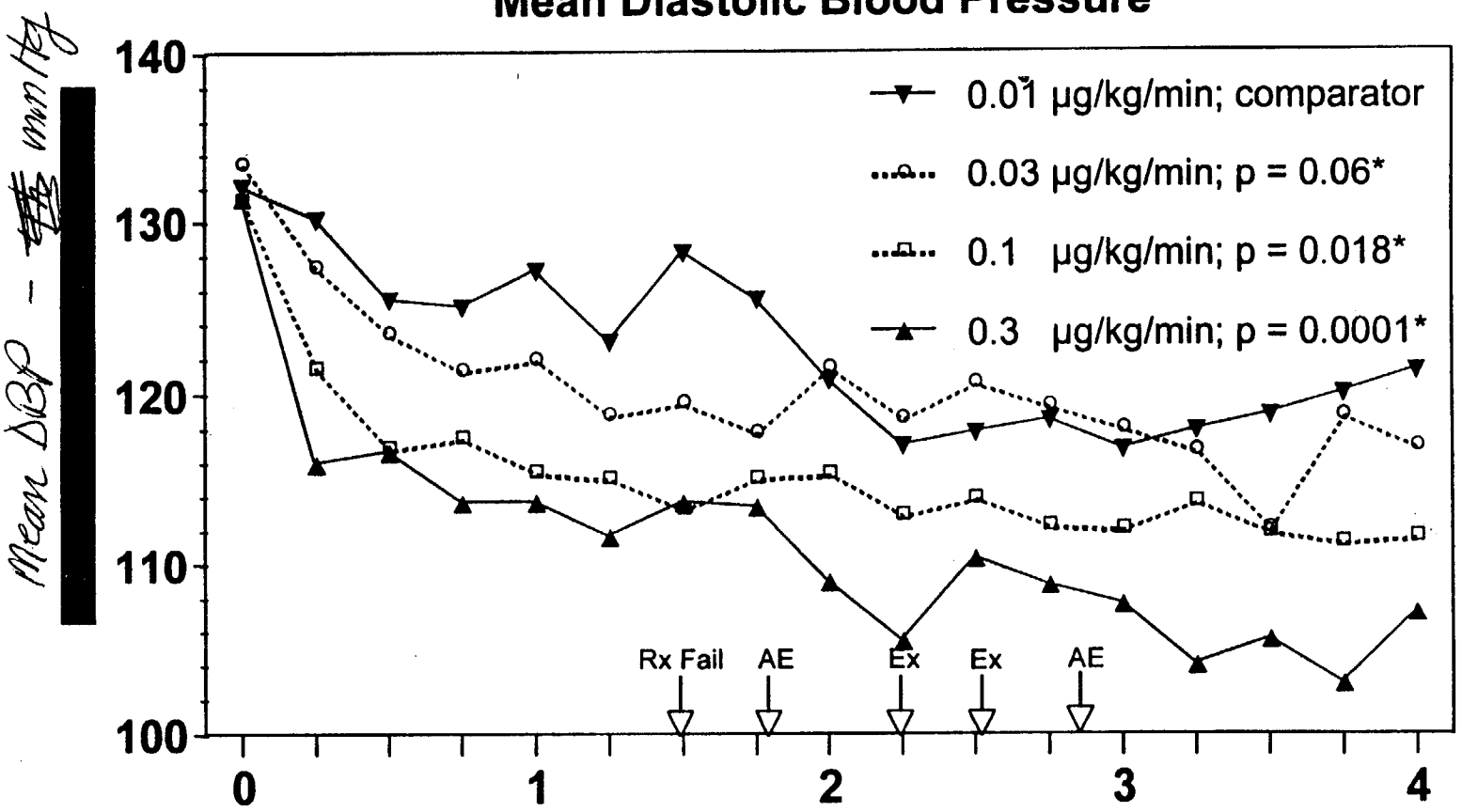
# Trial Conduct

- Only one patient unblinded before 4 hours
- 71% blinded throughout trial
- 76% maintained initial dose for 4 hours
  - 64% in 0.01 group → 87% in 0.3 group
- 47% maintained initial dose for 24 hours
  - 35% in 0.01 group → 59% in 0.3 group
- 5 patients transferred to nitroprusside
  - 2 discontinued prior to 4 hours
  - 3 discontinued after 4 hours

NEUREX

# Efficacy Endpoint

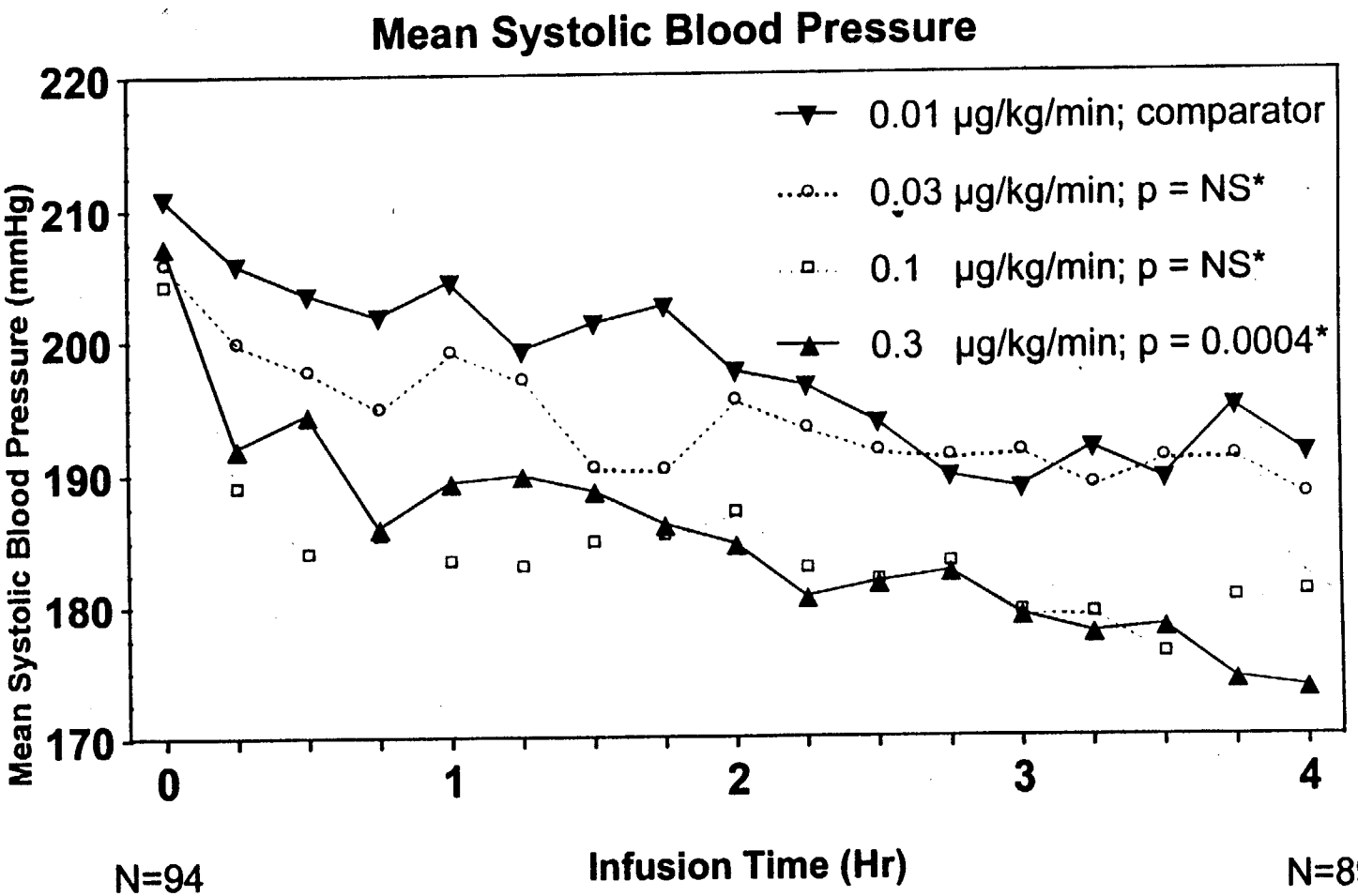
## Mean Diastolic Blood Pressure




* Paired t-test versus lowest dose group

NEUREX

# 4 Hour Systolic Blood Pressure



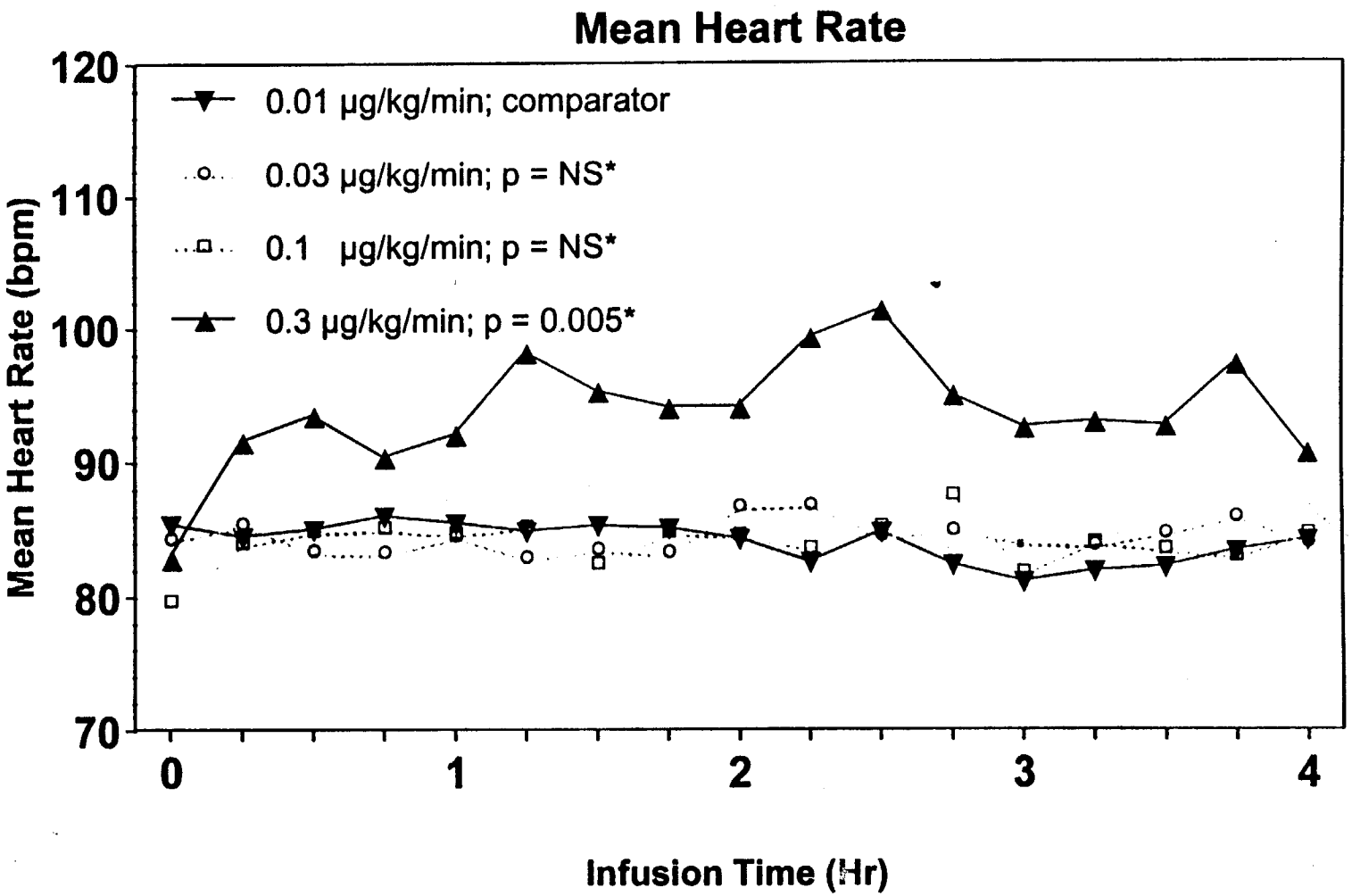

N=94

N=89

* Paired t-test versus lowest dose group

NEUREX

# 4 Hour Heart Rate




* Paired t-test versus lowest dose group

NEUREX

# Pharmacodynamic Effects in Renal Insufficiency
## SKF, B-74 (cont.)

No Duplicate Slide

- **Blood pressure effects (mean ± SEM) in patients receiving fenoldopam**

| Patient Group | N | Fenoldopam Baseline | Fenoldopam Maintenance | Fenoldopam Dose (μg/kg/min) |
|---|---|---|---|---|
| Impaired renal function | 9 | | | |
| Blood pressure (mm/Hg) | | 214 ± 8/139 ± 6 | 176 ± 8/107 ± 3* | 0.34 ± 0.06 |
| Heart rate (beats/min) | | 86 ± 6 | 86 ± 6 | |
| Nonimpaired renal function | 11 | | | |
| Blood pressure (mmHg) | | 208 ± 6/130 ± 2 | 170 ± 5/102 ±1* | 0.28 ± 0.03 |
| Heart rate (beats/min) | | 77 ± 2 | 83 ± 4 | |

* $p < 0.001$ for systolic and diastolic blood pressures compared with baseline

From: Shusterman, et al., *American Journal of Medicine* 1993, 95:161-168

# Conclusions

- Over 500 patients studied in 11 trials
- Wide range of patients studied
- Effects of fenoldopam are consistent
- Rapid onset
- Dose-dependent rate and magnitude of BP lowering
- Predictable effects

NEUREX

# Renal Function

**Vandana Mathur, M.D.**
**Neurex Corporation**

NEUREX

# Renal Function
## Introduction

- Summary of SKF hypertension studies addressing renal function
  - Blood pressure
  - Glomerular filtration
  - Renal blood flow

- Review of Neurex renal function study

- Review of independent renal function study by O'Connell, et al.

NEUREX

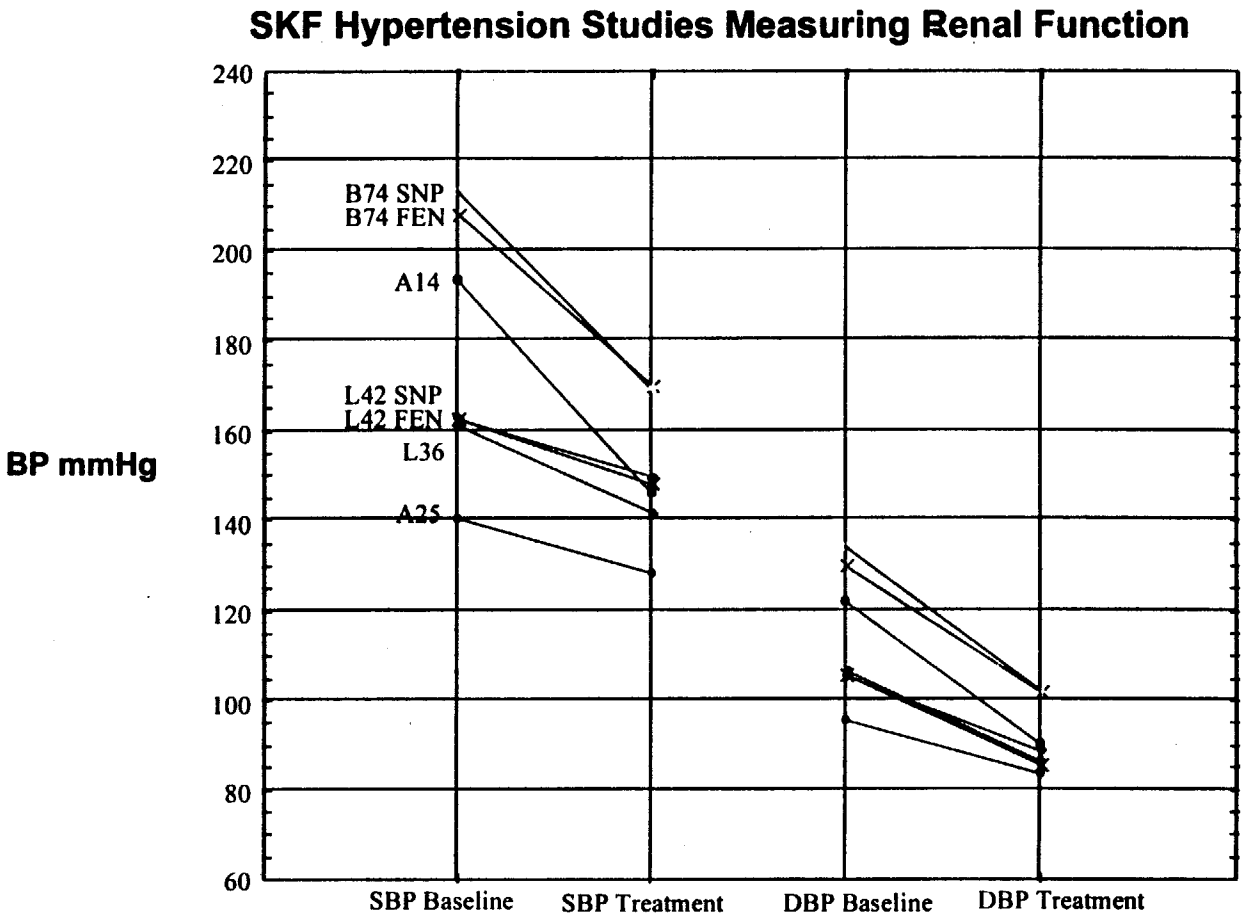
# Renal Function

## SKF Hypertension Studies

- 5 studies including 77 patients with various degrees of hypertension were studied on fenoldopam
- Placebo-controlled: 2
- Positive-control (sodium nitroprusside): 2
- Uncontrolled: 1

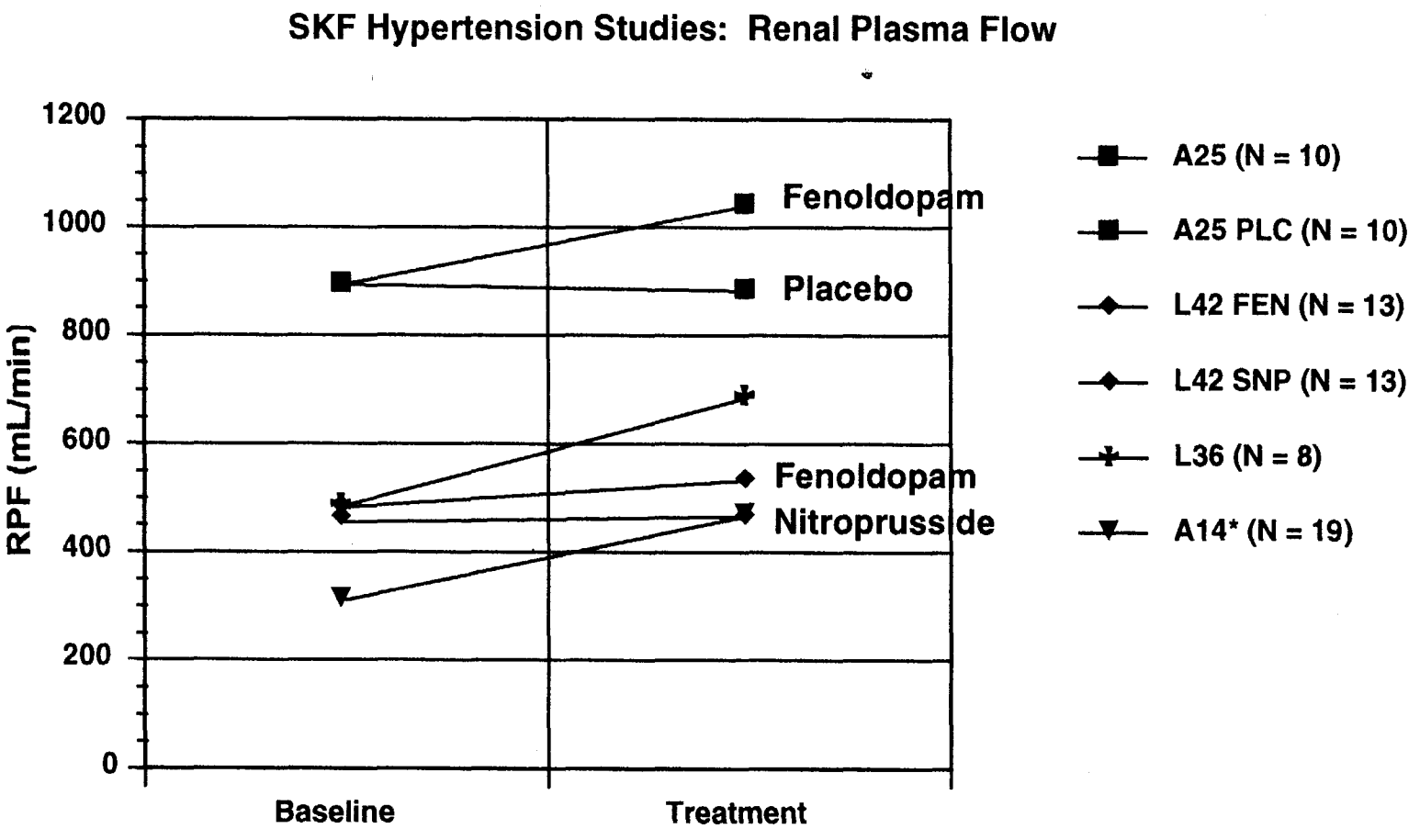
NEUREX

# Renal Function




NEUREX

# Renal Function

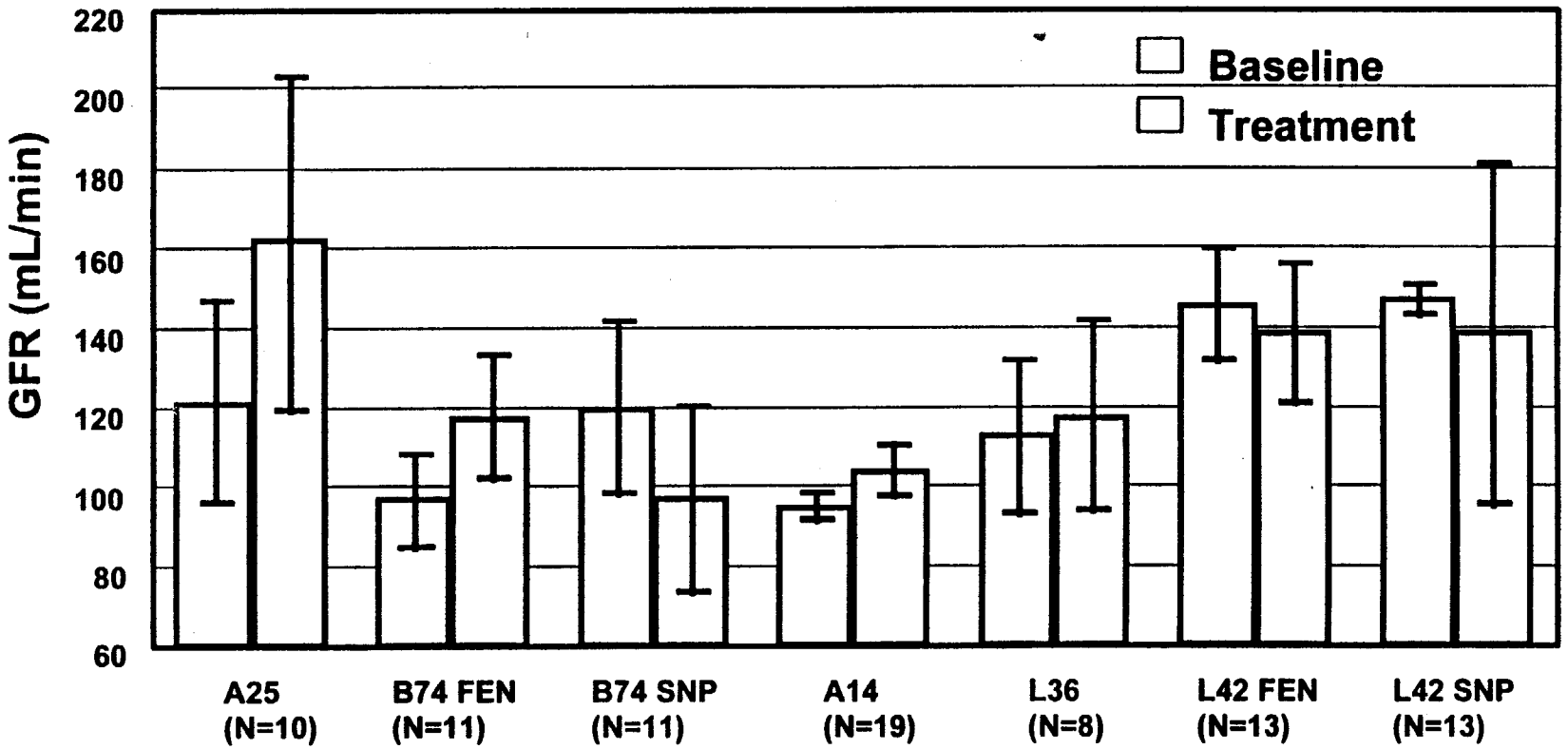



*p < 0.05 compared with baseline

NEUREX

# RENAL FUNCTION

## SKF HYPERTENSION STUDIES: GLOMERULAR FILTRATION




95% confidence intervals

NEUREX

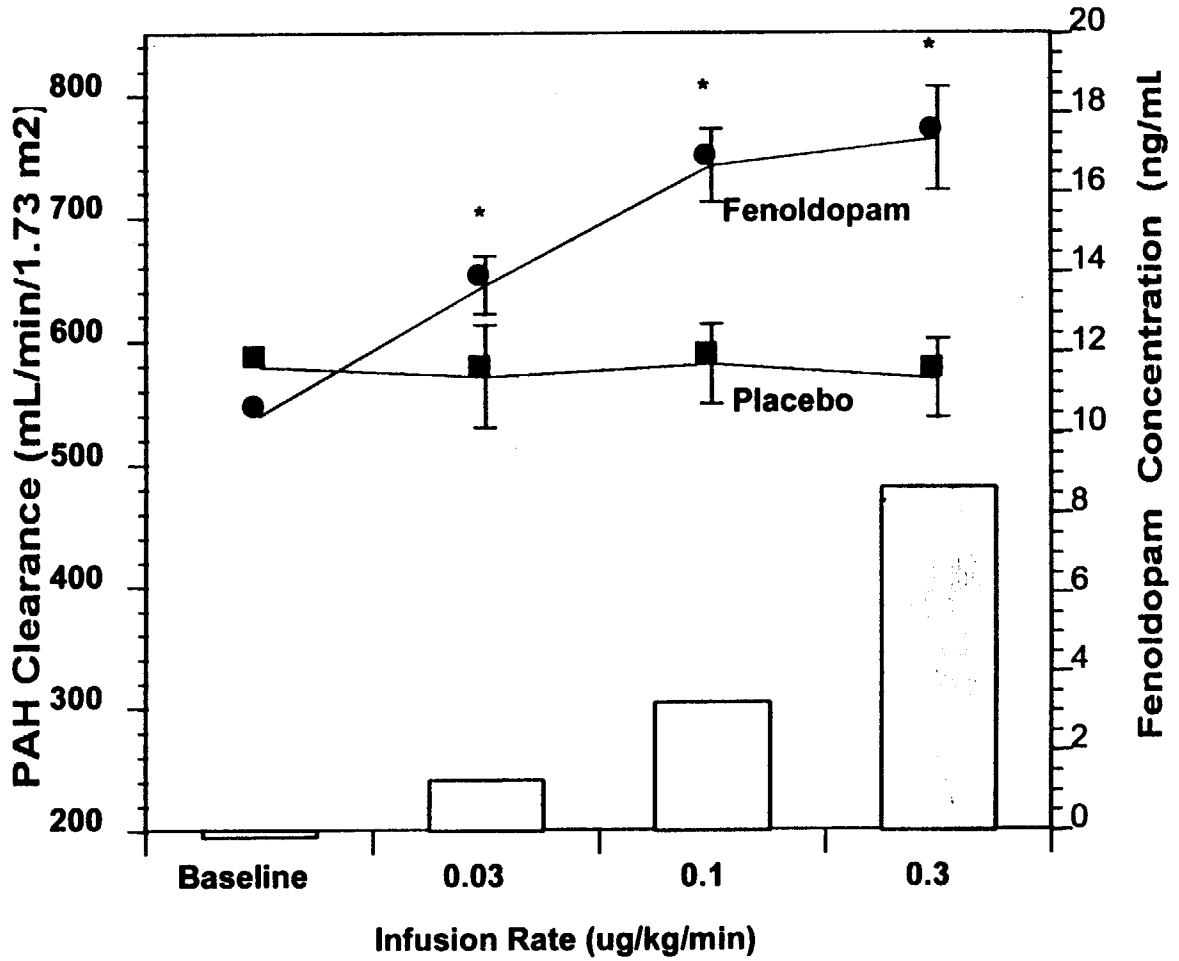
# Renal Function
## Neurex Study: Introduction

- Objective
  - To study the relationship of renal plasma flow to fenoldopam dose
- Subjects: 14 normal males
- Design: Randomized, placebo-controlled, double-blinded trial. Crossover to alternative sodium diet
- Doses: 0.03, 0.1, and 0.3 μg/kg/min fixed infusions
- Renal hemodynamics:
  - Renal plasma flow (PAH)
  - Glomerular filtration rate (inulin)
  - Electrolyte excretion
  - Hormone levels

NEUREX

# Renal Function

## Neurex Study: Renal Plasma Flow vs. Dose



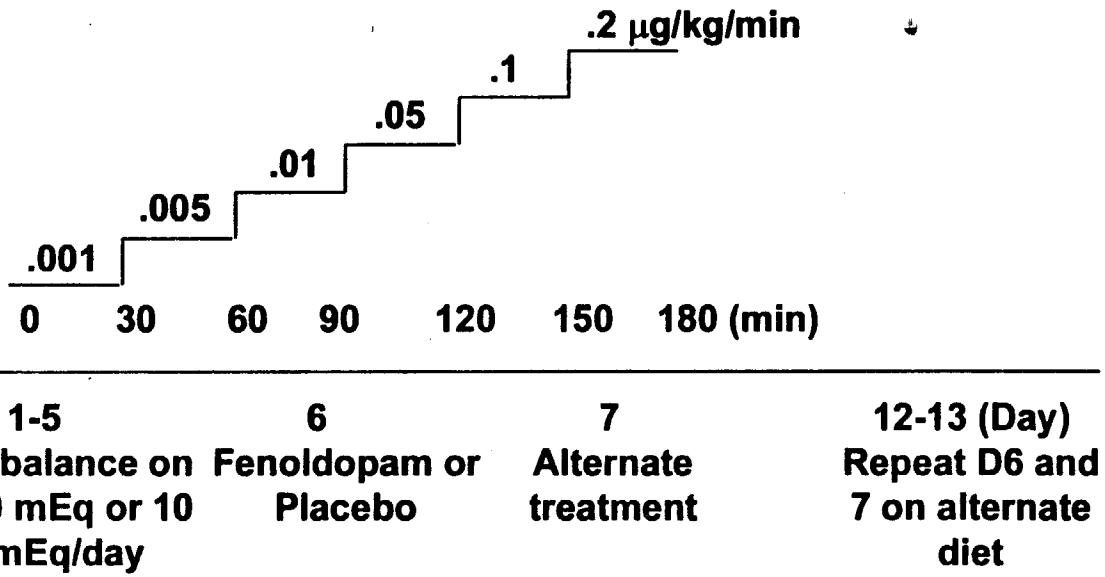

* p<0.05 compared with placebo with both diets combined

NEUREX

# Renal Function

## O'Connell, et al. Study*: Introduction

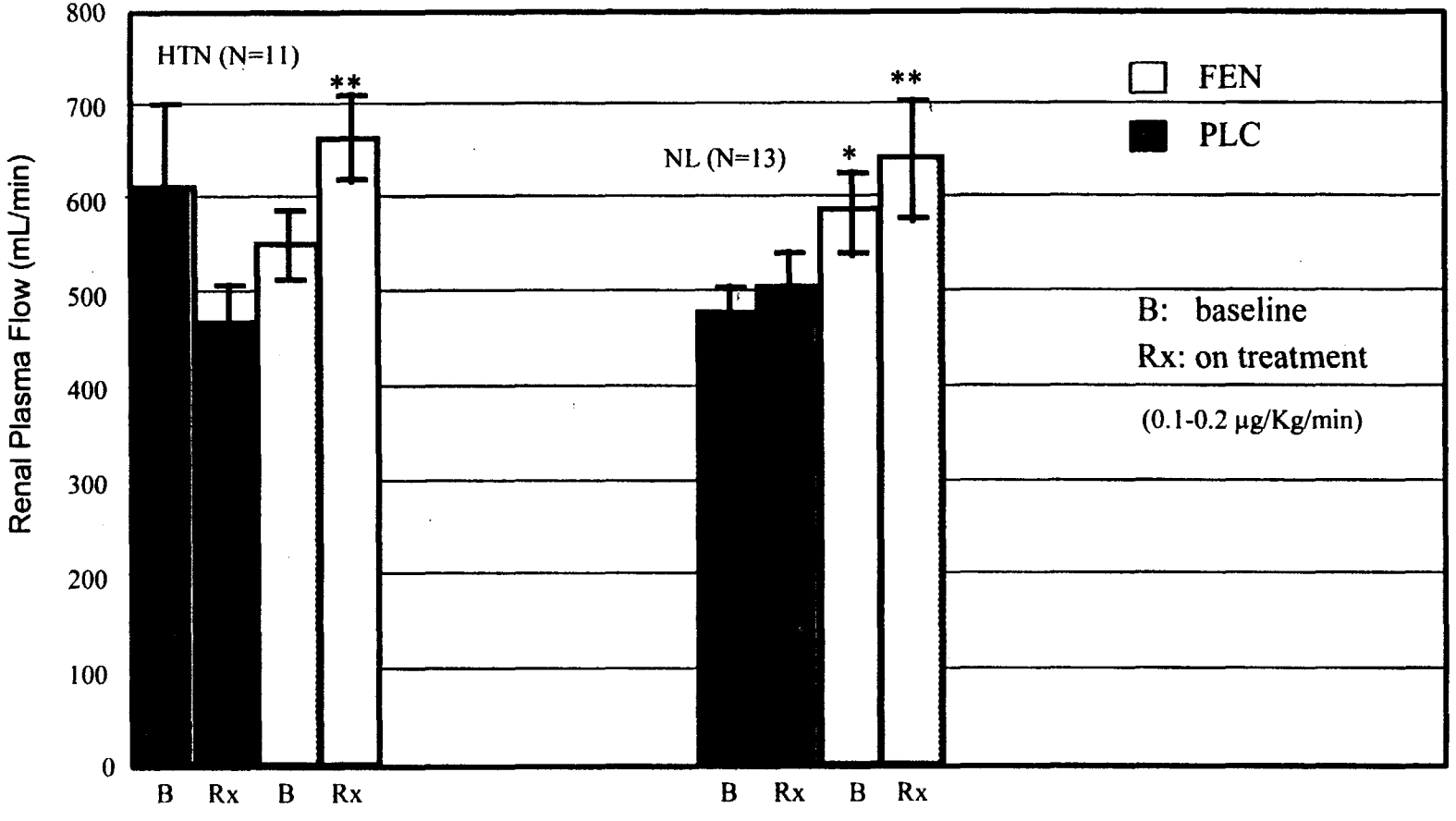
- **Objective: Determine if a proximal tubule DA1-like receptor defect is present in human essential hypertension**
- **Design: Randomized, double-blind, placebo-controlled, crossover study**
- **Subjects: 13 normal subjects, 11 patients with salt-sensitive hypertension with DBP (95-114 mmHg)**
- **Scheme:**




* O'Connell, Ragsdale, Boyd, Felder and Carey. *Hypertension* 1997 29:115-122

NEUREX

# O'Connell Study: Renal Plasma Flow




*p<0.05, **p<0.01 versus placebo SEM

Adapted from: O'Connell, Ragsdale, Boyd, Felder, and Carey. *Hypertension*. 1997;29: 115-122

NEUREX

# Renal Function

## Conclusions

- Fenoldopam increases or maintains renal plasma flow and maintains glomerular filtration while lowering systemic blood pressure
- Strongly suggests that the drug is unlikely to compromise renal function when used for blood pressure control
- Mainenance of renal perfusion and function during blood pressure lowering is an important pharmacologic and safety feature of this $DA_1$ receptor agonist

NEUREX

# Safety

**David Ellis, M.D., Ph.D.**

**Neurex Corporation**

NEUREX

# Safety Introduction

- Patient exposure
- Adverse events
- Serious adverse events
- Deaths
- EKG effects

NEUREX

# IV Experience

| Disease State | No. of Studies | No. of Patients/Subjects |
|---|---|---|
| Hypertensive emergency | 1 | 94 |
| Severe hypertension | 10 | 348 |
| Mild-to-moderate hypertension | 7 | 127 |
| Postoperative HT | 3 | 89 |
| CHF | 6 | 167 |
| Renal failure | 4 | 75 |
| Hepatic disease | 4 | 48 |
| Transplant | 2 | 21 |
| Other | 3 | 40 |
| Total patients | | 1,009 |
| Healthy subjects | | 258 |
| Total Experience | | 1,267 |

NEUREX

# Adverse Events*

| Clinical Events (N = 1,009) | Patients No. | (%) |
|---|---|---|
| Headache | 116 | (11) |
| Flushing | 53 | (5) |
| Nausea | 52 | (5) |
| Hypotension | 48 | (5) |
| Decreased serum potassium | 36 | (4) |
| ECG abnormalities | 29 | (3) |
| Tachycardia | 29 | (3) |
| Vomiting | 29 | (3) |
| Dizziness | 27 | (3) |
| Extrasystoles | 23 | (2) |
| Dyspnea | 16 | (2) |

* Occurrence > 2% in Combined SKF and Neurex Fenoldopam IV Therapeutic Studies

NEUREX

# Adverse Events*

| Event | Fenoldopam (n = 117) | Nitroprusside (n = 119) |
|---|---|---|
| Hypotension/Decreased BP | 10 | 15 |
| Flushing | 10 | 9 |
| ECG abnormal | 2 | -- |
| Nausea/vomiting | 20 | 18 |
| Headache | 18 | 19 |
| Dizziness | 4 | 5 |
| Hypokalemia (< 3.0) | 8 | 5 |

* Sum of two trials (B74, D1101)

NEUREX

# Serious Adverse Events

- 23 non-fatal serious adverse events
- Related or possibly related to study drug
- Resolved with treatment
- 18 related to cardiovascular system

NEUREX

059

# Serious Adverse Events

## Related or Possibly Related

| | |
|---|---|
| Hypotension | 6 |
| T-wave inversion | 5 |
| Extrasystoles | 2 |
| Tachycardia | 2 |
| Heart failure | 2 |
| Chest pain | 1 |
| Projectile vomiting | 1 |
| Severe abdominal pain | 1 |
| Postoperative bleeding | 1 |
| Creatinine increase | 1 |
| Mental status impairment | 1 |

NEUREX

# Deaths

- 19 deaths in total from 1,267 patients/normal subjects exposed to IV fenoldopam
  - No deaths in Neurex studies
  - 2 deaths in hypertension studies
  - 17 deaths in other diseases

NEUREX

# Deaths

- 2 deaths in hypertension studies
  - Occurred post-therapy
  - 1 due to presumed aortic dissection
  - 1 due to intracerebral hemorrhage

NEUREX

# Deaths

- 17 deaths in other diseases studied
  - 14 deaths occurred post-therapy
  - 3 deaths occurred on-therapy
    - 1 death in CHF patient, possibly related to study drug (ventricular fibrillation)
    - 2 deaths in transplant rejection patients, unrelated to study drug

NEUREX

06

# Complications in Hypertension Trials

- Cardiovascular complications
  - No deaths due to study drug
  - No myocardial infarctions
- Central nervous system complications
  - 3 CVAs
    - 2 documented intracerebral bleeds
    - 1 subarachnoid bleed
  - No deaths
- One case of ARF, post-infusion

NEUREX

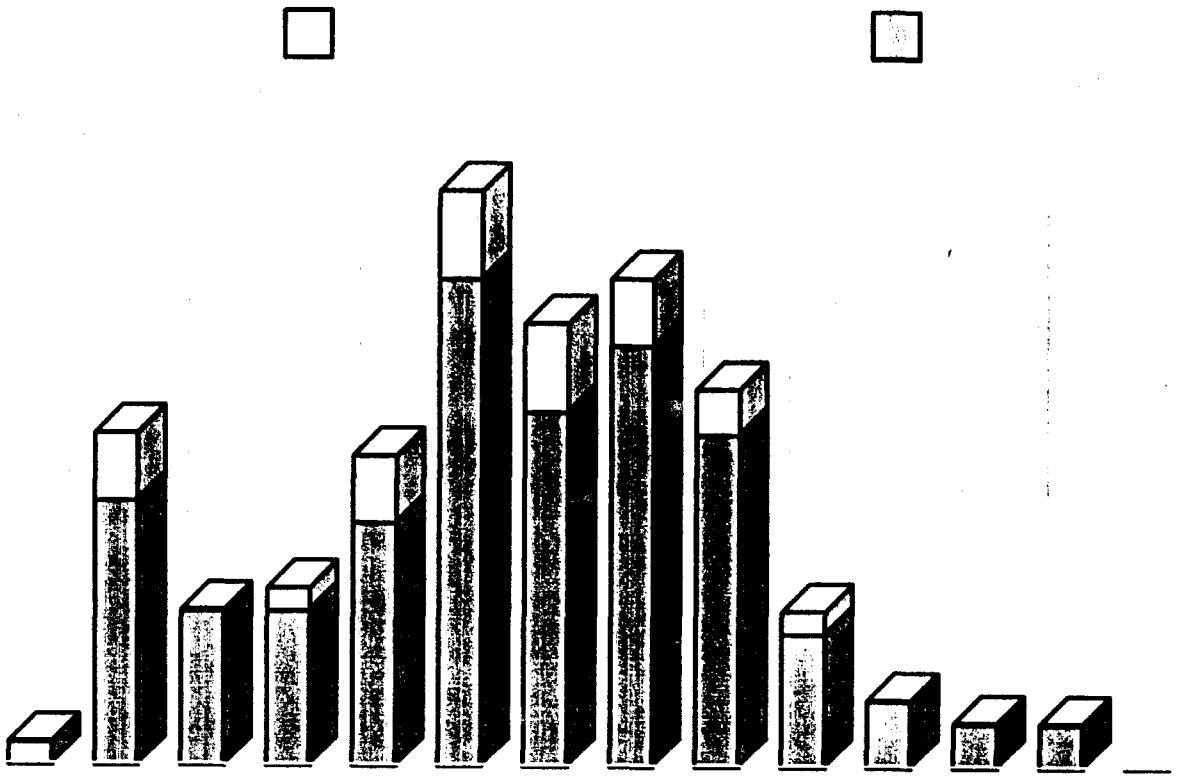
# Transition to Oral Medications

- No evidence of rebound effects
- Rapid disappearance of drug
- Administration before or after discontinuation of infusion
- Wide variety of drugs used
- Generally successful transfer to oral drugs

NEUREX

# Transition to Oral Medications

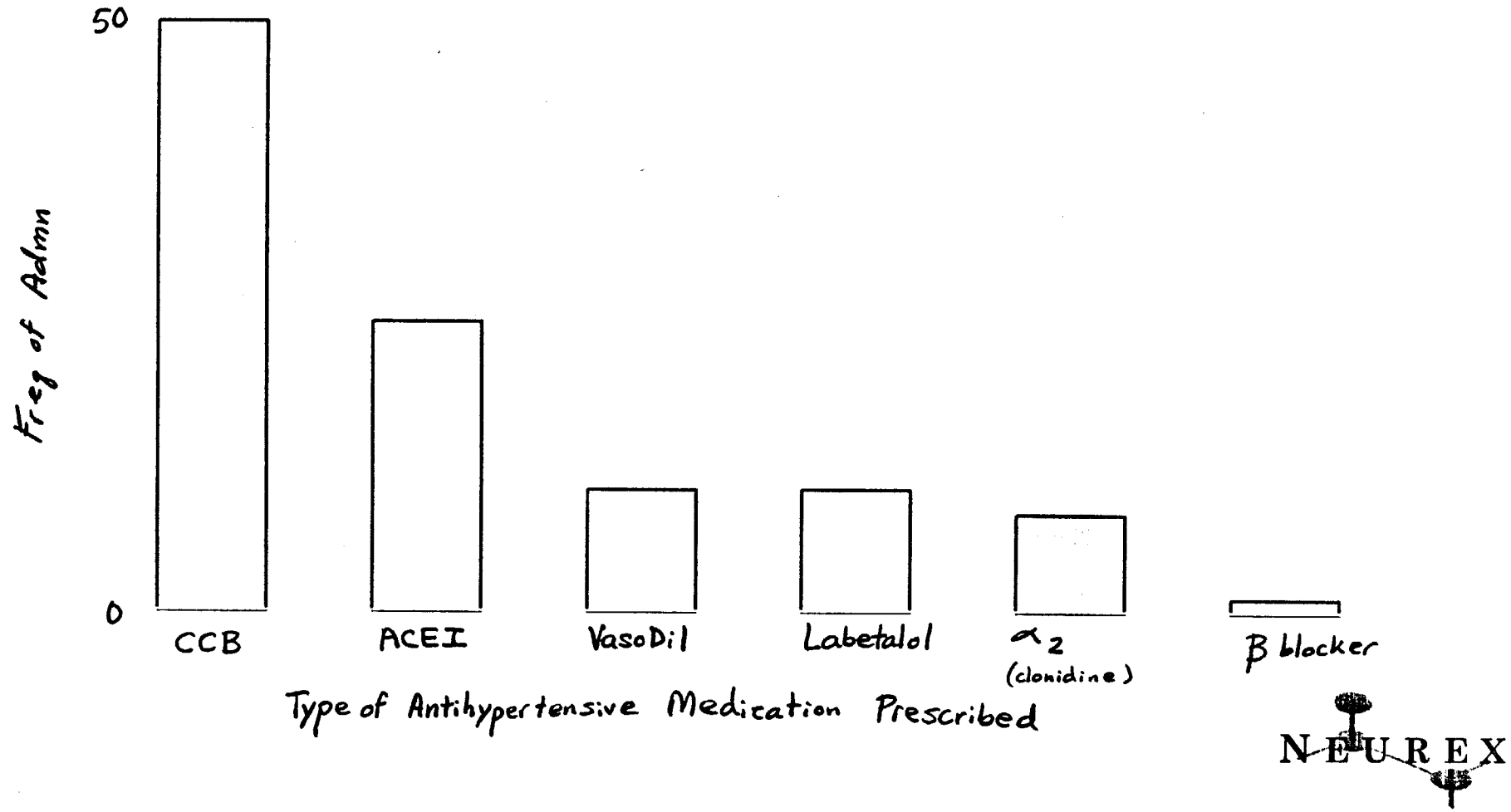
## Frequency of Administration of BP and Diuretic Oral Medications



NEUREX

# Transition to Oral Medications

## Frequency of Prescribed Oral Antihypertensive Medications




NEUREX

# QTc Intervals

- Uncontrolled severe hypertension trials suggested 1-2% prolongation
- Three trials reviewed by central reader
  - SKF: Severe hypertension (D1101)
  - Neurex: Mild to moderate hypertension (94-005)
  - Neurex: Hypertensive emergencies (94-006)

NEUREX

# Change in QTc on Therapy

## Mild to Moderate Hypertension - 94-005

| Dose | N | Baseline QTc msec | Change at 6 hours msec | # Pts. With 6 hr QTc ≥ 500 msec | # Pts. With 6 hr ▲ QTc ≥ 50 msec | # Pts. With 6 hr. ▲ QTc ≥ 10% |
|---|---|---|---|---|---|---|
| Placebo | 7 | 413 | -6.0 | 0 | 0 | 0 |
| 0.04 | 7 | 430 | -2.3 | 0 | 0 | 0 |
| 0.1 | 7 | 402 | 1.7 | 0 | 0 | 0 |
| 0.4 | 4 | 402 | -3.3 | 0 | 0 | 0 |
| 0.8 | 6 | 404 | 6.3 | 0 | 0 | 0 |

## Hypertensive Emergencies - 94-006

| | | | | | | |
|---|---|---|---|---|---|---|
| 0.01 | 18 | 449 | 5.4 | 2 | 1 | 1 |
| 0.03 | 23 | 448 | 3.7 | 2 | 2 | 2 |
| 0.1 | 16 | 445 | -9.1 | 0 | 0 | 0 |
| 0.3 | 19 | 437 | 7.4 | 1 | 2 | 2 |

## Severe Hypertension - D1101

| | | | | | | |
|---|---|---|---|---|---|---|
| Fenoldopam | 50 | 441 | 4.1 | 1 | 2 | 4 |
| Nitroprusside | 58 | 435 | 8.4 | 3 | 1 | 2 |

NEUREX

# QTc Summary

- No dose-related increase in number of patients with:
  - QTc > 500 msec
  - Δ QTc > 50 msec
  - Δ QTc > 10% increase
- No fatal events among 561 high risk severe hypertension patients

NEUREX

# Good Safety Profile

- Well-tolerated
- Adverse effects
  - Mostly exaggerated pharmacologic effects
- No evidence of fenoldopam-induced end-organ compromise
- No unexpected laboratory abnormalities
- QTc interval changes
  - No dose related
  - Without clinical sequelae

NEUREX

071

# Good Safety Characteristics

- No intra-arterial line required
- Short half-life
  - Fast offset and onset allows safe transition to oral therapy

NEUREX

# Summary

**Robert R. Luther, M.D.**
**Neurex Corporation**

NEUREX

# Efficacy: Dosing Recommendation

- Usual starting dose = 0.1 μg/kg/min
  - Rapid and substantial hypotensive effect
  - Little or no increase in heart rate
- Dosing increments at intervals not < 30 minutes
- Higher starting doses recommended when greater rate and/or magnitude of effect is desired

NEUREX

# Label Considerations

- Indications
  - Short-term treatment of hypertension when oral therapy is not feasible or possible
  - Treatment of severe hypertension with or without acute end-organ damage

- Renal pharmacology

NEUREX

3760 Haven Avenue, Menlo Park, California 94025-1012, (415) 853-1500, FAX (415) 853-1538

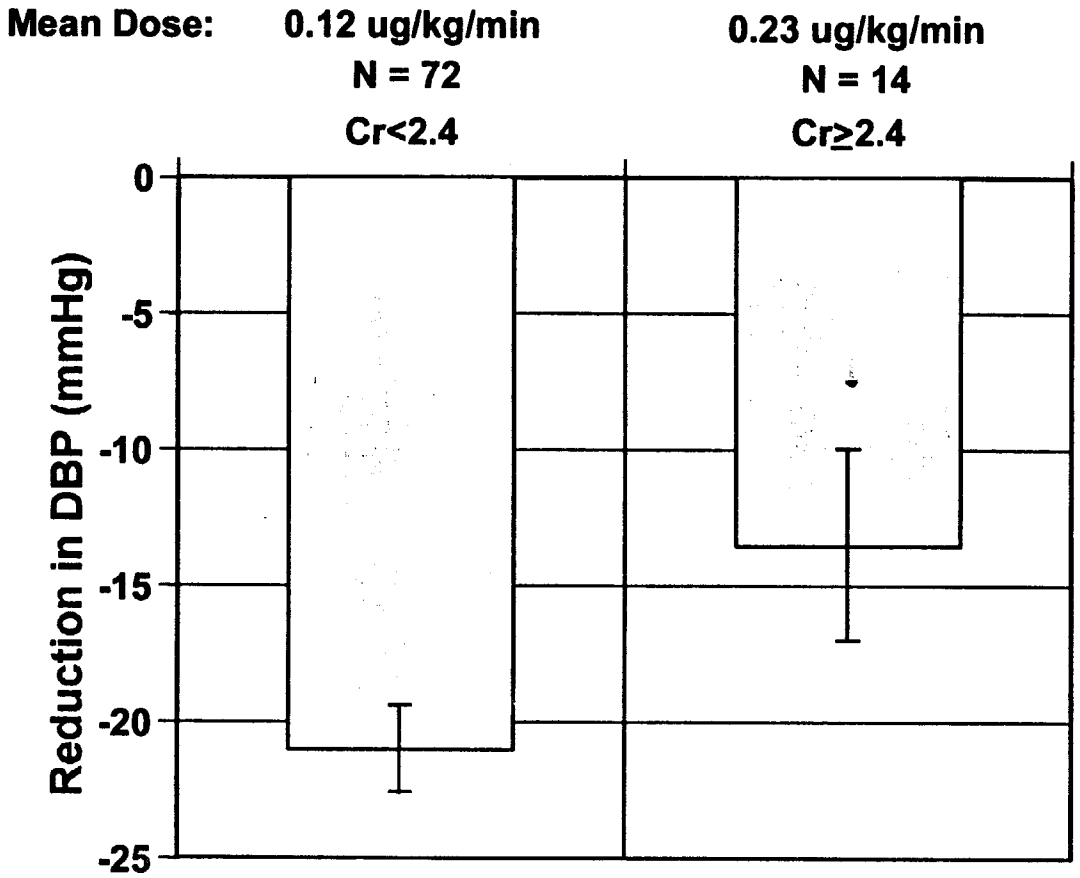


# Fenoldopam Benefits

- Ease of use
- Rapid, predictable, dose dependent blood pressure lowering without overshoot
- Short $t_{1/2}$, rapid attainment of $C_{ss}$, ease of titration
- Well-behaved, linear pharmacokinetics
- No cytochrome $P_{450}$ interactions
- Starting dose and dose-response curves well defined
- No dosing adjustment for pre-existing renal or hepatic disease
- Good safety profile with no evidence of end-organ compromise

# Effect versus Creatinine Level

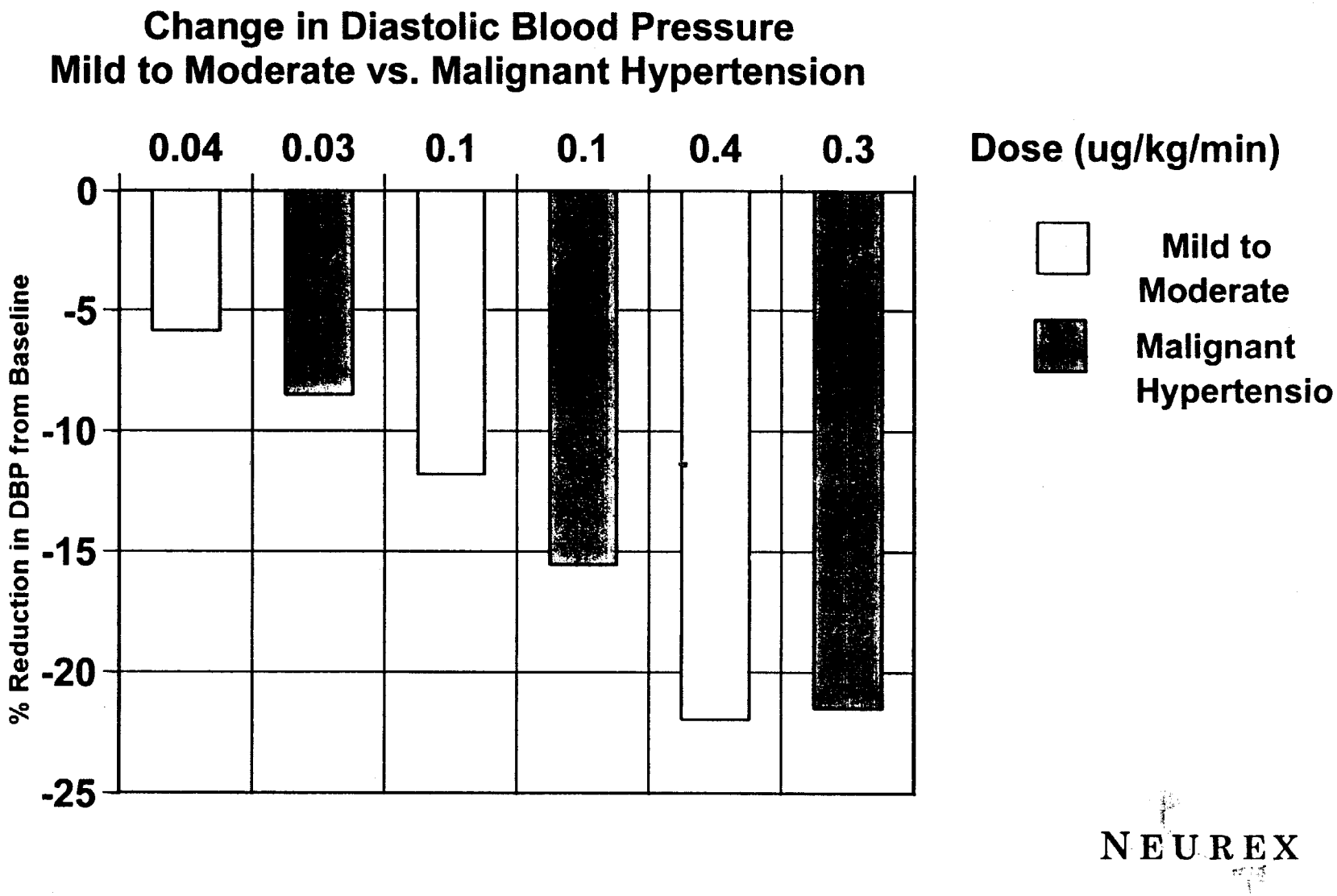
## Mean Reduction in DBP at 4 hours (All Doses Combined, 94-006)




Error bars ± S.E.

NEUREX

# Comparison of Diastolic Blood Pressure




NEUREX