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SBA

NDA No.: 19-032
Applicant Name: A. H. Robins Co.

Drug Generic Name: Guanfacine
Drug Trade Name: Tenex™

I. Indications for Use

Tenex (guanfacine hydrochloride) is indicated in the management of hypertension. Since dosing information (see DOSAGE and ADMINISTRATION) has been established in the presence of a thiazide-type diuretic, Tenex should, therefore, be used in patients who are already receiving a thiazide-type diuretic.

II. Dosage Form, Route of Administration and Recommended Dosage

Oral tablets containing 1 mg guanfacine hydrochloride. The recommended dose of Tenex (guanfacine hydrochloride) is 1 mg daily given at bedtime to minimize somnolence. Patients should already be receiving a thiazide-type diuretic.

If after 3 to 4 weeks of therapy, 1 mg does not give a satisfactory result, doses of 2 and then subsequently 3 mg may be given, although most of the effect of Tenex is seen at 1 mg (see Clinical Pharmacology). Some patients may show a rise in pressure toward the end of the dosing interval; in this event a divided dose may be utilized.

Higher daily doses (rarely up to 40 mg/day, in divided doses) have been used, but adverse reactions increase significantly with doses above 3 mg/day; and there is no evidence of increased efficacy. No studies have established an appropriate dose or dosing interval when Tenex (guanfacine hydrochloride) is given as the sole antihypertensive agent.

The frequency of rebound hypertension is low, but rebound can occur. When rebound occurs, it does so after 2-4 days, which is delayed compared with clonidine hydrochloride. This is consistent with the longer half-life of guanfacine. In most cases after abrupt withdrawal of guanfacine, blood pressure returns to pretreatment levels slowly (within 2-4 days) without ill effects.

III. Manufacturing and Control

A. Manufacturing and Control

The new drug substance, guanfacine hydrochloride, as supplied, is manufactured as defined in an appropriately written Drug Master File to which the applicant has authorized reference. The new drug substance is subject to such controls as are necessary to ensure its identity, purity, strength, and quality.

The tablet dosage form will be manufactured according to Current Good Manufacturing Practices by using only approved lots of active ingredients and excipients in plant facilities described in a reference Drug Master File.

This application contains Raw Material Specifications and Test Procedures, Manufacturing Procedures, Product Specifications and Test Procedures, and Packaging Material Specifications and Test Procedures supported where necessary by appropriate reference to Drug Master Files to ensure the identity, strength, quality, and purity of the finished drug product.

The product is a light-pink, diamond-shaped, compressed tablet with an embossed "1" engraved with "AHR" on one side and "Tenex" engraved on the opposite side. Test Procedures will ensure satisfactory dissolution and content uniformity of the finished tablet.

B. Stability

Stability studies of the drug product have been conducted and are continuing according to a defined protocol. In these studies the drug product is contained in amber glass containers, high-density polyethylene plastic containers, and in film/foil blister packaging. The data submitted adequately support the requested 2-year expiration date.

C. Methods Validation

Analytical methods used in testing the active ingredient and finished drug product, including an evaluation of its stability, have been appropriately validated.

D. Labeling

The immediate container label and carton labels are in compliance with technical requirements pertaining to the following: established name, ingredients statement, control number, expiration date, prescription caution, applicant's name and address, and net contents statement. Likewise, the "Description" and "How Supplied" sections of the package insert are satisfactory with respect to the technical requirements of the regulations.

E. Establishment Inspection

Inspections of A. H. Robins facilities have been performed to determine their compliance with Current Good Manufacturing Practice Regulations. A satisfactory report was received from the Office of Compliance, indicating no reason to withhold approval of the application. The applicant has the personnel, facilities, methods, and controls to produce the drug in accordance with the NDA procedures and commitments.

F. Environmental Impact Analysis Report

A report on the impact on the environment was submitted. There is expected to be little or no impact on the environment due to the manufacture of guanfacine hydrochloride.

IV. Pharmacology

A. Studies on Activities Related to the Primary Therapeutic Action

Guanfacine produced significant reductions of the elevated blood pressures in DOCA/salt, spontaneously and renal hypertensive rats and in renal hypertensive dogs when administered as a single oral dose. In DOCA/salt and renal hypertensive rats, the antihypertensive effect was dose-dependent between 0.3 to 5 mg/kg orally. In renal hypertensive rats the peak antihypertensive effect occurred 2-4 hrs after an oral dose of 2 mg/kg with a duration of action of over 6 but not more than 24 hours. In renal hypertensive dogs, peak reduction in blood pressure occurred 8 hours after 1 mg/kg orally and was paralleled by a pronounced bradycardia. Guanfacine was approximately one-tenth as potent, on a weight basis, as clonidine in DOCA/salt and spontaneously hypertensive rats and in renal hypertensive dogs. The daily administration of 3 mg/kg of guanfacine for a 5-week period to young spontaneously hypertensive rats blunted the progressive development of the hypertensive state.

Most of the antihypertensive action of guanfacine is exerted through stimulation of central α_2 -adrenergic receptors. Several observations indicate the primary importance of the central effect. Low levels of guanfacine elicited a fall in blood pressure and heart rate in anesthetized cats when injected intracerebroventricularly; larger doses were required for an effect by the intravenous route (Table I).

Table I

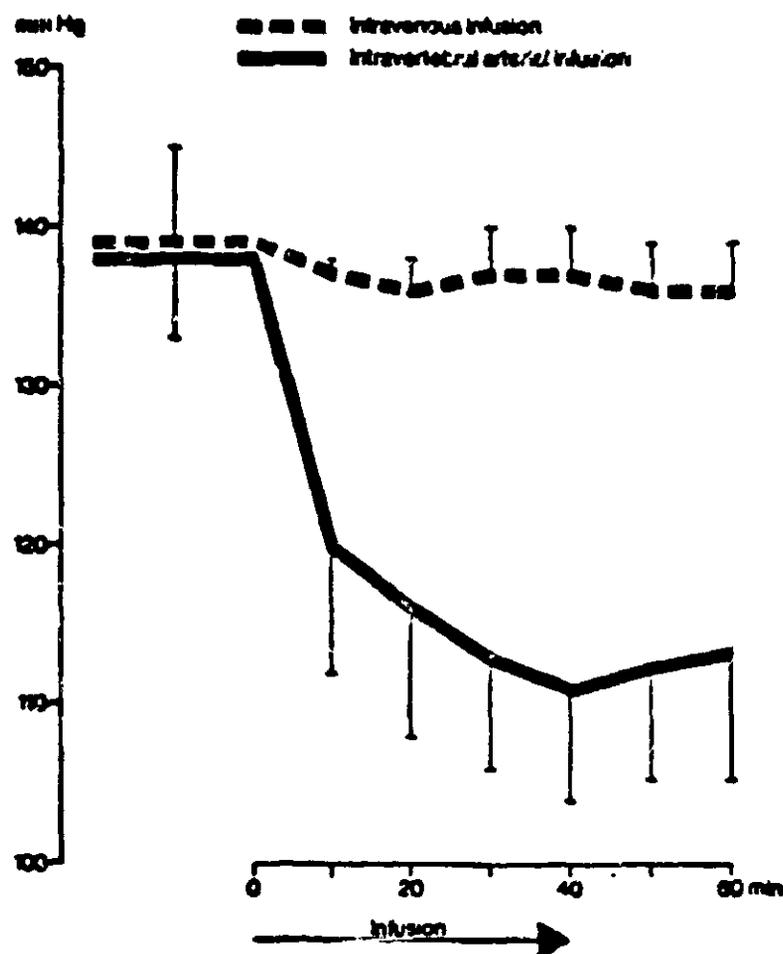
Route of Administration	ED ₅₀ (μ g/kg) ^a	Reference
Intravenous	83	Scholtysik, Laueraer et al. <i>Arzneim-Forsch.</i> 25(10) 1483-1491 (1975)
Intracerebroventricular	45	Scholtysik <i>Proc. 6th Int. Symposium on Med. Chem.</i> pp. 61-70 (1979).

^aApproximate dose that produces a 50% reduction of spontaneous preganglionic sympathetic nerve discharge activity.

Also, the infusion of guanfacine into the vertebral artery of anesthetized dogs produced a fall in blood pressure greater than that achieved with intravenous administration (Table II).

Table II

Effects of guanfacine (1 mg/kg/min) on the mean blood pressure in anesthetized dogs in response to intravertebral arterial and intravenous infusions. Mean values \pm SEM from eight experiments for each route of administration.



Scholtysik et al. "Guanfacine" in Pharmacology of Antihypertensive Drugs.
Raven

Press p. 79-98 (1980).

The blockade of central α_2 -receptors with selective antagonists phentolamine and piperoxan prevented the hypotension and bradycardia elicited by the central application of guanfacine (Table III).

Table III
Pharmacological Antagonism of Central Action of Guanfacine

Alpha Adrenergic Antagonist	Dose	Route of Administration	Test System	Response
Phentolamine ^a	50 mg/kg	i.c.v.	Anesthetized cat	Blocked guanfacine-induced hypotension and bradycardia
Piperoxan ^b	100 mg/kg	Vertebral artery	Anesthetized cat	Blocked guanfacine-induced hypotension and bradycardia

^aScholtysik, Lavener *et al.*, *Arzneim Forsch* 25(10) 1483-1491 (1975).

^bVan Zwiefen. *Brit. J. Clin. Pharmacol.* 10(1) 13s-20s (1980).

Guanfacine exhibited a much greater selectivity for α_2 - over α_1 -receptor sites in the brain than either clonidine or guanabenz, as determined from radioligand binding studies. Displacement of guanfacine from high affinity binding sites was most effected by antagonists and other agonists that are known to bind to α_2 -adrenergic receptors. Guanfacine produced transient vasopressor responses similar to those produced by clonidine and norepinephrine and is therefore not totally devoid of post synaptic α_1 -receptor stimulant properties.

Guanfacine inhibits peripheral sympathetic neurotransmission by stimulating presynaptic α_2 -receptors that regulate transmitter release from adrenergic nerves. In isolated hearts, the norepinephrine release and tachycardia induced by peripheral nerve stimulation is inhibited by guanfacine.

The abrupt cessation of chronic guanfacine treatment in animals resulted in less rebound hypertension and tachycardia than was observed with clonidine withdrawal. The slower rate of elimination of guanfacine relative to clonidine appears to be the underlying basis for the delayed and diminished symptoms associated with guanfacine withdrawal.

B. Other Pharmacological Actions

Guanfacine enhanced vagal inhibitory activity on the heart, as evidenced by enhanced reflex bradycardia elicited by transient

occlusion of the aorta in anesthetized dogs. The compensatory increase in blood pressure produced by carotid occlusion in dogs was also inhibited by guanfacine.

Guanfacine's action on renal function is correlated with the hemodynamic changes elicited on renal perfusion. In anesthetized dogs, intravenous doses of 3 and 10 $\mu\text{g}/\text{kg}$ caused dose-dependent increases in renal blood flow that occurred during the peak hypertensive phase and were attributed to an increase in renal perfusion pressure.

Guanfacine had no effect on dopamine turnover in rat brain and did not alter the norepinephrine reuptake mechanism. It had no dopamine agonist or antagonist actions.

Guanfacine differs from clonidine in its interaction with histamine receptors. Whereas clonidine stimulated gastric acid secretion in anesthetized rats via a histaminergic mechanism, guanfacine had no effect on gastric acid secretion in rats at antihypertensive levels.

Guanfacine, like clonidine, inhibited spontaneous motor activity in mice at an oral ED_{50} of 1.3 mg/kg. Neurotoxicity and motor impairment caused by guanfacine in mice occurred at doses approximately 300 times greater than doses affecting spontaneous motor activity.

At comparable antihypertensive doses, guanfacine (3 mg/kg, SC) was marginally sedative vs a strong sedative effect elicited by clonidine (0.3 mg/kg, SC) in dogs. In rats, guanfacine was 20-25 times less potent than clonidine in its sedative activity.

C. Pharmacokinetics

The absorption, distribution, metabolism, and excretion of guanfacine were investigated primarily in 2 animal species, i.e., the Wistar rat and the Beagle dog. After oral dosing, the absorption of guanfacine in both species was relatively rapid and essentially complete.

Guanfacine was widely distributed in the tissues of the rat. Autoradiographic studies identified the highest level of radioactivity in the gastrointestinal tract, followed by liver and kidneys.

The studies indicated that ^{14}C -Guanfacine crossed the placenta. Radioactivity was observed in the gastrointestinal tract, lung, and liver of the fetus and was also found in the milk of lactating rats.

Extensive metabolism of guanfacine occurred in the rat, only 1 to 3% of the dose being excreted in the urine as unchanged drug. Parent drug accounted for 25% of the dose in dog urine. The major urinary metabolites identified in the rat were the conjugates of 3-hydroxy guanfacine and in the dog the main metabolite was the

dihydrodiol derivative. The rate of elimination of guanfacine and its metabolites was rapid in these 2 species. Excretion of total radioactivity in the rat was equally divided between urine and feces. At least 75% of the fecal radioactivity was the result of biliary excretion. In the dog, 77 to 79% of the administered radioactivity appeared in urine.

D. Toxicology

In a one year oral toxicity study in dogs, daily doses of 0.3 mg/kg in capsules, approximately 6 times the maximum recommended human dose (MRHD) in a 60 kg person, were well tolerated. Higher doses of 1.0 and 3.0 mg/kg were associated with reduced food intake and body weight gains, reduced hemoglobin and hematocrit, reduced blood sugar, reduced urinary excretion of sodium and potassium, increased BUN, changes in EKG and atrophic and anemic spleens. Discoloration and centrilobular swelling of the liver, at incidences above concurrent control, were observed at 3.0 mg/kg.

A 102 week oral (drug in feed) toxicity/carcinogenicity study in rats revealed no evidence of drug related tumorigenicity at daily doses up to 5.0 mg/kg/day, 100 times the MRHD and a dose which reduced body weight gain and increased the incidence and severity of corneal clouding and subcapsular focal lenticular opacity observed in concurrent control rats. Clinical laboratory findings at this dosage were similar to findings reported at mid and high dose levels in the one year dog study. There were, however, no drug related gross or microscopic post-mortem findings.

Mice were treated for 78 weeks with guanfacine administered in feed at doses of 1.0, 3.0 and 10.0 mg/kg/day, i.e., up to 200 times the MRHD. There was no evidence of drug related tumorigenicity but high dose mice exhibited corneal opacity and lymphopenia at incidences above concurrent control.

Guanfacine was not mutagenic in four different test systems (Ames Test, Mouse Micronucleated Bone Marrow Test, Mouse Dominant Lethal Test and Chinese Hamster Bone Marrow Chromosome Aberration Test).

Reproduction studies in rats showed that guanfacine did not impair fertility of either males or females or affect postnatal development of offspring, even at maternally toxic doses. Teratology studies in rats and rabbits revealed no evidence of adverse effects on the development of embryo or fetus at 20 times the MRHD in the rabbit and 70 times the MRHD in the rat. Higher doses (100 and 200 times the MRHD in rabbits and rats, respectively) were associated with reduced fetal survival and maternal toxicity.

V. Medical

A. Clinical Pharmacology

1. Bioavailability and Pharmacokinetic Studies

1. Bioavailability and Pharmacokinetics Studies

Report No.	Principal Investigator/ Principal Monitor	Purpose of Study	Number of Subjects	Guanfacine Dose	Guanfacine Dosage Schedule
83-0407	Hanigan/ Melikian	Bioavailability Bioequivalence	23	1 mg	PO Tablet 1 mg qd x 6 days PO Capsule 1 mg qd x 6 days PO Solution (0.1 mg/mL) 1 mg qd x 6 days
83-0408	Hanigan/ Melikian	Bioavailability Bioequivalence	24	2 mg	PO Tablet 2.1 mg qd x 6 days PO Capsule 2.1 mg qd x 6 days PO Solution (0.1 mg/mL) 2 mg qd x 6 days
80-337	Kiechel	ADME	7	2 mg 3 mg	IV Solution 2 mg/2 mL - single dose PO Solution 3 mg/20 mL - single dose
80-0288	Beveridge	ADME	6	4 mg	PO Solution 4 mg/20 mL - single dose
83-0201	Poser	Protein binding	<u>in vitro</u>		
84-0573	Hanigan/ Carchman	Bioavailability	18	3 mg	PO Tablet 31-mg - single dose IV Solution - single dose
84-0582	Blackshear/ Carchman	Pharmacokinetics Mild to moderate hypertensives	20	1 mg	PO Chlorthalidone 25 mg x 3 weeks PO Chlorthalidone 25 mg w/PO Guanfacine Tablet 1 mg x 6 days

1. Bioavailability and Pharmacokinetic Studies (continued)

Report No.	Principal Investigator/ Principal Monitor	Purpose of Study	Number of Subjects	Guanfacine Dose	Guanfacine Dosage Schedule
Clin. Pharmacol. Ther. 25(3): 283-93, 1979. 200213	Weiss	ADME Dose Proportionality	9 10 15a	2 mg 4 mg 1-3 mg	P0 Tablet 2 mg - single dose P0 Tablet 4 mg - single dose P0 Tablet 1-3 mg b.i.d. x 60 days
Clin. Pharmacokin. 5(5) 476-83, 1980. 200127	Kirch	Effects of renal insufficiency	18 (6 GFR > 90 mL/min) (6 GFR 10-30 mL/min) (6 GFR < 10 mL/min)	3 mg 1 mg	IV Solution 3 mg/mL - single dose P0 Tablet 1 mg t.i.d. x 5 days
Nephrol. 1:73-81, 200125	Kiechel	Effect of renal insufficiency	10 (5 GFR < 30 mL/min 5 hemodialysis)	4 mg 3-4 mg	P0 Tablet 4 mg - single dose P0 Tablet 3-4 mg daily x 2 doses
Clin. Pharmacol. Thera. 35(5) 604-9, 1984	Hedner	Effects of long-term use of guanfacine	13	0.5-4 mg	Initially b.i.d., then o.d.

^aFifteen of the 19 patients were continued with multiple dosing.

The pharmacokinetics of guanfacine hydrochloride have been studied in normal volunteers and patients. Guanfacine was found to be rapidly and well (about 80%) absorbed from oral dosage forms. The elimination half-life in patients averaged about 17 hours but varied from 10 to 30 hours. Older patients (>50 years) tended to eliminate the drug more slowly, independent of renal function. In younger normal volunteers and patients (<50 years), the elimination half-life, on average, was found to be about 13-14 hours. In most instances steady state was attained within four days.

Two multiple dose studies were conducted to establish the extent of absorption of guanfacine from solid dosage forms in relation to solution (Melikian, 83-0407; Melikian, 83-0408). Each was a nonblinded, randomized, three-way, crossover study in healthy male volunteers. In the first study plasma levels of guanfacine were compared following 6 days of dosing with the A. H. Robins 1-mg tablet, 1-mg capsule, and a solution of 1-mg of guanfacine. In the second study the extent of absorption from two Sandoz solid dosage forms (2, 1-mg capsules; 2, 1-mg tablet) was established relative to a solution of 2-mg of guanfacine after dosing for 6 days. The mean plasma concentration-time curves from each study are shown in Figures 1 and 2. Pertinent pharmacokinetic parameters are listed in Tables IV and V.

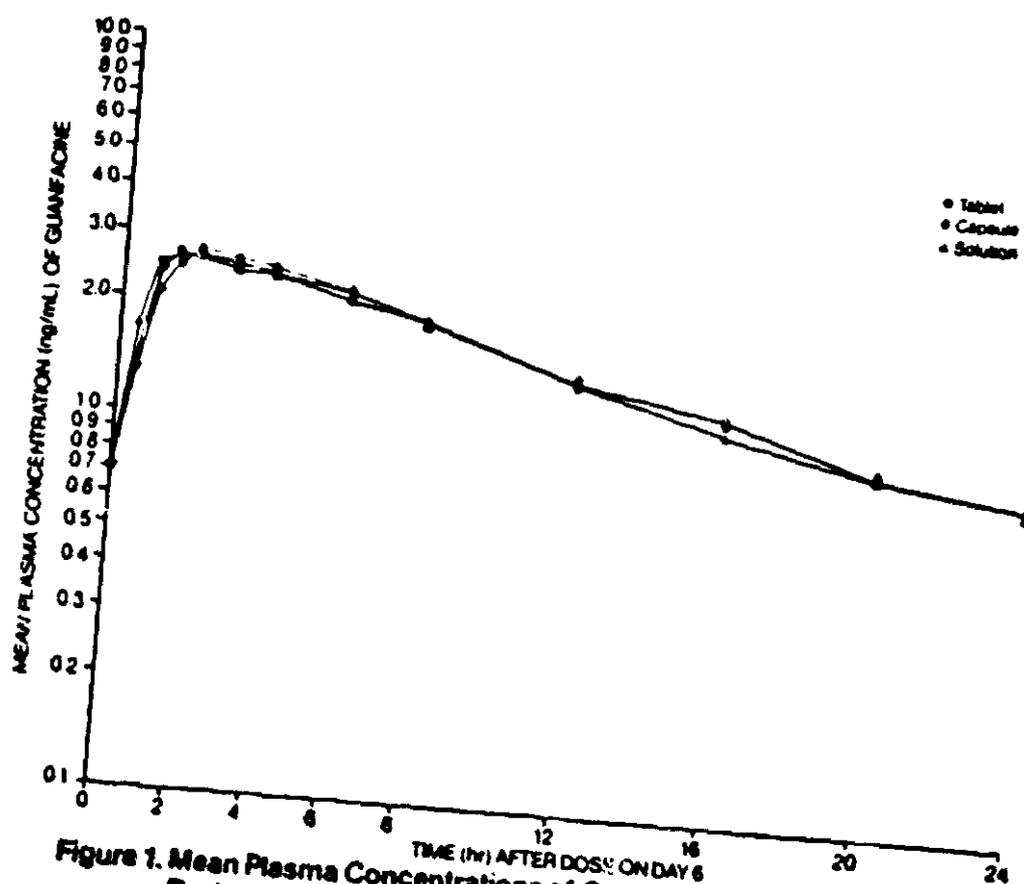


Figure 1. Mean Plasma Concentrations of Guanfacine in 23 Subjects During a 24-Hr. Interval on Day 6 After 6 Days of Single Daily Doses of 1 mg Guanfacine HCl/Day.

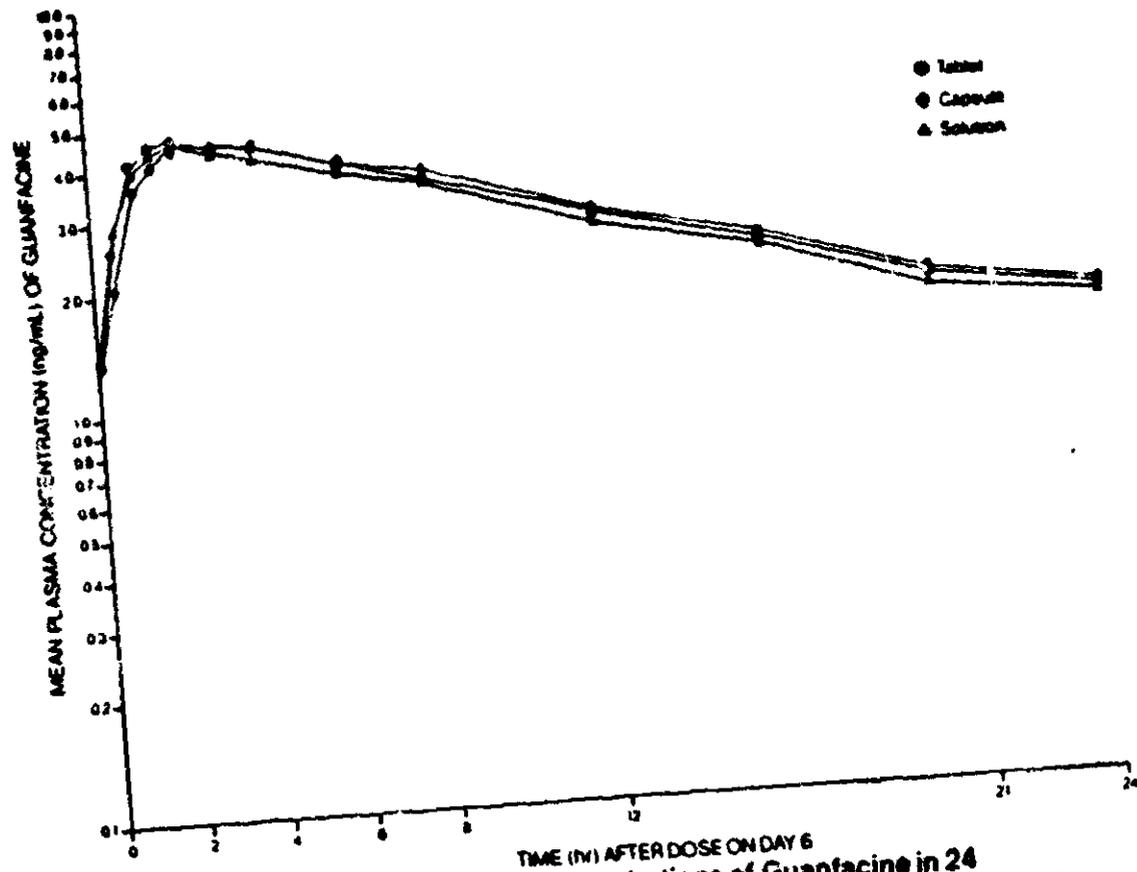


Figure 2. Mean Plasma Concentrations of Guanfacine in 24 Subjects During a 24-Hr Interval on Day 6 After 6 Days of Single Daily Doses of 2 mg Guanfacine HCl/Day.

These two studies established the equivalency of the solid dosage forms with a reference solution. Since both capsule and tablet formulations of the two studies were shown to be bioequivalent to the same reference solution, the capsule and tablet dosage forms developed by A. H. Robins and used in Sandoz studies in Europe were bioequivalent to one another.

In an open, single-dose, randomized, two-way, crossover study in 18 healthy male volunteers, the absolute bioavailability of guanfacine from a single oral dose of 3 mg was shown to be 81.2% with respect to the intravenous formulation (Carchman, 84-0573). The mean plasma concentration-time curves and mean cumulative collections in urine are shown in Figures 3 and 4, respectively. Pertinent pharmacokinetic parameters are listed in Table VI. The guanfacine-to-creatinine renal clearance ratio was greater than 1.0, suggesting that tubular secretion of drug is important for renal elimination.

TABLE IV
 Summary of Steady-State Mean Bioavailability Parameters After 6 Days of Guanfacine (1 mg/day orally)

Dosage Form	AUC (ng/mL-hr)	C _{max} (ng/mL)	T _{max} (hr)	C _{ave} (ng/mL)	kel (hr ⁻¹)	Elimination T _{1/2} (hr)	V ¹ (L)	V/kg ¹ (L/kg)	Clearance (mL/min)	Relative Bioavailability ² (%)
Tablet	37.19	2.9	2.0	1.6	0.059	11.7	659.6	9.35	458.0	101.0
Capsule	36.89	2.9	2.0	1.5	0.059	11.7	665.0	9.44	461.8	100.2
Solution	36.83	2.8	1.8	1.5	0.059	11.6	666.5	9.47	462.8	-

¹Calculated on the basis of assumed fraction of dose absorbed of 1.0.

²In reference to solution.

TABLE V
Summary of Steady-State Mean Bioavailability Parameters After 6 Days of Guanfacine
(2 mg/day orally)

Dosage Form	AUC (ng/mL-hr)	C _{max} (ng/mL)	T _{max} (hr)	C _{ave} (ng/mL)	kel (hr ⁻¹)	Elimination T _{1/2} (hr)	V ¹ (L)	V/kg ¹ (L/kg)	Clearance (mL/min)	Relative Bioavailability ² (%)
Tablet	69.43	5.0	2.2	2.9	0.056	12.4	704.7	9.21	489.4	104.5
Capsule	69.80	4.9	2.9	2.9	0.054	12.8	698.8	9.13	485.3	105.0
Solution	66.46	4.8	2.4	2.9	0.054	12.8	734.7	9.52	510.2	-

¹Calculated on the basis of assumed fraction of dose absorbed of 1.0.

²In reference to solution.

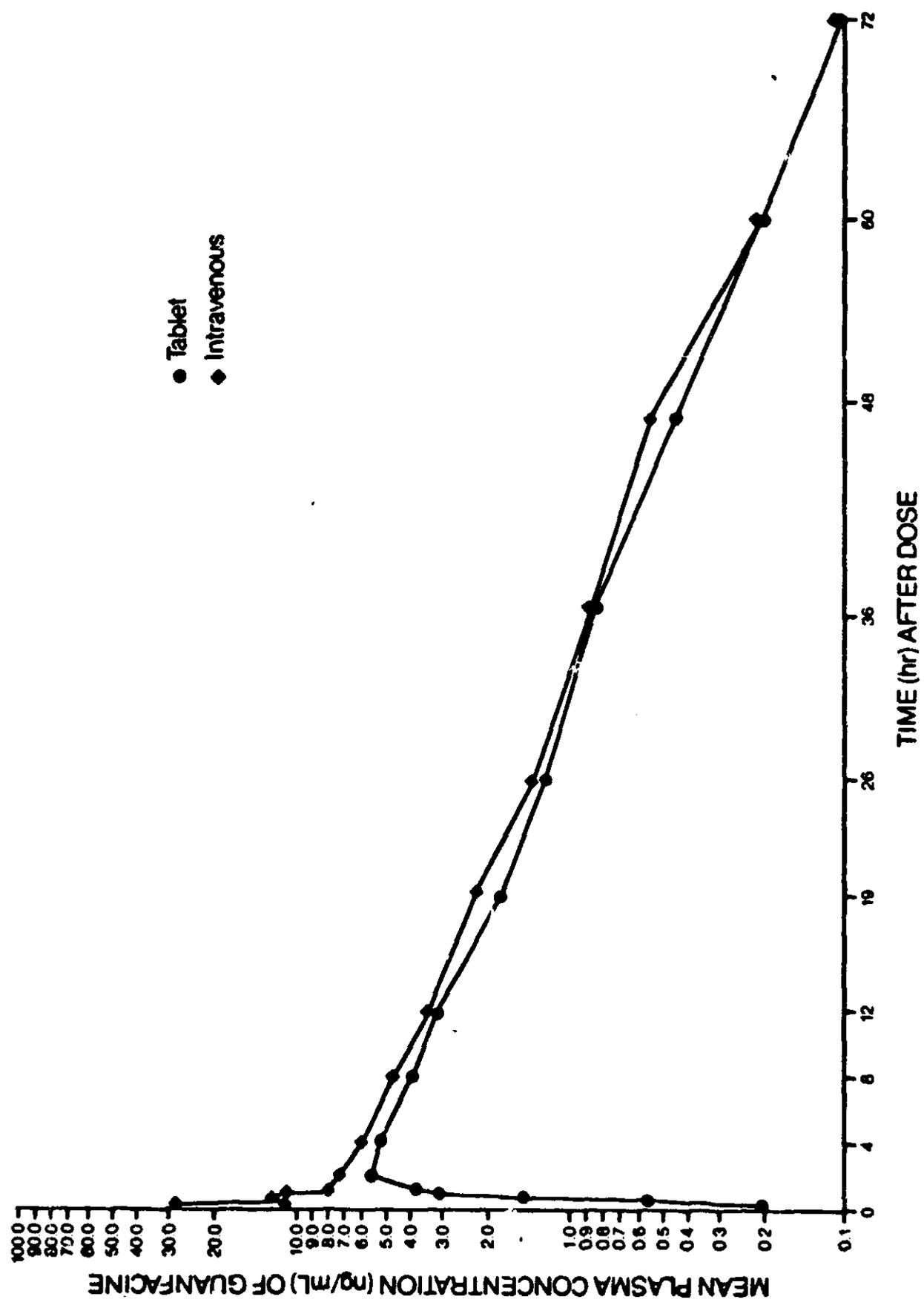


Figure 3. Mean Plasma Concentrations of Guanfacine in 18 Subjects After a Single Dose of 3mg of Guanfacine HCl.

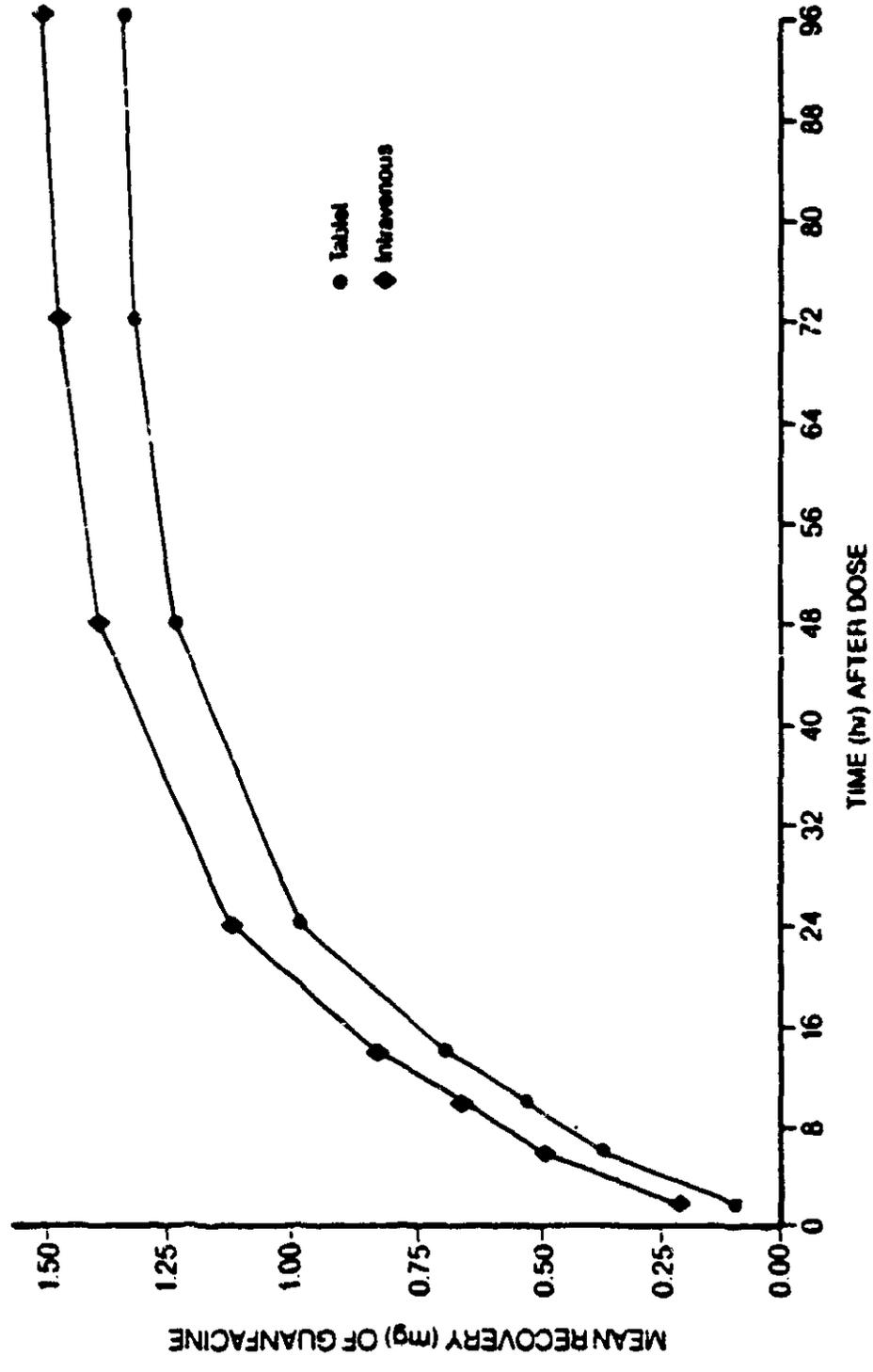


Figure 4. Mean Cumulative Urinary Excretion of Guanfacine

TABLE VI
 Summary of Mean Bioavailability Parameters of 3 mg of Guanfacine
 After Single Oral and Intravenous Administration

Route of Administration	AUC (ng/mL-hr)	C _{max} (ng/mL)	T _{max} (hr)	k _{el} (hr ⁻¹)	Elimination T _{1/2} (hr)	V (L/kg)	Total Clearance (mL/min)	Renal Clearance (mL/min)	Total Urinary Recovery (%)	Bioavailability (%)
Oral	100.64	5.49	2.6	0.052	13.8	6.5	-	-	44.7	81.2
Intravenous	123.99	29.57 ¹	0.2	0.053	13.4	6.3	414.4	210.7	50.0	-

¹Concentration immediately after the end of the infusion.

On comparison of the mean AUC and k_{el} values given by the specific dosage forms in the 3 above studies, it is apparent that good proportionality exists among these parameters and the dose. For example, the solution of 1 mg/day gave an AUC of 36.83 ng/mL-hr and a C_{max} of 7.9 ng/mL compared with an AUC of 66.46 ng/mL-hr and C_{max} of 5.0 ng/mL for the solution at 2 mg/day. In the single, 3-mg oral dose study the AUC was 100.64 ng/mL-hr. Although dose proportionality would be better assessed with several doses in a single study, the patient populations in these studies were sufficiently comparable with respect to demographic and elimination rate to conclude that there is no important nonlinearity.

The data provided by studies in patients with hypertension indicate that accumulation of guanfacine occurs as expected based on its half-life. Guanfacine concentrations in plasma at steady-state were well predicted by simulations of single-dose data (see Figure 4A) in one study in patients with hypertension (Weiss et al., 1979). Patients received either a 2-mg or 4-mg single dose followed by 1 to 3 mg guanfacine twice daily for up to 60 days. Actual plasma concentrations were compared with computer-simulated profiles from single-dose data. Linear regression of predicted vs. observed values gave a fit with an r value of 0.948 (see Figure 4B).

Hedner (1984) followed guanfacine blood levels in 13 hypertensive patients for 1 year. The mean daily dose of guanfacine was 2.0 ± 0.26 mg. After 1 year, the mean peak plasma level was 4.1 ± 0.6 ng/mL, similar to the mean peak of 4.9 ng/mL observed after 6 days of treatment with 2 mg/day of guanfacine.

An open, two-phase, multiple-dose study was conducted in patients with mild-to-moderate hypertension who were being treated with 25 mg chlorthalidone daily to determine the steady-state levels in plasma and pharmacokinetics of guanfacine in this population (Carchman, 84-0582). Patients received 25 mg chlorthalidone daily for three weeks, then 25 mg chlorthalidone with 1 mg guanfacine daily for six days. The results of the study are shown in Figure 5 and Table VII. There was no relationship between patient sex, creatinine clearance, or body weight to the mean elimination half-life. There did, however, appear to be a relationship between patient age and elimination half-life. Older patients tended to have a longer half-life in this study. The range of half-lives was 10.2 to 30.0 hr.

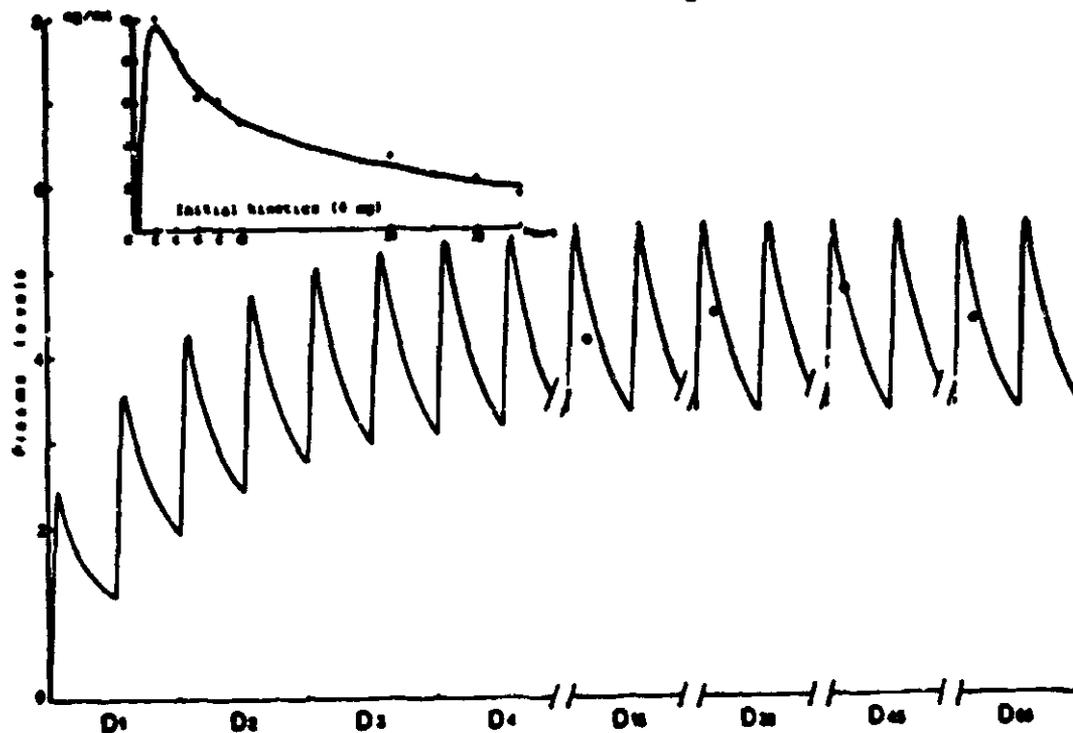


Figure 4A. Plasma concentration time profile of guanfacine following oral administration at 1 mg every 12 hr. Theoretical curve was generated by means of Eq. 3 with the parameters determined by program SAAM. Inset at top left position of figure illustrates profile of initial kinetics after single administration of 4 mg.

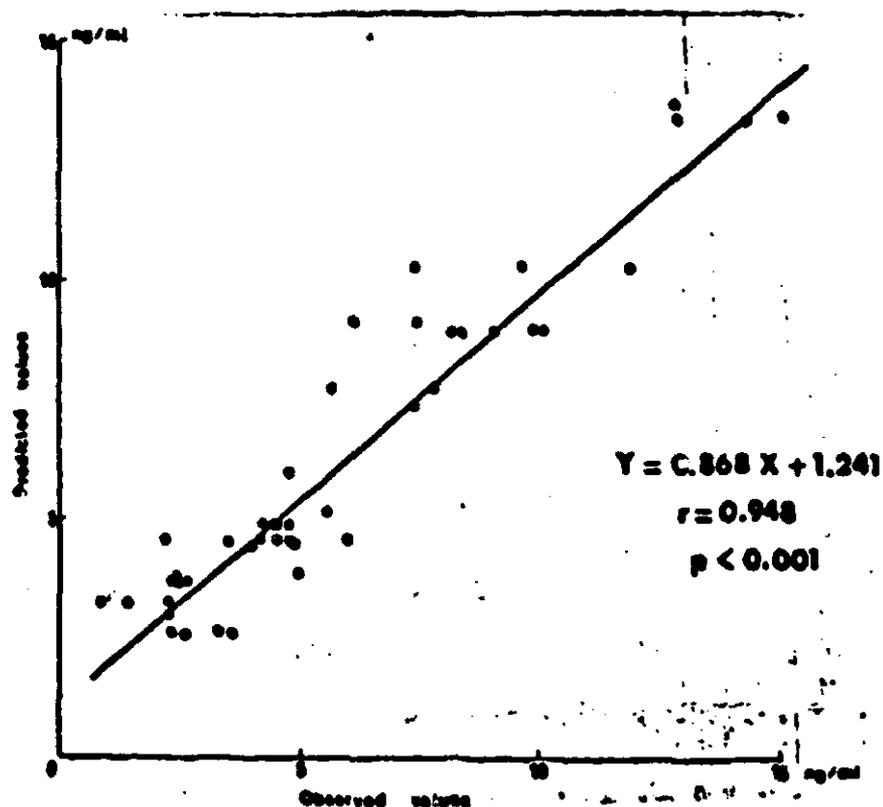


Figure 4B. Relationship between the observed plasma levels and the predicted values obtained after simulation with individual parameters in dosage regimen.

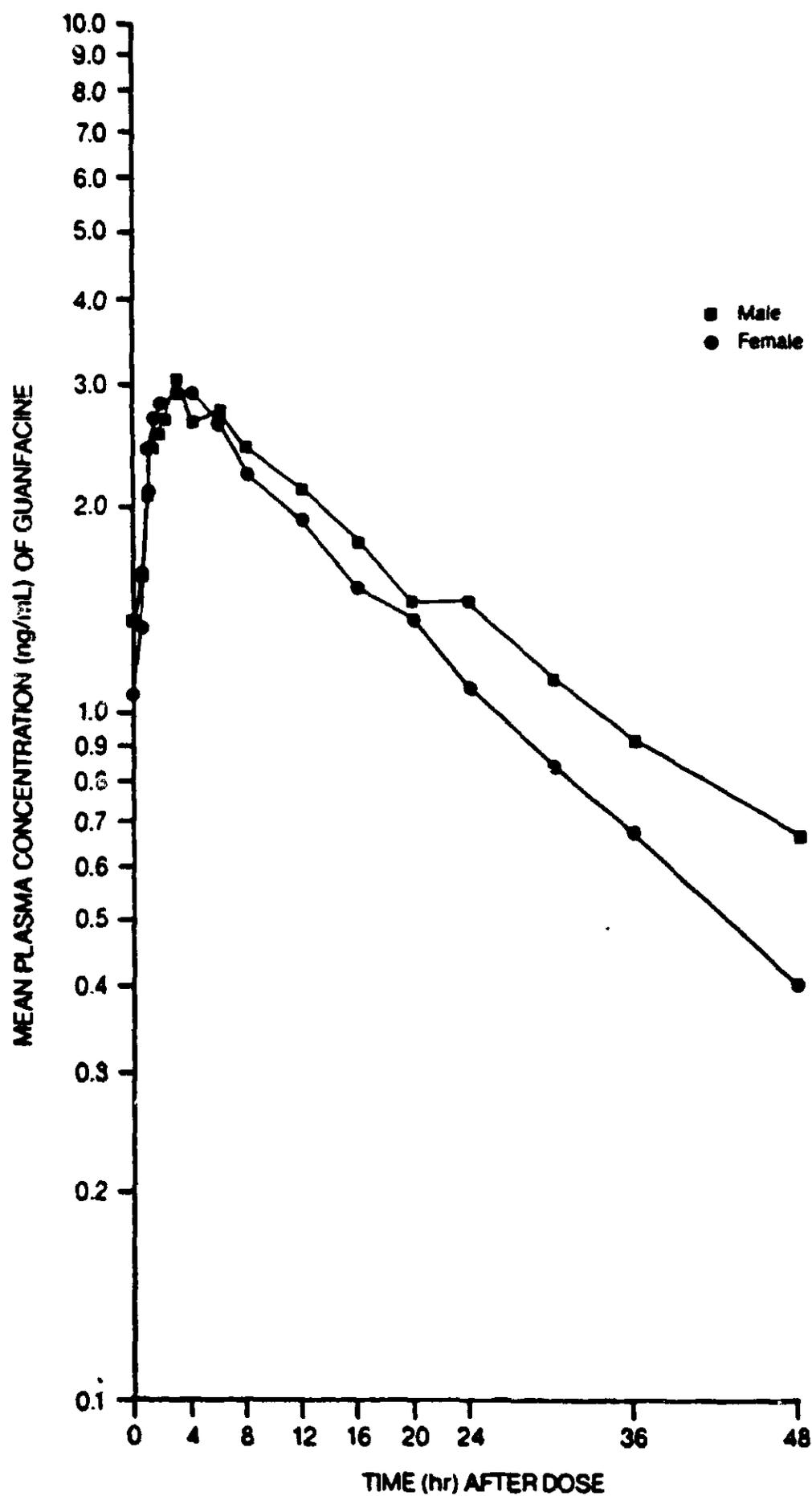


Figure 5. Mean Plasma Concentrations of Guanfacine in 10 Male and 10 Female Hypertensive Patients on Days 6-8 After 6 Days of Single Daily Doses of 1 mg Guanfacine HCl and 25 mg Chlorthalidone/Day.

TABLE VII

Summary of Mean Bioavailability Parameters of Guanfacine
at Steady State in Patients with Hypertension

AUC (ng/mL-hr)	C _{max} (ng/mL)	T _{max} (hr)	C _{ave} (ng/mL)	k _{el} (hr ⁻¹)	Elimination T 1/2 (hr)
48.04	3.12	2.7	2.00	0.042	17.66

The biological disposition of guanfacine was assessed in several studies following oral and intravenous administration of carbon-14 labeled guanfacine. The majority of administered radioactivity was recovered in urine. All of the metabolic products identified in human urine were previously found in animals. The biotransformation pathways in humans are shown in Figure 6. Parent drug(1) accounted for 28 to 32% of the radioactive content. The major compound, glucuronide(4) of 3-hydroxy guanfacine(3), accounted for about 30 to 40% of the drug content in urine excreted within 24 hr of administration (Kiechel et al., 80-3377).

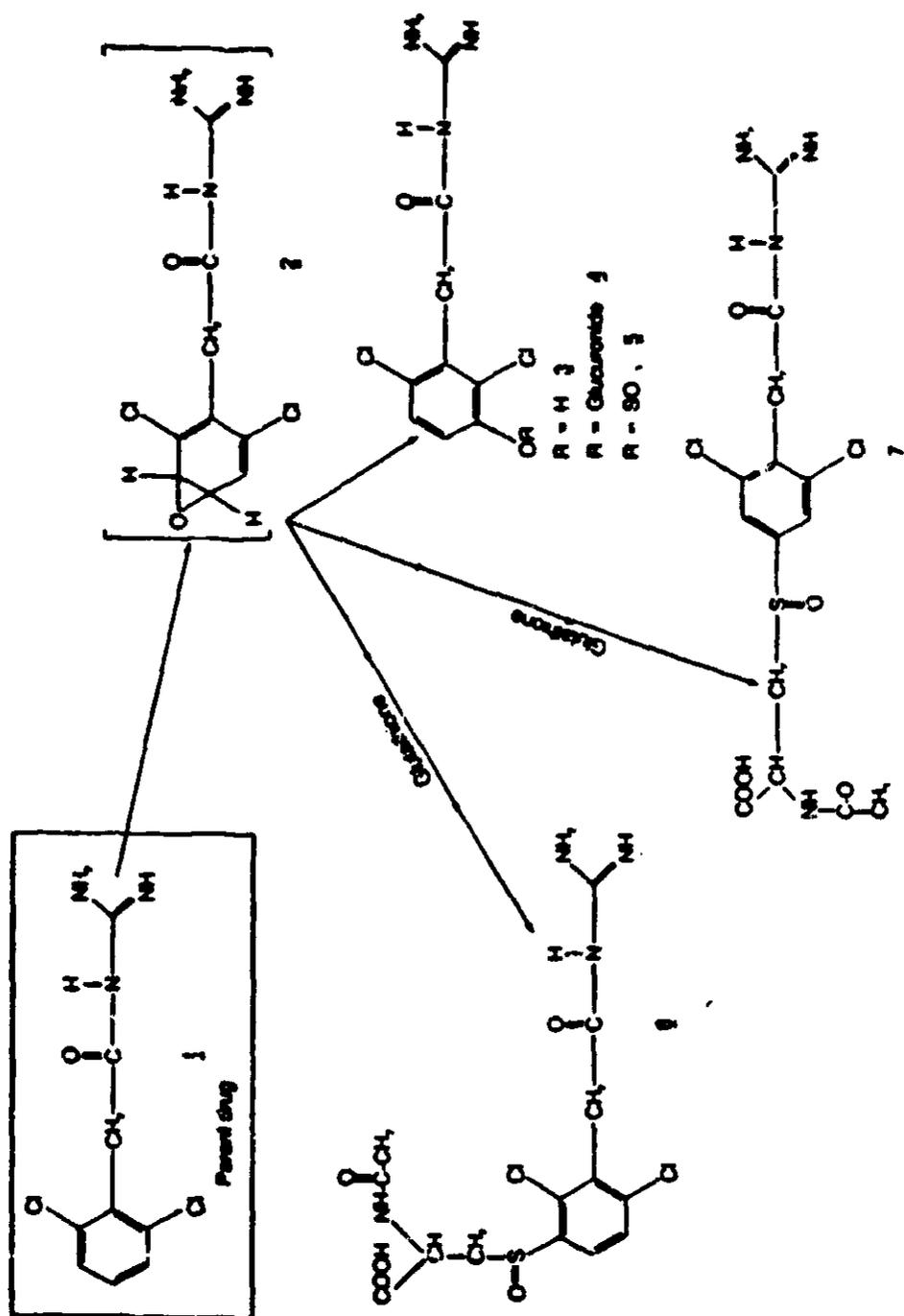


Figure 6. Proposed Metabolic Pathway of Guanfacine in Man
Based on Metabolites Identified in Urine.

Binding of ^{14}C -guanfacine to proteins in plasma from normal volunteers was evaluated by equilibrium dialysis. Guanfacine at concentrations from 0.02 to 5 $\mu\text{g}/\text{mL}$ was 68 to 71% bound to human plasma proteins after 6 hr of incubation *in vitro*. Moderate binding to erythrocytes was also observed (Poser, 83-0201).

Several studies have investigated the effect of renal insufficiency on the pharmacokinetics of guanfacine. In one study (Kirch *et al.*, 1980), 3 groups of hypertensive patients with various degrees of renal function (Group I = GFR >90 mL/min, Group II = GFR 10-30 mL/min, and Group III = GFR <10 mL/min). Renal clearance of guanfacine was reduced from 57% in Group I to 14% and 7.5% in Groups II and III respectively. The mean elimination half-life was 14 hr and found to be independent of the level of renal function. In spite of substantial interpatient variability, it was proposed that nonrenal clearance of guanfacine was enhanced in renal failure. Two other studies have demonstrated that the nonrenal clearance of guanfacine is unchanged in the context of renal insufficiency (Kiechel *et al.*, 1980; Carchman *et al.*, 1985). Total and renal clearances of guanfacine decreased in parallel with the decline in renal function which suggests that no compensatory increase in the metabolism of guanfacine by the liver occurred. The mean elimination half-life was about 20 to 24 hr, and the steady-state plasma levels were about twice as high in severe renal impairment as compared to subjects with normal renal function.

In a study with hemodialysis patients (Kiechel *et al.*, 1980), only 2.4% of the dose was extracted unchanged in the dialysate. Hemodialysis had no significant influence on the elimination of guanfacine.

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2. Duration of Action and Dose Response Study

Prot. No.	Principal Investigator	Purpose of Study	No. Subjects Receiving Tenex	No. Subjects Receiving Placebo	No. Subjects Receiving Comparative Drug	Tenex Doses (mg/day)	Tenex Dosing Schedule
S-02	Stephen Ayers, M.D.	To determine the hypotensive effects of single doses of guanfacine in normal volunteers. To evaluate safety of rising single doses in normal volunteers. To compare the efficacy and safety of 2 mg of guanfacine given as a single dose to 2 mg given on a 1 mg q12H x 2 schedule.	23	24	None	0.0mgx1 (n=24) 0.5mgx1 (n=6) 1.0mgx1 (n=7) 2.0mgx1 (n=5)	Once Once Once Once
						1mgq12hx2 (n=5)	q12hx2

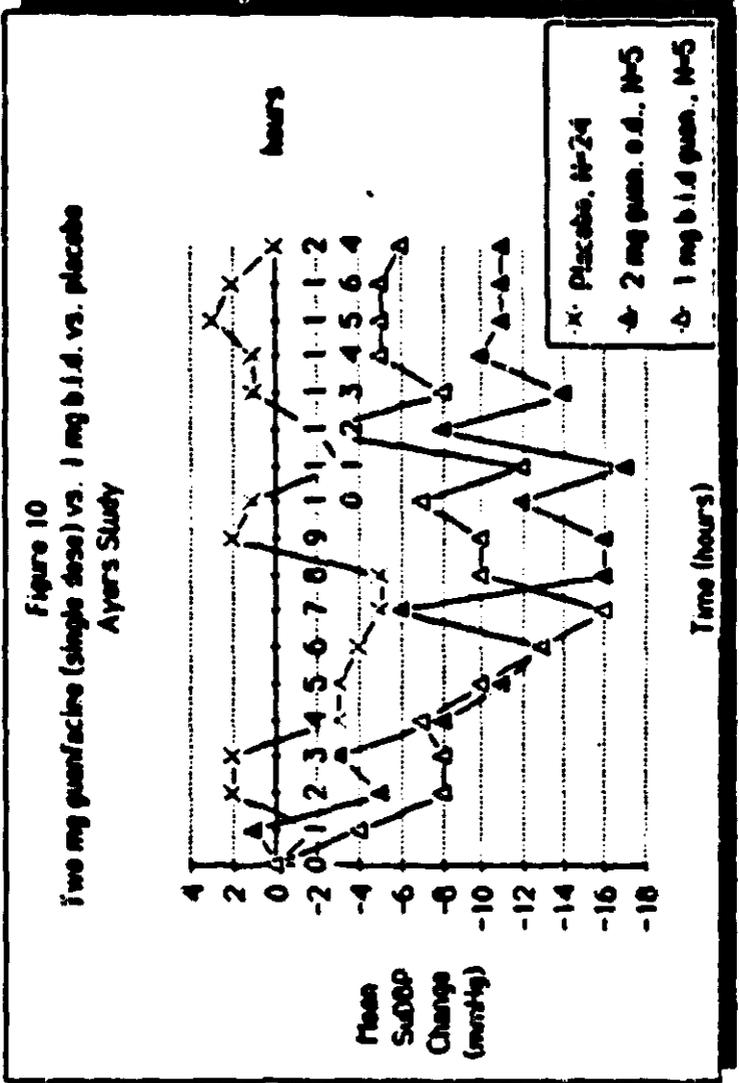
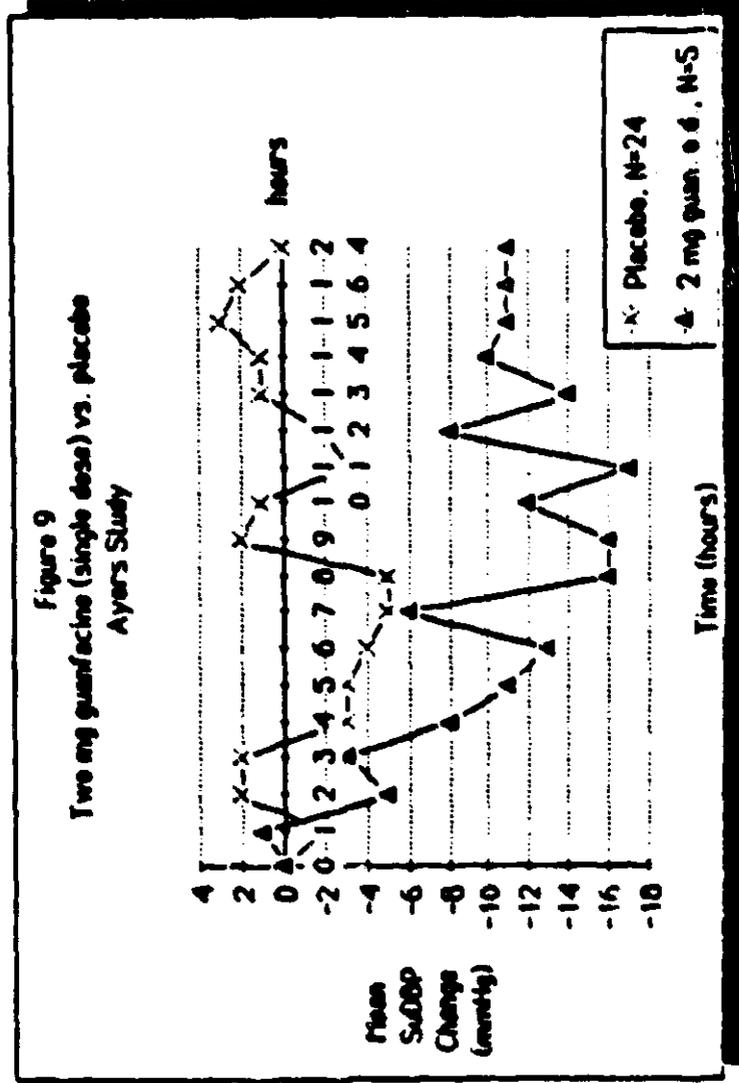
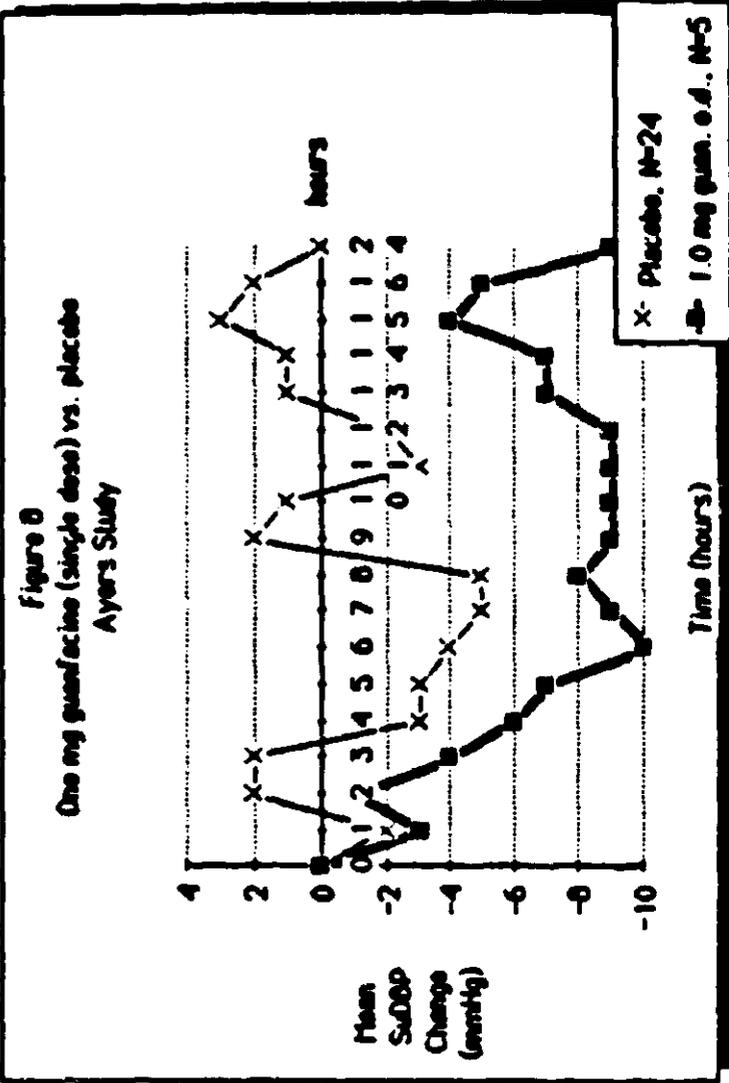
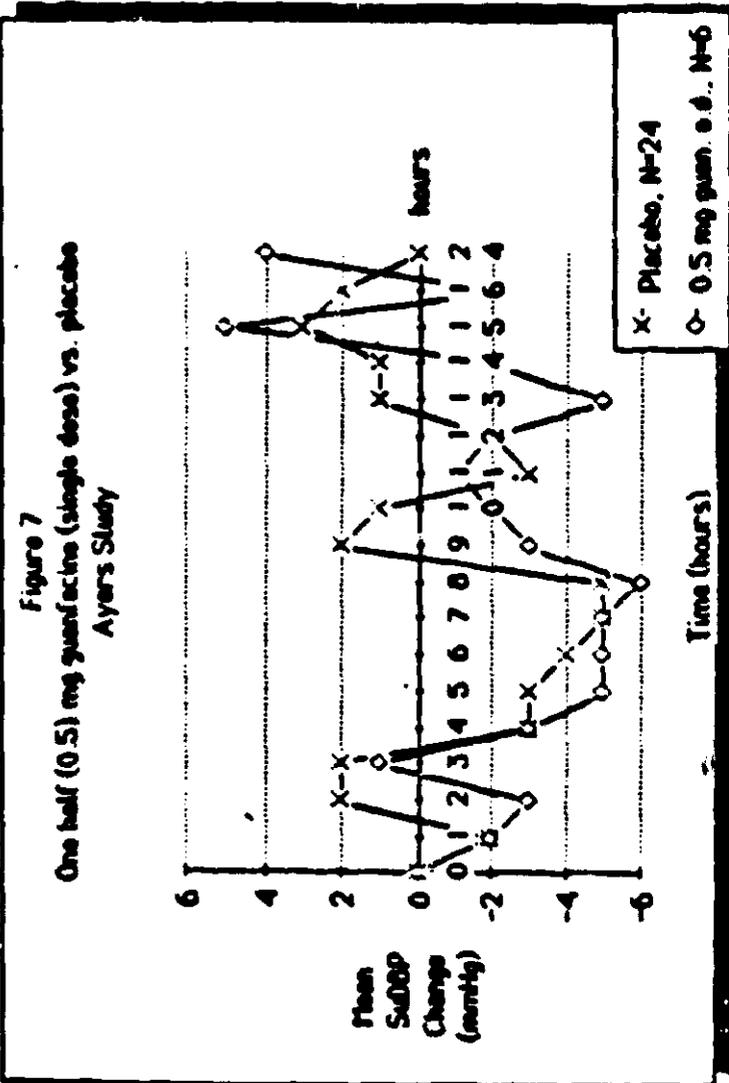
2. Duration of Action and Dose Response

A long-term (17-week) dose-response study of guanfacine when added to diuretic therapy is most relevant to the recommended clinical use of guanfacine and is described below under well-controlled clinical trials in hypertension. No similar data yet exist for guanfacine as monotherapy, so that monotherapy is not yet recommended. There are data in normal volunteers, however, that suggest the dose-response relationship for monotherapy will be similar to that seen when guanfacine is added to a diuretic. The single dose - dose-response study carried out was designed to look at maximum responses and duration of response.

The study (Ayers, S-02) was double-blind and placebo-controlled. Patients were randomized to placebo or 1 of 4 drug regimens, 0.5, 1.0, and 2.0 mg as a single dose and 1 mg given q12 for 2 doses. Observations were carried out for 48 hours. Results of blood pressure changes showed that there were mean diastolic blood pressure reductions over 24 hours of:

Placebo	1.4%
0.5 mg	3.6%
1.0 mg	7.5%
2.0 mg	11.5%
1.0 mg bid	11.0%

Hypotensive responses were dose related (see Figures 7-9). The duration of hypotensive effect was not altered by increasing the dose beyond 1 mg, but the 0.5 mg dose did not seem to have a 24-hour effect. The magnitude of reduction was dose related. When 2 mg as a single dose was compared to 1 mg q12h x 2, the patterns of response were quite similar (see Figure 10).



The incidence of side effects also appeared dose-related, as noted in Table VIII, although the small numbers of patients prevent any definitive conclusions.

Table VIII
Incidence of Side Effects
Ayers Study

Side Effect	Severity	Placebo (24 Subj.)	0.5 mg o.d. (6 Subj.)	1.0 mg o.d. (7 Subj.)	1.0 mg b.i.d. (5 Subj.)	2.0 mg o.d. (5 Subj.)
Lethargy	Mild					2
Headache	Mild	1	1	1		2
Muscle Ache	Mild					1
Drowsiness	Mild	1		1	2	2
	Moderate	1				1
Dry Mouth	Mild	1	1	2	1	1
Lightheadedness	Mild		1	1		
Vivid Dreams	Mild	2				
	Moderate	1				
% of Pts. with at least one side effect		29%	33%	43%	40%	80%

3. Rebound Hypertension

Protocol Number	Principal Investigator	Purpose of Study	No. Patients Receiving Tenex	No. Patients Receiving Placebo	No. Patients On Comparative Drug	Tenex Doses (mg/day)	Tenex Dosage Schedule
*	S. Mann, M.D.	Effect of guanfacine on acute & long-term treatment of hypertension & abrupt discontinuation of guanfacine	5	0	0	1-6	o.d.
**	P. Manhem, M.D.	Effect of guanfacine on acute & long-term treatment of hypertension & abrupt discontinuation of guanfacine	4	0	0	1-2	t.1.d.
241	I. Szam, M.D.	Effect of guanfacine on acute & long-term treatment of hypertension & abrupt discontinuation of guanfacine	11	0	0	1-5	o.d.
242	J. Reid, M.D.	Effect of guanfacine on acute & long-term treatment of hypertension & abrupt discontinuation of guanfacine	5	0	0	3-6	o.d.
Total No. Studies			25	0	0	1-6	o.d. & t.1.d.

*Brit. J. Clin. Pharmacol. 10, Suppl. 1, pp. 103S-107S (1980).

**Brit. J. Clin. Pharmacol. 10, Suppl. 1, pp. 109S-114S (1980).

3. Rebound Hypertension

Background. "Rebound" upon abrupt withdrawal of antihypertensive drugs has been described for central adrenergic agonists and beta-blockers. The "rebound phenomenon" is defined as a sudden rise in blood pressure accompanied by other symptoms of sympathetic overactivity which occur after abrupt discontinuation of drug therapy. Table IX shows that it has been reported with fairly high frequency for clonidine.

Table IX
Frequency of Rebound Phenomenon Following Clonidine

Author	No. of Patients	No. Patients with Rebound Phenomenon	Clonidine Dose mg/day
Hanson <u>et al.</u> ¹	5	5	0.3 - 2.4
Goldberg <u>et al.</u> ²	15	11	0.3 - 0.9
Goldberg <u>et al.</u> ³	9	9	0.3 - 0.6
Spach ⁴	14	7	0.15- 0.9
Reid ⁵	7	6	0.15->1.0
Geyskes <u>et al.</u> ⁶	14	14	0.9

¹Am. H. J. Vol. 85, No. 5, pp. 605-610 (May 1983)

²Postgrad. Med. J. 52(Suppl.), pp. 128-36 (1976)

³Br. Med. J., pp. 1243-46 (May 14, 1977)

⁴La Nouv. Press. Med. 6,(14), pp. 1201-5 (April 9, 1977)

⁵Lancet, pp 1171-74 (6/4/77)

⁶Br. J. Clin. Pharmacol., pp. 55-62 (1979)

Reid has postulated reasons for the rebound phenomenon:

"The central alpha-agonist effect of clonidine produces decreased peripheral sympathetic activity and increased vagal tone. The withdrawal syndrome represents a sudden reversal of these central drug induced effects with a transient increase in efferent sympathetic activity."

Clinical Trials. Early in the clinical investigation of guanfacine, 4 studies were performed with 25 hypertensive patients in order to evaluate the effects of cessation of guanfacine treatment. The "rebound phenomenon" was defined as (1) the presence of withdrawal symptoms and (2) a rise of 15 mmHg or more above the pretreatment systolic blood pressure. A summary of these results is given in Table X.

Table X
Summary of Guanfacine Clinical Studies Following Cessation of Treatment

Study No.	Investigator(s)	Treatment		No. Pts.	Observation Post-Drug		Results
		Duration	Dosage		Period of Obs./Frequency		
**	B. Mann, M.W. Miller-Craig, D. Melville, P. Cashman & E. Raftery	5-20 wks	1-6 mg o.d.	5	48 hrs./patients monitored continuously		No rebound phenomena
242	J.L. Reid, C. Zamboulis, C.A. Hamilton	8-10 wks.	3-6 mg daily	5	96 hrs./patients monitored continuously		No rebound phenomena
***	P. Manhem, B. Hökfelt	3-8 wks.	1-2 mg t.i.d.	4	96 hrs./continuous		No rebound phenomena
241	I. Szam	4-6 wks.	1-5 mg daily	11	7 days/patients monitored twice daily		No rebound* phenomena

*One patient's blood pressure exceeded pretreatment levels with no subjective symptoms of withdrawal.

**G. J. Clin. Pharmacol. (1980) 10, 1036-1075.

***Br. J. Clin. Pharmacol. (1980) 10, 1095-1145.

The return of blood pressure to pretreatment levels after guanfacine treatment was slower than had been observed with clonidine, perhaps because of the longer half-life of guanfacine. Unfortunately, these trials had no comparison clonidine group.

Several other trials (Table XI) of guanfacine for treatment of hypertension included observations of rebound phenomena, although these were not the prime objective of the studies.

Table XI

Summary of Rebound Phenomena with Guanfacine

Study Type	No. Pts. Monitored	Daily Dose Ranges (mg)	No. Pts. with Rebound	Frequency
1. Dose-finding and short-term tolerance (< 2 weeks)	63*	0.5-8.	0	0%
2. Comparative studies (6 weeks on guanfacine)	118	1-15	0	0%
3. Studies 2-4 months' duration	72	1-10	4	5.6%
4. Studies of 1 year's duration	407	0.5-20	9	2.2%
5. Studies of 2 years' duration	106	0.5-20	6	5.7%
Totals	766	0.5-20	19	2.5%

*Includes 43 normal volunteers.

After interruption of short-term treatment (lasting several days) no clinical signs of the rebound phenomenon were observed. The earliest occurrence of the rebound phenomenon was observed in patients who were treated for at least 7 weeks. The lowest daily dose of guanfacine followed by rebound on discontinuation was >5 mg/day.

While these observations suggested that guanfacine-treated patients faced a low risk of important rebound after cessation of treatment, they did not constitute a well-planned observation in an adequate patient population. Protocol 03, a multicenter study comparing the long-term effectiveness and tolerance of guanfacine and clonidine, each added to 25 mg of chlorthalidone, included a planned abrupt withdrawal phase after 24 weeks of treatment. It is described in detail under the Well-Controlled Clinical Trials section; it showed that rebound can occur with guanfacine, but it occurs much later (after several days) than clonidine and is almost always well tolerated.

* * * * *

4. Hemodynamic and Renal Effect Studies

Protocol Number	Principal Investigator	Purpose of Study	No. Patients Receiving Tenex	No. Patients Receiving Placebo	No. Patients On Comparative Drug	Tenex Doses (mg/day)	Tenex Dosage Schedule
<u>Hemodynamics</u>							
202	N. Schaefer, M.D.	Open label, hemodynamics	10	0	0	3-15	Single daily dose x 12 weeks
*	H. Erhinger, M.D.	Open label, hemodynamics	5	0	0	0.01-0.04 mg/kg	Single i.v. dose
**	Torok <u>et al.</u>	Long-term hemodynamics	10	0	0	4	Single daily doses
06	M. Strauss, M.D.	Effectiveness and plasma volume/ aldosterone; double-blind; placebo-controlled	17	9	0	1	q.d. x 28 days
**	Feldstein <u>et al.</u>	Open-label, hemodynamics	11	0	0	4 (mean)	i.v. single dose o.d. oral
Total No. Studies			53	9	0		
<u>Renal Effects</u>							
****	A. Roeckel, M.D.	Renal effects	21	0	0	2-15	q.d. x up to 24 months

*Brit. J. Clin. Pharmacol. 10 Suppl. 1, pp. 115S-122S, (1980).

**8th Scientific Meeting, Intern. Soc. of Hypertension, Milan, 1981.

***Clin. Therap. 6:325-34, 1984.

****Brit. J. Clin. Pharmacol. 10 Suppl. 1, pp. 141S-150S, (1980).

4. Hemodynamic and Renal Effect Studies (continued)

Introduction. Five clinical studies on the effects of guanfacine on hemodynamics and kidney function were performed. A total of 74 patients was studied.

In a hemodynamic study (Schaefer) of 10 hypertensive patients, guanfacine was given in daily dosages of 3-15 mg (mean = 7.3 mg) over a 12-week period to stabilize blood pressure. Hemodynamic studies were performed before and after treatment of these patients. No other drugs were taken during the study.

Systolic, diastolic, and mean arterial pressures in the right atrium and aorta were measured and heart rate was recorded at rest and during effort testing (bicycle ergometer, work loads of 25 watt/2 min, 50 watt/2 min, 75 watt/2 min, and 100 watt/2 min where possible). Cardiac output was also measured. From these data, the following were calculated: stroke volume and total peripheral resistance.

The results are given in Table XII.

Table XII

Hemodynamic Changes Between Pretreatment and Treatment (Schaefer)

Hemodynamic Parameter	Rest	Effort	After Effort
Systolic Pressure, aorta	+++	+++	+++
Diastolic Pressure, aorta	+++	+++	++
Mean Arterial Pressure, aorta	+++	++	++
Pressure, atrial	-	-	→
Mean Arterial Pressure, atrial	-	→	→
Heart Rate	+	+	+
Cardiac Output	-	-	-
Stroke Volume	→	→	↑
Total Peripheral Resistance	++	↓	↓
Heart Index	-	-	-

- = No change.
- = Relevant increase, not statistically significant.
- ← = Relevant decrease, not statistically significant.
- ↑ = Increase, statistically significant ($p < 0.05$).
- ↓ = Decrease, statistically significant ($p < 0.05$).
- ++ = Decrease, statistically significant ($p < 0.01$).
- +++ = Decrease, statistically significant ($p < 0.001$).

In a long-term hemodynamic trial (Torok, *et al.*, 8th Scientific Meeting, Intern. Soc. of Hypertension, Milan, 1981), ten patients received guanfacine at 4 mg/day for 12 months. Mean blood pressure and heart rate decreased significantly ($p < 0.01$). There was also a significant increase in stroke volume ($p < 0.05$) and a significant decrease in TPR ($p < 0.01$) with no changes in blood volume or cardiac index.

A third study (Feldstein, *et al.*, Clinical Therap. 6:325-34, 1984) evaluated 11 patients during six weeks of guanfacine therapy (mean daily dose of 4 mg). There were significant decreases in blood pressure, heart rate, and peripheral resistance. Increases were noted in pulmonary artery pressure, mean right atrial pressure, and stroke volume.

Erhinger and colleagues studied the effects of guanfacine on the circulation of 5 patients. The following doses of guanfacine were compared in random order with placebo: 0.01; 0.02; 0.04 mg/kg respectively. The drug was infused over a 5-minute period using a motorized pump.

The room temperature was controlled at constant 25°C following an adaptation period of 60 minutes for each patient. All patients remained in the supine position prior to and during the measurements of circulation. Blood flow in the calf and forefoot was measured simultaneously every 15 seconds using a strain gauge plethysmograph and an automatic venous occlusion device. The technique of Wood and Ecstein (J. Clin. Invest. 37:41, 1958) was utilized to measure blood flow.

There were dose-dependent drops in blood pressure and concurrent increases in blood flow in the foot. This observed action was interpreted by the authors as a decrease in peripheral resistance.

In a study by Strauss, the effects of guanfacine alone on plasma volume and plasma aldosterone were investigated. Twenty-six patients with essential hypertension (DBP 90-100 mmHg) were randomly assigned to either 1.0 mg/day guanfacine or placebo after a 1-month drug-free period. All medication was blinded, and the study was conducted in a double-blind fashion. Baseline values for plasma volume, plasma aldosterone, and vital signs were obtained immediately prior to the beginning of the drug evaluation period. All patients received the test agents daily for 28 days. At the end of the 28-day period, plasma volume, plasma aldosterone, and vital signs were obtained again for each patient. Plasma volume and plasma aldosterone were estimated using standard commercial laboratory methods.

There was no statistically significant or clinically relevant change from baseline in plasma aldosterone for any of the 17 guanfacine or 9 placebo patients. Plasma volume decreased 5.3% from baseline in those patients who received guanfacine, and a 2.4% decrease was observed in the placebo group. These differences were not statistically significant.

The mean blood pressures for the guanfacine group decreased from 149/97 mmHg at baseline to 140/84 mmHg at the end of treatment. The mean blood pressures for the placebo group changed from 163/97 mmHg to 156/99 mmHg at the end of treatment. The differences in the changes from baseline observed between the treatment groups for diastolic pressure were significant; the differences for systolic pressure were not. The mean heart rate decreased from 70 beats/min to 68 beats/min in the guanfacine group and remained unchanged in the placebo group.

RENAL FUNCTION

In a chronic study by Roeckel & Heidland, 21 hypertensive patients were treated orally with 2-15 mg/day of guanfacine for 24-42 months. The GFR for these patients ranged from 18.0-109.0 mL/min. Before, during, and after guanfacine, GFR and plasma creatinine were recorded.

In this study, patients who received guanfacine alone or in combination with hydrochlorothiazide and/or hydralazine did not show a significant change in GFR or plasma creatinine levels.

★ ★ ★ ★ ★

5. Metabolic Effects

Protocol Number	Principal Investigator	Purpose of Study	No. Patients Receiving Tenex	No. Patients Receiving Placebo	No. Patients On Comparative Drug	Tenex Doses (mg/day)	Tenex Dosage Schedule
222	S. Sailer, M.D.	Effect on glucose & insulin metabolism single-blind, cross-over	6	6	0	1	Single i.v. dose
*	J. Hauger-Klevene, M.D.	Effect on glucose tolerance	18	0	0	2.8	Mean daily dose
231	I. Lancranjan, M.D.	Effect on pituitary & pancreatic hormones 3 parts of the study	14 10 6	0 0 0	10 0 0	1-2 2-4 2	Single dose Single dose t.i.d.
Total No. Studies			54	6	10	1-4	

*Horm. Metabol. Res. 1985, pp. 613-14

5. Metabolic Effects (continued)

Three clinical studies were performed: (two) to evaluate the effects of guanfacine on glucose metabolism (S. Sailer and J. Hauger-Klevene) and (one) to evaluate effects on the secretion of pituitary and pancreatic hormones (I. Lancranjan).

Glucose Metabolism

Sailer conducted a single-blind, crossover experimental acute study, comparing guanfacine with placebo (isotonic saline solution) in their effects on glucose and insulin levels during a glucose tolerance test.

Guanfacine 1 mg or placebo was administered intravenously. After 20 minutes, 100 g of glucose p.o. was given. At time-points -90, 0, 30, 60, 90, and 120 min, glucose and insulin levels were measured.

There was no evidence that a single, 1-mg, intravenous dose of guanfacine has a hyperglycemic effect or altered insulin response.

An acute experiment cannot provide the definitive evidence on the effect of chronic oral administration of guanfacine on glucose metabolism. An analysis of the effect of guanfacine on serum glucose is included in the Well-Controlled Clinical Studies section of this clinical summary.

In a 12-month study in which 18, hypertensive, Type II diabetics were treated with guanfacine monotherapy (mean daily dose of 2.8 mg), Hauger-Klevene and Scornavacchi (Horm. Metab. Res. 1985, p. 613-4) glucose tolerance that was influenced by on-going diuretic therapy tended to improve during the period of observation. There were no changes in body weight during the period of observation.

The results are summarized in Tables XIII and XIV.

Table XIII

Changes in Plasma Glucose (mg/dL) During Oral Glucose Tolerance Tests
in Patients Treated with Guanfacine

	Time in minutes			
	0	60	120	180
Plasma glucose (mg%)				
Placebo (18)	134.6 ± 50.9	203.6 ± 49.1	212.7 ± 52.7	160.9 ± 52.7
3 months (18)	128.9 ± 40.0	180.0 ± 52.0	196.4 ± 57.6	147.1 ± 35.2
6 months (15)	111.3 ± 20.4	168.9 ± 40.0	179.1 ± 45.1*	138 ± 35.5
12 months (9)	99.6 ± 18.9*	160.9 ± 23.5*	165.5 ± 30.0*	118.9 ± 18.0

*p<0.001

Table XIV

Changes in Plasma Insulin During Oral GTT in Patients Treated with
Guanfacine

	Time in minutes			
	0	60	120	180
Plasma insulin (μU/mL)				
Placebo	12.5 ± 6.4	78.8 ± 57.4	98.5 ± 73.1	70.9 ± 64.9
3 months	18.9 ± 8.0	89.9 ± 64.2	111.4 ± 78.0	68.0 ± 57.3
6 months	22.3 ± 10.3**	95.8 ± 68.8	114.6 ± 67.1	72.3 ± 55.2
12 months	24.1 ± 6.3**	100.4 ± 53.1	135.8 ± 67.7	94.5 ± 42.0

**p<0.05 in relationship to placebo

Pituitary and Pancreatic Hormone Effects

Lancranjan conducted a study to determine the effects of guanfacine on the secretion of pituitary and pancreatic hormones.

Fourteen, non-obese, healthy volunteers aged 21-45 years, received 1 and 2 mg guanfacine as a single dose. A second group of 10 normal volunteers, aged 20-30 years, received single doses of 2 mg and 4 mg of guanfacine or 0.15 and 0.3 mg clonidine in a randomized crossover sequence. A third group of six male patients (44-60 years) with mild hypertension took 2 mg guanfacine t.i.d. for 10 days.

A significant stimulatory effect on growth hormone (GH) secretion occurred only after single oral doses of 2 and 4 mg guanfacine and 0.3 mg clonidine in normal subjects under 45 years. This effect did not occur in hypertensive patients aged 44-60 years, either after single doses of 2 mg guanfacine or after short-term treatment (2 mg t.i.d. for 10 days). Moreover GH plasma levels, measured in hypertensive patients during long-term treatment with guanfacine, were normal (Study No. 129).

Guanfacine had no effect on prolactin (PRL) resting plasma levels or on PRL released by agents acting on the pituitary, but significantly decreased PRL stimulated by insulin-induced hypoglycemia.

Single doses of 1 mg, 2 mg, and 4 mg guanfacine and short-term treatment (3 mg daily for 7 days) had no effect on "resting" glucose or insulin plasma levels.

Finally, no relevant biological effect on ACTH, LH, FSH or glucagon secretion was recorded after short-term treatment with guanfacine.

6. Clinical Laboratory Studies - Effectiveness

Protocol Number	Principal Investigator	Purpose of Study	No. Patients Receiving Tenex	No. Patients Receiving Placebo	No. Patients On Comparative Drug	Tenex Doses (mg/day)	Tenex Dosage Schedule
*	J. Rosenthal, M.D.	Effect on plasma renin activity	24	0	0	3-40	t.i.d.
**	M. Schoeppe, M.D.	Effect on BP, plasma renin, and norepinephrine	23	0	0	0.02 mg/kg 4 mg	i.v. single dose b.i.d.
***	P. Manahem, M.D.	Effect on BP/HR, catechols & PRA	5	0	0	1.5-6	t.i.d.
Total No. Studies			52	0	0	1.5-40	

*Br. J. Clin. Pharmacol. (1980) 10, 91S-96S.
 **Br. J. Clin. Pharmacol. (1980) 10, 97S-101S.
 ***Br. J. Clin. Pharmacol. (1980) 10, 109S-114S.

6. Clinical Laboratory Studies - Effectiveness (Continued)

Three studies of the effect of guanfacine on plasma renin activity and catecholamines were reviewed.

In the first study (Rosenthal), 26 hypertensive patients (21 essential hypertensives, 5 renal hypertensives) were evaluated in an open-label study in which 24 patients completed a 14-day placebo phase followed by 3 months of guanfacine with another 2-week placebo period at the end. All patients started at 3 mg/day and were titrated upward to achieve an effective maintenance dose. Blood and urine samples were collected for measurements of blood count, urinalysis, blood glucose, potassium urea, uric acid, serum creatinine, renin, and creatinine clearance.

The average daily dose of guanfacine was 6 mg (range 3-40 mg/day). Blood pressure was reduced from an average 197/115 mmHg to 147/83 mmHg after 12 weeks of treatment. Plasma renin decreased during treatment from a mean of 3.3 to 2.3 ng mL⁻¹ h⁻¹. This decrease could not be correlated with the decrease in blood pressure in individual patients.

In a second study (Schoeppe and Brecht), 23 patients with mild to moderate essential hypertension were studied. In the acute phase of the study, these previously untreated hypertensive patients received a single i.v. dose of 0.02 mg/kg guanfacine. At 15- and 60-minute intervals following the dose, blood pressure, heart rate, plasma noradrenaline, and plasma renin activity were measured in the supine position.

In the chronic phase of the study, the same patients were treated for 4 weeks with 1 mg b.i.d. orally. Blood pressure, heart rate, plasma noradrenaline, and plasma renin activity were measured before and after treatment under various physiological conditions, i.e., after 4 hours supine, after 7 minutes standing, and after 2 hours walking.

In both the acute and chronic phases of the study, there was a significant reduction in blood pressure. Plasma noradrenaline and renin (PRA) decreased significantly during the acute phase of the study. During the chronic phase of the study, there was a significant decrease in plasma noradrenaline and PRA under basal and orthostatic conditions. In individual patients, these reductions could not be correlated with a reduction in blood pressure.

In the third study (Manhem and Hökfelt), 5 patients with essential hypertension (WHO grades II-III) were hospitalized for 6-10 days during the institution of guanfacine treatment and then again 4-8 weeks later during the withdrawal of the drug. The dosage of guanfacine ranged from 0.5-2.0 mg t.i.d.

Blood pressure, heart rate, plasma and urinary catecholamines, and plasma renin activity were measured before and after treatment.

Blood pressure, plasma catechols, and PRA decreased during treatment, and all increased gradually upon discontinuation of the drug. No "rebound hypertension" was observed.

Guanfacine decreases plasma renin activity, but this decrease is not correlated with a reduction in blood pressure in individual subjects. Guanfacine decreases plasma catechols which return to normal levels after discontinuation of the drug.

* * * *

B. Well-Controlled Trials on Hypertension

Protocol Number	Principal Investigator	Purpose of Study	No. Patients Receiving Tenex	No. Patients Receiving Placebo	No. Patients On Comparative Drug	Tenex Doses (mg/day)	Tenex Dosage Schedule
01	F. Finnerty, M.D. W. Kessler, M.D. J. McMillen, M.D. A. Marlon, M.D. S. Savran, M.D. M. Alderman, M.D. F. Canosa, M.D. B. Materson, M.D.	Double-blind, parallel with placebo control to define dose response relationship of multiple Tenex doses with chlorthalidone for treatment of mild to moderate essential hypertension	288	73	NA	0.5-3	0.5 mg o.d. + 25 mg chlorthalidone o.d. 0.5 mg + 1.0 mg o.d. + 25 mg chlorthalidone o.d. 0.5 mg + 1.0 mg + 2.0 mg o.d. + 25 mg chlorthalidone o.d. 0.5 mg + 1.0 mg + 2.0 mg + 3.0 mg o.d. + 25 mg chlorthalidone o.d.
02	P. Black, M.D. J. Freudenburg, M.D. J. Hill, M.D. C. Holmburg, M.D. M. Rietbrock, M.D. M. Sullivan, M.D. M. Thompson, M.D. D. Wright, M.D.	Double-blind, parallel with placebo control to demonstrate the 24-hr duration of Tenex effectiveness with chlorthalidone for treatment of mild to moderate essential hypertension	126	123	NA	1-3	1-3 mg o.d. plus 25 mg chlorthalidone o.d.; free titration based upon response
03	O. Haring, M.D. A. Lewin, M.D. G. Bedsole, M.D. W. Stepansky, M.D. J. Fillingim, M.D. D. Hall, M.D. M. Roginsky, M.D. M. Wilson, M.D. P. Jagger, M.D. G. McMahon, M.D. M. Strauss, M.D.	Double-blind, parallel with clonidine control to demonstrate comparative efficacy/safety and to evaluate the effects of abrupt withdrawal of guanfacine vs. clonidine	279	NA	278	1-3	1-3 mg o.d. plus 25 mg chlorthalidone o.d.; free titration based upon patient response; 25 mg chlorthalidone continued for 1 week after withdrawal of clonidine or guanfacine

Protocol Number	Principal Investigator	Purpose of Study	No. Patients Receiving Tenex	No. Patients Receiving Placebo	No. Patients On Comparative Drug	Tenex Doses (mg/day)	Tenex Dosage Schedule
06	M. Strauss, M.D.	Double-blind, parallel with placebo control to determine efficacy and effect on plasma volume and plasma aldosterone	17	9	NA	1	1 mg o.d. monotherapy
11	J. Blackshear, M.D.	Double-blind, parallel with placebo control to determine efficacy and effect on plasma lipids	21	21	1	1	1 mg o.d. monotherapy
14	J. Fillingim, M.D. P. Boyles, M.D.	Double-blind, parallel with guanabenz as control to determine comparative efficacy/safety	45	NA	46	1	1 mg o.d. monotherapy
Total No. of Studies			776	226	278	0.5-3	
			6				

- 1) Dose response
- 2) duration of effectiveness
- 3) efficacy/safety vs. clonidine
- 4) effects on:
 - a) plasma volume
 - b) plasma aldosterone
 - c) plasma lipids
 - d) somnolence (No. 14)

Well-Controlled Trials on Hypertension
Investigators and Patient Accountability

Study Identification	Investigators	Location	No. Patients Studied
Protocol 01 - Dose Response Study	F. Finnerty, M.D.	Washington, D.C.	43
	W. Kessler, M.D.	Wallingford, PA	67
	J. McMillen, M.D.	Camp Hill, PA	36
	A. Marlon, M.D.	Las Vegas, NV	30
	S. Savran, M.D.	Reno, NV	37
	M. Alderman, M.D.	New York, NY	49
	F. Canosa	Miami, FL	50
	B. Materson	Miami, FL	49
	TOTAL		361
	Protocol 02 - 24-Hour Effectiveness Study	P. Black, M.D.	La Jolla, CA
J. Freudenburg, M.D.		Longmont, CO	31
J. Hill, M.D.		Vero Beach, FL	30
C. Holmburg, M.D.		Menomonee Falls, WI	32
M. Rietbrock, M.D.		Oconomowoc, WI	37
M. Sullivan, M.D.		Lafayette, NA	29
M. Thompson, M.D.		Redondo Beach, CA	24
D. Wright, M.D.		Rockford, IL	33
TOTAL			289
Protocol 03 - Clonidine Comparison		O. Haring, M.D.	Chicago, IL
	A. Lewin, M.D.	Los Angeles, CA	49
	G. Bedsole, M.D.	Montgomery, AL	51
	W. Stepansky, M.D.	Trappe, PA	27
	J. Fillingim, M.D.	Savannah, GA	100
	D. Hall, M.D.	Atlanta, GA	21
	M. Rosinsky, M.D.	East Meadow, NY	49
	M. Wilson, M.D.	Oklahoma City, OK	50
	P. Jagger, M.D.	San Diego, CA	19
	G. McMahon, M.D.	New Orleans, LA	49
M. Strauss, M.D.	Little Rock, AR	121	
TOTAL		557	

**Well-Controlled Trials on Hypertension
Investigators and Patient Accountability**

Study Identification	Investigators	Location	No. Patients Studied
Protocol 06 - Monotherapy Efficacy and Plasma Volume/Aldosterone Study	M. Strauss, M.D.	Little Rock, AR	26
Protocol 11 - Monotherapy Efficacy and Plasma Lipids	J. Blackshear, M.D.	Little Rock, AR	42
Protocol 14 - Monotherapy Efficacy and Safety vs. Guanabenz	J. Fillingim, M.D. P. Boyles, M.D.	Savannah, GA Cary, NC	91

continued:

8. Well-Controlled Trials on Hypertension (continued)

1. U.S. Trials: Stepped Care

a. Dose-Response Study (Study No. 01)

One multi-investigator, double-blind, randomized and placebo-controlled study to evaluate the dose response of guanfacine as Step II treatment for mild to moderate essential hypertension (95-114 mmHg, DBP) was completed.

Inclusion and Exclusion Criteria:

In order to be accepted in the study a patient was to be 21-60 years old and have a diagnosis of mild to moderate essential hypertension (DBP=95-114 mmHg). A patient was excluded, however, if he was obese, alcoholic or a drug addict, or if he/she had: unstable diabetes or grade III or IV hypertensive retinopathy, malignancy or advanced renal, hepatic, GI, pulmonary or hematological disease, congestive heart failure, unstable angina pectoris, MI within 6 months or clinically significant cerebrovascular disease, gout, or labile hypertension.

Excluded also were pregnant or nursing women or patients who had received guanethidine or reserpine therapy immediately prior to entering the study or patients taking anticholinergic, anticonvulsant, and antidepressant medication or adrenal steroids or β -blockers or ganglionic blockers, MAO inhibitors, phenothiazines, sympathomimetics or vasodilators for long-term therapy (more than 41 days).

Study Plan: This included two stages:

	<u>Duration</u>	<u>Treatment</u>
Stage I:	5 weeks	25 mg chlorthalidone O.D. in the morning
Stage II:	12 weeks	25 mg chlorthalidone and either placebo or one of the following:
		0.5 mg guanfacine)
		1.0 mg guanfacine)
		2.0 mg guanfacine)--O.D. at bedtime
		3.0 mg guanfacine)

In order to be advanced to Stage II a patient had to remain hypertensive (sitting diastolic blood pressure 95-114 mmHg) until the end of Stage I, if not, he was dropped from the study. Stage II was double-blind and the patients were assigned randomly into the 5 treatment groups. Guanfacine dosages for all groups started at 0.5 mg/day. For groups 3-5 the dosage was increased every 3 weeks until it reached the desired level by weeks 8, 10, and 12 respectively. Treatment during Stage II was administered at bedtime because guanfacine causes sedation in some patients which may interfere with the patient's daily activities.

The patients were evaluated at weeks 0, 2, 4, and 5 during Stage I (screening period) and every 2 weeks during Stage II (drug evaluation period). Evaluations were not at fixed times during the day, thus, representing measurements 12 or more hours post-dosing. The evaluated parameters at each study period are summarized in Table XV.

Table XV

Guanfacine-Clinical Protocol 01
Evaluations Schedule: Efficacy and Safety

Type of Evaluation	Week of Study										
	Step I				Step II						
	0	2	4	5	7	9	11	13	15	17	
<u>Efficacy</u>											
SISBP/SIDBP/SiHR	X	X	X	X	X	X	X	X	X	X	X
SISBP/SIDBP/StHR	X	X	X	X	X	X	X	X	X	X	X
Clinical Adverse Experiences	-	X	X	X	X	X	X	X	X	X	X
Body Weight	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram	X	X	-	X	-	-	-	-	-	-	X
<u>Safety</u>											
Laboratory											
CBC with Differential	X	-	-	X	-	-	X	-	-	-	X
Platelets	X	-	-	X	-	-	X	-	-	-	X
SMAC-16	X	-	-	X	-	-	X	-	-	-	X
Urinalysis	X	-	-	X	-	-	X	-	-	-	X
L.E. Test	-	-	-	X	-	-	-	-	-	-	X
Ophthalmic Exams (optional)	-	-	-	X	-	-	-	-	-	-	X

SiSBP = sitting systolic blood pressure
 SiDBP = sitting diastolic blood pressure
 SiHR = sitting heart rate
 StSBP = standing systolic blood pressure
 StDBP = standing diastolic blood pressure
 StHR = standing heart rate

Mean arterial pressure was calculated from $2/3$ DBP + $1/3$ SBP. Vital signs (blood pressure and pulse) were recorded 12-18 hours after the last dose of test medication. All data collected in the sitting position reflect an average of the last 3 of 5 measurements as was defined in the protocol. Data in the standing position were collected 2 and 5 minutes after standing erect, but the 2 minute reading was chosen for analysis because it provided a better estimation of orthostatic disturbances. The primary measurement of efficacy was the comparison of the values obtained at the end of Stage II to those obtained at the beginning of this stage just before treatment with guanfacine or placebo was initiated. Data from patients who dropped out of the study prior to week 13 were not included in this analysis since patients in the 1.0, 2.0, and 3.0 mg groups had not reached their pre-specified dosage levels. Data from patients who terminated prematurely between weeks 13-17 were "carried forward" and were included in the endpoint analysis.

The mean values of all efficacy data collected at each of the 10 observation periods were calculated and these results are also included in the efficacy analysis so that the overall responses to treatment over time can be appreciated.

RESULTS:

A total of 462 patients were admitted into Stage I by the 8 investigators. One hundred of these patients were terminated during this stage for the reasons indicated in Table XVI.

Table XVI

Patients Terminated During Stage I

<u>Reason</u>	<u>No. of Pts.</u>
DBP < 90 or > 114 mmHg	49
Clinical Adverse Reactions	12
Abnormal Lab Values	3
Administrative (patient failed to return, missed 20% of medication, etc.)	33
Other	<u>3</u>
	100

One additional patient was lost to follow-up early during Stage II. Thus, actually only 361 patients were treated during Stage II. Eighty (80) patients were terminated prematurely during Stage II for the reasons indicated in Table XVII.

Table XVII

Patients Terminated Prematurely During Stage II

Investigator	Number of Patients				Completed Study
	Entered	Terminated	Due to Side Effects Clinical	Lab	
Finnerty	43	6	0	1 (+ SGOT)	37
Kessler	67	24	12		43
McMillan	36	4	1		32
Maylor	30	5	4	1 (+ NPN)	25
Savran	37	7	0		30
Alderman	49	15	12	1 (+ glucose)	34
Canosa	50	9	4		41
Materson	50	10	8		40
	362	80	41	3	282

Other reasons for terminating patients prematurely during Stage II were: treatment failures (6, mainly placebo patients or patients receiving 0.5 mg guanfacine/day), loss to follow-up (7), uncooperation (8), failure to get more than 20% of medication (4), or failure to appear for 2 consecutive visits (4), taking excluded medication (3), intercurrent illness (4), personal reasons (4), (i.e., to have a baby, etc.). Some of the patients were excluded for more than one reason (side effect plus taking excluded medication, etc.).

The distribution of patients by investigator and treatment group is shown in Table XVIII. Comparison of the demographic characteristics of the patients (age, sex, race, height, weight, and mean duration of hypertension) showed no significant differences between the 5 groups as shown in Table XIX (all 362 patients), Table XX (patients who completed the study) and Table XXI (patients who did not complete the study).

Table XVIII

A. H. Robins Co.
Guanfacine-Clinical Protocol 01
Distribution of Patients Included in Endpoint Analysis
By Treatment Group and Investigator

Treatment Group	Investigator								Total
	1	2	3	4	5	6	7	8	
Placebo	8	11	6	3	7	10	9	9	63
0.5	8	12	7	5	7	6	9	9	63
1.0	7	11	5	5	7	10	9	10	64
2.0	8	9	7	5	6	8	8	7	58
3.0	7	8	7	5	7	9	9	7	59
Total	38	51	32	23	34	43	44	42	307

Table XIX

A. H. Robins Co.
Guanfacine - Clinical Protocol 01
Demography - All Patients

Characteristics	Treatment Groups				3.0 mg
	Placebo	0.5 mg	1.0 mg	2.0 mg	
N =	73	72	72	73	72
Sex: Male	56	53	55	57	49
Female	17	19	17	16	23
Race: Non-Blacks	53	49	46	46	45
Blacks	20	23	25	27	27
Age: Mean ± S.D. (yrs.)	48.6 ± 9.2	46.4 ± 10.2	48.6 ± 8.9	49.5 ± 8.9	47.7 ± 9.2
Height: Mean ± S.D. (in.)	68.3 ± 4.1	68.5 ± 4.1	68.2 ± 3.3	68.8 ± 3.7	68.3 ± 3.9
Weight: Mean ± S.D. (lbs.)	186.4 ± 34.3	187.9 ± 31.4	189.7 ± 34.3	185.8 ± 28.1	189.4 ± 37.2
Duration of Hypertension: Mean±S.D. (yrs.)	7.0 ± 6.0	7.3 ± 7.4	6.6 ± 7.5	6.7 ± 6.3	7.5 ± 7.8

Table XX

A. H. Robins Co.
Guanfacine - Clinical Protocol 01
Demography - Patients Who Completed Study

Characteristics	Treatment Groups				
	Placebo	0.5 mg	1.0 mg	2.0 mg	3.0 mg
N =	55	59	59	54	51
Sex: Male	41	44	46	44	36
Female	14	15	13	10	15
Race: Non-Blacks	40	39	37	34	32
Blacks	15	20	22	20	19
Age: Mean	49.7 ±	45.5 ±	48.9 ±	49.7 ±	47.4 ±
±S.D. (yrs.)	8.1	10.7	9.2	9.1	9.1
Height: Mean	68.2 ±	68.6 ±	68.5 ±	68.9 ±	68.6 ±
± S.D. (in.)	4.5	3.8	3.1	3.7	3.5
Weight: Mean	187.8 ±	187.7 ±	191.4 ±	185.9 ±	193.9 ±
± S.D. (lbs.)	35.9	30.9	33.2	27.6	39.9
Duration of Hypertension: Mean±S.D. (yrs).	6.7 ± 5.8	6.4 ± 7.1	6.1 ± 7.8	7.2 ± 6.5	6.7 ± 6.5

Table XXI

A. H. Robins Co.
Guanfacine - Clinical Protocol 01
Demography - Patients Who Did Not Complete Study

Characteristics	Treatment Groups				
	Placebo	0.5 mg	1.0 mg	2.0 mg	3.0 mg
N =	18	13	13	18	21
Sex: Male	16	9	9	12	13
Female	3	4	4	6	8
Race: Non-Blacks	13	10	9	13	13
Blacks	5	3	4	5	8
Age: Mean	45.4 ±	50.4 ±	47.0 ±	49.1 ±	48.4 ±
±S.D. (yrs.)	11.4	6.4	7.6	8.8	9.6
Height: Mean	68.4 ±	68.0 ±	66.9 ±	68.5 ±	67.6 ±
± S.D. (in.)	3.0	5.2	4.3	4.0	4.8
Weight: Mean	182.3 ±	188.9 ±	182.2 ±	183.5 ±	178.6 ±
± S.D. (lbs.)	29.5	34.7	39.6	30.3	27.6
Duration of Hypertension: Mean±S.D. (yrs).	7.9 ± 7.1	11.4 ± 7.8	9.0 ± 5.2	5.1 ± 5.7	9.4 ± 10.2

The baseline vital signs for all patients, patients who completed the study and for those who did not complete the study are shown in Tables XXII, XXIII, and XXIV, respectively. There were no significant differences in either systolic, diastolic, or mean arterial blood pressure or in heart rate between them.

Table XXII
Guanfacine - Clinical Protocol 01
Baseline Vital Signs - All Patients
Sitting Position

Vital Signs	Treatment Groups				
	Placebo	0.5 mg	1.0 mg	2.0 mg	3.0 mg
N =	73	72	72	73	72
Diastolic BP: Mean \pm S.D. (mmHg)	100.4 \pm 5.3	98.9 \pm 3.9	99.8 \pm 4.6	99.7 \pm 4.7	101.0 \pm 5.3
Systolic BP: Mean \pm S.D. (mmHg)	140.7 \pm 13.9	136.5 \pm 11.5	140.5 \pm 13.7	138.9 \pm 13.6	140.0 \pm 13.4
Mean Arterial BP: Mean \pm S.D. (mmHg)	113.8 \pm 7.1	111.5 \pm 5.3	113.4 \pm 6.2	112.8 \pm 6.4	114.0 \pm 6.6
Heart Rate: Mean \pm S.D. (beats/min)	79.6 \pm 10.7	77.4 \pm 9.2	79.9 \pm 10.2	80.5 \pm 10.7	78.5 \pm 9.1

Table XXIII

Guanfacine - Clinical Protocol 01
Baseline Vital Signs - Patients Who Completed Study
Sitting Position

Vital Signs	Treatment Groups				
	Placebo	0.5 mg	1.0 mg	2.0 mg	3.0 mg
N =	55	59	59	54	51
Diastolic BP: Mean \pm S.D. (mmHg)	99.5 \pm 4.9	99.1 \pm 4.1	99.9 \pm 4.6	99.6 \pm 4.7	100.3 \pm 5.1
Systolic BP: Mean \pm S.D. (mmHg)	139.1 \pm 13.9	136.2 \pm 11.3	139.9 \pm 13.6	139.4 \pm 14.9	139.8 \pm 12.8
Mean Arterial BP: Mean \pm S.D. (mmHg)	112.7 \pm 6.9	111.5 \pm 5.4	113.2 \pm 6.2	112.9 \pm 6.8	113.5 \pm 6.6
Heart Rate: Mean \pm S.D. (beats/min)	79.1 \pm 10.6	77.4 \pm 9.5	78.8 \pm 8.7	82.2 \pm 10.0	79.2 \pm 9.8

Table XXIV

Guanfacine - Clinical Protocol 01
Baseline Vital Signs - Patients Who Did Not Completed Study
Sitting Position

Vital Signs	Treatment Groups				
	Placebo	0.5 mg	1.0 mg	2.0 mg	3.0 mg
N =	18	13	13	18	21
Diastolic BP: Mean \pm S.D. (mmHg)	103.1 \pm 5.8	98.4 \pm 2.3	99.3 \pm 5.0	99.1 \pm 3.4	102.7 \pm 5.6
Systolic BP: Mean \pm S.D. (mmHg)	145.3 \pm 13.3	137.9 \pm 12.6	143.2 \pm 14.6	137.1 \pm 8.2	140.5 \pm 15.0
Mean Arterial BP: Mean \pm S.D. (mmHg)	117.1 \pm 7.2	111.6 \pm 4.7	113.9 \pm 6.6	111.7 \pm 4.2	115.3 \pm 6.4
Heart Rate: Mean \pm S.D. (beats/min)	81.2 \pm 11.3	77.5 \pm 8.3	84.6 \pm 14.8	75.2 \pm 11.6	77.1 \pm 7.2

The effect of the various dosages of guanfacine on the diastolic, systolic, and mean arterial blood pressures and on the heart rate in the sitting position is shown in Tables XXV, XXVI, XXVII, and XXVIII and is illustrated in Figs. 11, 12, 13, and 14. Tables XXIX, XXX, XXXI, and XXXII and Figs. 15, 16, 17, and 18 show the respective effects in the standing position.

Table XXV

Guanfacine - Clinical Protocol 01
Response Criterion = Diastolic Blood Pressure
Dose Group Means by Week of Study
Sitting Position

Week of Study	Statistic	Patient Randomized	Dose Group				
			Placebo	0.5	1.0	2.0	3.0
Baseline	N	361	-	-	-	-	-
	Mean	99.9	-	-	-	-	-
2	N	-	70	282	-	-	-
	Mean	-	94.3	89.9	-	-	-
4	N	-	69	66	198	-	-
	Mean	-	93.0	91.5	86.7	-	-
6	N	-	65	62	65	125	-
	Mean	-	93.8	91.2	86.7	85.4	-
8	N	-	60	62	62	58	59
	Mean	-	91.5	92.6	86.6	85.5	86.0
10	N	-	59	58	60	54	54
	Mean	-	92.3	91.3	87.0	86.4	86.0
12	N	-	57	59	60	54	52
	Mean	-	91.9	92.8	86.9	86.0	87.3

Figure 11

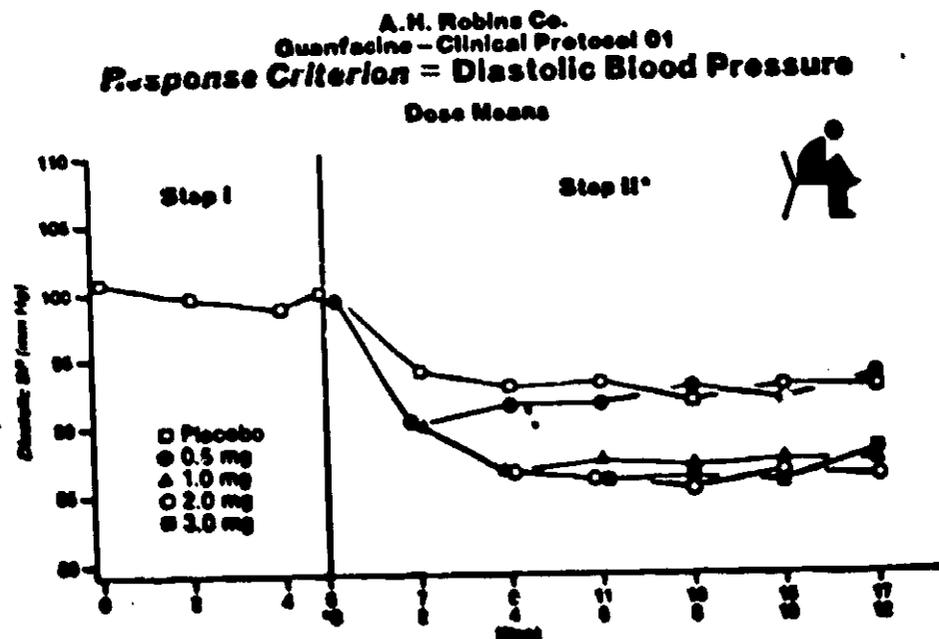


Table XXVI

Guanfacine - Clinical Protocol 01
 Response Criterion = Systolic Blood Pressure
 Dose Group Means by Week of Study
 Sitting Position

Week of Study	Statistic	Patient Randomized	Dose Group				
			Placebo	0.5	1.0	2.0	3.0
Baseline	N	361					
	Mean	139.3	-	-	-	-	-
2	N	-	70	282	-	-	-
	Mean	-	137.8	130.6	-	-	-
4	N	-	69	66	198	-	-
	Mean	-	137.0	130.2	125.4	-	-
6	N	-	65	62	65	125	-
	Mean	-	133.2	130.5	125.3	123.7	-
8	N	-	60	62	62	56	59
	Mean	-	133.7	131.7	128.5	125.0	122.1
10	N	-	59	58	60	54	54
	Mean	-	135.6	130.8	127.0	125.4	124.1
12	N	-	57	59	60	54	52
	Mean	-	134.4	131.3	126.3	125.9	123.8

Figure 12

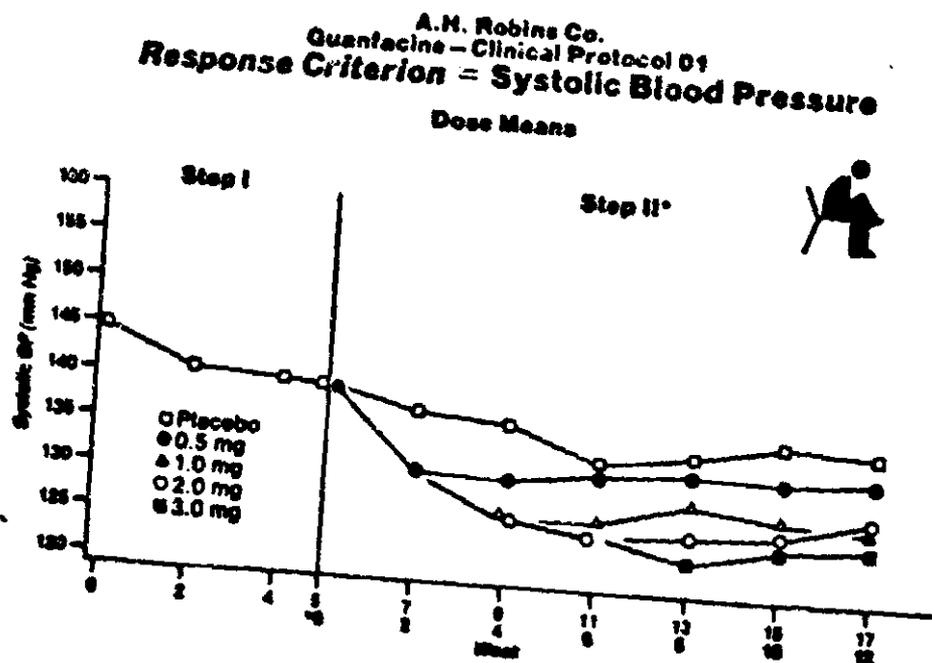


Table XXVII

Guanfacine - Clinical Protocol 01
 Response Criterion = Mean Arterial Pressure
 Dose Group Means by Week of Study
 Sitting Position

Week of Study	Statistic	Patient Randomized	Dose Group				
			Placebo	0.5	1.0	2.0	3.0
Baseline	N	361	-	-	-	-	-
	Mean	113.1					
2	N	-	70	282	-	-	-
	Mean		108.8	103.5			
4	N	-	69	66	198	-	-
	Mean		107.7	104.4	100.0		
6	N	-	65	62	65	125	-
	Mean		106.9	104.3	99.6	98.2	
8	N	-	60	62	62	58	59
	Mean		105.6	105.6	100.7	98.7	98.0
10	N	-	59	58	60	54	54
	Mean		106.7	104.5	100.3	99.4	98.7
12	N	-	57	59	60	54	52
	Mean		106.1	105.6	100.0	99.6	99.5

Figure 13

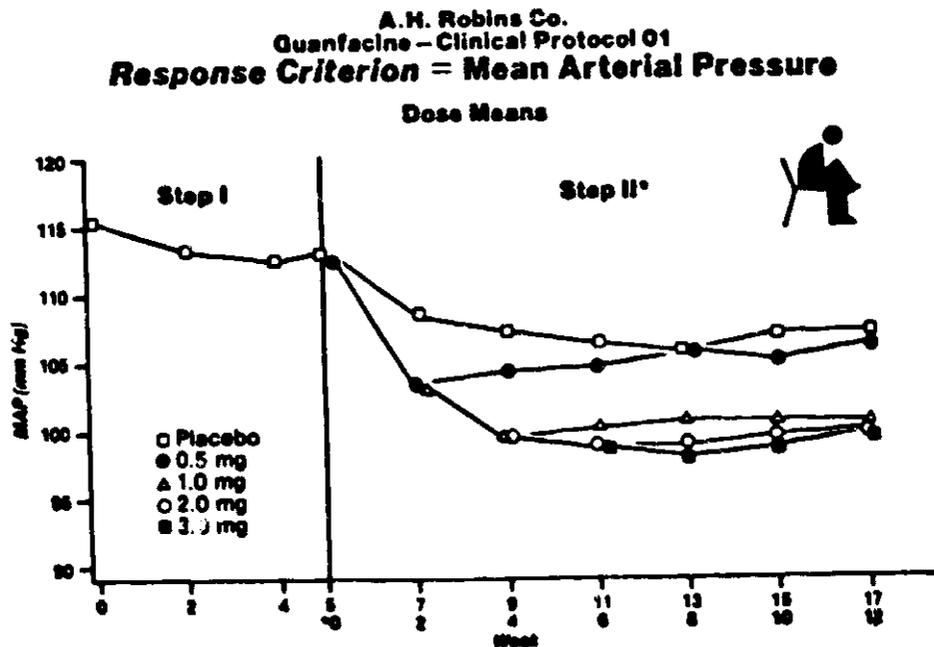


Table XXVIII

Guanfacine - Clinical Protocol 01
 Response Criterion = Heart Rate
 Dose Group Means by Week of Study
 Sitting Position

Week of Study	Statistic	Patients Randomized	Dose Group				
			Placebo	0.5	1.0	2.0	3.0
Baseline	N	361	-	-	-	-	-
	Mean	79.2					
2	N	-	70	282	-	-	-
	Mean		80.4	77.0			
4	N	-	69	66	198	-	-
	Mean		81.2	79.1	75.6		
6	N	-	65	62	65	124	-
	Mean		79.6	77.8	75.8	72.7	
8	N	-	60	62	62	58	59
	Mean		79.5	78.7	76.7	73.6	74.7
10	N	-	59	58	60	54	54
	Mean		77.7	77.1	74.9	74.1	74.4
12	N	-	57	59	60	54	52
	Mean		80.3	79.1	74.3	76.5	75.0

Figure 14

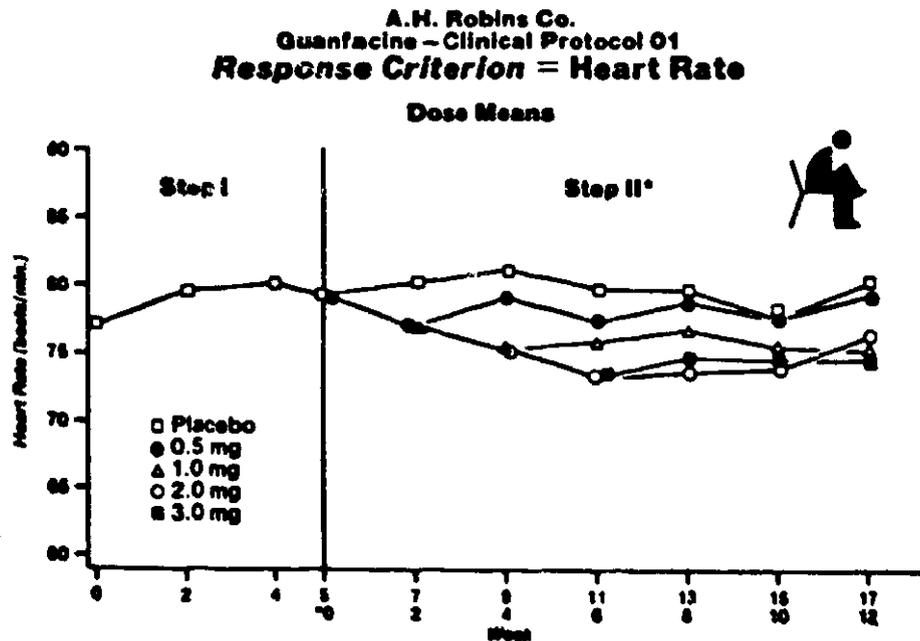


Table XXIX

Guanfacine - Clinical Protocol 01
 Response Criterion = Diastolic Blood Pressure
 Dose Group Means by Week of Study
 Standing Position

Week of Study	Statistic	Patients Randomized	Dose Group				
			Placebo	0.5	1.0	2.0	3.0
Baseline	N	361	-	-	-	-	-
	Mean	101.7	-	-	-	-	-
2	N	-	70	282	-	-	-
	Mean	-	98.7	93.5	-	-	-
4	N	-	69	66	198	-	-
	Mean	-	96.9	95.4	90.5	-	-
6	N	-	65	62	65	124	-
	Mean	-	98.7	95.0	90.3	89.8	-
8	N	-	60	62	62	58	59
	Mean	-	96.6	97.8	90.4	88.8	89.2
10	N	-	59	58	60	54	54
	Mean	-	96.9	95.7	90.1	90.9	89.7
12	N	-	57	59	60	54	52
	Mean	-	95.3	96.6	91.3	91.0	90.8

Figure 15

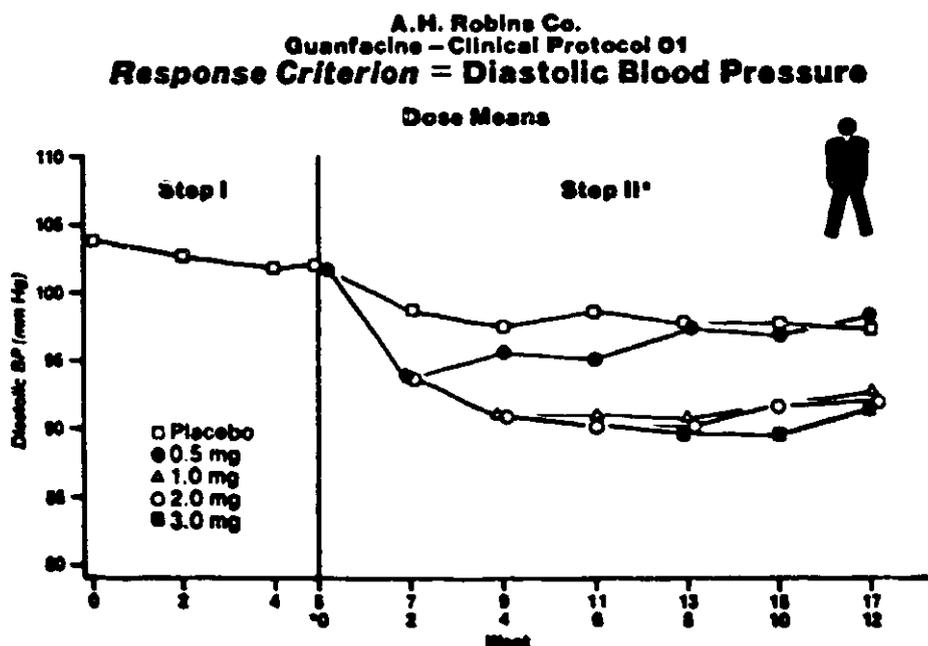


Table XXX

Guanfacine - Clinical Protocol 01
 Response Criterion = Systolic Blood Pressure
 Dose Group Means by Week of Study
 Standing Position

Week of Study	Statistic	Patients Randomized	Dose Group				
			Placebo	0.5	1.0	2.0	3.0
Baseline	N	361	-	-	-	-	-
	Mean	139.6	-	-	-	-	-
2	N	-	70	282	-	-	-
	Mean	-	140.1	132.4	-	-	-
4	N	-	69	66	198	-	-
	Mean	-	137.2	132.2	127.5	-	-
6	N	-	65	62	65	124	-
	Mean	-	135.2	130.8	126.3	125.7	-
8	N	-	60	62	62	58	59
	Mean	-	135.6	134.5	128.2	126.6	123.0
10	N	-	59	58	60	54	54
	Mean	-	135.9	130.4	127.5	127.5	125.3
12	N	-	57	59	60	54	52
	Mean	-	135.5	132.5	129.6	128.9	124.3

Figure 16

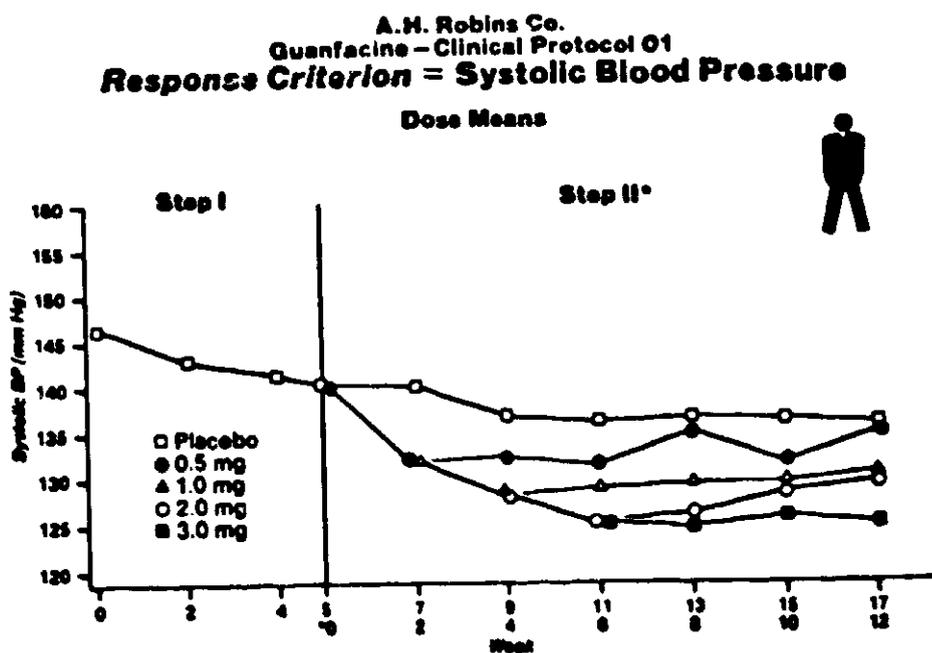


Table XXXI

Guanfacine - Clinical Protocol 01
 Response Criterion = Mean Arterial Pressure
 Dose Group Means by Week of Study
 Standing Position

Week of Study	Statistic	Patients Randomized	Dose Group				
			Placebo	0.5	1.0	2.0	3.0
Baseline	N	361					
2	Mean	114.3	-	-	-	-	-
4	N	-	70	282	-	-	-
	Mean	-	112.5	106.5	-	-	-
6	N	-	69	66	198	-	-
	Mean	-	110.3	107.7	102.8	-	-
8	N	-	65	62	65	124	-
	Mean	-	110.9	106.9	102.3	101.7	-
10	N	-	60	62	62	58	59
	Mean	-	109.6	110.0	113.0	101.4	100.5
12	N	-	59	58	60	54	54
	Mean	-	109.9	107.3	102.6	103.1	101.5
	Mean	-	57	59	60	54	52
	Mean	-	108.7	108.6	104.1	103.6	102.0

Figure 17

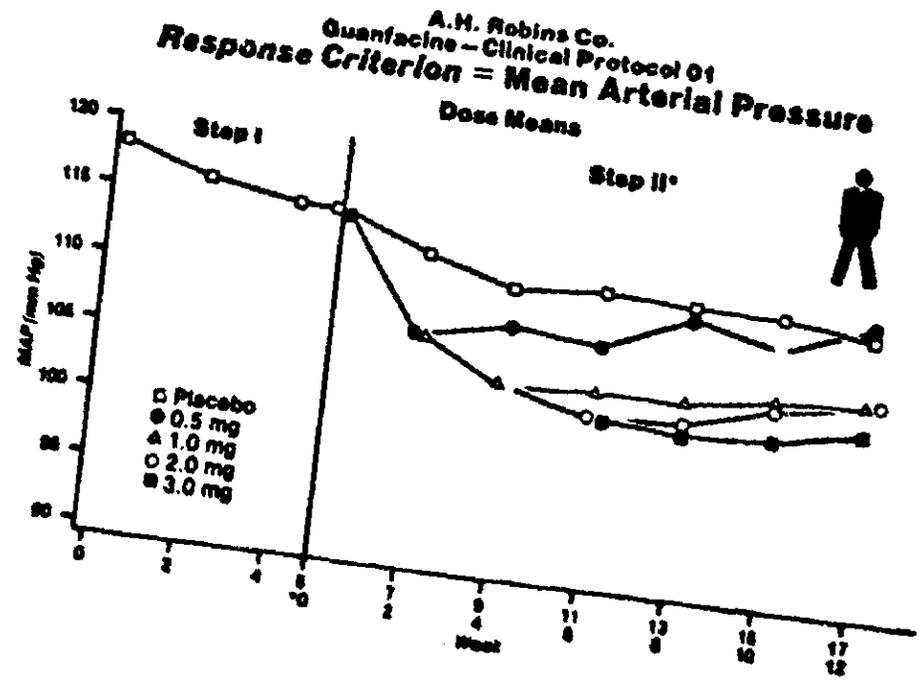
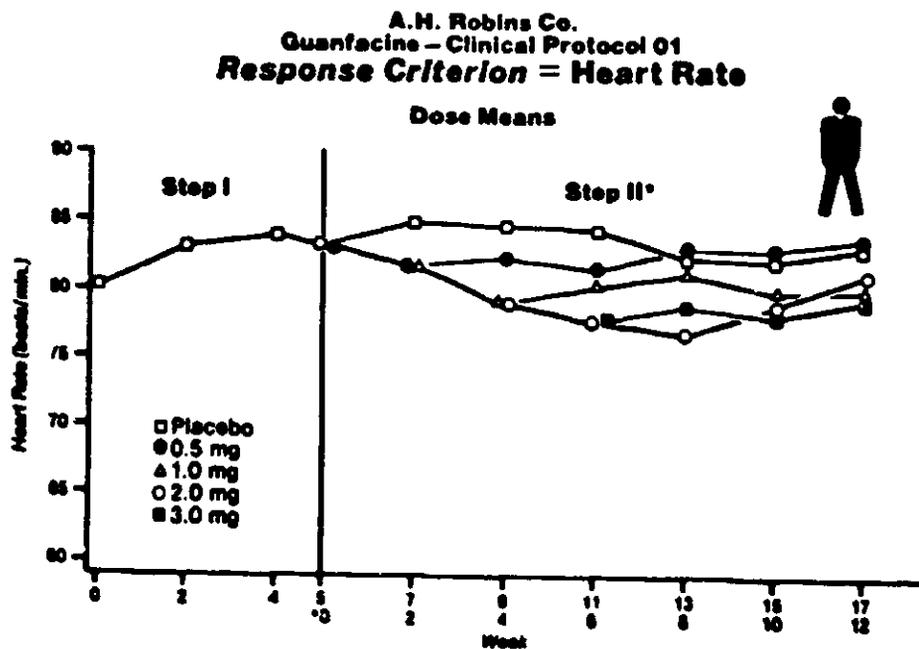


Table XXXII

Guanfacine - Clinical Protocol 01
 Response Criterion = Heart Rate
 Dose Group Means by Week of Study
 Standing Position

Week of Study	Statistic	Patient Randomized	Dose Group				
			Placebo	0.5	1.0	2.0	3.0
Baseline	N	361	-	-	-	-	-
	Mean	82.8					
2	N	-	70	282	-	-	-
	Mean		85.2	81.4			
4	N	-	69	66	198	-	-
	Mean		84.2	81.9	79.3		
6	N	-	65	62	65	123	-
	Mean		84.4	81.6	79.7	77.1	
8	N	-	60	62	62	58	59
	Mean		82.5	82.5	80.6	76.6	78.9
10	N	-	59	58	60	54	54
	Mean		81.8	82.5	78.6	78.7	78.5
12	N	-	57	59	60	54	52
	Mean		82.9	83.1	78.5	81.3	79.9

Figure 18



The results show that significant reductions in blood pressure were obtained with daily dosages of 1.0, 2.0, and 3.0 mg of guanfacine, while the 0.5-mg dosage was less effective, causing no significant reduction in pressure. The effect of the 1-3 mg dosages was similar, especially on diastolic pressure, where increasing the dosage from 1 to 3 mg gave no suggestion of an increased effect. There was, however, some indication of an increased effect on systolic pressure at the highest dose although the difference was not significant. Heart rate was decreased by 1-6 beats/min. Again, there was no significant difference between the effects of the 1-3 mg dosages.

Endpoint mean changes for each of the vital signs in the sitting and standing positions are shown in Tables XXXIII and XXXIV respectively. Addition of guanfacine at 1-3 mg to a regimen of 25 mg chlorthalidone per day reduced the diastolic, systolic and mean arterial pressure in the sitting position by 13, 12-16 and 13-14 mmHg respectively. The respective changes in the standing position were 9-12, 10-15, and 10-13 mmHg. The changes in heart rate were 4-5 beats/min in both positions.

Statistical analysis of the results in the sitting (Table XXXV) and standing position (Table XXXVI) showed that the reductions induced by the 1.0-3.0 mg dosages were statistically significant.

Table XXXIII

Guanfacine - Clinical Protocol 01
Endpoint Means by Treatment Group
Sitting Position

Response Criteria	Statistic	Treatment Group				
		Placebo	0.5	1.0	2.0	3.0
Diastolic Blood Pressure	N	63	63	64	58	59
	Mean	92.8	93.5	87.3	86.1	87.6
	Mean Change	-7.1	-5.6	-12.7	-13.3	-13.1
Systolic Blood Pressure	N	63	63	64	58	59
	Mean	134.5	132.5	126.5	127.6	124.2
	Mean Change	-4.7	-4.7	-14.0	-11.6	-15.6
Mean Arterial Pressure	N	63	63	64	58	59
	Mean	106.7	106.5	100.4	99.9	99.8
	Mean Change	-6.3	-5.3	-13.1	-12.8	-13.9
Heart Rate	N	63	63	64	58	59
	Mean	80.4	79.4	75.1	76.2	74.6
	Mean Change	+1.2	+2.1	-4.4	-4.7	-4.5

Table XXXIV

Guanfacine - Clinical Protocol 01
Endpoint Means by Treatment Group
Standing Position

Response Criteria	Statistic	Treatment Group				
		Placebo	0.5	1.0	2.0	3.0
Diastolic Blood Pressure	N	63	63	64	58	59
	Mean	96.3	97.2	92.0	91.2	91.1
	Mean Change	-5.5	-3.7	-8.9	-10.0	-11.7
Systolic Blood Pressure	N	63	63	64	58	59
	Mean	135.5	133.4	130.1	129.8	124.7
	Mean Change	-3.3	-4.9	-10.7	-9.5	-15.0
Mean Arterial Pressure	N	63	63	64	58	59
	Mean	109.4	109.3	104.7	104.0	102.3
	Mean Change	-4.8	-4.1	-9.5	-9.8	-12.8
Heart Rate	N	63	63	64	58	59
	Mean	83.3	83.2	79.3	80.9	79.5
	Mean Change	+2.1	+1.3	-3.9	-4.6	-3.7

Table XXXV

Guanfacine - Clinical Protocol 01
Statistical Analyses of Endpoint Efficacy Results
Sitting Position

Response Criterion	Treatment Effect ($\alpha=.05$)	4 Contrasts ($\alpha_1 = .05/4 = .0125$)			
		0 vs 0.5	0 vs 1.0	0 vs 2.0	0 vs 3.0
Diastolic Blood Pressure	p<.05	NS	p<.0125	p<.0125	p<.0125
Systolic Blood Pressure	p<.05	NS	p<.0125	p<.0125	p<.0125
Mean Arterial Pressure	p<.05	NS	p<.0125	p<.0125	p<.0125
Heart Rate	p<.05	NS	p<.0125	p<.0125	p<.0125

Table XXXVI

Guanfacine - Clinical Protocol 01
 Statistical Analyses of Endpoint Efficacy Results
 Standing Position

Response Criterion	Treatment Effect	4 Contrasts ($\alpha = .05/4 = .0125$)			
		0 vs 0.5	0 vs 1.0	0 vs 2.0	0 vs 3.0
Diastolic Blood Pressure	p<.05	NS	p=0.042	p<.0125	p<.0125
Systolic Blood Pressure	p<.05	NS	p<.0125	p=0.025	p<.0125
Mean Arterial Pressure	p<.05	NS	p<.0125	p<.0125	p<.0125
Heart Rate	p<.05	NS	p<.0125	p<.0125	p<.0125

Dose Response: The dose response curves for group mean blood pressures and heart rate at the end of the study (week 12) as a function of assigned dose are shown in Figures 19-26. It appears that the effect on the standing blood pressure increases with dosage although the differences between the 1.0-, 2.0-, and 3.0-mg dosages were not statistically significant, while there is little evidence of an increased diastolic pressure response with dose.

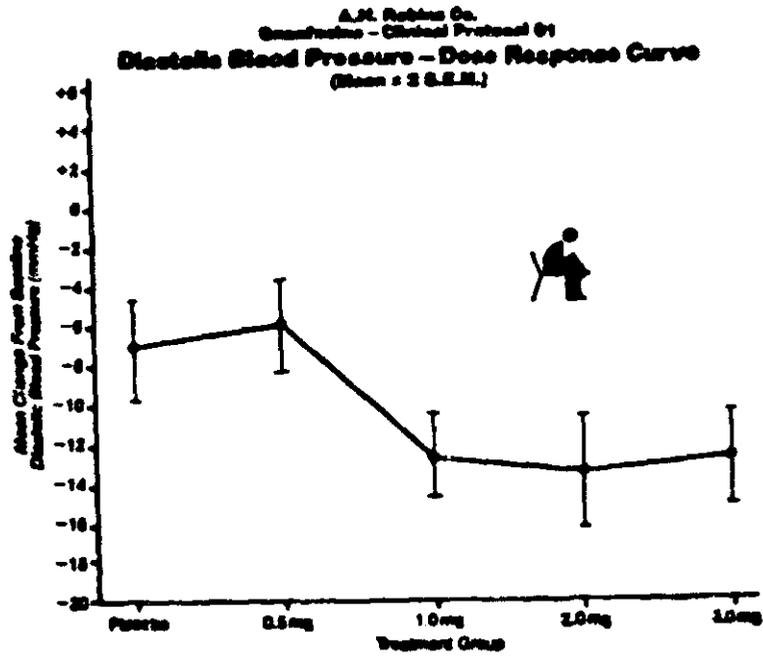


Figure 19

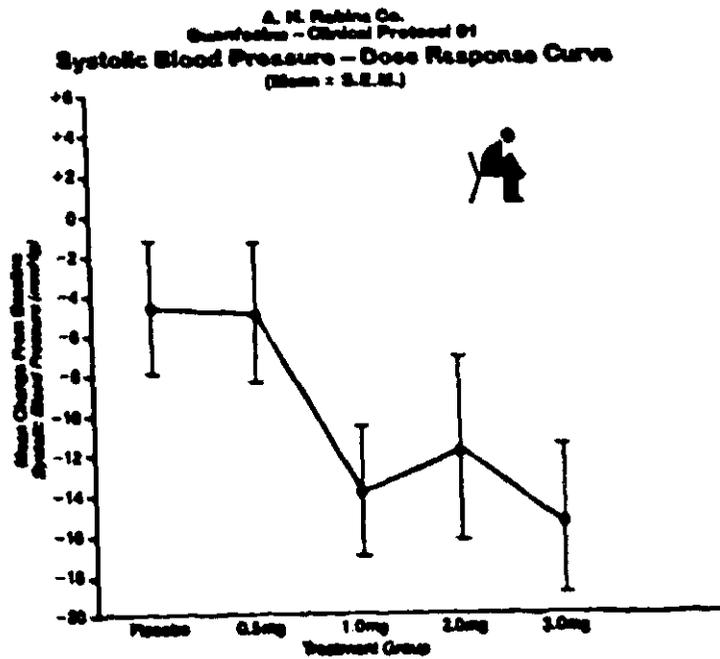


Figure 20

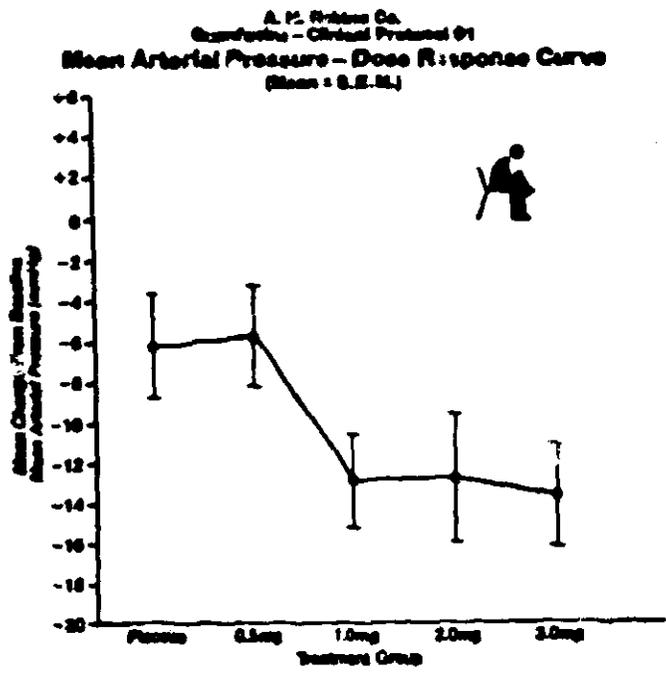


Figure 21

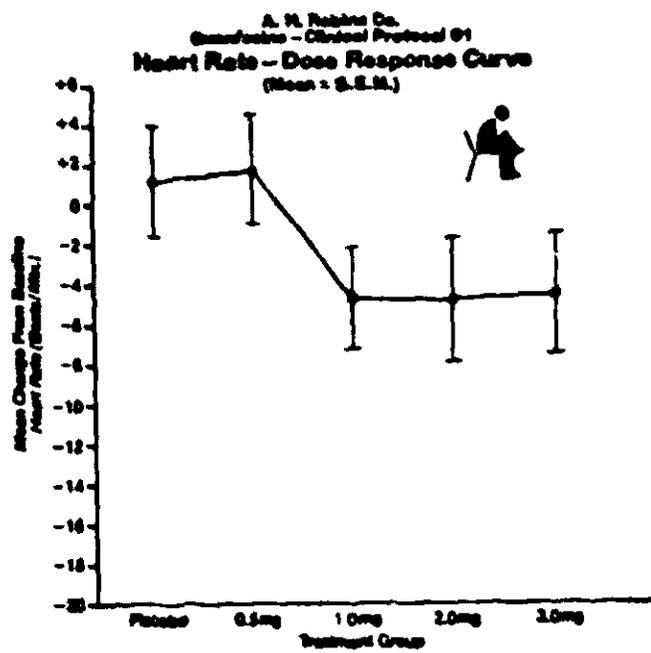


Figure 22

A. H. Robbins Co.
 Guanfacine - Clinical Protocol 01
Diaastolic Blood Pressure - Dose Response Curve
 (Mean ± S.E.M.)

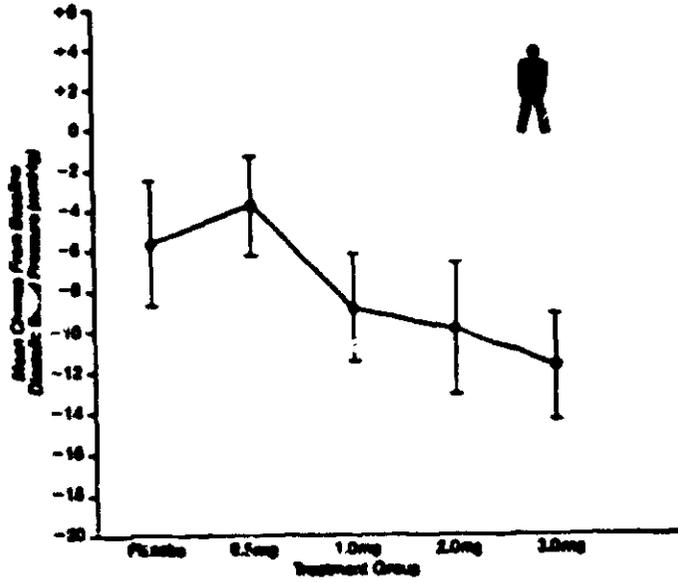


Figure 23

A. H. Robbins Co.
 Guanfacine - Clinical Protocol 01
Systolic Blood Pressure - Dose Response Curve
 (Mean ± S.E.M.)

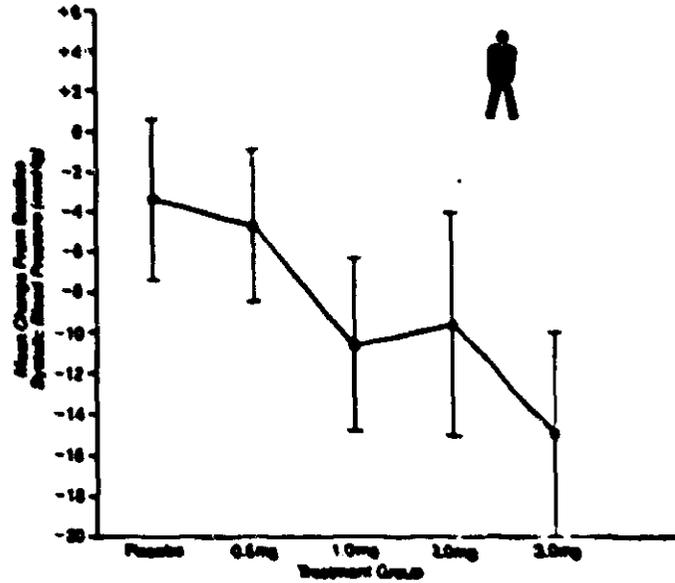


Figure 24

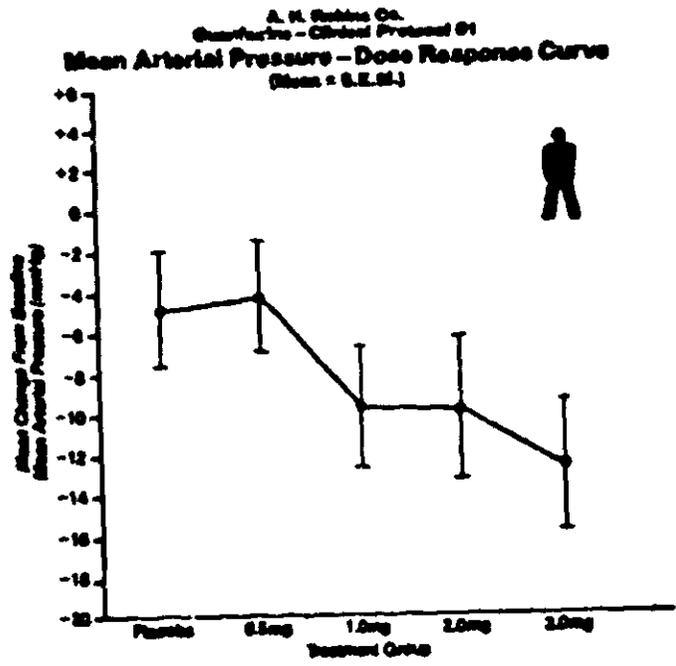


Figure 25

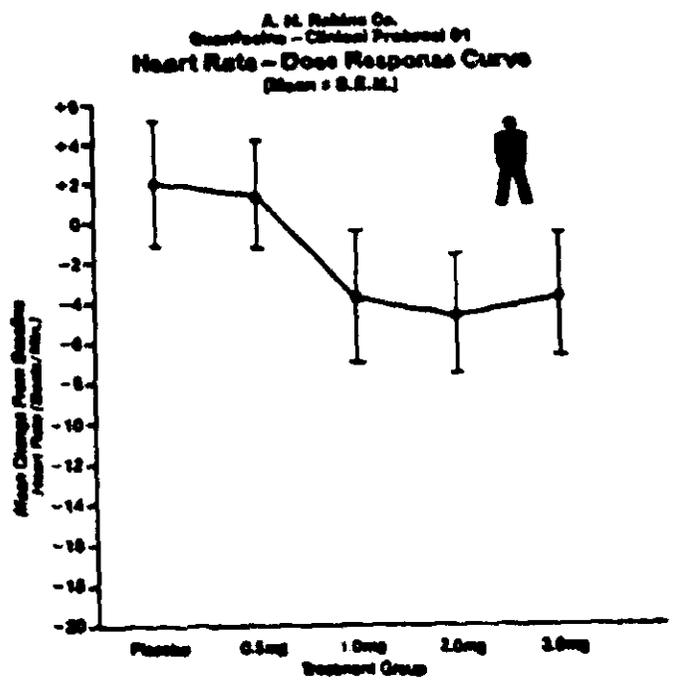


Figure 26

The endpoint mean diastolic blood pressures in the sitting position are tabulated in Table XXXVII according to the degree of the baseline diastolic pressures (95-99, 100-104, and greater than 104 mmHg). It is obvious that the lower the initial pressure was, the lower were the levels that the endpoint pressure reached, which suggest that the reductions in blood pressure due to guanfacine were the same in all 3 groups (a mean of about 12 mmHg). Table XXXVIII shows that the percentage of patients who reached an endpoint diastolic pressure less than 90 mmHg was inversely proportional to the degree of the baseline blood pressure. It also shows that the placebo effect was significant: 50% of the patients who had baseline diastolic blood pressure between 95-99 mmHg and 24% of those who had pressures between 110-114 mmHg became normotensive after taking placebo (in addition to chlorthalidone). Guanfacine at 0.5 mg/day was actually less effective (43% and 11% respectively) than placebo.

Table XXXVII

Guanfacine - Clinical Protocol 01
 Response Criterion = Diastolic Blood Pressure
 Mean Endpoint By Treatment Group and Baseline Value
 Sitting Position
 (mmHg)

Baseline	Treatment Groups (mg)									
	Placebo	Δ	0.5	Δ	1.0	Δ	2.0	Δ	3.0	Δ
95- 99	89.1 n=42	-8.0	91.1 n=44	-6.0	84.9 n=37	-12.0	85.0 n=40	-12.1	83.6 n=31	-13.3
100-104	96.7 n=12	-4.5	98.5 n=11	-3.0	87.9 n=16	-13.0	88.6 n=9	-12.3	92.2 n=16	- 9.2
>104	105.2 n=9	-6.1	100.6 n=8	-7.5	94.4 n=11	-14.6	89.1 n=9	-19.7	92.3 n=12	-17.8

Table XXXVIII

Guanfacine - Clinical Protocol 01
 Response Criteria = Diastolic Blood Pressure
 Number of Patients With Endpoint Diastolic
 Blood Pressure < 90 mmHg
 Sitting Position

Baseline Diastolic Blood Pressure (mmHg)	Treatment Group				
	Placebo	0.5	1.0	2.0	3.0
95- 99	50% n=42	43% n=44	73% n=37	68% n=40	71% n=31
100-114	24% n=21	11% n=19	41% n=27	61% n=18	39% n=28

Side Effects: Table XXXIX shows that only the higher dosages of guanfacine (2 and 3 mg/day) caused a clearly higher incidence of side effects than placebo. The 1.0-mg dose could not be distinguished from placebo. The most frequent side effects observed, especially at high dosages, were dry mouth, somnolence, and asthenia. It should be noted that because of the study design, patients assigned to the 3.0 mg/day group could also have experienced an adverse effect at a lower dose of guanfacine.

Table XL displays the frequency distribution of patients who were discontinued prematurely because of adverse experiences according to the dose level of the drug at the time of termination. There were no significant differences in the percentage of patients who were terminated because of side effects between the placebo and the 2.0 and 3.0 mg of guanfacine/day groups. This suggests that the side effects caused by guanfacine are rather mild and that patients can tolerate them.

Table XXXIX

Guanfacine - Clinical Protocol 01
Frequency Distribution of Patients with
Most Common Adverse Experiences
(Possibly or Probably Related Only)

Adverse Experience	Assigned Treatment Group				
	Placebo	0.5 mg	1.0 mg	2.0 mg	3.0 mg
	←----- 25 mg Chlorthalidone -----→				
N =	73	72	72	72	72
Dry Mouth	5	4	6	8	20
Somnolence	1	3	0	1	10
Asthenia	0	2	0	2	7
Dizziness	2	1	3	6	3
Headache	3	4	3	1	2
Impotence	1	1	0	1	3

Table XL

Guanfacine - Clinical Protocol 01
Premature Terminations Because of Adverse Experiences
Frequency Distribution of Patients

Week of Study	Dosage at Time of Termination				
	Placebo	0.5 mg	1.0 mg	2.0 mg	3.0 mg
	←----- 25 mg Chlorthalidone -----→				
2	0	8	-	-	-
4	0	2	5	-	-
6	1	0	1	10	-
8	1	1	1	0	3
10	3	1	0	1	3
12	0	0	0	0	0
Totals	5/73 6.9%	12/288 4.2%	7/216 3.2%	11/144 7.6%	6/72 8.3%

Tables XLI - XLV identify the individual patients in each group who experienced adverse reactions and the type of the reaction.

Table XLI

Guanfacine - Clinical Protocol 01
 Adverse Experiences as Reasons for Discontinuation of Placebo

Number of Patients with Adverse Experiences: 5

Number of Adverse Experiences : 6

<u>Patient Identification</u>	<u>Adverse Experience</u>
1403	hypertension
1406	nausea and vomiting
1604	headache
1709	fatigue
1816	somnolence

Table XLII

Guanfacine - Clinical Protocol 01
 Adverse Experiences as Reasons for Discontinuation of Guanfacine
 at the 0.5 mg Dosage Level

Number of Patients with Adverse Experiences: 12

Number of Adverse Experiences : 23

<u>Patient Identification</u>	<u>Adverse Experience</u>
12004	syncope
12014	headache, abnormal vision
12012	impotence
12019	conjunctivitis and iritis
12024	pain, headache and nausea
1411	impotence
1621	dry mouth, weight decrease and polyuria
1643	asthenia and nervousness
1615	urinary incontinence
1605	insomnia
1646	headache and dizziness
1707	asthenia, dizziness, headache and somnolence

Table XLIII

Guanfacine - Clinical Protocol 01
 Adverse Experiences as Reasons for Discontinuation of Guanfacine
 at the 1.0 mg Dosage Level

Number of Patients with Adverse Experiences: 7
 Number of Adverse Experiences : 12

<u>Patient Identification</u>	<u>Adverse Experience</u>
12001	dermatitis
1325	dizziness and nausea
1425	dry mouth and headache
1639	dizziness and headache
1623	pain, paresis and insomnia
1718	paraesthesia
1817	asthenia

Table XLIV

Guanfacine - Clinical Protocol 01
 Adverse Experiences as Reasons for Discontinuation of Guanfacine
 at the 2.0 mg Dosage Level

Number of Patients with Adverse Experiences: 11
 Number of Adverse Experiences : 29

<u>Patient Identification</u>	<u>Adverse Experience</u>
12052	constipation, taste perversion, and purpura bradycardia, dry mouth, dizziness and somnolence
12027	
12020	dry mouth, asthenia and somnolence
12073	dry mouth and substernal chest pain
12005	headache, vertigo and nausea
1421	asthenia, fatigue and depression
1835	asthenia
1802	somnolence and dry mouth
1810	dry mouth, asthenia, abdominal pain, taste perversion and somnolence
1825	dizziness and paraesthesia
1826	impotence

Table XLV

Guanfacine - Clinical Protocol 01
Adverse Experiences as Reasons for Discontinuation of Guanfacine
at the 3.0 mg Dosage Level

Number of Patients with Adverse Experiences: 6

Number of Adverse Experiences : 15

<u>Patient Identification</u>	<u>Adverse Experience</u>
12015	dry mouth, insomnia, somnolence and dermatitis
1601	dry mouth, dizziness and somnolence
1625	asthenia and somnolence
1635	asthenia
1636	asthenia and somnolence
1728	dry mouth, dysphagia and constipation

Laboratory Evaluations: There were no clinically significant changes in the mean values of any of the laboratory parameters which were evaluated. Two patients were discontinued from the study because of adverse lab results. One of these had received placebo and was discontinued because he had an elevated non-protein-N and albuminuria. The other, who was receiving a dose of 0.5 mg, developed dry mouth, polyuria and hyperglycemia at week 13. A third patient was discontinued at week 7 because of a high SGOT (605 units) but this patient had already a high value (244) at baseline. Similarly there were no significant changes in the ECG and ophthalmologic (slit lamp and intraocular pressure) evaluations.

Conclusion: This well-controlled, dose-response study shows that guanfacine is safe and effective with dose-related antihypertensive activity when used in combination with 25 mg of chlor-thalidone.

* * * * *

b. A Multi-Investigator, Double-blind, Randomized, and Parallel Clinical Study of Guanfacine Versus Placebo to Demonstrate the 24-Hour Duration of Effectiveness of Guanfacine for Treatment of Essential Hypertension (Study No. 02).

This study was similar in many respects to the previous one (Study 01) and was carried out by the following 8 investigators.

Paul Black, M.D.	LaJolla, CA
J.C. Freudenburg, M.D.	Longmont, CO
Joseph Hill, M.D.	Vero Beach, FL
C.E. Holmberg, M.S.	Menomonee Falls, WI
Michael Rietbrock, M.D.	Oconomowoc, WI
Maurice Sullivan, M.D.	Lafayette, LA
Mark Thompson, M.D.	Redondo Beach, CA
David Wright, M.D.	Rockford, IL

As in the previous study the design included two stages, the screening phase (Stage I) of 5 weeks duration (when the patients were weaned from any previous antihypertensive medication and were started on chlorthalidone 25 mg/day) and the treatment phase (Stage II) of 12 weeks duration. During this second stage the patients were stratified in either the A.M. or the P.M. group and then randomized double-blindly to receive guanfacine or placebo. Thus, there were two placebo and two guanfacine groups in this study. One pair was evaluated at 9 o'clock in the morning and the other at 9 o'clock in the evening (before taking their medication). Both groups ingested their assigned medications at 9 P.M. The starting guanfacine dosage was 1 mg/day. It could be titrated up in 1 mg increments (maximum 3 mg/day) or down at 3-week intervals. To maintain blindness, placebo was matched to the different doses of guanfacine and patients could be "titrated up or down" with placebo.

The inclusion and exclusion criteria, the evaluated parameters and the frequency and methodology of evaluation were the same as in the study 01.

Results

A total of 345 patients were admitted into the first phase. Of these, 96 (28%) were terminated during this phase because of:

Sitting diastolic Blood Pressure <90 mmHg:	64
Clinical Adverse Reactions:	3
Laboratory Adverse Reactions:	5
Other reasons (lost to follow-up, uncooperation or unreliability, intercurrent illness, use of excluded medication, etc.):	24

The remaining 249 patients entered the 12-week evaluation period. Four patients were terminated before week 2. Thus data from only 245 patients were evaluated for efficacy. The distribution of these patients by treatment group and investigator is shown in Table XLVI and their demographic characteristics in Table XLVII. It can be seen that there were no significant differences between the placebo and the guanfacine group regarding sex, race, age, or duration of hypertension.

Table XLVI
Distribution of Patients Included in Endpoint Analysis
By Treatment Group and Investigator

Treatment Group	Investigator								Total
	1	2	3	4	5	6	7	8	
Placebo									
A.M.	9	8	5	7	9	7	4	9	58
P.M.	6	7	8	9	9	8	8	7	62
Guanfacine									
A.M.	9	8	7	7	9	7	5	8	60
P.M.	8	8	8	9	10	7	7	8	65
Total	32	31	28	32	37	29	24	32	245

Table XLVII
Demography - All Patients

Characteristic	Treatment Group	
	Guanfacine	Placebo
Number of Patients	125	121
Sex: Male	80	76
Female	45	45
Race: Non-Blacks	122	116
Blacks	3	5
Age: Mean (SD) yrs.	46.4 (9.34)	48.3 (7.85)
Height: Mean (SD) in.	68.4 (3.61)	68.6 (3.85)
Weight: Mean (SD) lbs.	188.3 (34.33)	190.3 (33.32)
Duration of Hypertension: Mean (SD) yrs.	7.3 (7.34)	8.3 (6.85)

Twenty-two additional patients were terminated later during the same phase for reasons listed below (Table XLVIII includes the 3 patients who were terminated earlier):

Table XLVIII

	A.M.		P.M.	
	Placebo	Guanfacine	Placebo	Guanfacine
Clinical Adverse Reactions:	1	3	1	5
Miscellaneous*	<u>6</u>	<u>2</u>	<u>5</u>	<u>2</u>
Total	7	5	6	7

*(Lost to follow-up, high blood pressure, intercurrent illness, etc.)

Efficacy Data

A.M. Evaluation Groups. Results from 118 patients, who were evaluated in the morning at 9 a.m., i.e., 12 hours after they had received their medication, have been reported. Sixty of these patients had received guanfacine and 58 had received placebo. The two groups were comparable regarding blood pressure and heart rate at baseline as shown in Table XLIX. The blood

Table XLIX

Baseline Vital Signs - All Patients
Efficacy Analysis Group = A.M.

Vital Sign	Treatment Group	
	Guanfacine	Placebo
Number of Patient	60	58
Diastolic Blood Pressure mean (s.d.) mmHg	98.4 (4.80)	99.8 (4.37)
Systolic Blood Pressure mean (s.d.) mmHg	142.3 (13.78)	141.9 (12.32)
Mean Arterial Pressure mean (s.d.) mmHg	113.0 (6.47)	113.8 (5.82)
Heart Rate mean (s.d.) beats/min.	79.1 (11.12)	81.2 (9.08)

pressures decreased in both groups during the treatment period. The mean diastolic blood pressure of the placebo group fell from 99.1 mmHg to 93.5 mmHg at the end of 12 weeks of treatment (Table L, Fig. 27) in the sitting position and from 100 mmHg to 96.0 mmHg in the standing position (Table LI, Fig. 28), i.e., it dropped by a mean value of 5.6 and 4.0 mmHg respectively. The diastolic blood pressure of the guanfacine group dropped by 14.0 mmHg in the sitting position and by 12.2 mmHg in the standing position (Tables LI and Figs. 27 and 28). Statistical analysis of the differences, about 8 mmHg, were not reported. It appears, however, that these differences are significant.

Similar changes were reported regarding the systolic blood pressure (Tables LII and LIII; Figs. 29 and 30). The mean systolic blood pressure in the placebo group fell from 142.1 mmHg to 136.4 (-5.7 mmHg) in the sitting position and from 140.4 to 137.0 (-3.4) mmHg in the standing position. The respective reductions in the guanfacine group were 16.2 and 14.9 mmHg, i.e., about 10-11 mmHg greater than the placebo group. The heart rate was decreased by guanfacine by 8.1 (sitting) and 6.5 (standing) beats/minute from around 80 to 72-77 beats per minute (Tables LIV and LV; Figs. 31 and 32).

Thus, compared to placebo, guanfacine gave a fall in blood pressure of 10-11/8 mmHg and a change in heart rate of about -5 beats per minute.

Table L

Response Criterion = Diastolic Blood Pressure
 Treatment Group Means by Week of Study
 Efficacy Analysis Group = A.M.
 Sitting Position

Week of Study	Statistic	Patients Randomized	Treatment Groups	
			Guanfacine	Placebo
Baseline	N	118	-	-
	Mean	99.1	-	-
1.5	N	-	60	58
	Mean	-	88.3	95.3
3	N	-	60	58
	Mean	-	87.1	95.0
6	N	-	60	57
	Mean	-	87.7	93.2
9	N	-	56	54
	Mean	-	86.2	93.6
12	N	-	56	52
	Mean	-	85.1	93.5

Figure 27

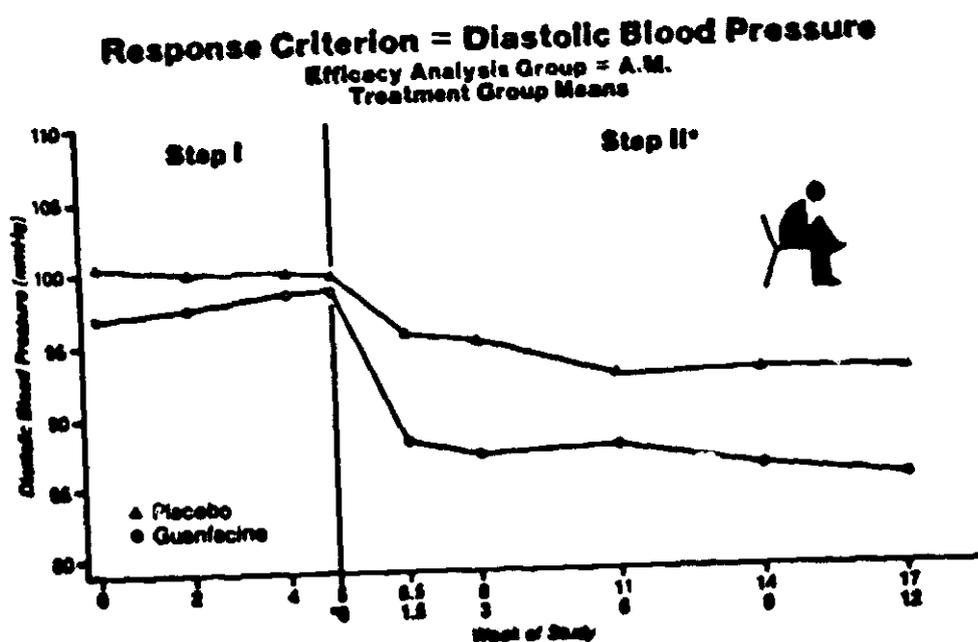


Table LI

Response Criterion = Diastolic Blood Pressure
 Treatment Group Means by Week of Study
 Efficacy Analysis Group = A.M.
 Standing Position

Week of Study	Statistic	Patients Randomized	Treatment Groups	
			Guanfacine	Placebo
Baseline	N	118	-	-
	Mean	100.0		
1.5	N	-	60	58
	Mean		90.4	98.2
3	N	-	60	58
	Mean		89.9	97.3
6	N	-	60	57
	Mean		89.3	97.0
9	N	-	56	54
	Mean		88.4	95.9
12	N	-	56	52
	Mean		87.8	96.0

Figure 28

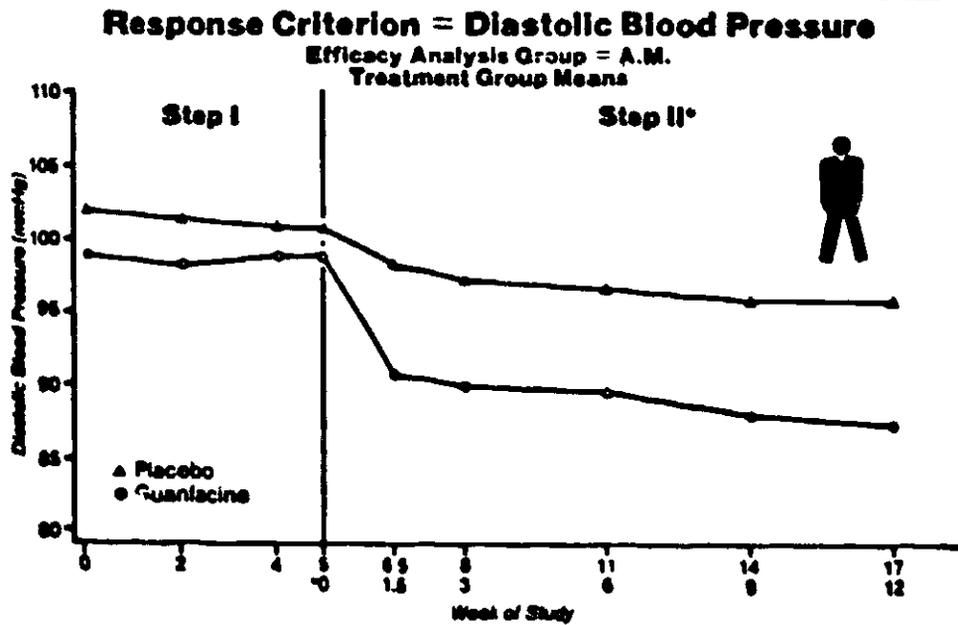


Table L11
 Response Criterion = Systolic Blood Pressure
 Treatment Group Means by Week of Study
 Efficacy Analysis Group = A.M.
 Sitting Position

Week of Study	Statistic	Patients Randomized	Treatment Groups	
			Guanfacine	Placebo
Baseline	N	118	-	-
	Mean	142.1	60	58
1.5	N	-	128.4	138.7
	Mean	-	60	58
3	N	-	128.3	138.2
	Mean	-	60	57
6	N	-	129.9	136.5
	Mean	-	56	54
9	N	-	128.6	137.0
	Mean	-	56	52
12	N	-	125.9	136.4
	Mean	-	-	-

Figure 29

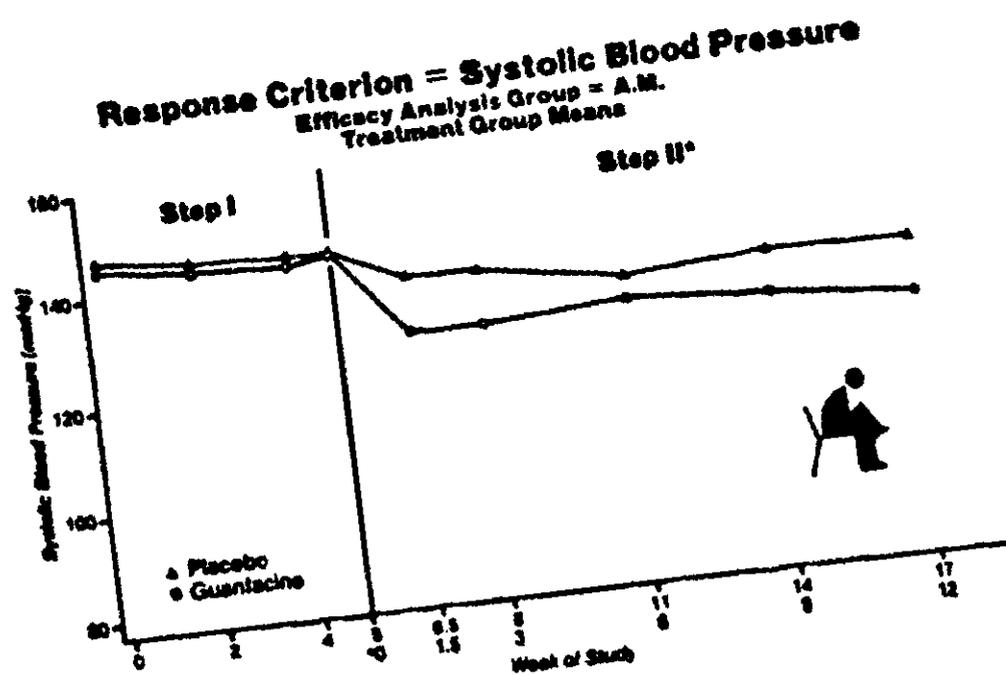


Table LIII

Response Criterion = Systolic Blood Pressure
 Treatment Group Means by Week of Study
 Efficacy Analysis Group = A.M.
 Standing Position

Week of Study	Statistic	Patients Randomized	Treatment Groups	
			Guanfacine	Placebo
Baseline	N	118	-	-
	Mean	140.4		
1.5	N	-	60	58
	Mean		126.4	137.8
3	N	-	60	58
	Mean		127.9	136.5
6	N	-	60	57
	Mean		127.1	137.5
9	N	-	56	54
	Mean		125.3	137.1
12	N	-	56	52
	Mean		125.5	137.0

Figure 30

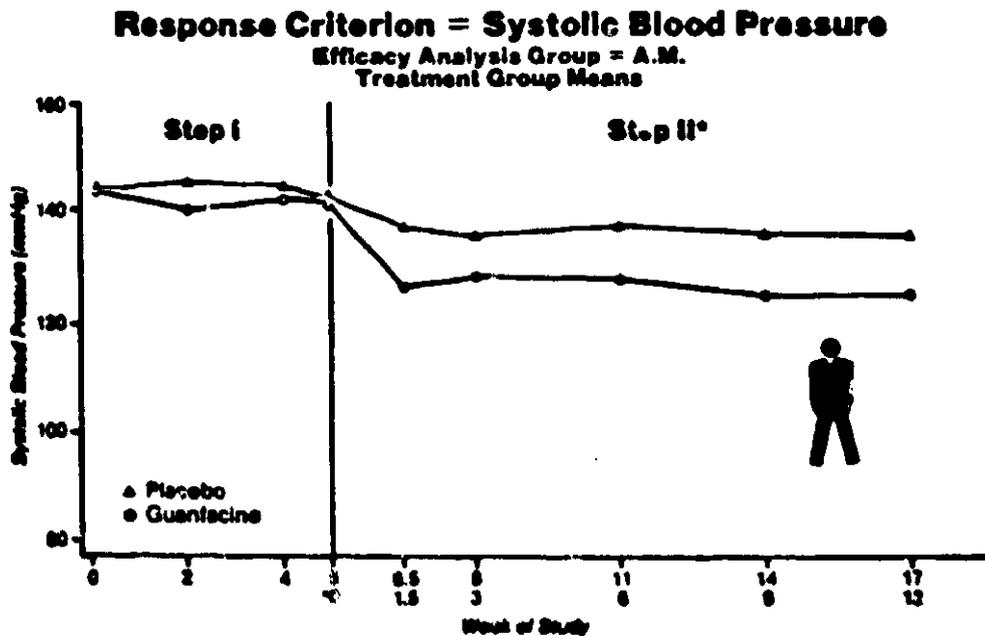
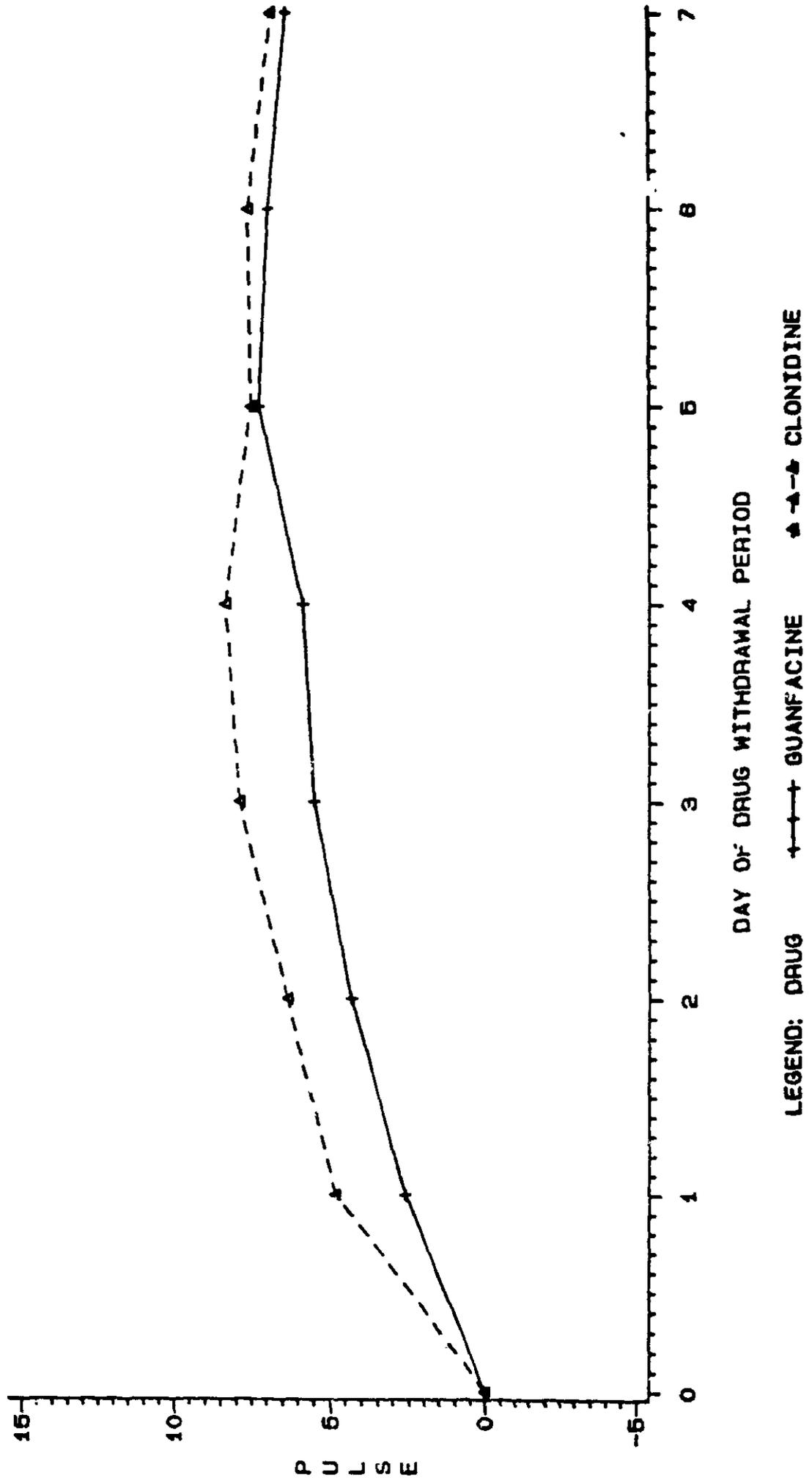


Figure 48

AHR 4458 PROTOCOL 03
MEAN CHANGE IN PULSE
WEEK 30 - WEEK 28
OVERALL OUTPATIENT



The mean DBP, SBP, and HR for each day during Weeks 5 and 30 are shown for each treatment group in figures 49-51. The mean DBP for both guanfacine and clonidine during Week 30 failed to "rebound" to the baseline mean DBP established during Week 5. The mean SBP during Week 30 for both treatment groups slightly exceeded the baseline mean SBP, and the mean SBP in the clonidine group rose at a much faster rate compared with the guanfacine group. Heart rate during Week 30 rose upon discontinuation of treatment, and the mean HRs at the end of Week 30 were slightly higher than at the end of Week 5. These results suggest that, on average, blood pressure and heart rate for patients treated with either guanfacine or clonidine on the doses and dosing schedule used in this study rise upon abrupt discontinuation of either drug, but the vital signs do not "overshoot" a control baseline.

The frequency distribution of patients with increases in diastolic blood pressure >5 or >10 mmHg were analyzed. There were no significant differences between treatment groups on any day of the Drug Withdrawal Period.

Figure 49

AMR 4458 PROTOCOL 09
MEAN DIASTOLIC BLOOD PRESSURE
OVER WEEKS 6 AND 30
OVERALL OUTPATIENT

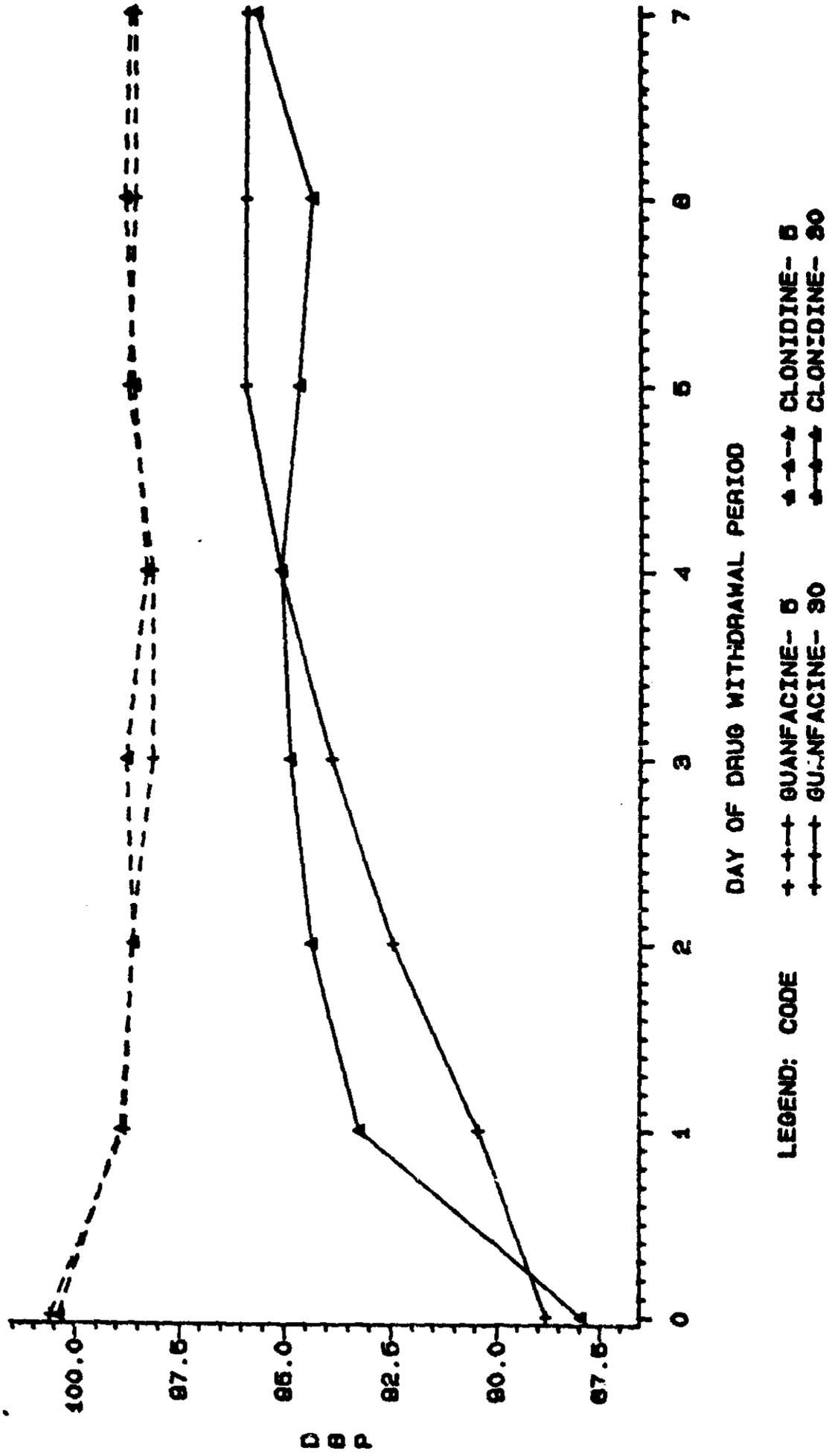


Figure 50

AHR 4488 PROTOCOL 03
MEAN SYSTOLIC BLOOD PRESSURE
OVER WEEKS 6 AND 30
OVERALL OUTPATIENT

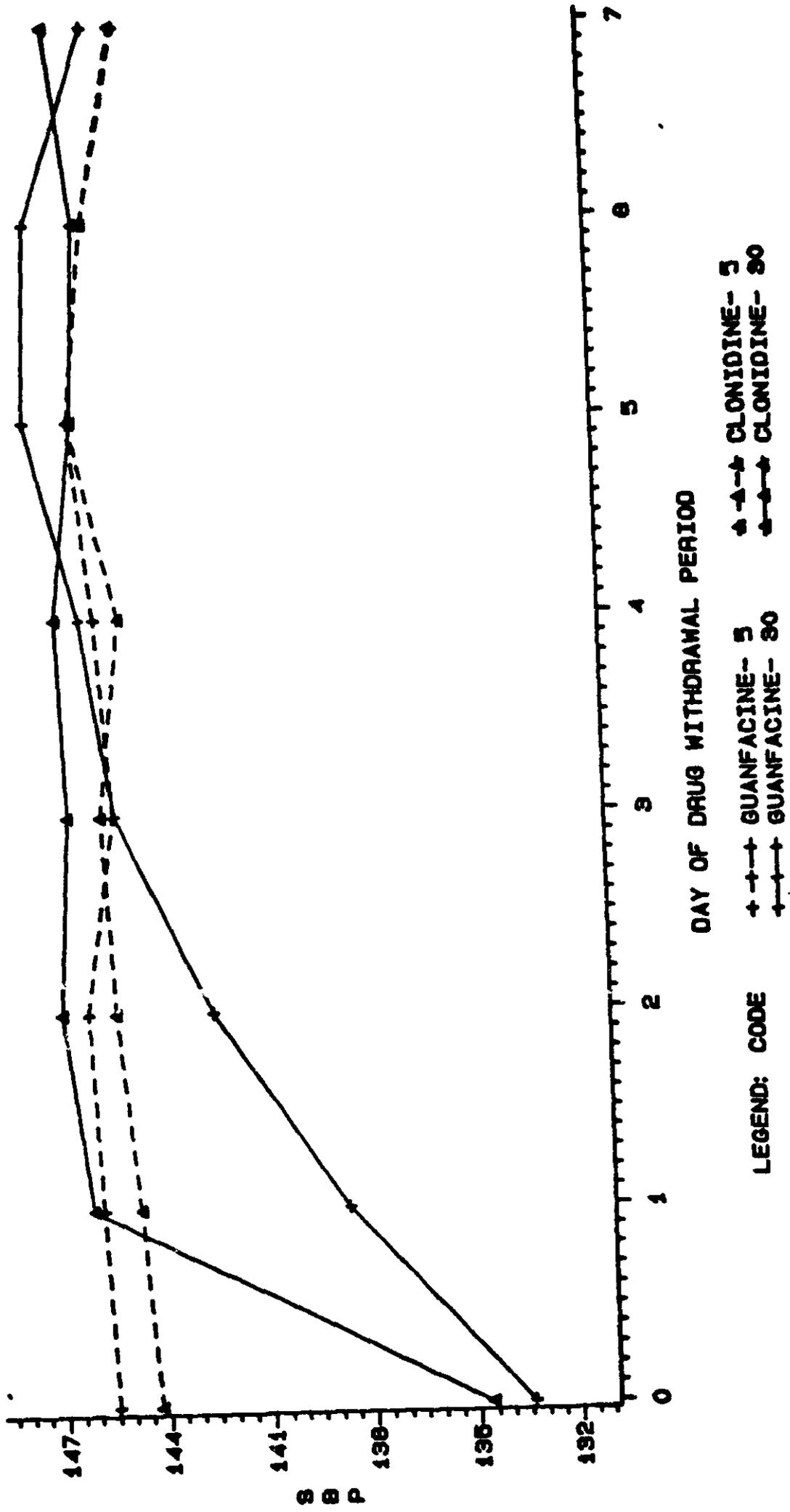
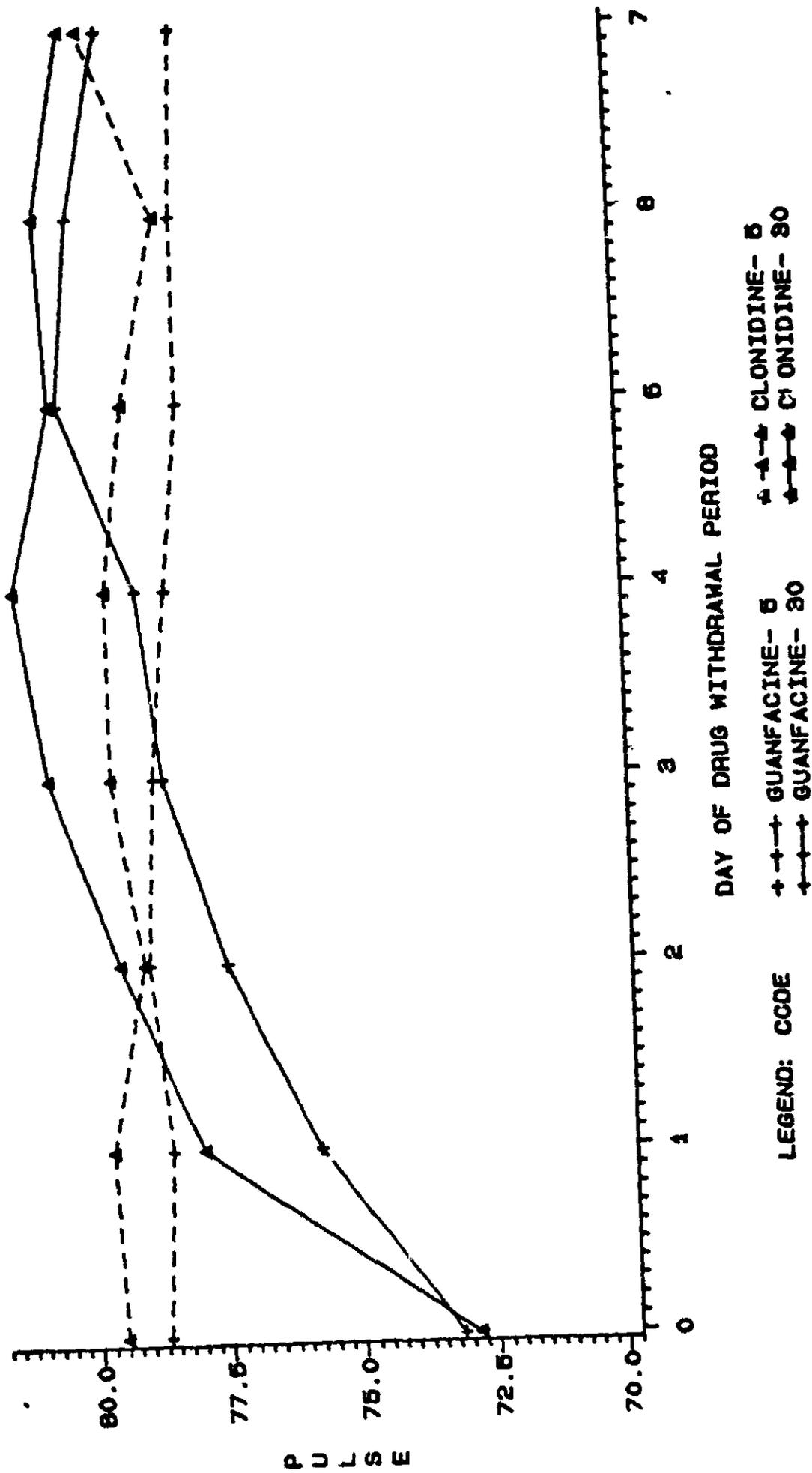


Figure 51

AHR 4458 PROTOCOL 03
MEAN PULSE
OVER WEEKS 5 AND 23
OVERALL OUTPATIENT



Symptoms of Drug Withdrawal

The frequency distribution of patients with 1, 2, 3, or >4 symptoms of drug withdrawal during Week 30 is given in Table LXXXV. The frequency distribution of patients who reported a particular symptom of drug withdrawal is also given.

Eight patients in the clonidine/chlorthalidone treatment group were discontinued from the study during the Drug Withdrawal Period (Week 30) because of symptoms of drug withdrawal and/or rapid elevation of blood pressure.

Five patients in the guanfacine/chlorthalidone treatment group were discontinued from the study during the Drug Withdrawal Period (Week 30) because of symptoms of drug withdrawal and/or rapid elevations of blood pressure.

Table LXXXV

Summary of Drug Withdrawal Period Symptoms
 Week 30
 AHR-4458, Protocol 03
 Overall Outpatient

	<u>Guanfacine</u>	<u>Clonidine</u>
Number of Patients Evaluated	160	156
Number Patients Experiencing 1 Symptom	27	19
Number Patients Experiencing 2 Symptoms	18	15
Number Patients Experiencing 3 Symptoms	8	10
Number Patients Experiencing ≥ 4 Symptoms	20	28

<u>Symptom</u>	<u>Treatment Group</u>	<u>Number Patients Experiencing Symptom</u>
Headache	Guanfacine	44 (28%)
	Clonidine	51 (33%)
Tiredness	Guanfacine	26 (16%)
	Clonidine	33 (21%)
Dizziness	Guanfacine	23 (14%)
	Clonidine	19 (12%)
Nausea	Guanfacine	22 (14%)
	Clonidine	28 (18%)
Agitation/Anxiety	Guanfacine	20 (13%)
	Clonidine	20 (13%)
Flushing	Guanfacine	15 (9%)
	Clonidine	16 (10%)
Palpitation	Guanfacine	14 (9%)
	Clonidine	22 (14%)
Insomnia	Guanfacine	14 (9%)
	Clonidine	20 (13%)
Sweating	Guanfacine	12 (8%)
	Clonidine	15 (10%)
Apprehension	Guanfacine	11 (7%)
	Clonidine	9 (6%)

Table LXXXV (continued)
 Summary of Drug Withdrawal Period Symptoms
 Week 30
 AHR-4458, Protocol 03
 Overall Outpatient

Symptom	Treatment Group	Number Patients Experiencing Symptom
Abdominal Cramps	Guanfacine	9 (6%)
	Clonidine	10 (6%)
Chest Pains	Guanfacine	5 (3%)
	Clonidine	5 (3%)
Blurred Vision	Guanfacine	4 (3%)
	Clonidine	3 (2%)
Vomiting	Guanfacine	3 (2%)
	Clonidine	7 (4%)
Fainting	Guanfacine	3 (2%)
	Clonidine	3 (2%)

DISCUSSION

This was the first prospective, randomized, double-blind evaluation of the long-term use of guanfacine vs. clonidine that was ever done. Because it was a pioneer effort and involved a large number of patients, certain points demonstrated in the trial are quite important.

In this study, both drugs produced clinically significant reductions in blood pressure in patients with mild and moderate essential hypertension and, since titration was allowed, a good idea of the equipotent daily doses of the two agents can be discerned. In this trial, daily doses of guanfacine and clonidine in the ratio of 5:1 produced equal reductions in blood pressure.

Prior to the study it was postulated that, due to the long elimination half life of guanfacine relative to clonidine, the former could be effectively dosed once daily. In addition, it was felt that this long elimination half life would, upon sudden withdrawal of the drug, lengthen the time before the symptoms and/or signs of "rebound" hypertension appeared thus attenuating any risk to the patient should he miss a dose or two of the drug.

Yet another hypothesis based upon the long half life in humans and basic animal data, was that h.s. dosing of guanfacine would result in less sedation when compared to clonidine dosed b.i.d.

The 24-hour effectiveness was proven in Study 02.

The ability of guanfacine to produce a relatively benign rebound picture was shown in the present study. The number of patients with symptoms and/or signs of rebound was lower with guanfacine than with clonidine (although not significantly different) but was quite low with both agents thus supporting reports in the literature that suggest that rebound with clonidine is primarily seen after withdrawal of large daily doses and in patients with more severe hypertension.

Abrupt withdrawal of guanfacine produced, in this carefully controlled study, a slower return of blood pressure to pretreatment levels than did clonidine. After abrupt withdrawal of both alpha agonists, blood pressure and heart rate increases occurred earlier (days 1-3) with clonidine than with guanfacine (days 3-7). Since clonidine can provoke a withdrawal reaction within 24 hours, guanfacine is potentially advantageous, since should the patient miss a dose or two for any reason, the risk of rebound is less than with clonidine.

Due to the fact that guanfacine can be taken qd before bedtime, patients treated with it feel less somnolence during the day than patients treated with clonidine which is administered bid.

* * * * *

3. U.S. Trials: Monotherapy

Three well-controlled clinical studies (2 placebo-controlled and 1 positive-controlled) of guanfacine monotherapy were completed with 83 patients receiving guanfacine, 1 mg, at bedtime. These studies provided some evidence of the efficacy of guanfacine given as 1 mg/day monotherapy (Table LXXXVI).

Study 06 was designed to elucidate the effects of guanfacine on blood pressure, heart rate, plasma aldosterone and plasma volume in patients with mild to moderate essential hypertension (DBP = 90-114 mmHg). The study was double-blind, randomized, placebo-controlled with a parallel design. After a 4-week wash-out period, patients were randomized in a 2:1 (guanfacine: placebo) ratio to therapy. The treatment period lasted 4 weeks (Weeks 5-8). Plasma volume and plasma aldosterone were measured immediately prior to randomization and at the end of treatment. Blood pressure and heart rate were measured at entry into the screening period, Week 2, 4 (baseline, just prior to treatment), 6 and 8 (end of treatment). Blood pressure and heart rate were measured 12-18 hours after dosing. Seventeen patients received 1 mg of guanfacine and 9 received placebo. All patients took their medications at bedtime.

TABLE LXXXVI

Overall Summary of Results of Guanfacine Monotherapy Clinical Studies

Study Investigator	n	Baseline		Endpoint		Blood Pressures		Net Difference from Placebo					
		Guanf. Place.	Guanab. Place.	Guanf. Place.	Guanab. Place.	Guanf. Place.	Guanab. Place.						
06 M. Strauss	17	9	-	149/97	163/97	NA	140/84	156/99	NA	-9*/-13	-7/+2	NA	-2/-15
11 J. Black-shear	21	21	-	150/97	159/97	NA	148/84	156/96	NA	-2*/-13	-3/-1	NA	+1/-12
1401 J. Fillingim	27	-	28	145/97	NA	147/97	141/88	NA	142/87	-4**/-9	NA	-5/-7	-
1402 P. Boyles	18	-	18	151/95	NA	149/97	142/87	NA	135/84	-9**/-8	NA	-14/-13	-

*Compared to placebo p<0.05.

**Compared with guanfacine = NS.

Guanfacine had no significant effect on either plasma volume or plasma aldosterone. Guanfacine significantly reduced diastolic blood pressure from a mean of 97 to 84 (-13 mmHg change) during the 1-month treatment period ($p < 0.0001$). Diastolic blood pressure in the 9 patients receiving placebo went up on average by 2 mmHg. The effect on systolic pressure was less clear pressure falling only 2.6 mmHg more than placebo. The mean decrease in diastolic blood pressure with 1 mg guanfacine over a 1-month treatment period was approximately equal to the mean decrease (-12.6 mmHg) observed in a dose-response study with 25 mg chlorthalidone (Study 01), but the systolic response was clearly smaller. No patients reported side effects in this study.

Blackshear (Study 11) investigated the effects of guanfacine on blood pressure, heart rate, blood glucose and plasma lipids using the same study design as Strauss with the exception of the treatment group sizes which were equal. Twenty-one patients received 1 mg guanfacine at bedtime for 4 weeks and 21 patients took placebo during the same period. Measurements of blood pressure, heart rate, and plasma lipids were done at the same time intervals as in Strauss' study. The baseline blood glucose samples were lysed during shipment to National Health Laboratories for analysis, and therefore, this variable could not be evaluated. Plasma lipids were not significantly altered by guanfacine treatment.

Diastolic blood pressure in guanfacine treatment group decreased (an average of 13 mmHg) by the end of treatment versus a mean decrease of 2 mmHg in the placebo group. These differences were highly significant ($p < 0.0001$). Systolic blood pressure, however, actually fell more in the placebo group (3.2 mmHg vs. 1.3 mmHg). The decrease in diastolic blood pressure with 1 mg of guanfacine was approximately the same as that observed in Study 01 (mean 12.6 mmHg). One patient reported dry mouth and 3 patients experienced drowsiness during treatment with guanfacine.

These two placebo controlled studies suggest the effectiveness of 1 mg/day guanfacine for the treatment of mild to moderate essential hypertension, but are limited in their interpretation by the absence of a clear effect on systolic pressure.

A third study of guanfacine as monotherapy (Studies 1401 and 1402) was conducted. The aim of this study was to compare the safety and efficacy of guanfacine versus guanabenz for the treatment of mild to moderate essential hypertension (seated DBP average of 90-114 mmHg). Of particular interest was the comparative incidence of somnolence.

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The study was double-blind with a parallel design. The study was divided into a 2-week screening period during which placebo capsules (b.i.d.) were substituted for previously effective antihypertensive agents. Patients who completed this screening period, who met all other requirements for entry into the study, and whose average seated DBP was in the 90-114 mmHg range were randomized to either guanfacine or guanabenz. Guanfacine was given at bedtime as a 1-mg capsule, and a dummy placebo capsule was administered each morning to maintain the blind. Guanabenz was dosed at 4 mg, b.i.d. for the first 7 days followed by 8 mg b.i.d. for the remaining 7 weeks of treatment. All test medications (including placebo) were identical in appearance. Blood pressure and heart rate were measured 12-18 hours after the evening dose.

Ninety-one patients (45 guanfacine and 46 guanabenz) were randomized to treatment, and 89 patients (44 guanfacine and 45 guanabenz) completed the study. Comparative efficacy was measured by the percentage of patients normalized (DBP <90 mmHg) by the end of treatment. In the guanfacine treatment group, 62% were normalized versus 70% in the guanabenz group, but the differences were not statistically significant. The mean decrease in DBP in the guanfacine treatment group of both investigators was approximately the same (9 mmHg for Fillingim and 8 mmHg for Boyles). However, the mean decrease in DBP in Dr. Boyles' guanabenz treatment group were 13 mmHg versus 7 mmHg for Dr. Fillingim. These differences prevented the pooling of data for this type of efficacy analysis. It is possible that the differences between investigators could be explained because of Dr. Boyles' evaluation of patients during the morning versus Dr. Fillingim's evaluations which were generally done throughout the day. The guanabenz group in Dr. Boyles' study would have had their blood pressure measured closer to their last dose of guanabenz. If so, this could suggest some loss of effect of guanfacine toward the end of the 24-hour dose interval. The modest falls in BP in this active control study limit its persuasiveness as evidence of effectiveness. Note especially the very small change in systolic pressure.

The percentage of patients reporting an adverse experience was greater in the guanabenz group than in the guanfacine group (57% vs. 33%). The percentage of patient experiencing an increase in somnolence was also greater in the guanabenz group than in the guanfacine group (59% vs. 31%), and this difference was statistically significant ($p=0.008$).

Safety of Guanfacine Monotherapy

The frequency of the most common side effects with guanfacine monotherapy was low, lower than most of the studies in which guanfacine was combined with chlorthalidone. These results are given in Table LXXXVII. Different types of reported side effects were more numerous when guanfacine was given with chlorthalidone. Overall, the type of side effects reported with guanfacine are not unexpected for a centrally acting alpha-adrenergic agonist, and the frequency of selected bothersome side effects (somnolence) is less than that observed with guanabenz.

While these studies of 1 mg doses, as well as published studies of larger doses used in active control trials, indicate guanfacine is active as monotherapy, they do not yet show what the appropriate dose is, or, more precisely, do not describe dose-response and dose-adverse effect relationships.

Table LXXXVII

Comparison of Side Effects with Guanfacine as Monotherapy
or with Chlorthalidone

Frequency Distribution of Patients with Most Common Side Effects				
Side Effect	Study 01 n = 72	Study 06 n = 17	Study 11 n = 21	Study 14 n = 45
Dry mouth	6 (8.3%)	0	1 (4.8%)	6 (13.3%)
Dizziness	3 (4.2%)	0	0	2 (4.4%)
Headache	3 (4.2%)	0	0	2 (4.4%)
Somnolence	0	0	3 (14.3%)	*

*A special rating scale was used in this study to measure somnolence and the results cannot properly be compared with the other studies because information on somnolence was solicited from each patient by direct questioning.

Discussion

A single-rising dose tolerance study in normotensive volunteers (Study S-02, See Clinical Pharmacology Section of this document) suggested a dose-response relationship for the maximum effect of single doses of guanfacine (0.5, 1, 1.5, and 2 mg) given once daily and the evidence cited above suggests that a 1 mg dose as monotherapy has some effect in hypertensive patients. There are no well-controlled, dose-response studies in hypertensive patients on guanfacine monotherapy. Western European experience with guanfacine provides a historical perspective of the issues of proper dose. In Europe, the initially recommended dosage schedules resulted in doses 3-10 times higher than those now recommended as a result of the dose-response data now available. The recommended dose of guanfacine in Western Europe has been decreasing over the last 10 years, however, and investigators have shown excellent blood pressure response with 1-2 mg doses of guanfacine, given as a single, daily dose.

Overall Discussion and Conclusion

Data from patients treated with guanfacine alone and in combination with other antihypertensive agents (diuretics, beta-blockers, vasodilators) for time periods up to 24 months provide adequate information on the long-term safety of the drug for treatment of essential hypertension. Dosages of guanfacine utilized in these studies were usually 2-25 times higher than the recommended starting dosage of 1 mg h.s. and side effects occurred more frequently with these higher doses. The frequency of reported side effects diminishes over time if a patient can tolerate the initial annoyance of a side effect.

The antihypertensive effect of guanfacine after 24 months was not different from the results obtained after 12 months of treatment. The dosage of guanfacine did not have to be increased during the 2nd year in order to maintain the hypotensive action. Thus, tolerance did not develop.

No undesirable interactions with concomitantly prescribed medications were noted.

E. The Safety of Guanfacine

1. Deaths. Guanfacine has been given to more than 1,690 patients in clinical trials in many parts of the world. In addition, 11,270 patients have been evaluated in a postmarketing surveillance program. Despite this large patient exposure, there has been no death reported that could be ascribed to the drug.

2. Adverse Effects

Incidence and Types

In open-labeled safety studies lasting from 6 to 12 months. There were 1,063 adverse effects reported in 655 patients (1.6 adverse effects/patients) taking a mean daily dose of 4.7 mg (range 0.5-25 mg). During the year 55 patients (8%) dropped out because of adverse effects:

Dry mouth	23
Sedation	15
Constipation	7
Nausea	3
Orthostatic Hypo.	2
Headache	1
Nightmare	1
Rash	1
Insomnia	1
Depression	1

When treatment was extended to 24 months in 169 patients, there were 92 adverse effects reported (0.54/patient). Mean daily dose of guanfacine was 3.6 mg. There were 2 dropouts during the second year, one with rash and the other with dry mouth.

Adverse effects were dose related. In a double-blind, placebo controlled evaluation, the following adverse effects were seen.

Table CX

Adverse Effect	Daily Doses		
	Placebo (n=73)	1.0 mg (n=72)	3.0 mg (n=72)
Dry mouth	5	6	20
Sedation	1	0	10
Weakness	0	0	7
Dizziness	2	3	3
Headache	3	3	2
Impotence	1	0	3

In another placebo-controlled study, side effects were evaluated over time to determine the course of these adverse effects with time. Adverse effects on drug, in completers, were as shown in Figure 56.

VI. Approved Package Insert

A copy of the package insert is attached.

10032

SRF

SUMMARY BASIS OF APPROVAL

NOV 10 1988

NDA No.: 19-032
Applicant Name: A. H. Robins Co.

Drug Generic Name: Guanfacine
Drug Trade Name: Tenex™

I. Indications for Use

Tenex (guanfacine hydrochloride) is indicated in the management of hypertension. Since dosing information (see DOSAGE and ADMINISTRATION) has been established in the presence of a thiazide-type diuretic, Tenex should, therefore, be used in patients who are already receiving a thiazide-type diuretic.

II. Dosage Form, Route of Administration and Recommended Dosage

Oral tablets containing 1 mg guanfacine hydrochloride. The recommended dose of Tenex (guanfacine hydrochloride) is 1 mg daily given at bedtime to minimize somnolence. Patients should already be receiving a thiazide-type diuretic.

If after 3 to 4 weeks of therapy, 1 mg does not give a satisfactory result, doses of 2 and then subsequently 3 mg may be given, although most of the effect of Tenex is seen at 1 mg (see Clinical Pharmacology). Some patients may show a rise in pressure toward the end of the dosing interval; in this event a divided dose may be utilized.

Higher daily doses (rarely up to 40 mg/day, in divided doses) have been used, but adverse reactions increase significantly with doses above 3 mg/day; and there is no evidence of increased efficacy. No studies have established an appropriate dose or dosing interval when Tenex (guanfacine hydrochloride) is given as the sole antihypertensive agent.

The frequency of rebound hypertension is low, but rebound can occur. When rebound occurs, it does so after 2-4 days, which is delayed compared with clonidine hydrochloride. This is consistent with the longer half-life of guanfacine. In most cases after abrupt withdrawal of guanfacine, blood pressure returns to pretreatment levels slowly (within 2-4 days) without ill effects.

III. Manufacturing and Control

A. Manufacturing and Control

The new drug substance, guanfacine hydrochloride, as supplied, is manufactured as defined in an appropriately written Drug Master File to which the applicant has authorized reference. The new drug substance is subject to such controls as are necessary to ensure its identity, purity, strength, and quality.

The tablet dosage form will be manufactured according to Current Good Manufacturing Practices by using only approved lots of active ingredients and excipients in plant facilities described in a reference Drug Master File.

This application contains Raw Material Specifications and Test Procedures, Manufacturing Procedures, Product Specifications and Test Procedures, and Packaging Material Specifications and Test Procedures supported where necessary by appropriate reference to Drug Master Files to ensure the identity, strength, quality, and purity of the finished drug product.

The product is a light-pink, diamond-shaped, compressed tablet with an embossed "1" engraved with "AHR" on one side and "Tenex" engraved on the opposite side. Test Procedures will ensure satisfactory dissolution and content uniformity of the finished tablet.

B. Stability

Stability studies of the drug product have been conducted and are continuing according to a defined protocol. In these studies the drug product is contained in amber glass containers, high-density polyethylene plastic containers, and in film/foil blister packaging. The data submitted adequately support the requested 2-year expiration date.

C. Methods Validation

Analytical methods used in testing the active ingredient and finished drug product, including an evaluation of its stability, have been appropriately validated.

D. Labeling

The immediate container label and carton labels are in compliance with technical requirements pertaining to the following: established name, ingredients statement, control number, expiration date, prescription caution, applicant's name and address, and net contents statement. Likewise, the "Description" and "How Supplied" sections of the package insert are satisfactory with respect to the technical requirements of the regulations.

E. Establishment Inspection

Inspections of A. H. Robins facilities have been performed to determine their compliance with Current Good Manufacturing Practice Regulations. A satisfactory report was received from the Office of Compliance, indicating no reason to withhold approval of the application. The applicant has the personnel, facilities, methods, and controls to produce the drug in accordance with the NDA procedures and commitments.

F. Environmental Impact Analysis Report

A report on the impact on the environment was submitted. There is expected to be little or no impact on the environment due to the manufacture of guanfacine hydrochloride.

IV. Pharmacology

A. Studies on Activities Related to the Primary Therapeutic Action

Guanfacine produced significant reductions of the elevated blood pressures in DOCA/salt, spontaneously and renal hypertensive rats and in renal hypertensive dogs when administered as a single oral dose. In DOCA/salt and renal hypertensive rats, the antihypertensive effect was dose-dependent between 0.3 to 5 mg/kg orally. In renal hypertensive rats the peak antihypertensive effect occurred 2-4 hrs after an oral dose of 2 mg/kg with a duration of action of over 6 but not more than 24 hours. In renal hypertensive dogs, peak reduction in blood pressure occurred 8 hours after 1 mg/kg orally and was paralleled by a pronounced bradycardia. Guanfacine was approximately one-tenth as potent, on a weight basis, as clonidine in DOCA/salt and spontaneously hypertensive rats and in renal hypertensive dogs. The daily administration of 3 mg/kg of guanfacine for a 5-week period to young spontaneously hypertensive rats blunted the progressive development of the hypertensive state.

Most of the antihypertensive action of guanfacine is exerted through stimulation of central α_2 -adrenergic receptors. Several observations indicate the primary importance of the central effect. Low levels of guanfacine elicited a fall in blood pressure and heart rate in anesthetized cats when injected intracerebroventricularly; larger doses were required for an effect by the intravenous route (Table I).

Table I

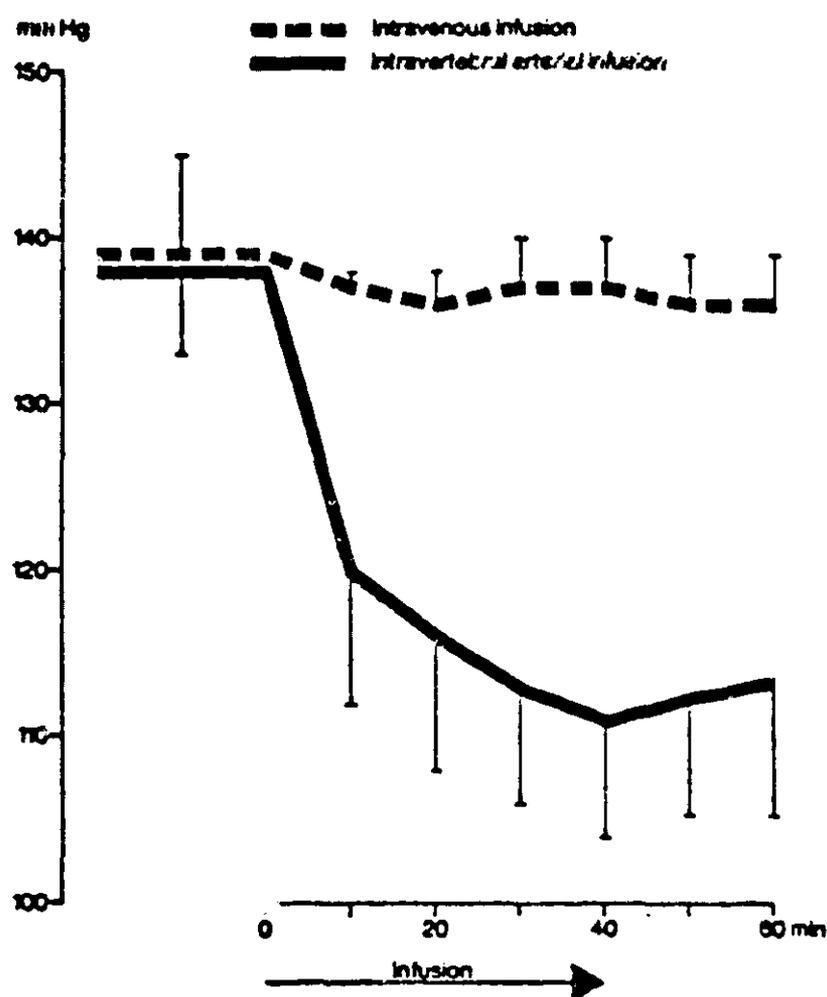
Route of Administration	ED ₅₀ (μ g/kg) ^a	Reference
Intravenous	83	Scholtysik, Laueraer et al. <i>Arzneim-Forsch.</i> 25(10) 1483-1491 (1975)
Intracerebroventricular	45	Scholtysik <i>Proc. 6th Int. Symposium on Med. Chem.</i> pp. 61-70 (1979).

^aApproximate dose that produces a 50% reduction of spontaneous preganglionic sympathetic nerve discharge activity.

Also, the infusion of guanfacine into the vertebral artery of anesthetized dogs produced a fall in blood pressure greater than that achieved with intravenous administration (Table II).

Table II

Effects of guanfacine (1 mg/kg/min) on the mean blood pressure in anesthetized dogs in response to intravertebral arterial and intravenous infusions. Mean values \pm SEM from eight experiments for each route of administration.



Scholtysik et al. "Guanfacine" in Pharmacology of Antihypertensive Drugs.
Raven
Press p. 79-98 (1980).

The blockade of central α_2 -receptors with selective antagonists phentolamine and piperoxan prevented the hypotension and bradycardia elicited by the central application of guanfacine (Table III).

Table III
Pharmacological Antagonism of Central Action of Guanfacine

Alpha Adrenergic Antagonist	Dose	Route of Administration	Test System	Response
Phentolamine ^a	50 mg/kg	i.c.v.	Anesthetized cat	Blocked guanfacine-induced hypotension and bradycardia
Piperoxan ^b	100 mg/kg	Vertebral artery	Anesthetized cat	Blocked guanfacine-induced hypotension and bradycardia

^aScholtysik, Lavener *et al.*, *Arzneim Forsch* 25(10) 1483-1491 (1975).

^bVan Zwiefen. *Brit. J. Clin. Pharmacol.* 10(1) 13s-20s (1980).

Guanfacine exhibited a much greater selectivity for α_2 - over α_1 -receptor sites in the brain than either clonidine or guanabenz, as determined from radioligand binding studies. Displacement of guanfacine from high affinity binding sites was most effected by antagonists and other agonists that are known to bind to α_2 -adrenergic receptors. Guanfacine produced transient vasopressor responses similar to those produced by clonidine and norepinephrine and is therefore not totally devoid of post synaptic α_1 -receptor stimulant properties.

Guanfacine inhibits peripheral sympathetic neurotransmission by stimulating presynaptic α_2 -receptors that regulate transmitter release from adrenergic nerves. In isolated hearts, the norepinephrine release and tachycardia induced by peripheral nerve stimulation is inhibited by guanfacine.

The abrupt cessation of chronic guanfacine treatment in animals resulted in less rebound hypertension and tachycardia than was observed with clonidine withdrawal. The slower rate of elimination of guanfacine relative to clonidine appears to be the underlying basis for the delayed and diminished symptoms associated with guanfacine withdrawal.

B. Other Pharmacological Actions

Guanfacine enhanced vagal inhibitory activity on the heart, as evidenced by enhanced reflex bradycardia elicited by transient

occlusion of the aorta in anesthetized dogs. The compensatory increase in blood pressure produced by carotid occlusion in dogs was also inhibited by guanfacine.

Guanfacine's action on renal function is correlated with the hemodynamic changes elicited on renal perfusion. In anesthetized dogs, intravenous doses of 3 and 10 $\mu\text{g}/\text{kg}$ caused dose-dependent increases in renal blood flow that occurred during the peak hypertensive phase and were attributed to an increase in renal perfusion pressure.

Guanfacine had no effect on dopamine turnover in rat brain and did not alter the norepinephrine reuptake mechanism. It had no dopamine agonist or antagonist actions.

Guanfacine differs from clonidine in its interaction with histamine receptors. Whereas clonidine stimulated gastric acid secretion in anesthetized rats via a histaminergic mechanism, guanfacine had no effect on gastric acid secretion in rats at antihypertensive levels.

Guanfacine, like clonidine, inhibited spontaneous motor activity in mice at an oral ED_{50} of 1.3 mg/kg. Neurotoxicity and motor impairment caused by guanfacine in mice occurred at doses approximately 300 times greater than doses affecting spontaneous motor activity.

At comparable antihypertensive doses, guanfacine (3 mg/kg, SC) was marginally sedative vs a strong sedative effect elicited by clonidine (0.3 mg/kg, SC) in dogs. In rats, guanfacine was 20-25 times less potent than clonidine in its sedative activity.

C. Pharmacokinetics

The absorption, distribution, metabolism, and excretion of guanfacine were investigated primarily in 2 animal species, i.e., the Wistar rat and the Beagle dog. After oral dosing, the absorption of guanfacine in both species was relatively rapid and essentially complete.

Guanfacine was widely distributed in the tissues of the rat. Autoradiographic studies identified the highest level of radioactivity in the gastrointestinal tract, followed by liver and kidneys.

The studies indicated that ^{14}C -Guanfacine crossed the placenta. Radioactivity was observed in the gastrointestinal tract, lung, and liver of the fetus and was also found in the milk of lactating rats.

Extensive metabolism of guanfacine occurred in the rat, only 1 to 3% of the dose being excreted in the urine as unchanged drug. Parent drug accounted for 25% of the dose in dog urine. The major urinary metabolites identified in the rat were the conjugates of 3-hydroxy guanfacine and in the dog the main metabolite was the

dihydrodiol derivative. The rate of elimination of guanfacine and its metabolites was rapid in these 2 species. Excretion of total radioactivity in the rat was equally divided between urine and feces. At least 75% of the fecal radioactivity was the result of biliary excretion. In the dog, 77 to 79% of the administered radioactivity appeared in urine.

D. Toxicology

In a one year oral toxicity study in dogs, daily doses of 0.3 mg/kg in capsules, approximately 6 times the maximum recommended human dose (MRHD) in a 60 kg person, were well tolerated. Higher doses of 1.0 and 3.0 mg/kg were associated with reduced food intake and body weight gains, reduced hemoglobin and hematocrit, reduced blood sugar, reduced urinary excretion of sodium and potassium, increased BUN, changes in EKG and atrophic and anemic spleens. Discoloration and centrilobular swelling of the liver, at incidences above concurrent control, were observed at 3.0 mg/kg.

A 102 week oral (drug in feed) toxicity/carcinogenicity study in rats revealed no evidence of drug related tumorigenicity at daily doses up to 5.0 mg/kg/day, 100 times the MRHD and a dose which reduced body weight gain and increased the incidence and severity of corneal clouding and subcapsular focal lenticular opacity observed in concurrent control rats. Clinical laboratory findings at this dosage were similar to findings reported at mid and high dose levels in the one year dog study. There were, however, no drug related gross or microscopic post-mortem findings.

Mice were treated for 78 weeks with guanfacine administered in feed at doses of 1.0, 3.0 and 10.0 mg/kg/day, i.e., up to 200 times the MRHD. There was no evidence of drug related tumorigenicity but high dose mice exhibited corneal opacity and lymphopenia at incidences above concurrent control.

Guanfacine was not mutagenic in four different test systems (Ames Test, Mouse Micronucleated Bone Marrow Test, Mouse Dominant Lethal Test and Chinese Hamster Bone Marrow Chromosome Aberration Test).

Reproduction studies in rats showed that guanfacine did not impair fertility of either males or females or affect postnatal development of offspring, even at maternally toxic doses. Teratology studies in rats and rabbits revealed no evidence of adverse effects on the development of embryo or fetus at 20 times the MRHD in the rabbit and 70 times the MRHD in the rat. Higher doses (100 and 200 times the MRHD in rabbits and rats, respectively) were associated with reduced fetal survival and maternal toxicity.

V. Medical

A. Clinical Pharmacology

1. Bioavailability and Pharmacokinetic Studies

1. Bioavailability and Pharmacokinetic Studies

Report No.	Principal Investigator/ Principal Monitor	Purpose of Study	Number of Subjects	Guanfacine Dose	Guanfacine Dosage Schedule
83-0407	Hanigan/ Melikian	Bioavailability Bioequivalence	23	1 mg	PO Tablet 1 mg qd x 6 days PO Capsule 1 mg qd x 6 days PO Solution (0.1 mg/mL) 1 mg qd x 6 days
83-0408	Hanigan/ Melikian	Bioavailability Bioequivalence	24	2 mg	PO Tablet 2,1 mg qd x 6 days PO Capsule 2,1 mg qd x 6 days PO Solution (0.1 mg/mL) 2 mg qd x 6 days
80-337	Kiechel	ADME	7	2 mg 3 mg	IV Solution 2 mg/2 mL - single dose PO Solution 3 mg/20 mL - single dose
80-0288	Beveridge	ADME	6	4 mg	PO Solution 4 mg/20 mL - single dose
83-0201	Poser	Protein binding	<u>in vitro</u>		
84-0573	Hanigan/ Carchman	Bioavailability	18	3 mg	PO Tablet 31-mg - single dose IV Solution - single dose
84-0582	Blackshear/ Carchman	Pharmacokinetics Mild to moderate hypertensives	20	1 mg	PO Chlorthalidone 25 mg x 3 weeks PO Chlorthalidone 25 mg w/PO Guanfacine Tablet 1 mg x 6 days

1. Bioavailability and Pharmacokinetic Studies (continued)

Report No.	Principal Investigator/ Principal Monitor	Purpose of Study	Number of Subjects	Guanfacine Dose	Guanfacine Dosage Schedule
Clin. Pharmacol. Ther. 25(3): 283-93, 1979. 2(2)213	Weiss	ADME Dose Proportionality	9 10 15a	2 mg 4 mg 1-3 mg	P0 Tablet 2 mg - single dose P0 Tablet 4 mg - single dose P0 Tablet 1-3 mg b.i.d. x 60 days
Clin. Pharmacokin. 5(5) 476-83, 1980. 200127	Kirch	Effects of renal insufficiency	18 (6 GFR > 90 mL/min) (6 GFR 10-30 mL/min) (6 GFR < 10 mL/min)	3 mg 1 mg	IV Solution 3 mg/mL - single dose P0 Tablet 1 mg t.i.d. x 5 days
Nephrol. 1:73-81, 200125	Kiechel	Effect of renal insufficiency	10 (5 GFR < 30 mL/min 5 hemodialysis)	4 mg 3-4 mg	P0 Tablet 4 mg - single dose P0 Tablet 3-4 mg daily x 2 doses
Clin. Pharmacol. Thera. 35(5) 604-9, 1984	Hedner	Effects of long-term use of guanfacine	13	0.5-4 mg	Initially b.i.d., then o.d.

aFifteen of the 19 patients were continued with multiple dosing.

The pharmacokinetics of guanfacine hydrochloride have been studied in normal volunteers and patients. Guanfacine was found to be rapidly and well (about 80%) absorbed from oral dosage forms. The elimination half-life in patients averaged about 17 hours but varied from 10 to 30 hours. Older patients (>50 years) tended to eliminate the drug more slowly, independent of renal function. In younger normal volunteers and patients (<50 years), the elimination half-life, on average, was found to be about 13-14 hours. In most instances steady state was attained within four days.

Two multiple dose studies were conducted to establish the extent of absorption of guanfacine from solid dosage forms in relation to solution (Melikian, 83-0407; Melikian, 83-0408). Each was a nonblinded, randomized, three-way, crossover study in healthy male volunteers. In the first study plasma levels of guanfacine were compared following 6 days of dosing with the A. H. Robins 1-mg tablet, 1-mg capsule, and a solution of 1-mg of guanfacine. In the second study the extent of absorption from two Sandoz solid dosage forms (2, 1-mg capsules; 2, 1-mg tablet) was established relative to a solution of 2-mg of guanfacine after dosing for 6 days. The mean plasma concentration-time curves from each study are shown in Figures 1 and 2. Pertinent pharmacokinetic parameters are listed in Tables IV and V.

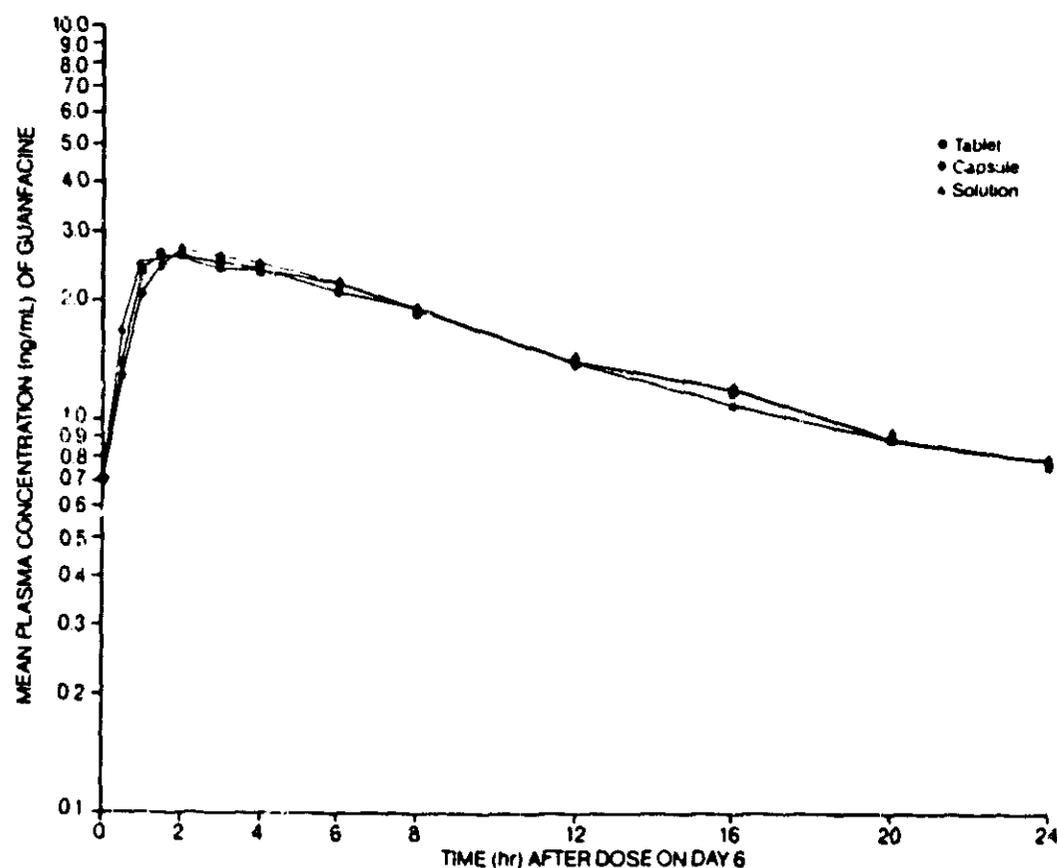


Figure 1. Mean Plasma Concentrations of Guanfacine in 23 Subjects During a 24-Hr. Interval on Day 6 After 6 Days of Single Daily Doses of 1 mg Guanfacine HCl/Day.

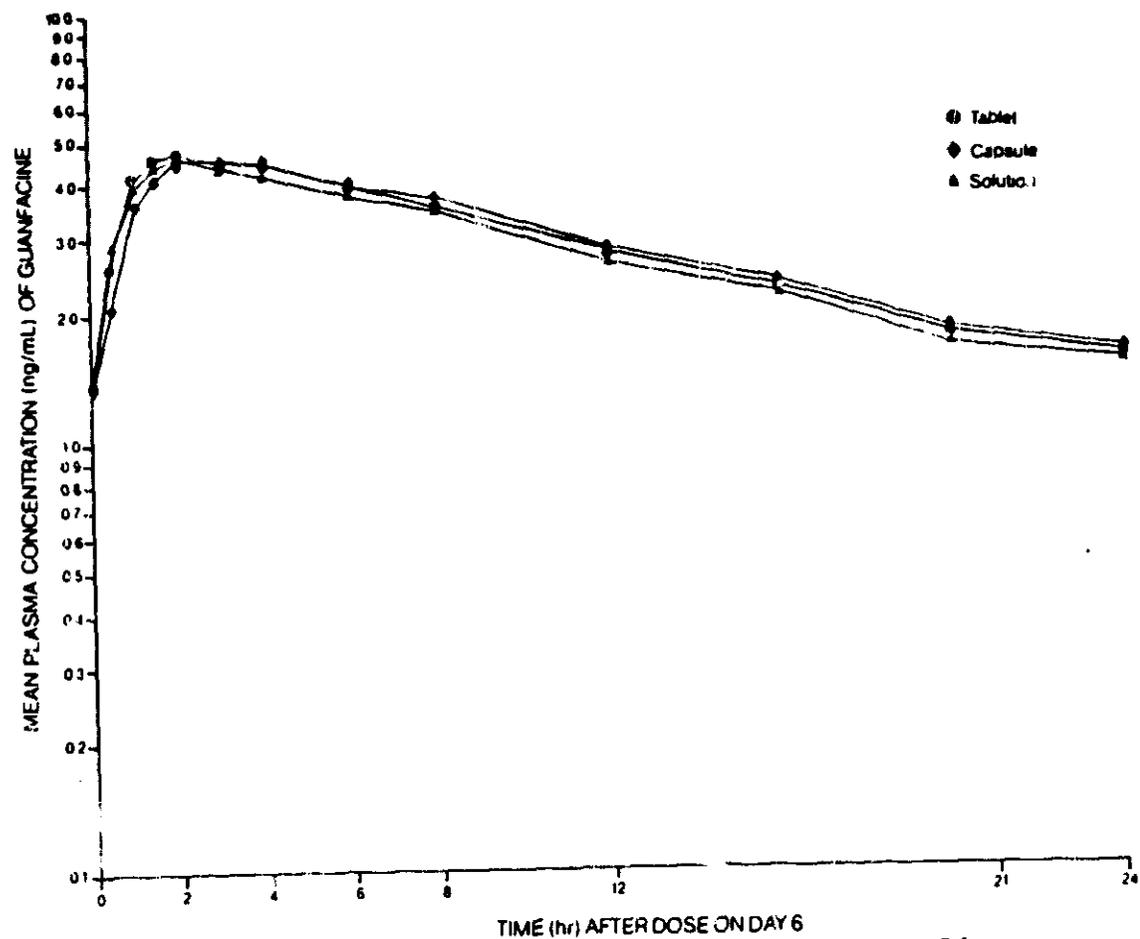


Figure 2 Mean Plasma Concentrations of Guanfacine in 24 Subjects During a 24-Hr Interval on Day 6 After 6 Days of Single Daily Doses of 2 mg Guanfacine HCl/Day.

These two studies established the equivalency of the solid dosage forms with a reference solution. Since both capsule and tablet formulations of the two studies were shown to be bioequivalent to the same reference solution, the capsule and tablet dosage forms developed by A. H. Robins and used in Sandoz studies in Europe were bioequivalent to one another.

In an open, single-dose, randomized, two-way, crossover study in 18 healthy male volunteers, the absolute bioavailability of guanfacine from a single oral dose of 3 mg was shown to be 81.2% with respect to the intravenous formulation (Carchman, 84-0573). The mean plasma concentration-time curves and mean cumulative collections in urine are shown in Figures 3 and 4, respectively. Pertinent pharmacokinetic parameters are listed in Table VI. The guanfacine-to-creatinine renal clearance ratio was greater than 1.0, suggesting that tubular secretion of drug is important for renal elimination.

TABLE IV
Summary of Steady-State Mean Bioavailability Parameters After 6 Days of Guanfacine (1 mg/day orally)

Dosage Form	AUC (ng/mL-hr)	C _{max} (ng/mL)	T _{max} (hr)	C _{ave} (ng/mL)	k _{el} (hr ⁻¹)	Elimination T _{1/2} (hr)	V ¹ (L)	V/kg ¹ (L/kg)	Clearance (mL/min)	Relative Bioavailability ² (%)
Tablet	37.19	2.9	2.0	1.6	0.059	11.7	659.6	9.35	458.0	101.0
Capsule	36.89	2.9	2.0	1.5	0.059	11.7	665.0	9.44	461.8	100.2
Solution	36.83	2.8	1.8	1.5	0.059	11.6	666.5	9.47	462.8	-

¹Calculated on the basis of assumed fraction of dose absorbed of 1.0.

²In reference to solution.

TABLE V
 Summary of Steady-State Mean Bioavailability Parameters After 6 Days of Guanfacine
 (2 mg/day orally)

Dosage Form	AUC (ng/mL-hr)	C _{max} (ng/mL)	T _{max} (hr)	C _{ave} (ng/mL)	kel (hr ⁻¹)	Elimination T _{1/2} (hr)	V ¹ (L)	V/kg ¹ (L/kg)	Clearance (mL/min)	Relative Bioavailability ² (%)
Tablet	69.43	5.0	2.2	2.9	0.056	12.4	704.7	9.21	489.4	104.5
Capsule	69.80	4.9	2.9	2.9	0.054	12.8	698.8	9.13	485.3	105.0
Solution	66.46	4.8	2.4	2.9	0.054	12.8	734.7	9.52	510.2	-

¹Calculated on the basis of assumed fraction of dose absorbed of 1.0.

²In reference to solution.

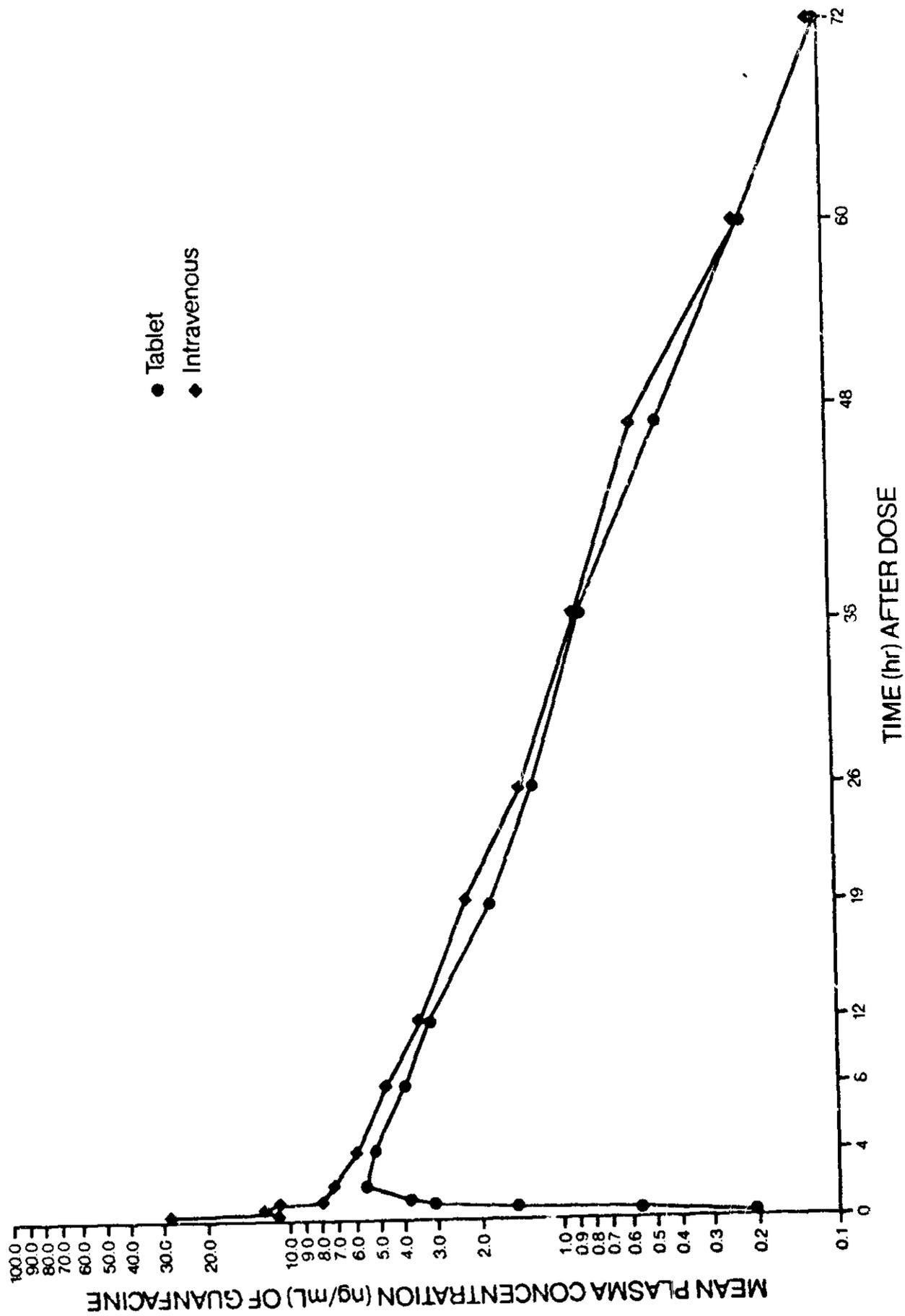


Figure 3. Mean Plasma Concentrations of Guanfacine in 18 Subjects After a Single Dose of 3mg of Guanfacine HCl.

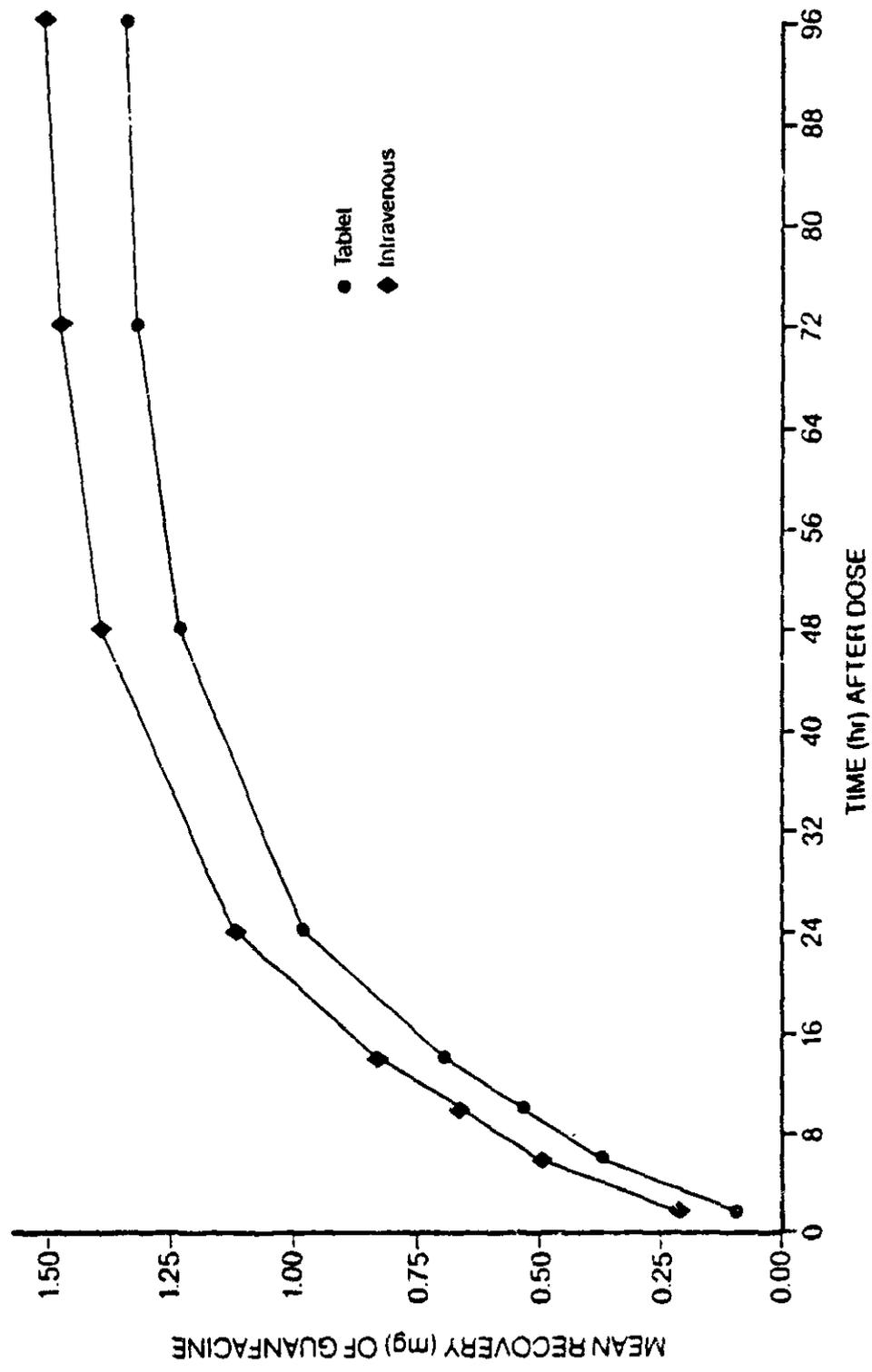


Figure 4. Mean Cumulative Urinary Excretion of Guanfacine

TABLE VI
 Summary of Mean Bioavailability Parameters of 3 mg of Guanfacine
 After Single Oral and Intravenous Administration

Route of Administration	AUC (ng/mL-hr)	C _{max} (ng/mL)	T _{max} (hr)	k _{el} (hr ⁻¹)	Elimination T _{1/2} (hr)	V (L/kg)	Total Clearance (mL/min)	Renal Clearance (mL/min)	Total Urinary Recovery (%)	Bioavailability (%)
Oral	100.64	5.49	2.6	0.052	13.8	6.5	-	-	44.7	81.2
Intravenous	123.99	29.57 ¹	0.2	0.053	13.4	6.3	414.4	210.7	50.0	-

¹Concentration immediately after the end of the infusion.

On comparison of the mean AUC and k_{el} values given by the specific dosage forms in the 3 above studies, it is apparent that good proportionality exists among these parameters and the dose. For example, the solution of 1 mg/day gave an AUC of 36.83 ng/mL-hr and a C_{max} of 2.9 ng/mL compared with an AUC of 66.46 ng/mL-hr and C_{max} of 5.0 ng/mL for the solution at 2 mg/day. In the single, 3-mg oral dose study the AUC was 100.64 ng/mL-hr. Although dose proportionality would be better assessed with several doses in a single study, the patient populations in these studies were sufficiently comparable with respect to demographic and elimination rate to conclude that there is no important nonlinearity.

The data provided by studies in patients with hypertension indicate that accumulation of guanfacine occurs as expected based on its half-life. Guanfacine concentrations in plasma at steady-state were well predicted by simulations of single-dose data (see Figure 4A) in one study in patients with hypertension (Weiss *et al.*, 1979). Patients received either a 2-mg or 4-mg single dose followed by 1 to 3 mg guanfacine twice daily for up to 60 days. Actual plasma concentrations were compared with computer-simulated profiles from single-dose data. Linear regression of predicted vs. observed values gave a fit with an r value of 0.948 (see Figure 4B).

Hedner (1984) followed guanfacine blood levels in 13 hypertensive patients for 1 year. The mean daily dose of guanfacine was 2.0 ± 0.26 mg. After 1 year, the mean peak plasma level was 4.1 ± 0.6 ng/mL, similar to the mean peak of 4.9 ng/mL observed after 6 days of treatment with 2 mg/day of guanfacine.

An open, two-phase, multiple-dose study was conducted in patients with mild-to-moderate hypertension who were being treated with 25 mg chlorthalidone daily to determine the steady-state levels in plasma and pharmacokinetics of guanfacine in this population (Carchman, 84-0582). Patients received 25 mg chlorthalidone daily for three weeks, then 25 mg chlorthalidone with 1 mg guanfacine daily for six days. The results of the study are shown in Figure 5 and Table VII. There was no relationship between patient sex, creatinine clearance, or body weight to the mean elimination half-life. There did, however, appear to be a relationship between patient age and elimination half-life. Older patients tended to have a longer half-life in this study. The range of half-lives was 10.2 to 30.0 hr.

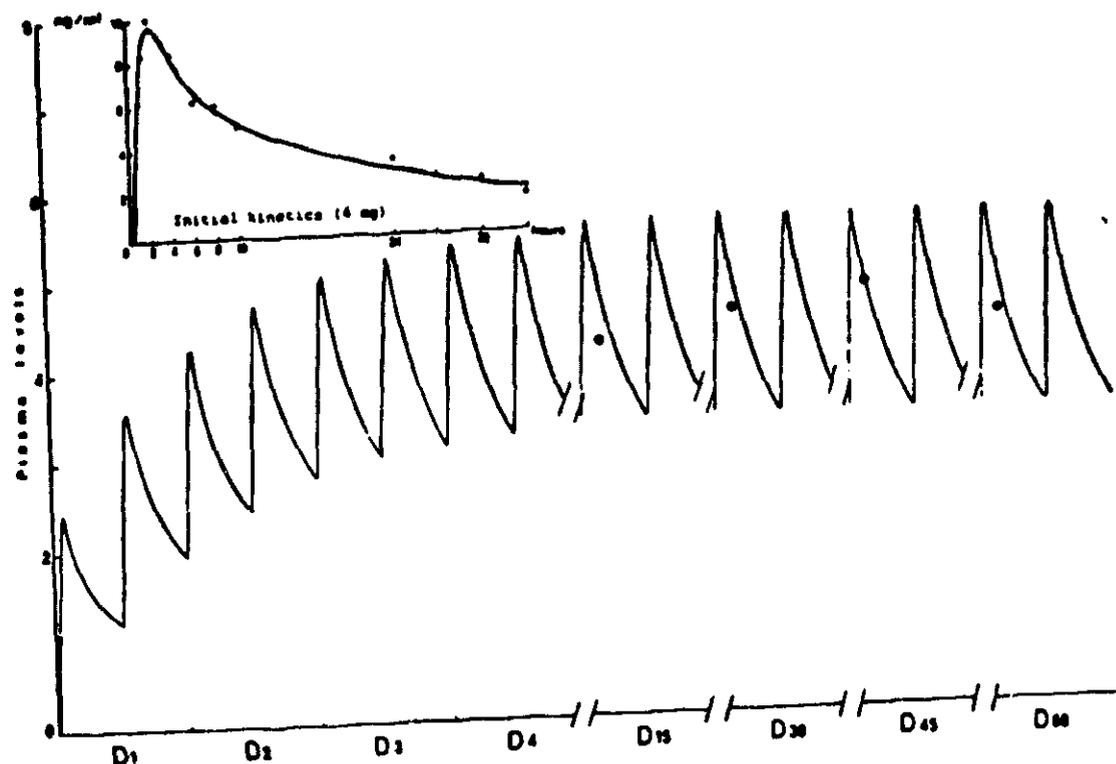


Figure 4A. Plasma concentration time profile of guanfacine following oral administration at 1 mg every 12 hr. Theoretical curve was generated by means of Eq. 3 with the parameters determined by program SAAM. Inset at top left position of figure illustrates profile of initial kinetics after single administration of 4 mg.

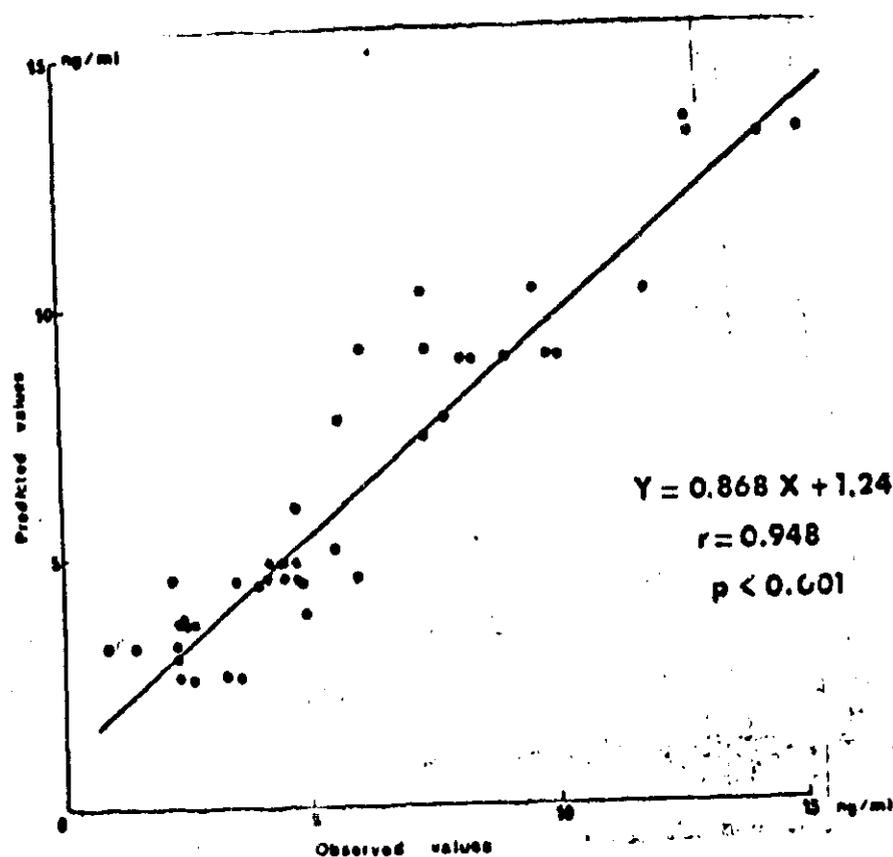


Figure 4B. Relationship between the observed plasma levels and the predicted values obtained after simulation with individual parameters in dosage regimen.

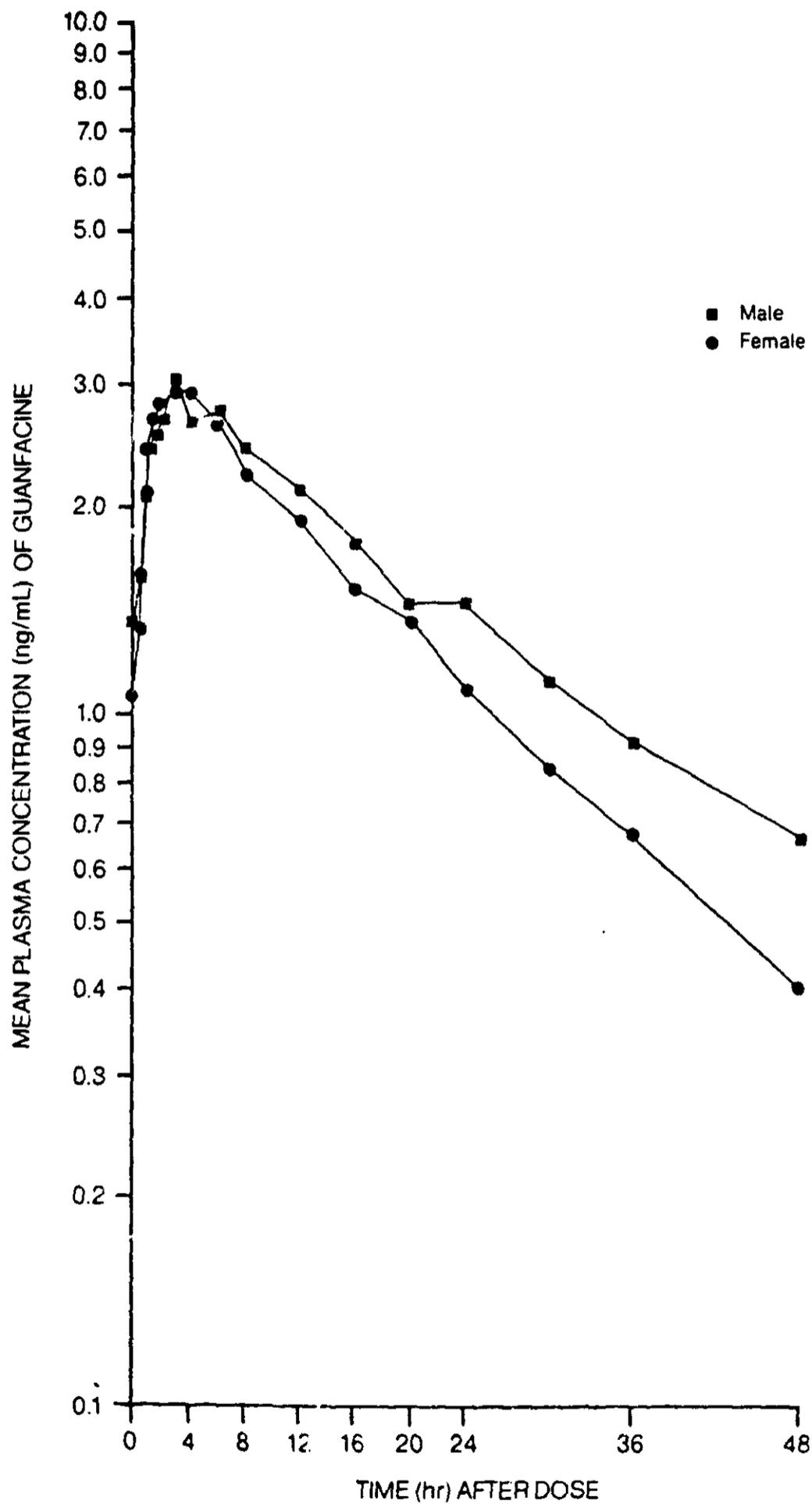


Figure 5. Mean Plasma Concentrations of Guanfacine in 10 Male and 10 Female Hypertensive Patients on Days 6-8 After 6 Days of Single Daily Doses of 1 mg Guanfacine HCl and 25 mg Chlorthalidone/Day.

TABLE VII

Summary of Mean Bioavailability Parameters of Guanfacine at Steady State in Patients with Hypertension

AUC (ng/mL-hr)	C _{max} (ng/mL)	T _{max} (hr)	C _{ave} (ng/mL)	k _{el} (hr ⁻¹)	Elimination T 1/2 (hr)
48.04	3.12	2.7	2.00	0.042	17.66

The biological disposition of guanfacine was assessed in several studies following oral and intravenous administration of carbon-14 labeled guanfacine. The majority of administered radioactivity was recovered in urine. All of the metabolic products identified in human urine were previously found in animals. The biotransformation pathways in humans are shown in Figure 6. Parent drug(1) accounted for 28 to 32% of the radioactive content. The major compound, glucuronide(4) of 3-hydroxy guanfacine(3), accounted for about 30 to 40% of the drug content in urine excreted within 24 hr of administration (Kiechel et al., 80-3377).

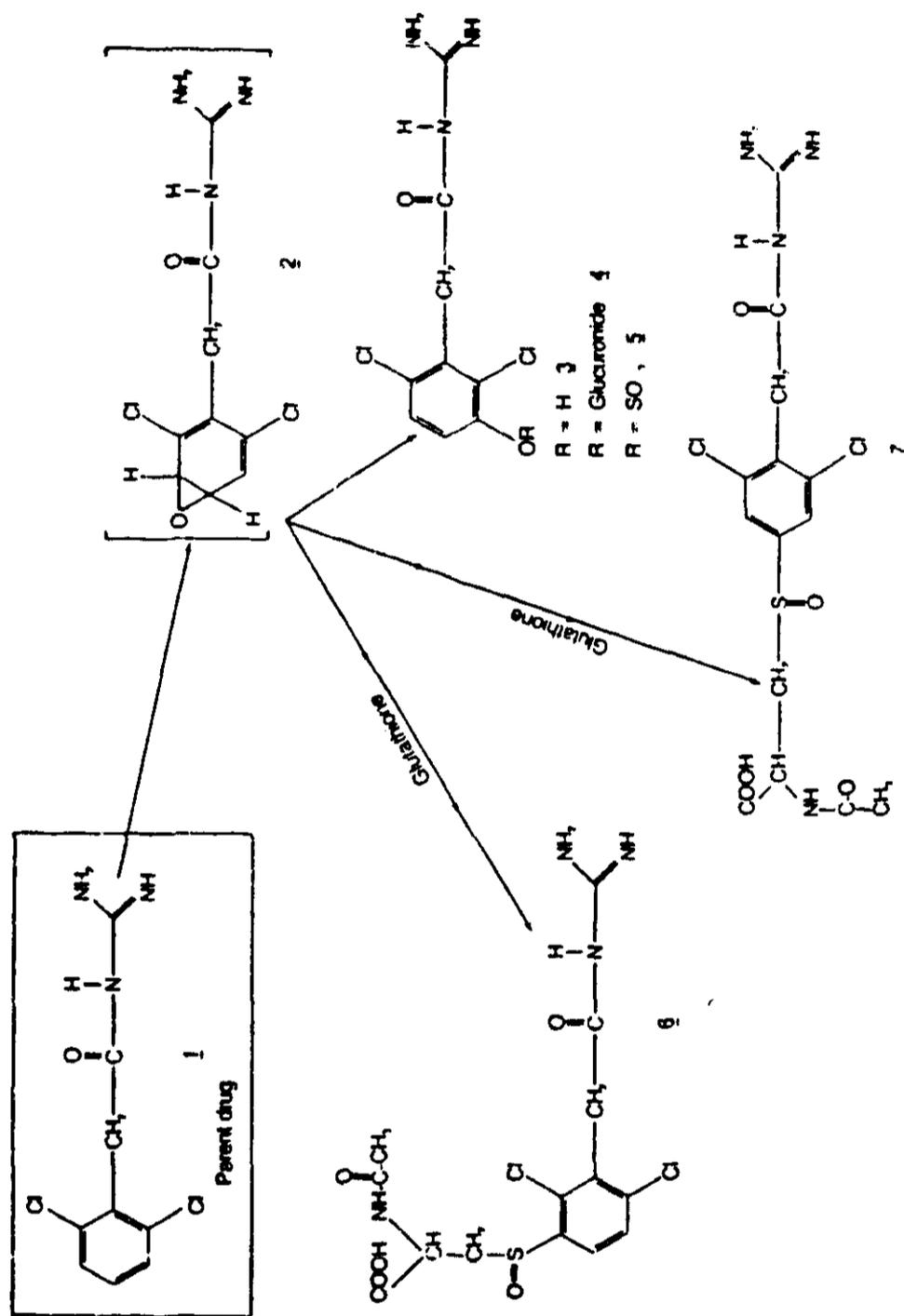


Figure 6. Proposed Metabolic Pathway of Guanfacine in Man Based on Metabolites Identified in Urine.

Binding of ^{14}C -guanfacine to proteins in plasma from normal volunteers was evaluated by equilibrium dialysis. Guanfacine at concentrations from 0.02 to 5 mcg/mL was 68 to 71% bound to human plasma proteins after 6 hr of incubation in vitro. Moderate binding to erythrocytes was also observed (Poser, 83-0201).

Several studies have investigated the effect of renal insufficiency on the pharmacokinetics of guanfacine. In one study (Kirch et al., 1980), 3 groups of hypertensive patients with various degrees of renal function (Group I = GFR >90 mL/min, Group II = GFR 10-30 mL/min, and Group III = GFR <10 mL/min). Renal clearance of guanfacine was reduced from 57% in Group I to 14% and 7.5% in Groups II and III respectively. The mean elimination half-life was 14 hr and found to be independent of the level of renal function. In spite of substantial interpatient variability, it was proposed that nonrenal clearance of guanfacine was enhanced in renal failure. Two other studies have demonstrated that the nonrenal clearance of guanfacine is unchanged in the context of renal insufficiency (Kiechel et al., 1980; Carchman et al., 1985). Total and renal clearances of guanfacine decreased in parallel with the decline in renal function which suggests that no compensatory increase in the metabolism of guanfacine by the liver occurred. The mean elimination half-life was about 20 to 24 hr, and the steady-state plasma levels were about twice as high in severe renal impairment as compared to subjects with normal renal function.

In a study with hemodialysis patients (Kiechel et al., 1980), only 2.4% of the dose was extracted unchanged in the dialysate. Hemodialysis had no significant influence on the elimination of guanfacine.

* * * * *

2. Duration of Action and Dose Response Study

Prot. No.	Principal Investigator	Purpose of Study	No. Subjects Receiving Tenex	No. Subjects Receiving Placebo	No. Subjects Receiving Comparative Drug	Tenex Doses (mg/day)	Tenex Dosing Schedule
S-02	Stephen Ayers, M.D.	To determine the hypotensive effects of single doses of guanfacine in normal volunteers. To evaluate safety of rising single doses in normal volunteers. To compare the efficacy and safety of 2 mg of guanfacine given as a single dose to 2 mg given on a 1 mg q12H x 2 schedule.	23	24	None	0.0mgx1 (n=24) 0.5mgx1 (n=6) 1.0mgx1 (n=7) 2.0mgx1 (n=5) 1mgq12hx2 (n=5)	Once Once Once Once q12hx2

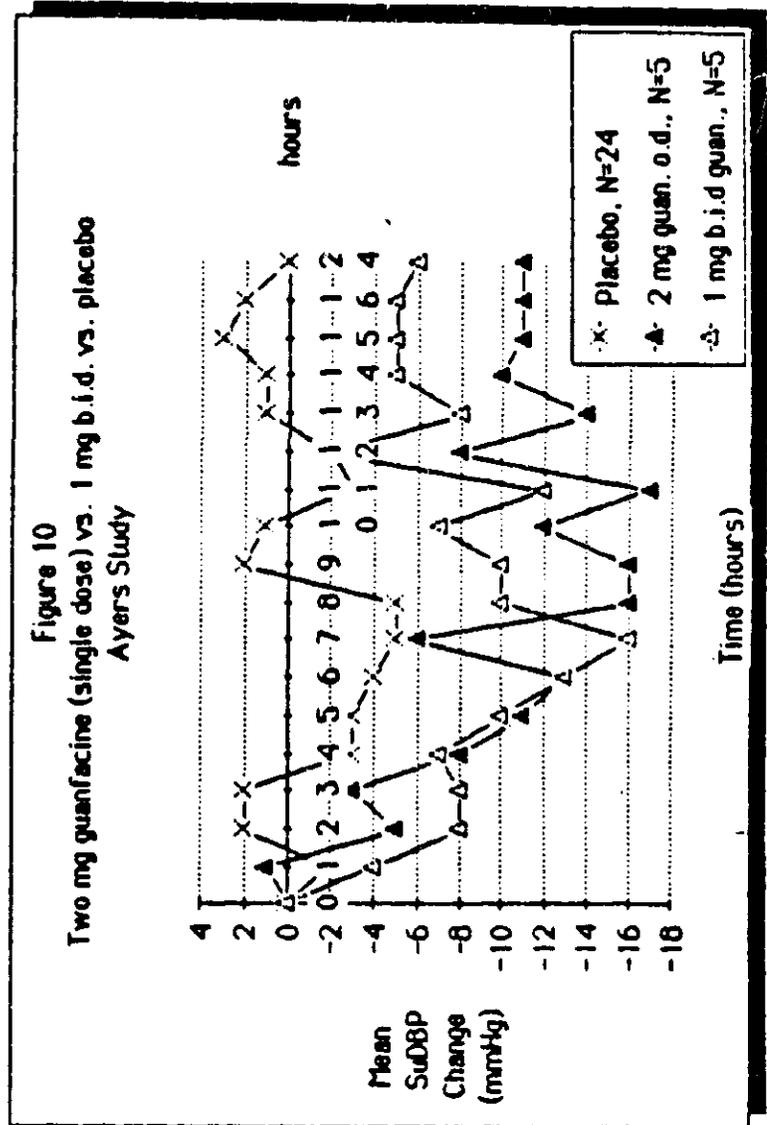
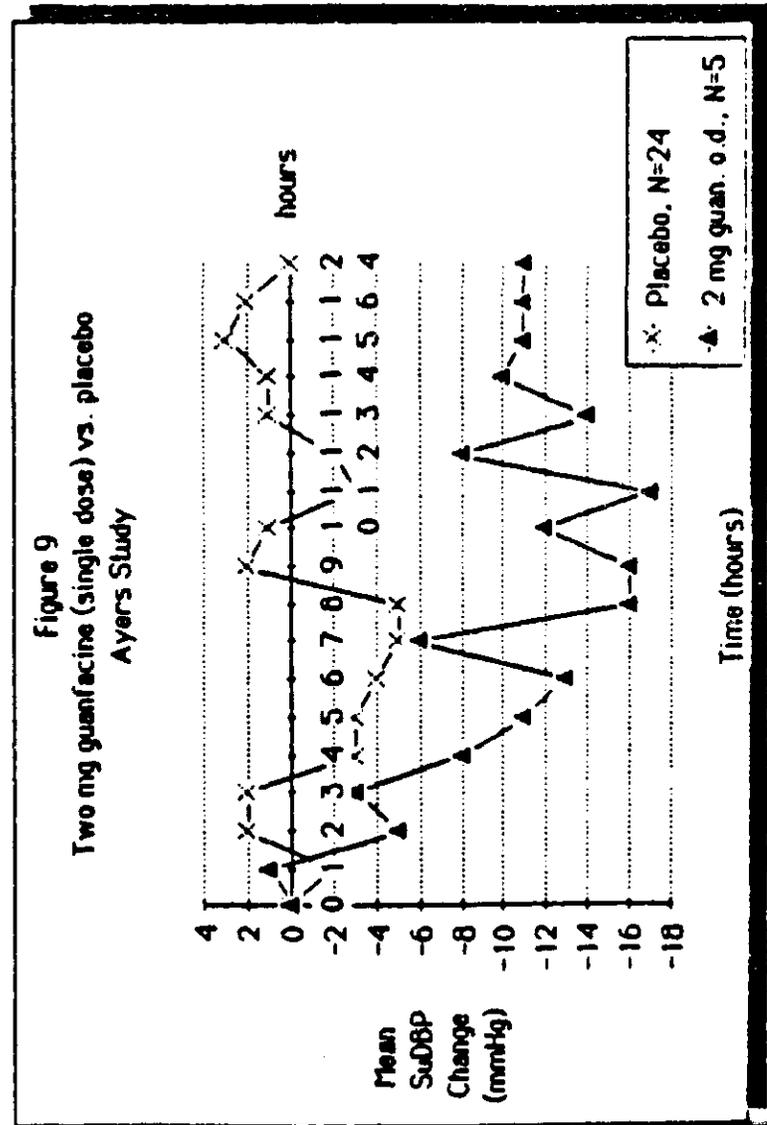
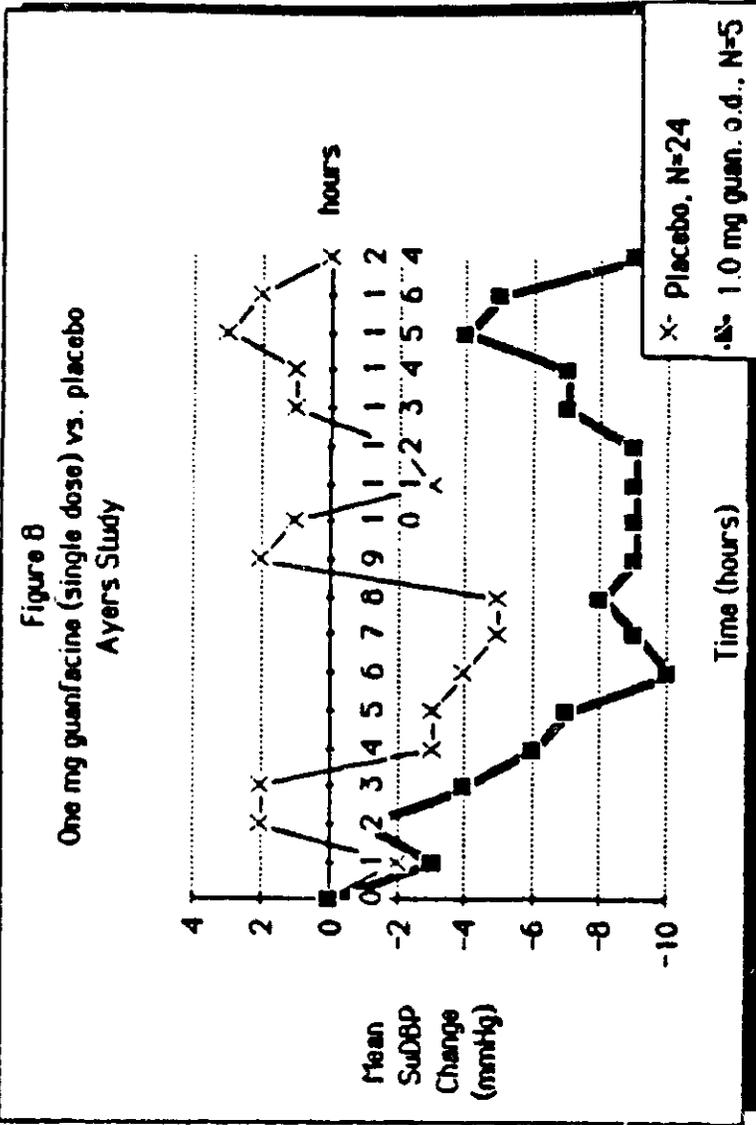
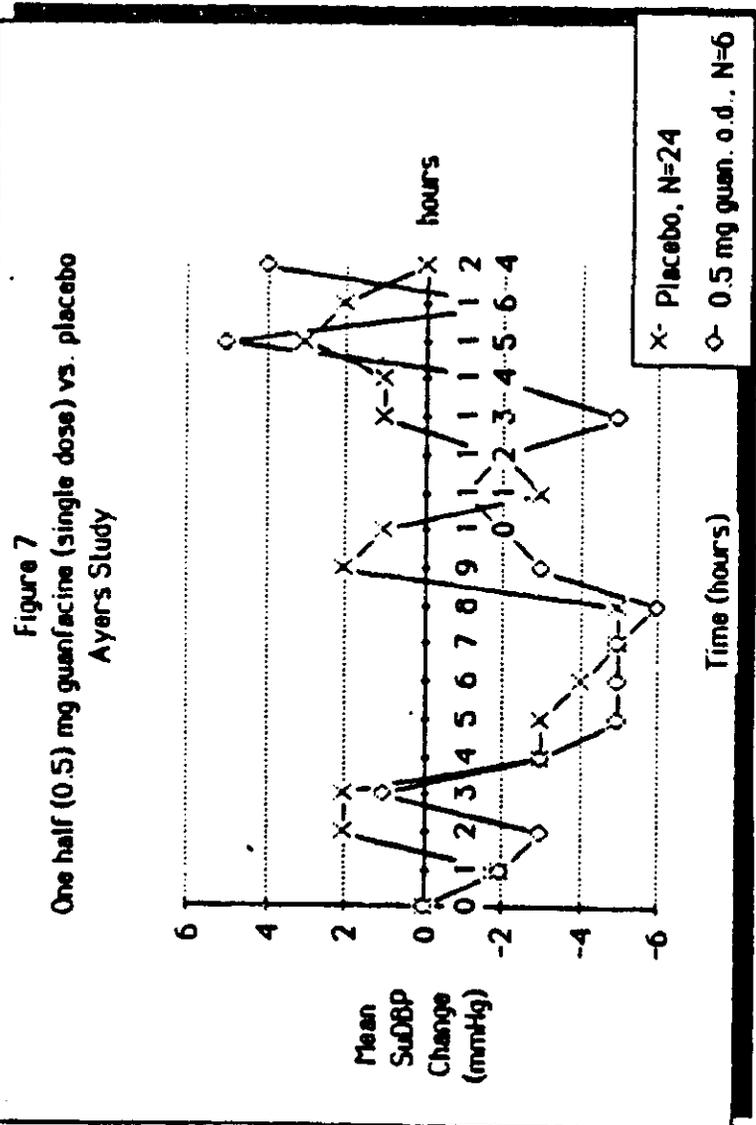
2. Duration of Action and Dose Response

A long-term (17-week) dose-response study of guanfacine when added to diuretic therapy is most relevant to the recommended clinical use of guanfacine and is described below under well-controlled clinical trials in hypertension. No similar data yet exist for guanfacine as monotherapy, so that monotherapy is not yet recommended. There are data in normal volunteers, however, that suggest the dose-response relationship for monotherapy will be similar to that seen when guanfacine is added to a diuretic. The single dose - dose-response study carried out was designed to look at maximum responses and duration of response.

The study (Ayers, S-02) was double-blind and placebo-controlled. Patients were randomized to placebo or 1 of 4 drug regimens, 0.5, 1.0, and 2.0 mg as a single dose and 1 mg given q12 for 2 doses. Observations were carried out for 48 hours. Results of blood pressure changes showed that there were mean diastolic blood pressure reductions over 24 hours of:

Placebo	1.4%
0.5 mg	3.6%
1.0 mg	7.5%
2.0 mg	11.5%
1.0 mg bid	11.0%

Hypotensive responses were dose related (see Figures 7-9). The duration of hypotensive effect was not altered by increasing the dose beyond 1 mg, but the 0.5 mg dose did not seem to have a 24-hour effect. The magnitude of reduction was dose related. When 2 mg as a single dose was compared to 1 mg q12h x 2, the patterns of response were quite similar (see Figure 10).



The incidence of side effects also appeared dose-related, as noted in Table VIII, although the small numbers of patients prevent any definitive conclusions.

Table VIII
Incidence of Side Effects
Ayers Study

Side Effect	Severity	Placebo (24 Subj.)	0.5 mg o.d. (6 Subj.)	1.0 mg o.d. (7 Subj.)	1.0 mg b.i.d. (5 Subj.)	2.0 mg o.d. (5 Subj.)
Lethargy	Mild					2
Headache	Mild	1	1	1		2
Muscle Ache	Mild					1
Drowsiness	Mild	1		1	2	2
	Moderate	1				1
Dry Mouth	Mild	1	1	2	1	1
Lightheadedness	Mild		1	1		
Vivid Dreams	Mild	2				
	Moderate	1				
% of Pts. with at least one side effect		29%	33%	43%	40%	80%

3. Rebound Hypertension

Protocol Number	Principal Investigator	Purpose of Study	No. Patients Receiving Tenex	No. Patients Receiving Placebo	No. Patients On Comparative Drug	Tenex Doses (mg/day)	Tenex Dosage Schedule
*	S. Mann, M.D.	Effect of guanfacine on acute & long-term treatment of hypertension & abrupt discontinuation of guanfacine	5	0	0	1-6	o.d.
**	P. Manhem, M.D.	Effect of guanfacine on acute & long-term treatment of hypertension & abrupt discontinuation of guanfacine	4	0	0	1-2	t.i.d.
241	I. Szam, M.D.	Effect of guanfacine on acute & long-term treatment of hypertension & abrupt discontinuation of guanfacine	11	0	0	1-5	o.d.
242	J. Reid, M.D.	Effect of guanfacine on acute & long-term treatment of hypertension & abrupt discontinuation of guanfacine	5	0	0	3-6	o.d.
Total No. Studies			25	0	0	1-6	o.d. & t.i.d.

*Brit. J. Clin. Pharmacol. 10, Suppl. 1, pp. 103S-107S (1980).

**Brit. J. Clin. Pharmacol. 10, Suppl. 1, pp. 109S-114S (1980).

3. Rebound Hypertension

Background. "Rebound" upon abrupt withdrawal of antihypertensive drugs has been described for central adrenergic agonists and beta-blockers. The "rebound phenomenon" is defined as a sudden rise in blood pressure accompanied by other symptoms of sympathetic overactivity which occur after abrupt discontinuation of drug therapy. Table IX shows that it has been reported with fairly high frequency for clonidine.

Table IX
Frequency of Rebound Phenomenon Following Clonidine

Author	No. of Patients	No. Patients with Rebound Phenomenon	Clonidine Dose mg/day
Hanson et al. ¹	5	5	0.3 - 2.4
Goldberg et al. ²	15	11	0.3 - 0.9
Goldberg et al. ³	9	9	0.3 - 0.6
Spach ⁴	14	7	0.15- 0.9
Reid ⁵	7	6	0.15->1.0
Geyskes et al. ⁶	14	14	0.9

¹Am. H. J. Vol. 85, No. 5, pp. 605-610 (May 1983)

²Postgrad. Med. J. 52(Suppl.), pp. 128-36 (1976)

³Br. Med. J., pp. 1243-46 (May 14, 1977)

⁴La Nouv. Press. Med. 6,(14), pp. 1201-5 (April 9, 1977)

⁵Lancet, pp 1171-74 (6/4/77)

⁶Br. J. Clin. Pharmacol., pp. 55-62 (1979)

Reid has postulated reasons for the rebound phenomenon:

"The central alpha-agonist effect of clonidine produces decreased peripheral sympathetic activity and increased vagal tone. The withdrawal syndrome represents a sudden reversal of these central drug induced effects with a transient increase in efferent sympathetic activity."

Clinical Trials. Early in the clinical investigation of guanfacine, 4 studies were performed with 25 hypertensive patients in order to evaluate the effects of cessation of guanfacine treatment. The "rebound phenomenon" was defined as (1) the presence of withdrawal symptoms and (2) a rise of 15 mmHg or more above the pretreatment systolic blood pressure. A summary of these results is given in Table X.

Table X
Summary of Guanfacine Clinical Studies Following Cessation of Treatment

Study No.	Investigator(s)	Treatment		No. Pts.	Observation Post-Drug Period of Obs./Frequency	Results
		Duration	Dosage			
**	B. Mann, M.W. Miller- Craig, D. Melville, P. Cashman & E. Raftery	5-20 wks	1-6 mg o.d.	5	48 hrs./patients monitored continuously	No rebound phenomena
242	J.L. Reid, C. Zamboulis, C.A. Hamilton	8-10 wks.	3-6 mg daily	5	96 hrs./patients monitored continuously	No rebound phenomena
***	P. Manhem, B. Hökfelt	3-8 wks.	1-2 mg t.i.d.	4	96 hrs./continuous	No rebound phenomena
241	I. Szam	4-6 wks.	1-5 mg daily	11	7 days/patients monitored twice daily	No rebound* phenomena

*One patient's blood pressure exceeded pretreatment levels with no subjective symptoms of withdrawal.
 **G. J. Clin. Pharmacol. (1980) 10, 1036-1075.
 ***Br. J. Clin. Pharmacol. (1980) 10, 1095-1145.

The return of blood pressure to pretreatment levels after guanfacine treatment was slower than had been observed with clonidine, perhaps because of the longer half-life of guanfacine. Unfortunately, these trials had no comparison clonidine group.

Several other trials (Table XI) of guanfacine for treatment of hypertension included observations of rebound phenomena, although these were not the prime objective of the studies.

Table XI

Summary of Rebound Phenomena with Guanfacine

Study Type	No. Pts. Monitored	Daily Dose Ranges (mg)	No. Pts. with Rebound	Frequency
1. Dose-finding and short-term tolerance (< 2 weeks)	63*	0.5-8	0	0%
2. Comparative studies (6 weeks on guanfacine)	118	1-15	0	0%
3. Studies 2-4 months' duration	72	1-10	4	5.6%
4. Studies of 1 year's duration	407	0.5-20	9	2.2%
5. Studies of 2 years' duration	106	0.5-20	6	5.7%
Totals	766	0.5-20	19	2.5%

*Includes 43 normal volunteers.

After interruption of short-term treatment (lasting several days) no clinical signs of the rebound phenomenon were observed. The earliest occurrence of the rebound phenomenon was observed in patients who were treated for at least 7 weeks. The lowest daily dose of guanfacine followed by rebound on discontinuation was >5 mg/day.

While these observations suggested that guanfacine-treated patients faced a low risk of important rebound after cessation of treatment, they did not constitute a well-planned observation in an adequate patient population. Protocol 03, a multicenter study comparing the long-term effectiveness and tolerance of guanfacine and clonidine, each added to 25 mg of chlorthalidone, included a planned abrupt withdrawal phase after 24 weeks of treatment. It is described in detail under the Well-Controlled Clinical Trials section; it showed that rebound can occur with guanfacine, but it occurs much later (after several days) than clonidine and is almost always well tolerated.

* * * * *

4. Hemodynamic and Renal Effect Studies

Protocol Number	Principal Investigator	Purpose of Study	No. Patients Receiving Tenex	No. Patients Receiving Placebo	No. Patients On Comparative Drug	Tenex Doses (mg/day)	Tenex Dosage Schedule
<u>Hemodynamics</u>							
202	N. Schaefer, M.D.	Open label, hemodynamics	10	0	0	3-15	Single daily dose x 12 weeks
*	H. Erhinger, M.D.	Open label, hemodynamics	5	0	0	0.01-0.04 mg/kg	Single i.v. dose
**	Torok <u>et al.</u>	Long-term hemodynamics	10	0	0	4	Single daily doses
06	M. Strauss, M.D.	Effectiveness and plasma volume/plasma aldosterone; double-blind; placebo-controlled	17	9	0	1	q.d. x 28 days
**	Feldstein <u>et al.</u>	Open-label, hemodynamics	11	0	0	4 (mean)	i.v. single dose o.d. oral
<u>Total No. Studies</u>			53	9	0		
<u>Renal Effects</u>							
****	A. Roeckel, M.D.	Renal effects	21	0	0	2-15	q.d. x up to 24 months

*Brit. J. Clin. Pharmacol. 10 Suppl. 1, pp. 115S-122S, (1980).
 **8th Scientific Meeting, Intern. Soc. of Hypertension, Milan, 1981.
 ***Clin. Therap. 6:325-34, 1984.
 ****Brit. J. Clin. Pharmacol. 10 Suppl. 1, pp. 141S-150S, (1980).

4. Hemodynamic and Renal Effect Studies (continued)

Introduction. Five clinical studies on the effects of guanfacine on hemodynamics and kidney function were performed. A total of 74 patients was studied.

In a hemodynamic study (Schaefer) of 10 hypertensive patients, guanfacine was given in daily dosages of 3-15 mg (mean = 7.3 mg) over a 12-week period to stabilize blood pressure. Hemodynamic studies were performed before and after treatment of these patients. No other drugs were taken during the study.

Systolic, diastolic, and mean arterial pressures in the right atrium and aorta were measured and heart rate was recorded at rest and during effort testing (bicycle ergometer, work loads of 25 watt/2 min, 50 watt/2 min, 75 watt/2 min, and 100 watt/2 min where possible). Cardiac output was also measured. From these data, the following were calculated: stroke volume and total peripheral resistance.

The results are given in Table XII.

Table XII

Hemodynamic Changes Between Pretreatment and Treatment (Schaefer)

Hemodynamic Parameter	Rest	Effort	After Effort
Systolic Pressure, aorta	+++	+++	+++
Diastolic Pressure, aorta	+++	+++	++
Mean Arterial Pressure, aorta	+++	++	++
Pressure, atrial	-	-	→
Mean Arterial Pressure, atrial	-	→	→
Heart Rate	←	←	←
Cardiac Output	-	-	-
Stroke Volume	→	→	↑
Total Peripheral Resistance	↓↓	↓	↓
Heart Index	-	-	-

- = No change.

→ = Relevant increase, not statistically significant.

← = Relevant decrease, not statistically significant.

↑ = Increase, statistically significant ($p < 0.05$).

↓ = Decrease, statistically significant ($p < 0.05$).

↓↓ = Decrease, statistically significant ($p < 0.01$).

+++ = Decrease, statistically significant ($p < 0.001$).

In a long-term hemodynamic trial (Torok, *et al.*, 8th Scientific Meeting, Intern. Soc. of Hypertension, Milan, 1981), ten patients received guanfacine at 4 mg/day for 12 months. Mean blood pressure and heart rate decreased significantly ($p < 0.01$). There was also a significant increase in stroke volume ($p < 0.05$) and a significant decrease in TPR ($p < 0.01$) with no changes in blood volume or cardiac index.

A third study (Feldstein, *et al.*, Clinical Therap. 6:325-34, 1984) evaluated 11 patients during six weeks of guanfacine therapy (mean daily dose of 4 mg). There were significant decreases in blood pressure, heart rate, and peripheral resistance. Increases were noted in pulmonary artery pressure, mean right atrial pressure, and stroke volume.

Erhinger and colleagues studied the effects of guanfacine on the circulation of 5 patients. The following doses of guanfacine were compared in random order with placebo: 0.01; 0.02; 0.04 mg/kg respectively. The drug was infused over a 5-minute period using a motorized pump.

The room temperature was controlled at constant 25°C following an adaptation period of 60 minutes for each patient. All patients remained in the supine position prior to and during the measurements of circulation. Blood flow in the calf and forefoot was measured simultaneously every 15 seconds using a strain gauge plethysmograph and an automatic venous occlusion device. The technique of Wood and Ecstein (J. Clin. Invest. 37:41, 1958) was utilized to measure blood flow.

There were dose-dependent drops in blood pressure and concurrent increases in blood flow in the foot. This observed action was interpreted by the authors as a decrease in peripheral resistance.

In a study by Strauss, the effects of guanfacine alone on plasma volume and plasma aldosterone were investigated. Twenty-six patients with essential hypertension (DBP 90-100 mmHg) were randomly assigned to either 1.0 mg/day guanfacine or placebo after a 1-month drug-free period. All medication was blinded, and the study was conducted in a double-blind fashion. Baseline values for plasma volume, plasma aldosterone, and vital signs were obtained immediately prior to the beginning of the drug evaluation period. All patients received the test agents daily for 28 days. At the end of the 28-day period, plasma volume, plasma aldosterone, and vital signs were obtained again for each patient. Plasma volume and plasma aldosterone were estimated using standard commercial laboratory methods.

There was no statistically significant or clinically relevant change from baseline in plasma aldosterone for any of the 17 guanfacine or 9 placebo patients. Plasma volume decreased 5.3% from baseline in those patients who received guanfacine, and a 2.4% decrease was observed in the placebo group. These differences were not statistically significant.

The mean blood pressures for the guanfacine group decreased from 149/97 mmHg at baseline to 140/84 mmHg at the end of treatment. The mean blood pressures for the placebo group changed from 163/97 mmHg to 156/99 mmHg at the end of treatment. The differences in the changes from baseline observed between the treatment groups for diastolic pressure were significant; the differences for systolic pressure were not. The mean heart rate decreased from 70 beats/min to 68 beats/min in the guanfacine group and remained unchanged in the placebo group.

RENAL FUNCTION

In a chronic study by Roedel & Heidland, 21 hypertensive patients were treated orally with 2-15 mg/day of guanfacine for 24-42 months. The GFR for these patients ranged from 18.0-109.0 mL/min. Before, during, and after guanfacine, GFR and plasma creatinine were recorded.

In this study, patients who received guanfacine alone or in combination with hydrochlorothiazide and/or hydralazine did not show a significant change in GFR or plasma creatinine levels.

★ ★ ★ ★ ★

5. Metabolic Effects

Protocol Number	Principal Investigator	Purpose of Study	No. Patients Receiving Tenex	No. Patients Receiving Placebo	No. Patients On Comparative Drug	Tenex Doses (mg/day)	Tenex Dosage Schedule
222	S. Sailer, M.D.	Effect on glucose & insulin metabolism single-blind, cross-over	6	6	0	1	Single i.v. dose
*	J. Hauger-Kleve, M.D.	Effect on glucose tolerance	18	0	0	2.8	Mean daily dose
231	I. Lancranjan, M.D.	Effect on pituitary & pancreatic hormones 3 parts of the study	14 10 6	0 0 0	10 0 0	1-2 2-4 2	Single dose Single dose t.i.d.
Total No. Studies			54	6	10	1-4	

*Horm. Metabol. Res. 1985, pp. 613-14

5. Metabolic Effects (continued)

Three clinical studies were performed: (two) to evaluate the effects of guanfacine on glucose metabolism (S. Sailer and J. Hauger-Klevene) and (one) to evaluate effects on the secretion of pituitary and pancreatic hormones (I. Lancranjan).

Glucose Metabolism

Sailer conducted a single-blind, crossover experimental acute study, comparing guanfacine with placebo (isotonic saline solution) in their effects on glucose and insulin levels during a glucose tolerance test.

Guanfacine 1 mg or placebo was administered intravenously. After 20 minutes, 100 g of glucose p.o. was given. At time-points -90, 0, 30, 60, 90, and 120 min, glucose and insulin levels were measured.

There was no evidence that a single, 1-mg, intravenous dose of guanfacine has a hyperglycemic effect or altered insulin response.

An acute experiment cannot provide the definitive evidence on the effect of chronic oral administration of guanfacine on glucose metabolism. An analysis of the effect of guanfacine on serum glucose is included in the Well-Controlled Clinical Studies section of this clinical summary.

In a 12-month study in which 18, hypertensive, Type II diabetics were treated with guanfacine monotherapy (mean daily dose of 2.8 mg), Hauger-Klevene and Scornavacchi (Horm. Metab. Res. 1985, p. 613-4) glucose tolerance that was influenced by on-going diuretic therapy tended to improve during the period of observation. There were no changes in body weight during the period of observation.

The results are summarized in Tables XIII and XIV.

Table XIII

Changes in Plasma Glucose (mg/dL) During Oral Glucose Tolerance Tests
in Patients Treated with Guanfacine

	Time in minutes			
	0	60	120	180
Plasma glucose (mg%)				
Placebo (18)	134.6 ± 50.9	203.6 ± 49.1	212.7 ± 52.7	160.9 ± 52.7
3 months (18)	128.9 ± 40.0	180.0 ± 52.0	196.4 ± 57.6	147.1 ± 38.2
6 months (15)	111.3 ± 20.4	168.9 ± 40.0	179.1 ± 45.1*	138 ± 35.5
12 months (9)	99.6 ± 18.9*	160.9 ± 23.5*	165.5 ± 30.0*	118.9 ± 18.0

*p<0.001

Table XIV

Changes in Plasma Insulin During Oral GTT in Patients Treated with
Guanfacine

	Time in minutes			
	0	60	120	180
Plasma insulin (μU/mL)				
Placebo	12.5 ± 6.4	78.8 ± 57.4	98.5 ± 73.1	70.9 ± 64.9
3 months	18.9 ± 8.0	89.9 ± 64.2	111.4 ± 78.0	68.0 ± 57.3
6 months	22.3 ± 10.3**	95.8 ± 68.8	114.6 ± 67.1	72.3 ± 55.2
12 months	24.1 ± 6.3**	100.4 ± 53.1	135.8 ± 67.7	94.5 ± 42.0

**p<0.05 in relationship to placebo

Pituitary and Pancreatic Hormone Effects

Lancranjan conducted a study to determine the effects of guanfacine on the secretion of pituitary and pancreatic hormones.

Fourteen, non-obese, healthy volunteers aged 21-45 years, received 1 and 2 mg guanfacine as a single dose. A second group of 10 normal volunteers, aged 20-30 years, received single doses of 2 mg and 4 mg of guanfacine or 0.15 and 0.3 mg clonidine in a randomized crossover sequence. A third group of six male patients (44-60 years) with mild hypertension took 2 mg guanfacine t.i.d. for 10 days.

A significant stimulatory effect on growth hormone (GH) secretion occurred only after single oral doses of 2 and 4 mg guanfacine and 0.3 mg clonidine in normal subjects under 45 years. This effect did not occur in hypertensive patients aged 44-60 years, either after single doses of 2 mg guanfacine or after short-term treatment (2 mg t.i.d. for 10 days). Moreover GH plasma levels, measured in hypertensive patients during long-term treatment with guanfacine, were normal (Study No. 129).

Guanfacine had no effect on prolactin (PRL) resting plasma levels or on PRL released by agents acting on the pituitary, but significantly decreased PRL stimulated by insulin-induced hypoglycemia.

Single doses of 1 mg, 2 mg, and 4 mg guanfacine and short-term treatment (3 mg daily for 7 days) had no effect on "resting" glucose or insulin plasma levels.

Finally, no relevant biological effect on ACTH, LH, FSH or glucagon secretion was recorded after short-term treatment with guanfacine.

* * * * *

6. Clinical Laboratory Studies - Effectiveness

Protocol Number	Principal Investigator	Purpose of Study	No. Patients Receiving Tenex	No. Patients Receiving Placebo	No. Patients On Comparative Drug	Tenex Doses (mg/day)	Tenex Dosage Schedule
*	J. Rosenthal, M.D.	Effect on plasma renin activity	24	0	0	3-40	t.i.d.
**	W. Schoeppe, M.D.	Effect on BP, plasma renin, and norepinephrine	23	0	0	0.02 mg/kg 4 mg	i.v. single dose b.i.d.
***	P. Manahem, M.D.	Effect on BP/HR, catechols & PRA	5	0	0	1.5-6	t.i.d.
Total No. Studies			52	0	0	1.5-40	

*Br. J. Clin. Pharmacol. (1980) 10, 91S-96S.
 **Br. J. Clin. Pharmacol. (1980) 10, 97S-101S.
 ***Br. J. Clin. Pharmacol. (1980) 10, 109S-114S.

6. Clinical Laboratory Studies - Effectiveness (Continued)

Three studies of the effect of guanfacine on plasma renin activity and catecholamines were reviewed.

In the first study (Rosenthal), 26 hypertensive patients (21 essential hypertensives, 5 renal hypertensives) were evaluated in an open-label study in which 24 patients completed a 14-day placebo phase followed by 3 months of guanfacine with another 2-week placebo period at the end. All patients started at 3 mg/day and were titrated upward to achieve an effective maintenance dose. Blood and urine samples were collected for measurements of blood count, urinalysis, blood glucose, potassium urea, uric acid, serum creatinine, renin, and creatinine clearance.

The average daily dose of guanfacine was 6 mg (range 3-40 mg/day). Blood pressure was reduced from an average 197/115 mmHg to 147/83 mmHg after 12 weeks of treatment. Plasma renin decreased during treatment from a mean of 3.3 to 2.3 ng mL⁻¹ h⁻¹. This decrease could not be correlated with the decrease in blood pressure in individual patients.

In a second study (Schoeppe and Brecht), 23 patients with mild to moderate essential hypertension were studied. In the acute phase of the study, these previously untreated hypertensive patients received a single i.v. dose of 0.02 mg/kg guanfacine. At 15- and 60-minute intervals following the dose, blood pressure, heart rate, plasma noradrenaline, and plasma renin activity were measured in the supine position.

In the chronic phase of the study, the same patients were treated for 4 weeks with 1 mg b.i.d. orally. Blood pressure, heart rate, plasma noradrenaline, and plasma renin activity were measured before and after treatment under various physiological conditions, i.e., after 4 hours supine, after 7 minutes standing, and after 2 hours walking.

In both the acute and chronic phases of the study, there was a significant reduction in blood pressure. Plasma noradrenaline and renin (PRA) decreased significantly during the acute phase of the study. During the chronic phase of the study, there was a significant decrease in plasma noradrenaline and PRA under basal and orthostatic conditions. In individual patients, these reductions could not be correlated with a reduction in blood pressure.

In the third study (Manhem and Hökfelt), 5 patients with essential hypertension (WHO grades II-III) were hospitalized for 6-10 days during the institution of guanfacine treatment and then again 4-8 weeks later during the withdrawal of the drug. The dosage of guanfacine ranged from 0.5-2.0 mg t.i.d.

Blood pressure, heart rate, plasma and urinary catecholamines, and plasma renin activity were measured before and after treatment.

Blood pressure, plasma catechols, and PRA decreased during treatment, and all increased gradually upon discontinuation of the drug. No "rebound hypertension" was observed.

Guanfacine decreases plasma renin activity, but this decrease is not correlated with a reduction in blood pressure in individual subjects. Guanfacine decreases plasma catechols which return to normal levels after discontinuation of the drug.

* * * *

B. Well-Controlled Trials on Hypertension

Protocol Number	Principal Investigator	Purpose of Study	No. Patients Receiving Tenex	No. Patients Receiving Placebo	No. Patients On Comparative Drug	Tenex Doses (mg/day)	Tenex Dosage Schedule
01	F. Finnerty, M.D. W. Kessler, M.D. J. McMillen, M.D. A. Marlon, M.D. S. Savran, M.D. M. Alderman, M.D. F. Canosa, M.D. B. Materson, M.D.	Double-blind, parallel with placebo control to define dose response relationship of multiple Tenex doses with chlorthalidone for treatment of mild to moderate essential hypertension	288	73	NA	0.5-3	0.5 mg o.d. + 25 mg chlorthalidone o.d. 0.5 mg + 1.0 mg o.d. + 25 mg chlorthalidone o.d. 0.5 mg + 1.0 mg + 2.0 mg o.d. + 25 mg chlorthalidone o.d. 0.5 mg + 1.0 mg + 2.0 mg + 3.0 mg o.d. + 25 mg chlorthalidone o.d.
02	P. Black, M.D. J. Freudenburg, M.D. J. Hill, M.D. C. Holmburg, M.D. M. Rietbrock, M.D. M. Sullivan, M.D. M. Thompson, M.D. D. Wright, M.D.	Double-blind, parallel with placebo control to demonstrate the 24-hr duration of Tenex effectiveness with chlorthalidone for treatment of mild to moderate essential hypertension	126	123	NA	1-3	1-3 mg o.d. plus 25 mg chlorthalidone o.d.; free titration based upon response
03	O. Haring, M.D. A. Lewin, M.D. G. Bedsole, M.D. W. Stepansky, M.D. J. Fillingim, M.D. D. Hall, M.D. M. Roginsky, M.D. M. Wilson, M.D. P. Jagger, M.D. G. McMahon, M.D. M. Strauss, M.D.	Double-blind, parallel with clonidine control to demonstrate comparative efficacy/safety and to evaluate the effects of abrupt withdrawal of guanfacine vs. clonidine	279	NA	278	1-3	1-3 mg o.d. plus 25 mg chlorthalidone o.d.; free titration based upon patient response; 25 mg chlorthalidone continued for 1 week after withdrawal of clonidine or guanfacine

Protocol Number	Principal Investigator	Purpose of Study	No. Patients Receiving Tenex	No. Patients Receiving Placebo	No. Patients On Comparative Drug	Tenex Doses (mg/day)	Tenex Dosage Schedule
06	M. Strauss, M.D.	Double-blind, parallel with placebo control to determine efficacy and effect on plasma volume and plasma aldosterone	17	9	NA	1	1 mg o.d. monotherapy
11	J. Blackshear, M.D.	Double-blind, parallel with placebo control to determine efficacy and effect on plasma lipids	21	21		1	1 mg o.d. monotherapy
14	J. Fillingim, M.D. P. Boyles, M.D.	Double-blind, parallel with guanabenz as control to determine comparative efficacy/safety	45	NA	46	1	1 mg o.d. monotherapy
Total No. of Studies			776	226	278	0.5-3	
			6				

Well-Controlled Trials on Hypertension
Investigators and Patient Accountability

Study Identification	Investigators	Location	No. Patients Studied
Protocol 01 - Dose Response Study	F. Finnerty, M.D.	Washington, D.C.	43
	W. Kessler, M.D.	Wallingford, PA	67
	J. McMillen, M.D.	Camp Hill, PA	36
	A. Marlon, M.D.	Las Vegas, NV	30
	S. Savran, M.D.	Reno, NV	37
	M. Alderman, M.D.	New York, NY	49
	F. Canosa	Miami, FL	50
	B. Materson	Miami, FL	49
	TOTAL		361
	Protocol 02 - 24-Hour Effectiveness Study	P. Black, M.D.	La Jolla, CA
J. Freudenburg, M.D.		Longmont, CO	31
J. Hill, M.D.		Vero Beach, FL	30
C. Holmburg, M.D.		Menomonee Falls, WI	32
M. Rietbrock, M.D.		Oconomowoc, WI	37
M. Sullivan, M.D.		Lafayette, NA	29
M. Thompson, M.D.		Redondo Beach, CA	24
D. Wright, M.D.		Rockford, IL	33
TOTAL			289
Protocol 03 - Clonidine Comparison		O. Haring, M.D.	Chicago, IL
	A. Lewin, M.D.	Los Angeles, CA	49
	G. Bedsole, M.D.	Montgomery, AL	51
	W. Stepansky, M.D.	Trappe, PA	27
	J. Fillingim, M.D.	Savannah, GA	100
	D. Hall, M.D.	Atlanta, GA	21
	M. Rosinsky, M.D.	East Meadow, NY	49
	M. Wilson, M.D.	Oklahoma City, OK	50
	P. Jagger, M.D.	San Diego, CA	19
	G. McMahon, M.D.	New Orleans, LA	49
M. Strauss, M.D.	Little Rock, AR	121	
TOTAL		557	

Well-Controlled Trials on Hypertension
Investigators and Patient Accountability

Study Identification	Investigators	Location	No. Patients Studied
Protocol 06 - Monotherapy Efficacy and Plasma Volume/Aldosterone Study	M. Strauss, M.D.	Little Rock, AR	26
Protocol 11 - Monotherapy Efficacy and Plasma Lipids	J. Blackshear, M.D.	Little Rock, AR	42
Protocol 14 - Monotherapy Efficacy and Safety vs. Guanabenz	J. Fillingim, M.D. P. Boyles, M.D.	Savannah, GA Cary, NC	91

continued:

B. Well-Controlled Trials on Hypertension (continued)

1. U.S. Trials: Stepped Care

a. Dose-Response Study (Study No. 01)

One multi-investigator, double-blind, randomized and placebo-controlled study to evaluate the dose response of guanfacine as Step II treatment for mild to moderate essential hypertension (95-114 mmHg, DBP) was completed.

Inclusion and Exclusion Criteria:

In order to be accepted in the study a patient was to be 21-60 years old and have a diagnosis of mild to moderate essential hypertension (DBP=95-114 mmHg). A patient was excluded, however, if he was obese, alcoholic or a drug addict, or if he/she had: unstable diabetes or grade III or IV hypertensive retinopathy, malignancy or advanced renal, hepatic, GI, pulmonary or hematological disease, congestive heart failure, unstable angina pectoris, MI within 6 months or clinically significant cerebrovascular disease, gout, or labile hypertension.

Excluded also were pregnant or nursing women or patients who had received guanethidine or reserpine therapy immediately prior to entering the study or patients taking anticholinergic, anticonvulsant, and antidepressant medication or adrenal steroids or β -blockers or ganglionic blockers, MAO inhibitors, phenothiazines, sympathomimetics or vasodilators for long-term therapy (more than 41 days).

Study Plan: This included two stages:

	<u>Duration</u>	<u>Treatment</u>
Stage I:	5 weeks	25 mg chlorthalidone O.D. in the morning
Stage II:	12 weeks	25 mg chlorthalidone and either placebo or one of the following:
		0.5 mg guanfacine)
		1.0 mg guanfacine)
		2.0 mg guanfacine)--O.D. at bedtime
		3.0 mg guanfacine)

In order to be advanced to Stage II a patient had to remain hypertensive (sitting diastolic blood pressure 95-114 mmHg) until the end of Stage I, if not, he was dropped from the study. Stage II was double-blind and the patients were assigned randomly into the 5 treatment groups. Guanfacine dosages for all groups started at 0.5 mg/day. For groups 3-5 the dosage was increased every 3 weeks until it reached the desired level by weeks 8, 10, and 12 respectively. Treatment during Stage II was administered at bedtime because guanfacine causes sedation in some patients which may interfere with the patient's daily activities.

The patients were evaluated at weeks 0, 2, 4, and 5 during Stage I (screening period) and every 2 weeks during Stage II (drug evaluation period). Evaluations were not at fixed times during the day, thus, representing measurements 12 or more hours post-dosing. The evaluated parameters at each study period are summarized in Table XV.

Table XV

Guanfacine-Clinical Protocol 01
Evaluations Schedule: Efficacy and Safety

Type of Evaluation	Week of Study									
	Step I					Step II				
	0	2	4	5	7	9	11	13	15	17
<u>Efficacy</u>										
SISBP/SIDBP/SiHR	X	X	X	X	X	X	X	X	X	X
SISBP/SIDBP/StHR	X	X	X	X	X	X	X	X	X	X
Clinical Adverse Experiences	-	X	X	X	X	X	X	X	X	X
Body Weight	X	X	X	X	X	X	X	X	X	X
Electrocardiogram	X	X	-	X	-	-	-	-	-	-
<u>Safety</u>										
Laboratory										
CBC with Differential	X	-	-	X	-	-	X	-	-	X
Platelets	X	-	-	X	-	-	X	-	-	X
SMAC-16	X	-	-	X	-	-	X	-	-	X
Urinalysis	X	-	-	X	-	-	-	-	-	X
L.E. Test	-	-	-	X	-	-	-	-	-	X
Ophthalmic Exams (optional)	-	-	-	X	-	-	-	-	-	-

SiSBP = sitting systolic blood pressure
 SiDBP = sitting diastolic blood pressure
 SiHR = sitting heart rate
 StSBP = standing systolic blood pressure
 StDBP = standing diastolic blood pressure
 StHR = standing heart rate

Mean arterial pressure was calculated from $2/3$ DBP + $1/3$ SBP. Vital signs (blood pressure and pulse) were recorded 12-18 hours after the last dose of test medication. All data collected in the sitting position reflect an average of the last 3 of 5 measurements as was defined in the protocol. Data in the standing position were collected 2 and 5 minutes after standing erect, but the 2 minute reading was chosen for analysis because it provided a better estimation of orthostatic disturbances. The primary measurement of efficacy was the comparison of the values obtained at the end of Stage II to those obtained at the beginning of this stage just before treatment with guanfacine or placebo was initiated. Data from patients who dropped out of the study prior to week 13 were not included in this analysis since patients in the 1.0, 2.0, and 3.0 mg groups had not reached their pre-specified dosage levels. Data from patients who terminated prematurely between weeks 13-17 were "carried forward" and were included in the endpoint analysis.

The mean values of all efficacy data collected at each of the 10 observation periods were calculated and these results are also included in the efficacy analysis so that the overall responses to treatment over time can be appreciated.

RESULTS:

A total of 462 patients were admitted into Stage I by the 8 investigators. One hundred of these patients were terminated during this stage for the reasons indicated in Table XVI.

Table XVI
Patients Terminated During Stage I

<u>Reason</u>	<u>No. of Pts.</u>
DBP < 90 or > 114 mmHg	49
Clinical Adverse Reactions	12
Abnormal Lab Values	3
Administrative (patient failed to return, missed 20% of medication, etc.)	33
Other	<u>3</u>
	100

One additional patient was lost to follow-up early during Stage II. Thus, actually only 361 patients were treated during Stage II. Eighty (80) patients were terminated prematurely during Stage II for the reasons indicated in Table XVII.

Table XVII
 Patients Terminated Prematurely During Stage II

Investigator	Number of Patients				Completed Study
	Entered	Terminated	Due to Side Effects Clinical	Lab	
Finnerty	43	6	0	1 (+ SGOT)	37
Kessler	67	24	12		43
McMillan	36	4	1		32
Mavlon	30	5	4	1 (+ NPN)	25
Savran	37	7	0		30
Alderman	49	15	12	1 (+ glucose)	34
Canosa	50	9	4		41
Materson	50	10	8		40
	362	80	41	3	282

Other reasons for terminating patients prematurely during Stage II were: treatment failures (6, mainly placebo patients or patients receiving 0.5 mg guanfacine/day), loss to follow-up (7), uncooperation (8), failure to get more than 20% of medication (4), or failure to appear for 2 consecutive visits (4), taking excluded medication (3), intercurrent illness (4), personal reasons (4), (i.e., to have a baby, etc.). Some of the patients were excluded for more than one reason (side effect plus taking excluded medication, etc.).

The distribution of patients by investigator and treatment group is shown in Table XVIII. Comparison of the demographic characteristics of the patients (age, sex, race, height, weight, and mean duration of hypertension) showed no significant differences between the 5 groups as shown in Table XIX (all 362 patients), Table XX (patients who completed the study) and Table XXI (patients who did not complete the study).

Table XVIII

A. H. Robins Co.
Guanfacine-Clinical Protocol 01
Distribution of Patients Included in Endpoint Analysis
By Treatment Group and Investigator

Investigator

Treatment Group	1	2	3	4	5	6	7	8	Total
Placebo	8	11	6	3	7	10	9	9	63
0.5	8	12	7	5	7	6	9	9	63
1.0	7	11	5	5	7	10	9	10	64
2.0	8	9	7	5	6	8	8	7	58
3.0	7	8	7	5	7	9	9	7	59
Total	38	51	32	23	34	43	44	42	307

Table XIX

A. H. Robins Co.
Guanfacine - Clinical Protocol 01
Demography - All Patients

Characteristics	Treatment Groups				
	Placebo	0.5 mg	1.0 mg	2.0 mg	3.0 mg
N =	73	72	72	73	72
Sex: Male	56	53	55	57	49
Female	17	19	17	16	23
Race: Non-Blacks	53	49	46	46	45
Blacks	20	23	25	27	27
Age: Mean ± S.D. (yrs.)	48.6 ± 9.2	46.4 ± 10.2	48.6 ± 8.9	49.5 ± 8.9	47.7 ± 9.2
Height: Mean ± S.D. (in.)	68.3 ± 4.1	68.5 ± 4.1	68.2 ± 3.3	68.8 ± 3.7	68.3 ± 3.9
Weight: Mean ± S.D. (lbs.)	186.4 ± 34.3	187.9 ± 31.4	189.7 ± 34.3	185.8 ± 28.1	189.4 ± 37.2
Duration of Hypertension: Mean=S.D. (yrs.)	7.0 ± 6.0	7.3 ± 7.4	6.6 ± 7.5	6.7 ± 6.3	7.5 ± 7.8

Table XX

A. H. Robins Co.
Guanfacine - Clinical Protocol 01
Demography - Patients Who Completed Study

Characteristics	Treatment Groups				
	Placebo	0.5 mg	1.0 mg	2.0 mg	3.0 mg
N =	55	59	59	54	51
Sex: Male	41	44	46	44	36
Female	14	15	13	10	15
Race: Non-Blacks	40	39	37	34	32
Blacks	15	20	22	20	19
Age: Mean	49.7 ±	45.5 ±	48.9 ±	49.7 ±	47.4 ±
±S.D. (yrs.)	8.1	10.7	9.2	9.1	9.1
Height: Mean	68.2 ±	68.5 ±	68.5 ±	68.9 ±	68.6 ±
± S.D. (in.)	4.5	3.8	3.1	3.7	3.5
Weight: Mean	187.8 ±	187.7 ±	191.4 ±	185.9 ±	193.9 ±
± S.D. (lbs.)	35.9	30.9	33.2	27.6	39.9
Duration of Hypertension: Mean±S.D. (yrs).	6.7 ± 5.8	6.4 ± 7.1	6.1 ± 7.8	7.2 ± 6.5	6.7 ± 6.5

Table XXI

A. H. Robins Co.
Guanfacine - Clinical Protocol 01
Demography - Patients Who Did Not Complete Study

Characteristics	Treatment Groups				
	Placebo	0.5 mg	1.0 mg	2.0 mg	3.0 mg
N =	18	13	13	18	21
Sex: Male	16	9	9	12	13
Female	3	4	4	6	8
Race: Non-Blacks	13	10	9	13	13
Blacks	5	3	4	5	8
Age: Mean	45.4 ±	50.4 ±	47.0 ±	49.1 ±	48.4 ±
±S.D. (yrs.)	11.4	6.4	7.6	8.8	9.6
Height: Mean	68.4 ±	68.0 ±	66.9 ±	68.5 ±	67.6 ±
± S.D. (in.)	3.0	5.2	4.3	4.0	4.8
Weight: Mean	182.3 ±	188.9 ±	182.2 ±	183.5 ±	178.6 ±
± S.D. (lbs.)	29.5	34.7	39.6	30.3	27.6
Duration of Hypertension: Mean±S.D. (yrs).	7.9 ± 7.1	11.4 ± 7.8	9.0 ± 5.2	5.1 ± 5.7	9.4 ± 10.2

The baseline vital signs for all patients, patients who completed the study and for those who did not complete the study are shown in Tables XXII, XXIII, and XXIV, respectively. There were no significant differences in either systolic, diastolic, or mean arterial blood pressure or in heart rate between them.

Table XXII
Guanfacine - Clinical Protocol 01
Baseline Vital Signs - All Patients
Sitting Position

Vital Signs	Treatment Groups				
	Placebo	0.5 mg	1.0 mg	2.0 mg	3.0 mg
N =	73	72	72	73	72
Diastolic BP: Mean \pm S.D. (mmHg)	100.4 \pm 5.3	98.9 \pm 3.9	99.8 \pm 4.6	99.7 \pm 4.7	101.0 \pm 5.3
Systolic BP: Mean \pm S.D. (mmHg)	140.7 \pm 13.9	136.5 \pm 11.5	140.5 \pm 13.7	138.9 \pm 13.6	140.0 \pm 13.4
Mean Arterial BP: Mean \pm S.D. (mmHg)	113.8 \pm 7.1	111.5 \pm 5.3	113.4 \pm 6.2	112.8 \pm 6.4	114.0 \pm 6.6
Heart Rate: Mean \pm S.D. (beats/min)	79.6 \pm 10.7	77.4 \pm 9.2	79.9 \pm 10.2	80.5 \pm 10.7	78.5 \pm 9.1

Table XXIII
 Guanfacine - Clinical Protocol 01
 Baseline Vital Signs - Patients Who Completed Study,
 Sitting Position

Vital Signs	Treatment Groups				
	Placebo	0.5 mg	1.0 mg	2.0 mg	3.0 mg
N =	55	59	59	54	51
Diastolic BP: Mean \pm S.D. (mmHg)	99.5 \pm 4.9	99.1 \pm 4.1	99.9 \pm 4.6	99.6 \pm 4.7	100.3 \pm 5.1
Systolic BP: Mean \pm S.D. (mmHg)	139.1 \pm 13.9	136.2 \pm 11.3	139.9 \pm 13.6	139.4 \pm 14.9	139.8 \pm 12.8
Mean Arterial BP: Mean \pm S.D. (mmHg)	112.7 \pm 6.9	111.5 \pm 5.4	113.2 \pm 6.2	112.9 \pm 6.8	113.5 \pm 6.6
Heart Rate: Mean \pm S.D. (beats/min)	79.1 \pm 10.6	77.4 \pm 9.5	78.8 \pm 8.7	82.2 \pm 10.0	79.2 \pm 9.8

Table XXIV
 Guanfacine - Clinical Protocol 01
 Baseline Vital Signs - Patients Who Did Not Completed Study
 Sitting Position

Vital Signs	Treatment Groups				
	Placebo	0.5 mg	1.0 mg	2.0 mg	3.0 mg
N =	18	13	13	18	21
Diastolic BP: Mean \pm S.D. (mmHg)	103.1 \pm 5.8	98.4 \pm 2.3	99.3 \pm 5.0	99.1 \pm 3.4	102.7 \pm 5.6
Systolic BP: Mean \pm S.D. (mmHg)	145.3 \pm 13.3	137.9 \pm 12.6	143.2 \pm 14.6	137.1 \pm 8.2	140.5 \pm 15.0
Mean Arterial BP: Mean \pm S.D. (mmHg)	117.1 \pm 7.2	111.6 \pm 4.7	113.9 \pm 6.6	111.7 \pm 4.2	115.3 \pm 6.4
Heart Rate: Mean \pm S.D. (beats/min)	81.2 \pm 11.3	77.5 \pm 8.3	84.6 \pm 14.8	75.2 \pm 11.6	77.1 \pm 7.2

The effect of the various dosages of guanfacine on the diastolic, systolic, and mean arterial blood pressures and on the heart rate in the sitting position is shown in Tables XXV, XXVI, XXVII, and XXVIII and is illustrated in Figs. 11, 12, 13, and 14. Tables XXIX, XXX, XXXI, and XXXII and Figs. 15, 16, 17, and 18 show the respective effects in the standing position.

Table XXV

Guanfacine - Clinical Protocol 01
Response Criterion = Diastolic Blood Pressure
Dose Group Means by Week of Study
Sitting Position

Week of Study	Statistic	Patient Randomized	Dose Group				
			Placebo	0.5	1.0	2.0	3.0
Baseline	N	361	-	-	-	-	-
	Mean	99.9					
2	N	-	70	282	-	-	-
	Mean		94.3	89.9			
4	N	-	69	66	198	-	-
	Mean		93.0	91.5	86.7		
6	N	-	65	62	65	125	-
	Mean		93.8	91.2	86.7	85.4	
8	N	-	60	62	62	58	59
	Mean		91.5	92.6	86.6	85.5	86.0
10	N	-	59	58	60	54	54
	Mean		92.3	91.3	87.0	86.4	86.0
12	N	-	57	59	60	54	52
	Mean		91.9	92.8	86.9	86.0	87.3

Figure 11

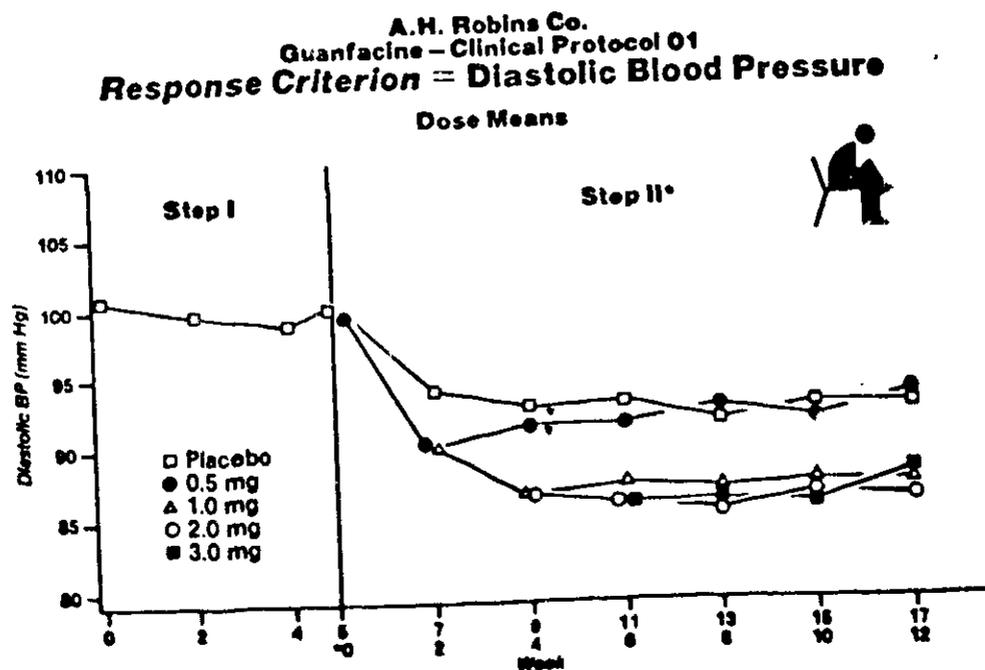


Table XXVI

Guanfacine - Clinical Protocol 01
 Response Criterion = Systolic Blood Pressure
 Dose Group Means by Week of Study
 Sitting Position

Week of Study	Statistic	Patient Randomized	Dose Group				
			Placebo	0.5	1.0	2.0	3.0
Baseline	N	361	-	-	-	-	-
	Mean	139.3					
2	N	-	70	282	-	-	-
	Mean		137.8	130.6			
4	N	-	69	66	198	-	-
	Mean		137.0	130.2	126.4		
6	N	-	65	62	65	125	-
	Mean		133.2	130.5	125.3	123.7	
8	N	-	60	62	62	58	59
	Mean		133.7	131.7	128.5	125.0	122.1
10	N	-	59	58	60	54	54
	Mean		135.6	130.8	127.0	125.4	124.1
12	N	-	57	59	60	54	52
	Mean		134.4	131.3	126.3	126.9	123.8

Figure 12

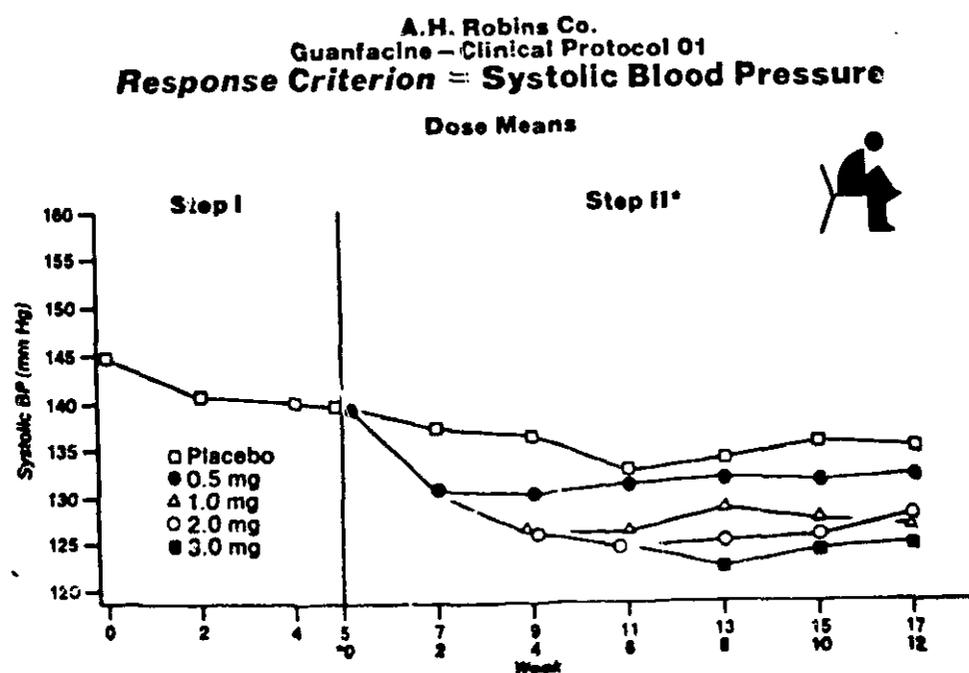


Table XXVII

Guanfacine - Clinical Protocol 01
 Response Criterion = Mean Arterial Pressure
 Dose Group Means by Week of Study
 Sitting Position

Week of Study	Statistic	Patient Randomized	Dose Group				
			Placebo	0.5	1.0	2.0	3.0
Baseline	N	361	-	-	-	-	-
	Mean	113.1					
2	N	"	70	282	-	-	-
	Mean		108.8	103.5			
4	N	-	69	66	198	-	-
	Mean		107.7	104.4	100.0		
6	N	-	65	62	65	125	-
	Mean		106.9	104.3	99.6	98.2	
8	N	-	60	62	62	58	59
	Mean		105.6	105.6	100.7	98.7	98.0
10	N	-	59	58	60	54	54
	Mean		106.7	104.5	100.3	99.4	98.7
12	N	-	57	59	60	54	52
	Mean		106.1	105.6	100.0	99.6	99.5

Figure 13

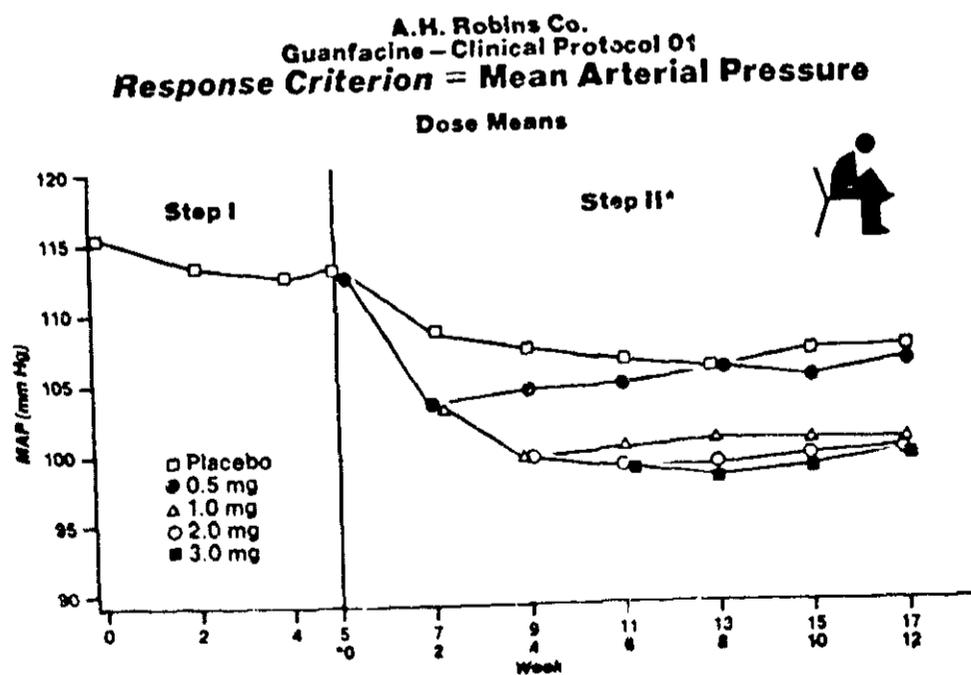


Table XXVIII

Guanfacine - Clinical Protocol 01
 Response Criterion = Heart Rate
 Dose Group Means by Week of Study
 Sitting Position

Week of Study	Statistic	Patients Randomized	Dose Group				
			Placebo	0.5	1.0	2.0	3.0
Baseline	N	361	-	-	-	-	-
	Mean	79.2					
2	N	-	70	282	-	-	-
	Mean		80.4	77.0			
4	N	-	69	66	198	-	-
	Mean		81.2	79.1	75.6		
6	N	-	65	62	65	124	-
	Mean		79.6	77.8	75.8	72.7	
8	N	-	60	62	62	58	59
	Mean		79.5	78.7	76.7	73.6	74.7
10	N	-	59	58	60	54	54
	Mean		77.7	77.1	74.9	74.1	74.4
12	N	-	57	59	60	54	52
	Mean		80.3	79.1	74.3	76.5	75.0

Figure 14

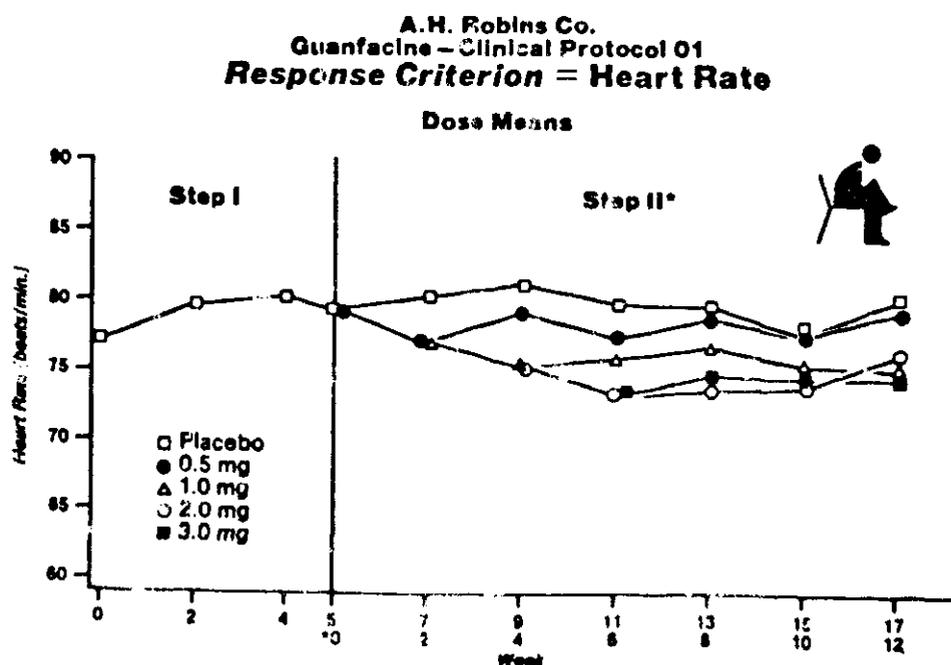


Table XXIX

Guanfacine - Clinical Protocol 01
 Response Criterion = Diastolic Blood Pressure
 Dose Group Means by Week of Study
 Standing Position

Week of Study	Statistic	Patients Randomized	Dose Group				
			Placebo	0.5	1.0	2.0	3.0
Baseline	N	361	-	-	-	-	-
	Mean	101.7					
2	N	-	70	282	-	-	-
	Mean		98.7	93.5			
4	N	-	69	66	198	-	-
	Mean		96.9	95.4	90.5		
6	N	-	65	62	65	124	-
	Mean		98.7	95.0	90.3	89.8	
8	N	-	60	62	62	58	59
	Mean		96.6	97.8	90.4	88.8	89.2
10	N	-	59	58	60	54	54
	Mean		96.9	95.7	90.1	90.9	89.7
12	N	-	57	59	60	54	52
	Mean		95.3	96.6	91.3	91.0	90.8

Figure 15

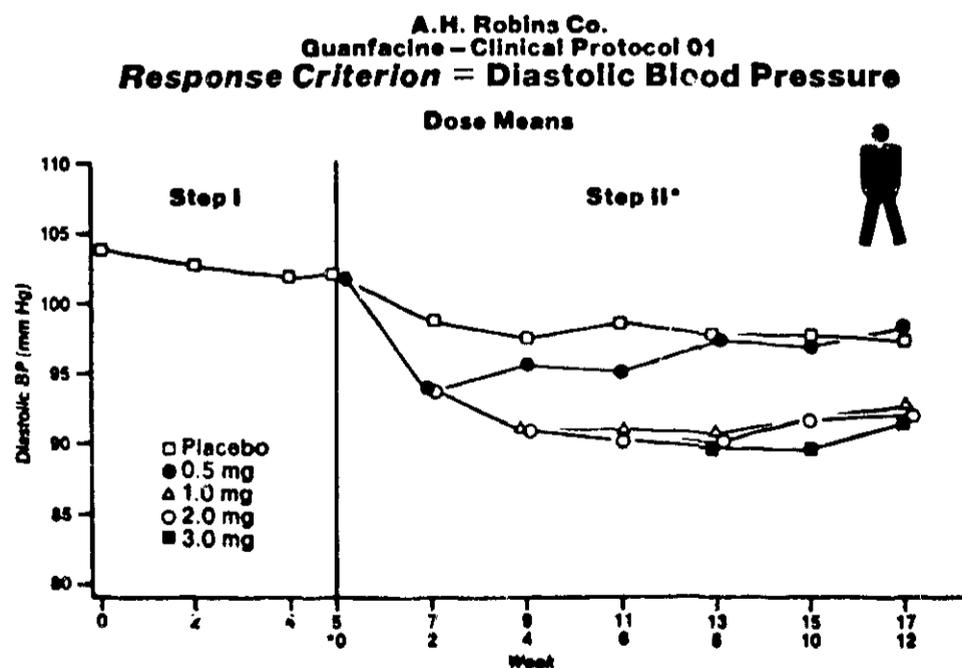


Table XXX

Guanfacine - Clinical Protocol 01
 Response Criterion = Systolic Blood Pressure
 Dose Group Means by Week of Study
 Standing Position

Week of Study	Statistic	Patients Randomized	Dose Group				
			Placebo	0.5	1.0	2.0	3.0
Baseline	N	361	-	-	-	-	-
	Mean	139.6					
2	N	-	70	282	-	-	-
	Mean		140.1	132.4			
4	N	-	69	66	198	-	-
	Mean		137.2	132.2	127.5		
6	N	-	65	62	65	124	-
	Mean		135.2	130.8	126.3	125.7	
8	N	-	60	62	62	58	59
	Mean		135.6	134.5	128.2	126.6	123.0
10	N	-	59	58	60	54	54
	Mean		135.9	130.4	127.5	127.5	125.3
12	N	-	57	59	60	54	52
	Mean		135.5	132.5	129.6	128.9	124.3

Figure 16

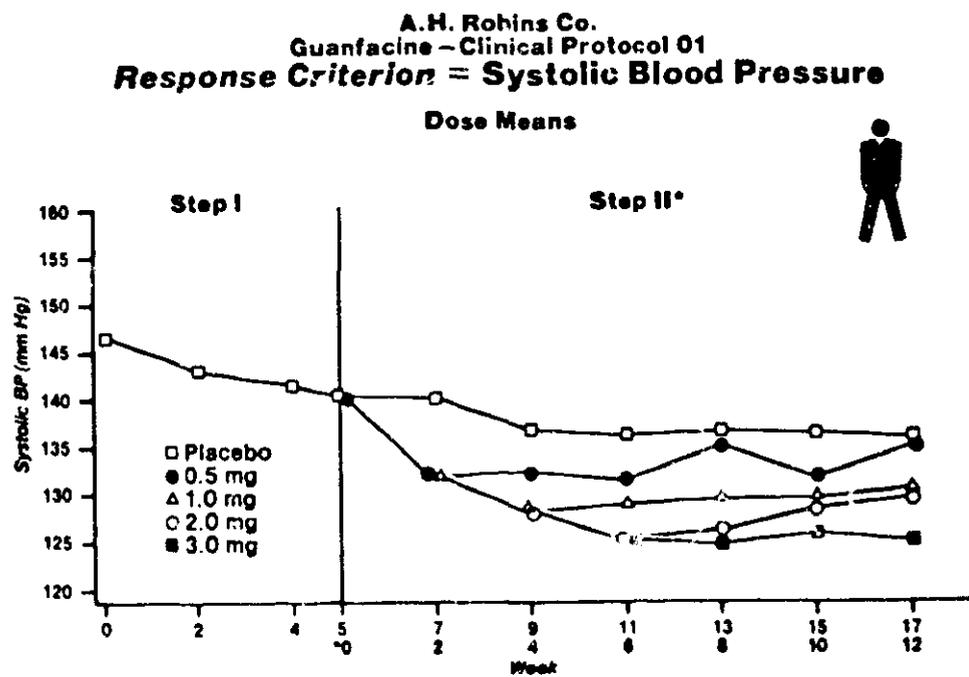


Table XXXI

Guanfacine - Clinical Protocol 01
 Response Criterion = Mean Arterial Pressure
 Dose Group Means by Week of Study
 Standing Position

Week of Study	Statistic	Patients Randomized	Dose Group				
			Placebo	0.5	1.0	2.0	3.0
Baseline	N	361	-	-	-	-	-
	Mean	114.3					
2	N	-	70	282	-	-	-
	Mean		112.5	106.5			
4	N	-	69	66	198	-	-
	Mean		110.3	107.7	102.8		
6	N	-	65	62	65	124	-
	Mean		110.9	106.9	102.3	101.7	
8	N	-	60	62	62	58	59
	Mean		109.6	110.0	113.0	101.4	100.5
10	N	-	59	58	60	54	54
	Mean		109.9	107.3	102.6	103.1	101.5
12	N	-	57	59	60	54	52
	Mean		108.7	108.6	104.1	103.6	102.0

Figure 17

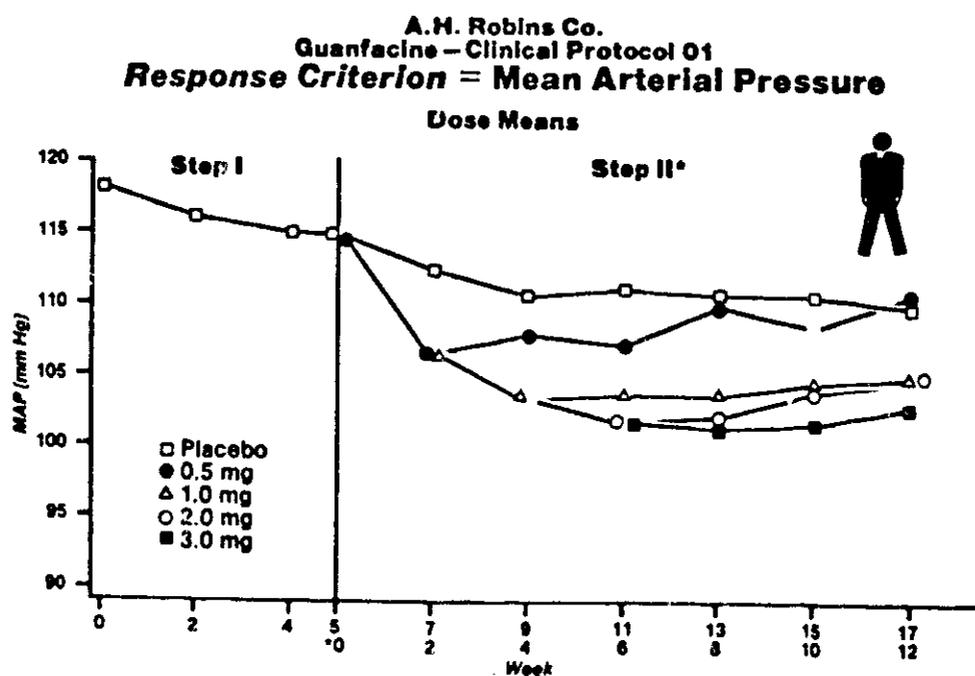
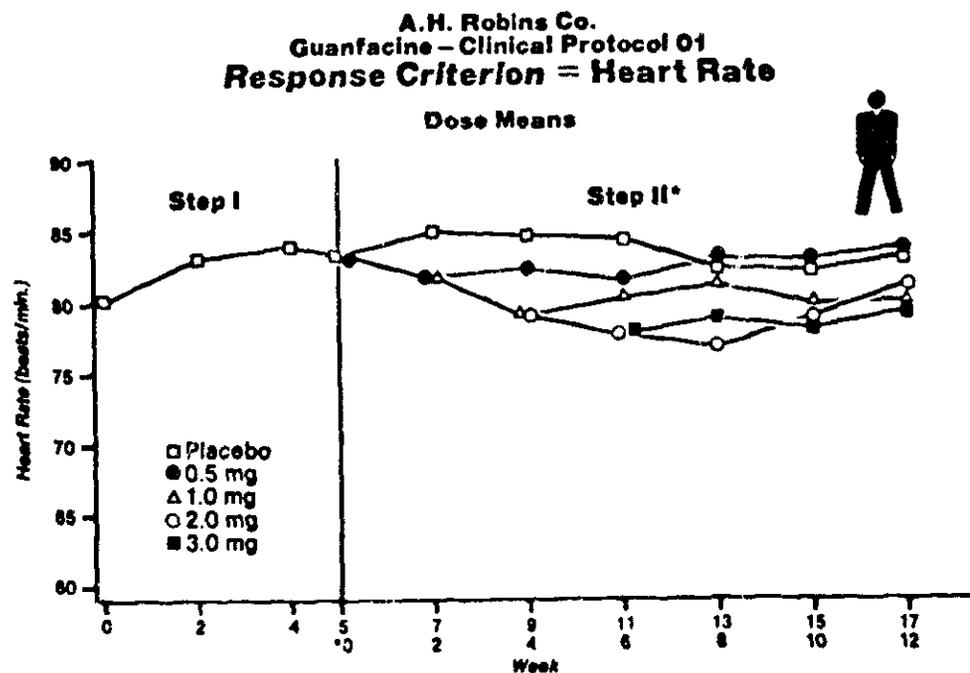


Table XXXII

Guanfacine - Clinical Protocol 01
 Response Criterion = Heart Rate
 Dose Group Means by Week of Study
 Standing Position

Week of Study	Statistic	Patient Randomized	Dose Group				
			Placebo	0.5	1.0	2.0	3.0
Baseline	N	361	-	-	-	-	-
	Mean	82.8	-	-	-	-	-
2	N	-	70	282	-	-	-
	Mean	-	85.2	81.4	-	-	-
4	N	-	69	66	198	-	-
	Mean	-	84.2	81.9	79.3	-	-
6	N	-	65	62	65	123	-
	Mean	-	84.4	81.6	79.7	77.1	-
8	N	-	60	62	62	58	59
	Mean	-	82.5	82.5	80.6	76.6	78.9
10	N	-	59	58	60	54	54
	Mean	-	81.8	82.5	78.6	78.7	78.5
12	N	-	57	59	60	54	52
	Mean	-	82.9	83.1	78.5	81.3	79.9

Figure 18



The results show that significant reductions in blood pressure were obtained with daily dosages of 1.0, 2.0, and 3.0 mg of guanfacine, while the 0.5-mg dosage was less effective, causing no significant reduction in pressure. The effect of the 1-3 mg dosages was similar, especially on diastolic pressure, where increasing the dosage from 1 to 3 mg gave no suggestion of an increased effect. There was, however, some indication of an increased effect on systolic pressure at the highest dose although the difference was not significant. Heart rate was decreased by 1-6 beats/min. Again, there was no significant difference between the effects of the 1-3 mg dosages.

Endpoint mean changes for each of the vital signs in the sitting and standing positions are shown in Tables XXXIII and XXXIV respectively. Addition of guanfacine at 1-3 mg to a regimen of 25 mg chlorthalidone per day reduced the diastolic, systolic and mean arterial pressure in the sitting position by 13, 12-16 and 13-14 mmHg respectively. The respective changes in the standing position were 9-12, 10-15, and 10-13 mmHg. The changes in heart rate were 4-5 beats/min in both positions.

Statistical analysis of the results in the sitting (Table XXXV) and standing position (Table XXXVI) showed that the reductions induced by the 1.0-3.0 mg dosages were statistically significant.

Table XXXIII

Guanfacine - Clinical Protocol 01
Endpoint Means by Treatment Group
Sitting Position

Response Criteria	Statistic	Treatment Group				
		Placebo	0.5	1.0	2.0	3.0
Diastolic Blood Pressure	N	63	63	64	58	59
	Mean	92.8	93.5	87.3	86.1	87.6
	Mean Change	-7.1	-5.6	-12.7	-13.3	-13.1
Systolic Blood Pressure	N	63	63	64	58	59
	Mean	134.5	132.5	126.5	127.6	124.2
	Mean Change	-4.7	-4.7	-14.0	-11.6	-15.6
Mean Arterial Pressure	N	63	63	64	58	59
	Mean	106.7	106.5	100.4	99.9	99.8
	Mean Change	-6.3	-5.3	-13.1	-12.8	-13.9
Heart Rate	N	63	63	64	58	59
	Mean	80.4	79.4	75.1	76.2	74.6
	Mean Change	+1.2	+2.1	-4.4	-4.7	-4.5

Table XXXIV

Guanfacine - Clinical Protocol 01
Endpoint Means by Treatment Group
Standing Position

Response Criteria	Statistic	Treatment Group				
		Placebo	0.5	1.0	2.0	3.0
Diastolic Blood Pressure	N	63	63	64	58	59
	Mean	96.3	97.2	92.0	91.2	91.1
	Mean Change	-5.5	-3.7	-8.9	-10.0	-11.7
Systolic Blood Pressure	N	63	63	64	58	59
	Mean	135.5	133.4	130.1	129.8	124.7
	Mean Change	-3.3	-4.9	-10.7	-9.5	-15.0
Mean Arterial Pressure	N	63	63	64	58	59
	Mean	109.4	109.3	104.7	104.0	102.3
	Mean Change	-4.8	-4.1	-9.5	-9.8	-12.8
Heart Rate	N	63	63	64	58	59
	Mean	83.3	83.2	79.3	80.9	79.5
	Mean Change	+2.1	+1.3	-3.9	-4.6	-3.7

Table XXXV

Guanfacine - Clinical Protocol 01
Statistical Analyses of Endpoint Efficacy Results
Sitting Position

Response Criterion	Treatment Effect ($\alpha=.05$)	4 Contrasts ($\alpha_1 = .05/4 = .0125$)			
		0 vs 0.5	0 vs 1.0	0 vs 2.0	0 vs 3.0
Diastolic Blood Pressure	p<.05	NS	p<.0125	p<.0125	p<.0125
Systolic Blood Pressure	p<.05	NS	p<.0125	p<.0125	p<.0125
Mean Arterial Pressure	p<.05	NS	p<.0125	p<.0125	p<.0125
Heart Rate	p<.05	NS	p<.0125	p<.0125	p<.0125

Table XXXVI
 Guanfacine - Clinical Protocol 01
 Statistical Analyses of Endpoint Efficacy Results
 Standing Position

Response Criterion	Treatment Effect	4 Contrasts ($\alpha = .05/4 = .0125$)			
		0 vs 0.5	0 vs 1.0	0 vs 2.0	0 vs 3.0
Diastolic Blood Pressure	p<.05	NS	p=0.042	p<.0125	p<.0125
Systolic Blood Pressure	p<.05	NS	p<.0125	p=0.025	p<.0125
Mean Arterial Pressure	p<.05	NS	p<.0125	p<.0125	p<.0125
Heart Rate	p<.05	NS	p<.0125	p<.0125	p<.0125

Dose Response: The dose response curves for group mean blood pressures and heart rate at the end of the study (week 12) as a function of assigned dose are shown in Figures 19-26. It appears that the effect on the standing blood pressure increases with dosage although the differences between the 1.0-, 2.0-, and 3.0-mg dosages were not statistically significant, while there is little evidence of an increased diastolic pressure response with dose.

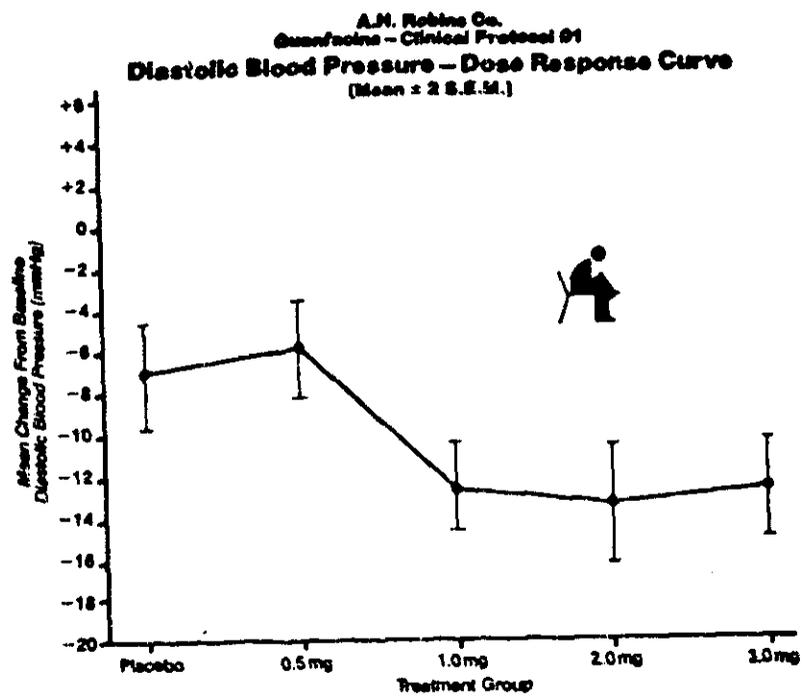


Figure 19

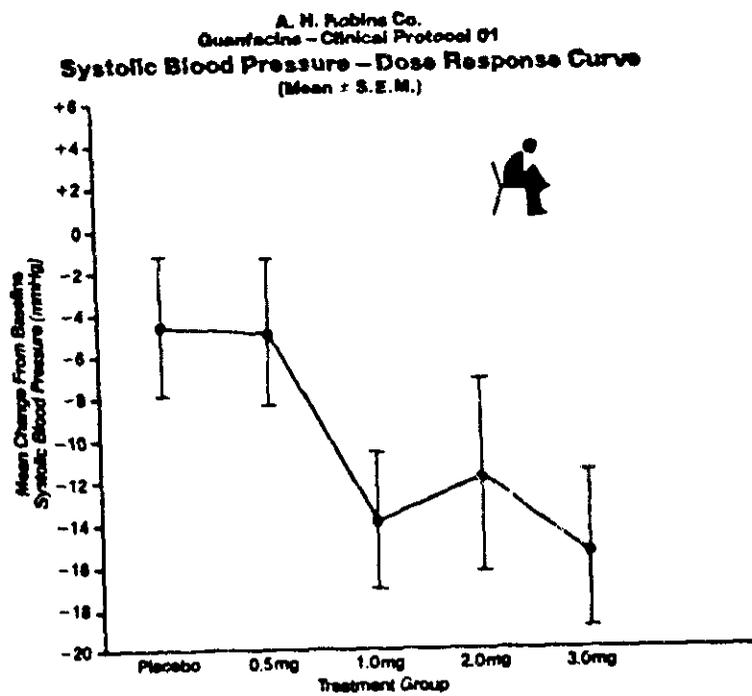


Figure 20

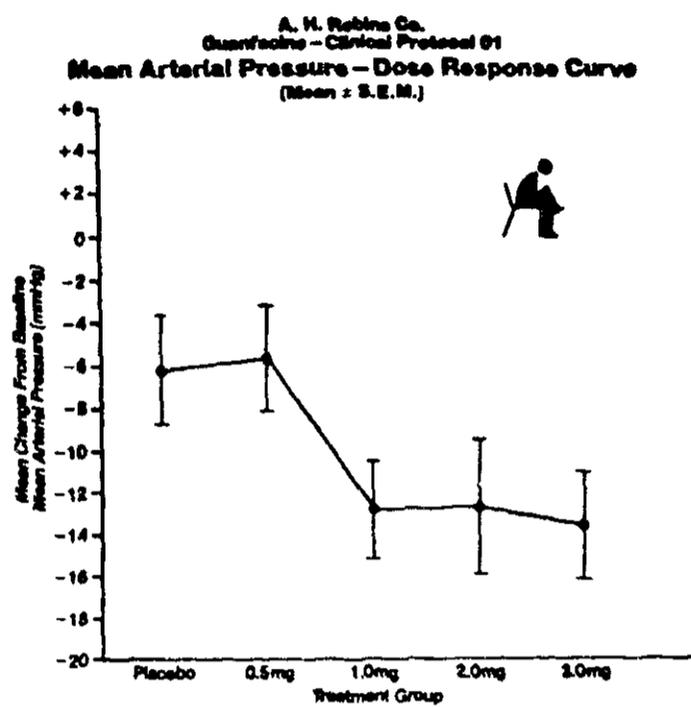


Figure 21

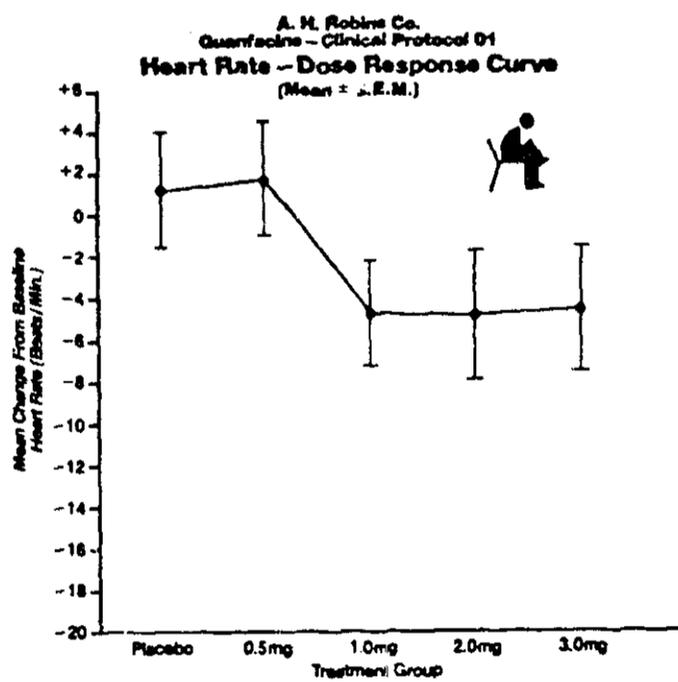


Figure 22

A. H. Robins Co.
Quarfaine - Clinical Protocol 01
Diastolic Blood Pressure - Dose Response Curve
(Mean \pm S.E.M.)

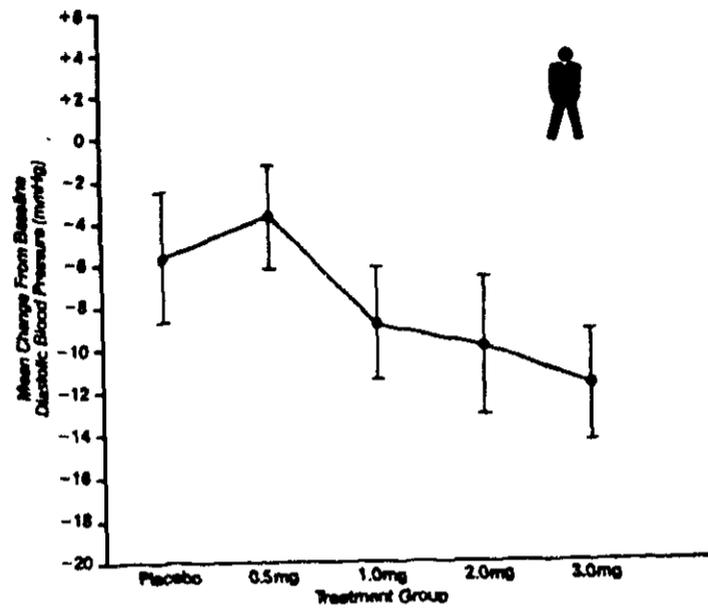


Figure 23

A. H. Robins Co.
Quarfaine - Clinical Protocol 01
Systolic Blood Pressure - Dose Response Curve
(Mean \pm S.E.M.)

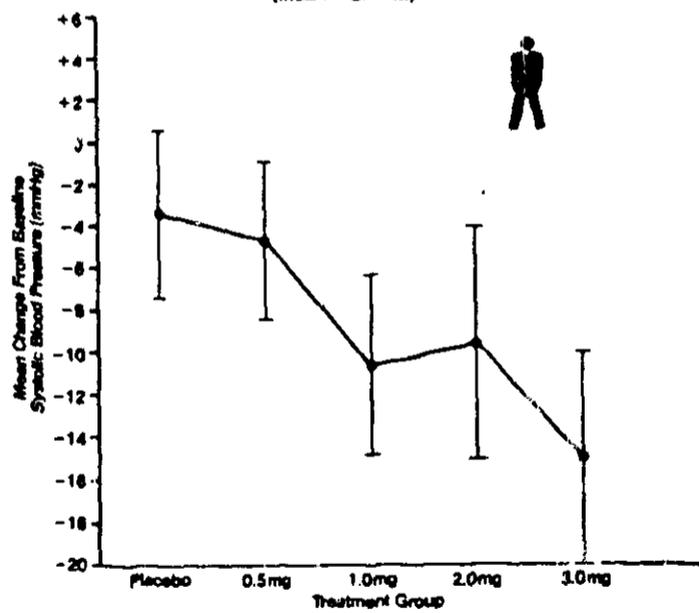


Figure 24

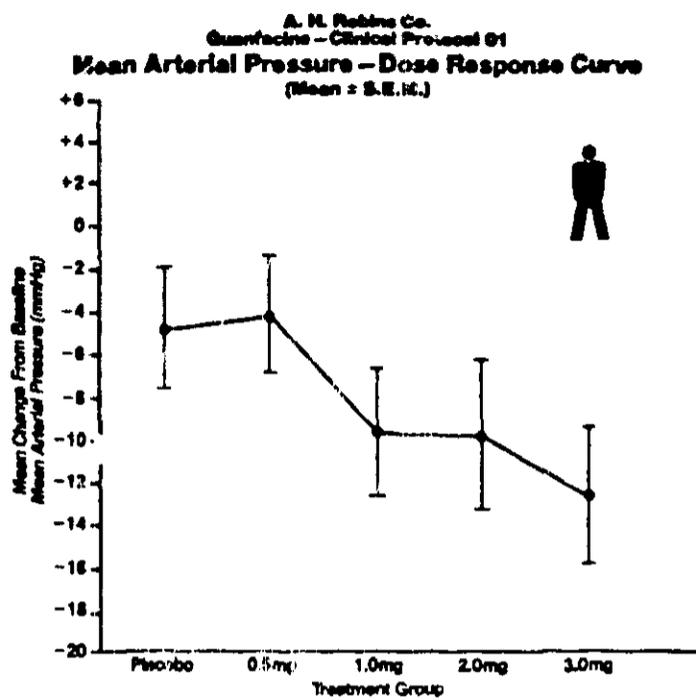


Figure 25

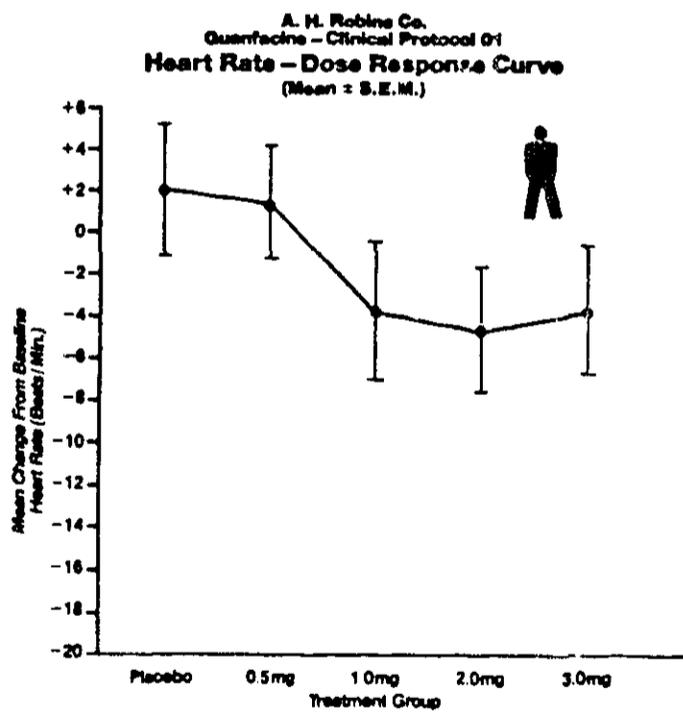


Figure 26

The endpoint mean diastolic blood pressures in the sitting position are tabulated in Table XXXVII according to the degree of the baseline diastolic pressures (95-99, 100-104, and greater than 104 mmHg). It is obvious that the lower the initial pressure was, the lower were the levels that the endpoint pressure reached, which suggest that the reductions in blood pressure due to guanfacine were the same in all 3 groups (a mean of about 12 mmHg). Table XXXVIII shows that the percentage of patients who reached an endpoint diastolic pressure less than 90 mmHg was inversely proportional to the degree of the baseline blood pressure. It also shows that the placebo effect was significant: 50% of the patients who had baseline diastolic blood pressure between 95-99 mmHg and 24% of those who had pressures between 110-114 mmHg became normotensive after taking placebo (in addition to chlorthalidone). Guanfacine at 0.5 mg/day was actually less effective (43% and 11% respectively) than placebo.

Table XXXVII

Guanfacine - Clinical Protocol 01
Response Criterion = Diastolic Blood Pressure
Mean Endpoint By Treatment Group and Baseline Value
Sitting Position
(mmHg)

Baseline	Treatment Groups (mg)									
	Placebo	Δ	0.5	Δ	1.0	Δ	2.0	Δ	3.0	Δ
95- 99	89.1 n=42	-8.0	91.1 n=44	-6.0	84.9 n=37	-12.0	85.0 n=40	-12.1	83.6 n=31	-13.3
100-104	96.7 n=12	-4.5	98.5 n=11	-3.0	87.9 n=16	-13.0	88.6 n=9	-12.3	92.2 n=16	- 9.2
>104	105.2 n=9	-6.1	100.6 n=8	-7.5	94.4 n=11	-14.6	89.1 n=9	-19.7	92.3 n=12	-17.8

Table XXXVIII

Guanfacine - Clinical Protocol 01
 Response Criteria = Diastolic Blood Pressure
 Number of Patients With Endpoint Diastolic
 Blood Pressure < 90 mmHg
 Sitting Position

Baseline Diastolic Blood Pressure (mmHg)	Treatment Group				
	Placebo	0.5	1.0	2.0	3.0
95- 99	50% n=42	43% n=44	73% n=37	68% n=40	71% n=31
100-114	24% n=21	11% n=19	41% n=27	61% n=18	39% n=28

Side Effects: Table XXXIX shows that only the higher dosages of guanfacine (2 and 3 mg/day) caused a clearly higher incidence of side effects than placebo. The 1.0-mg dose could not be distinguished from placebo. The most frequent side effects observed, especially at high dosages, were dry mouth, somnolence, and asthenia. It should be noted that because of the study design, patients assigned to the 3.0 mg/day group could also have experienced an adverse effect at a lower dose of guanfacine.

Table XL displays the frequency distribution of patients who were discontinued prematurely because of adverse experiences according to the dose level of the drug at the time of termination. There were no significant differences in the percentage of patients who were terminated because of side effects between the placebo and the 2.0 and 3.0 mg of guanfacine/day groups. This suggests that the side effects caused by guanfacine are rather mild and that patients can tolerate them.

Table XXXIX

Guanfacine - Clinical Protocol 01
 Frequency Distribution of Patients with
 Most Common Adverse Experiences
 (Possibly or Probably Related Only)

Adverse Experience	Assigned Treatment Group				
	Placebo	0.5 mg	1.0 mg	2.0 mg	3.0 mg
	←----- 25 mg Chlorthalidone-----→				
N =	73	72	72	72	72
Dry Mouth	5	4	6	8	20
Somnolence	1	3	0	1	10
Asthenia	0	2	0	2	7
Dizziness	2	1	3	6	3
Headache	3	4	3	1	2
Impotence	1	1	0	1	3

Table XL

Guanfacine - Clinical Protocol 01
 Premature Terminations Because of Adverse Experiences
 Frequency Distribution of Patients

Week of Study	Dosage at Time of Termination				
	Placebo	0.5 mg	1.0 mg	2.0 mg	3.0 mg
	←----- 25 mg Chlorthalidone-----→				
2	0	8	-	-	-
4	0	2	5	-	-
6	1	0	1	10	-
8	1	1	1	0	3
10	3	1	0	1	3
12	0	0	0	0	0
Totals	5/73 6.9%	12/288 4.2%	7/216 3.2%	11/144 7.6%	6/72 8.3%

Tables XLI - XLV identify the individual patients in each group who experienced adverse reactions and the type of the reaction.

Table XLI

Guanfacine - Clinical Protocol 01
Adverse Experiences as Reasons for Discontinuation of Placebo

Number of Patients with Adverse Experiences: 5
Number of Adverse Experiences : 6

<u>Patient Identification</u>	<u>Adverse Experience</u>
1403	hypertension
1406	nausea and vomiting
1604	headache
1709	fatigue
1816	somnolence

Table XLII

Guanfacine - Clinical Protocol 01
Adverse Experiences as Reasons for Discontinuation of Guanfacine
at the 0.5 mg Dosage Level

Number of Patients with Adverse Experiences: 12
Number of Adverse Experiences : 23

<u>Patient Identification</u>	<u>Adverse Experience</u>
12004	syncope
12014	headache, abnormal vision
12012	impotence
12019	conjunctivitis and iritis
12024	pain, headache and nausea
1411	impotence
1621	dry mouth, weight decrease and polyuria
1643	asthenia and nervousness
1615	urinary incontinence
1605	insomnia
1646	headache and dizziness
1707	asthenia, dizziness, headache and somnolence

Table XLIII

Guanfacine - Clinical Protocol 01
Adverse Experiences as Reasons for Discontinuation of Guanfacine
at the 1.0 mg Dosage Level

Number of Patients with Adverse Experiences: 7
Number of Adverse Experiences : 12

<u>Patient Identification</u>	<u>Adverse Experience</u>
12001	dermatitis
1325	dizziness and nausea
1425	dry mouth and headache
1639	dizziness and headache
1623	pain, paresis and insomnia
1718	paraesthesia
1817	asthenia

Table XLIV

Guanfacine - Clinical Protocol 01
Adverse Experiences as Reasons for Discontinuation of Guanfacine
at the 2.0 mg Dosage Level

Number of Patients with Adverse Experiences: 11
Number of Adverse Experiences : 29

<u>Patient Identification</u>	<u>Adverse Experience</u>
12052	constipation, taste perversion, and purpura
12027	bradycardia, dry mouth, dizziness and somnolence
12020	dry mouth, asthenia and somnolence
12073	dry mouth and substernal chest pain
12005	headache, vertigo and nausea
1421	asthenia, fatigue and depression
1835	asthenia
1802	somnolence and dry mouth
1810	dry mouth, asthenia, abdominal pain, taste perversion and somnolence
1825	dizziness and paraesthesia
1826	impotence

Table XLV

Guanfacine - Clinical Protocol 01
Adverse Experiences as Reasons for Discontinuation of Guanfacine
at the 3.0 mg Dosage Level

Number of Patients with Adverse Experiences: 6

Number of Adverse Experiences : 15

<u>Patient Identification</u>	<u>Adverse Experience</u>
12015	dry mouth, insomnia, somnolence and dermatitis
1601	dry mouth, dizziness and somnolence
1625	asthenia and somnolence
1635	asthenia
1636	asthenia and somnolence
1728	dry mouth, dysphagia and constipation

Laboratory Evaluations: There were no clinically significant changes in the mean values of any of the laboratory parameters which were evaluated. Two patients were discontinued from the study because of adverse lab results. One of these had received placebo and was discontinued because he had an elevated non-protein-N and albuminuria. The other, who was receiving a dose of 0.5 mg, developed dry mouth, polyuria and hyperglycemia at week 13. A third patient was discontinued at week 7 because of a high SGOT (605 units) but this patient had already a high value (244) at baseline. Similarly there were no significant changes in the ECG and ophthalmologic (slit lamp and intraocular pressure) evaluations.

Conclusion: This well-controlled, dose-response study shows that guanfacine is safe and effective with dose-related antihypertensive activity when used in combination with 25 mg of chlor-thalidone.

* * * * *

- b. A Multi-Investigator, Double-blind, Randomized, and Parallel Clinical Study of Guanfacine Versus Placebo to Demonstrate the 24-Hour Duration of Effectiveness of Guanfacine for Treatment of Essential Hypertension (Study No. 02).

This study was similar in many respects to the previous one (Study 01) and was carried out by the following 8 investigators.

Paul Black, M.D.	LaJolla, CA
J.C. Freudenburg, M.D.	Longmont, CO
Joseph Hill, M.D.	Vero Beach, FL
C.E. Holmberg, M.S.	Menomonee Falls, WI
Michael Rietbrock, M.D.	Oconomowoc, WI
Maurice Sullivan, M.D.	Lafayette, LA
Mark Thompson, M.D.	Redondo Beach, CA
David Wright, M.D.	Rockford, IL

As in the previous study the design included two stages, the screening phase (Stage I) of 5 weeks duration (when the patients were weaned from any previous antihypertensive medication and were started on chlorthalidone 25 mg/day) and the treatment phase (Stage II) of 12 weeks duration. During this second stage the patients were stratified in either the A.M. or the P.M. group and then randomized double-blindly to receive guanfacine or placebo. Thus, there were two placebo and two guanfacine groups in this study. One pair was evaluated at 9 o'clock in the morning and the other at 9 o'clock in the evening (before taking their medication). Both groups ingested their assigned medications at 9 P.M. The starting guanfacine dosage was 1 mg/day. It could be titrated up in 1 mg increments (maximum 3 mg/day) or down at 3-week intervals. To maintain blindness, placebo was matched to the different doses of guanfacine and patients could be "titrated up or down" with placebo.

The inclusion and exclusion criteria, the evaluated parameters and the frequency and methodology of evaluation were the same as in the study 01.

Results

A total of 345 patients were admitted into the first phase. Of these, 96 (28%) were terminated during this phase because of:

Sitting diastolic Blood Pressure <90 mmHg:	64
Clinical Adverse Reactions:	3
Laboratory Adverse Reactions:	5
Other reasons (lost to follow-up, uncooperation or unreliability, intercurrent illness, use of excluded medication, etc.):	24
	<hr/> 96

The remaining 249 patients entered the 12-week evaluation period. Four patients were terminated before week 2. Thus data from only 245 patients were evaluated for efficacy. The distribution of these patients by treatment group and investigator is shown in Table XLVI and their demographic characteristics in Table XLVII. It can be seen that there were no significant differences between the placebo and the guanfacine group regarding sex, race, age, or duration of hypertension.

Table XLVI

Distribution of Patients Included in Endpoint Analysis
By Treatment Group and Investigator

Treatment Group	Investigator								Total
	1	2	3	4	5	6	7	8	
Placebo									
A.M.	9	8	5	7	9	7	4	9	58
P.M.	6	7	8	9	9	8	8	7	62
Guanfacine									
A.M.	9	8	7	7	9	7	5	8	60
P.M.	8	8	8	9	10	7	7	8	65
Total	32	31	28	32	37	29	24	32	245

Table XLVII

Demography - All Patients

Characteristic	Treatment Group	
	Guanfacine	Placebo
Number of Patients	125	121
Sex: Male	80	76
Female	45	45
Race: Non-Blacks	122	116
Blacks	3	5
Age: Mean (SD) yrs.	46.4 (9.34)	48.3 (7.85)
Height: Mean (SD) in.	68.4 (3.61)	68.6 (3.85)
Weight: Mean (SD) lbs.	188.3 (34.33)	190.3 (33.32)
Duration of Hypertension: Mean (SD) yrs.	7.3 (7.34)	8.3 (5.85)

Twenty-two additional patients were terminated later during the same phase for reasons listed below (Table XLVIII includes the 3 patients who were terminated earlier):

Table XLVIII

	A.M.		P.M.	
	Placebo	Guanfacine	Placebo	Guanfacine
Clinical Adverse Reactions:				
Miscellaneous*	<u>1</u> 6	<u>3</u> 2	<u>1</u> 5	<u>5</u> 2
Total	7	5	6	7

*(Lost to follow-up, high blood pressure, intercurrent illness, etc.)

Efficacy Data

A.M. Evaluation Groups. Results from 118 patients, who were evaluated in the morning at 9 a.m., i.e., 12 hours after they had received their medication, have been reported. Sixty of these patients had received guanfacine and 58 had received placebo. The two groups were comparable regarding blood pressure and heart rate at baseline as shown in Table XLIX. The blood

Table XLIX

Baseline Vital Signs - All Patients
Efficacy Analysis Group = A.M.

Vital Sign	Treatment Group	
	Guanfacine	Placebo
Number of Patient	60	58
Diastolic Blood Pressure mean (s.d.) mmHg	98.4 (4.80)	99.8 (4.37)
Systolic Blood Pressure mean (s.d.) mmHg	142.3 (13.78)	141.9 (12.32)
Mean Arterial Pressure mean (s.d.) mmHg	113.0 (6.47)	113.8 (5.82)
Heart Rate mean (s.d.) beats/min.	79.1 (11.12)	81.2 (9.08)

pressures decreased in both groups during the treatment period. The mean diastolic blood pressure of the placebo group fell from 99.1 mmHg to 93.5 mmHg at the end of 12 weeks of treatment (Table L, Fig. 27) in the sitting position and from 100 mmHg to 96.0 mmHg in the standing position (Table LI, Fig. 28), i.e., it dropped by a mean value of 5.6 and 4.0 mmHg respectively. The diastolic blood pressure of the guanfacine group dropped by 14.0 mmHg in the sitting position and by 12.2 mmHg in the standing position (Tables LI and Figs. 27 and 28). Statistical analysis of the differences, about 8 mmHg, were not reported. It appears, however, that these differences are significant.

Similar changes were reported regarding the systolic blood pressure (Tables LII and LIII; Figs. 29 and 30). The mean systolic blood pressure in the placebo group fell from 142.1 mmHg to 136.4 (-5.7 mmHg) in the sitting position and from 140.4 to 137.0 (-3.4) mmHg in the standing position. The respective reductions in the guanfacine group were 16.2 and 14.9 mmHg, i.e., about 10-11 mmHg greater than the placebo group. The heart rate was decreased by guanfacine by 8.1 (sitting) and 6.5 (standing) beats/minute from around 80 to 72-77 beats per minute (Tables LIV and LV; Figs. 31 and 32).

Thus, compared to placebo, guanfacine gave a fall in blood pressure of 10-11/8 mmHg and a change in heart rate of about -5 beats per minute.

Table L

Response Criterion = Diastolic Blood Pressure
 Treatment Group Means by Week of Study
 Efficacy Analysis Group = A.M.
 Sitting Position

Week of Study	Statistic	Patients Randomized	Treatment Groups	
			Guanfacine	Placebo
Baseline	N	118	-	-
	Mean	99.1	-	-
1.5	N	-	60	58
	Mean	-	88.3	95.3
3	N	-	60	58
	Mean	-	87.1	95.0
6	N	-	60	57
	Mean	-	87.7	93.2
9	N	-	56	54
	Mean	-	86.2	93.6
12	N	-	56	52
	Mean	-	85.1	93.5

Figure 27

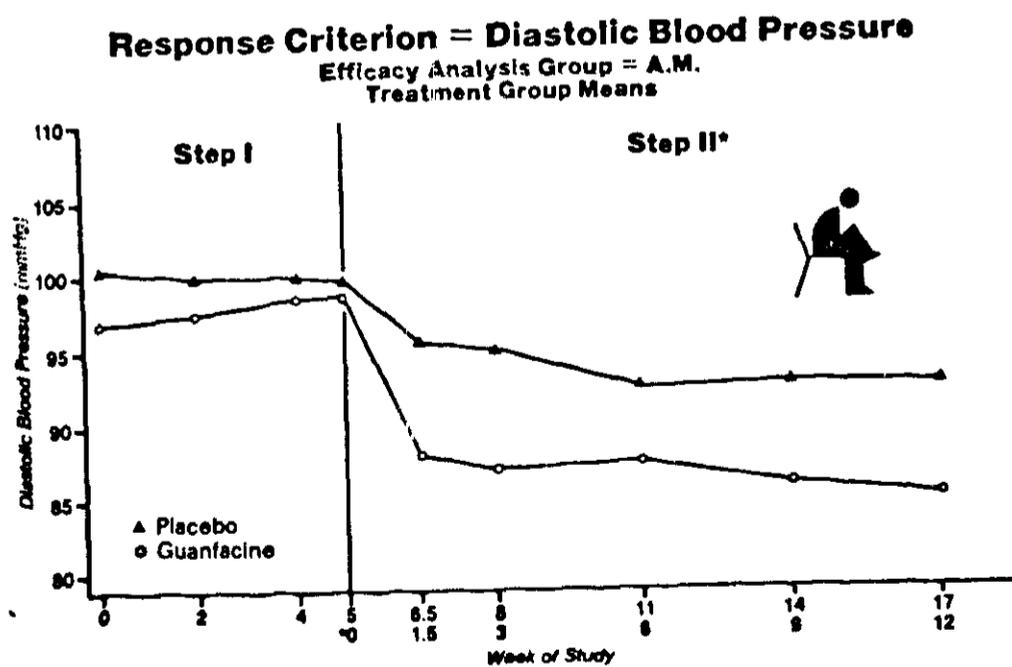


Table LI

Response Criterion = Diastolic Blood Pressure
 Treatment Group Means by Week of Study
 Efficacy Analysis Group = A.M.
 Standing Position

Week of Study	Statistic	Patients Randomized	Treatment Groups	
			Guanfacine	Placebo
Baseline	N	118	-	-
	Mean	100.0	-	-
1.5	N	-	60	58
	Mean	-	90.4	98.2
3	N	-	60	58
	Mean	-	89.9	97.3
6	N	-	60	57
	Mean	-	89.3	97.0
9	N	-	56	54
	Mean	-	88.4	95.9
12	N	-	56	52
	Mean	-	87.8	96.0

Figure 28

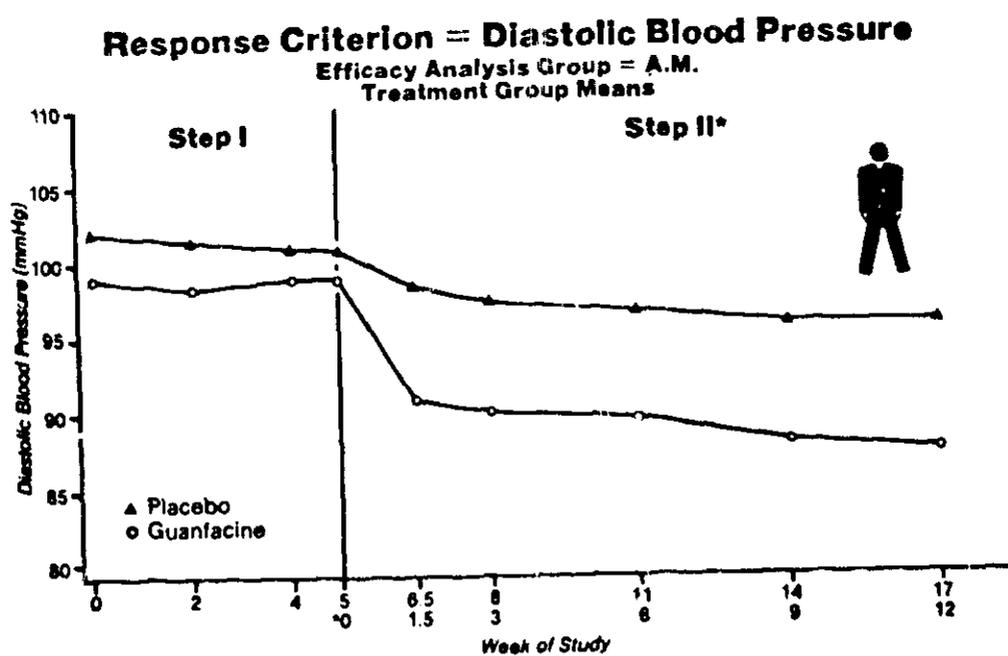


Table LII

Response Criterion = Systolic Blood Pressure
 Treatment Group Means by Week of Study
 Efficacy Analysis Group = A.M.
 Sitting Position

Week of Study	Statistic	Patients Randomized	Treatment Groups	
			Guanfacine	Placebo
Baseline	N	118	-	-
	Mean	142.1	-	-
1.5	N	-	60	58
	Mean	-	128.4	138.7
3	N	-	60	58
	Mean	-	128.3	138.2
6	N	-	60	57
	Mean	-	129.9	136.5
9	N	-	56	54
	Mean	-	128.6	137.0
12	N	-	56	52
	Mean	-	125.9	136.4

Figure 29

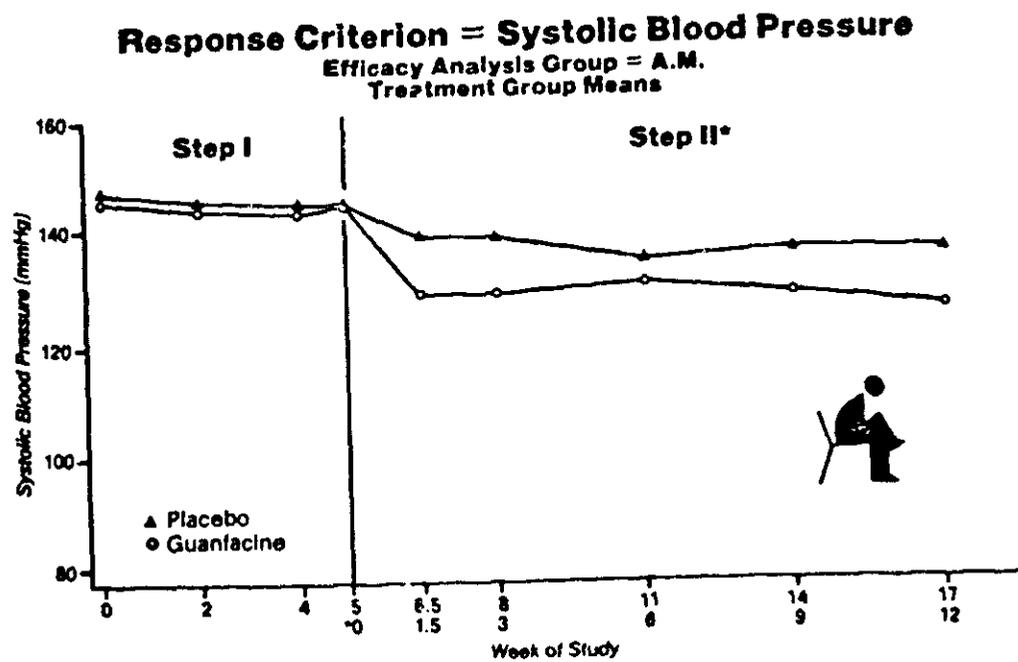


Table LIII

Response Criterion = Systolic Blood Pressure
 Treatment Group Means by Week of Study
 Efficacy Analysis Group = A.M.
 Standing Position

Week of Study	Statistic	Patients Randomized	Treatment Groups	
			Guanfacine	Placebo
Baseline	N	118	-	-
	Mean	140.4	-	-
1.5	N	-	60	58
	Mean	-	126.4	137.8
3	N	-	60	58
	Mean	-	127.9	136.5
6	N	-	60	57
	Mean	-	127.1	137.5
9	N	-	56	54
	Mean	-	125.3	137.1
12	N	-	56	52
	Mean	-	125.5	137.0

Figure 30

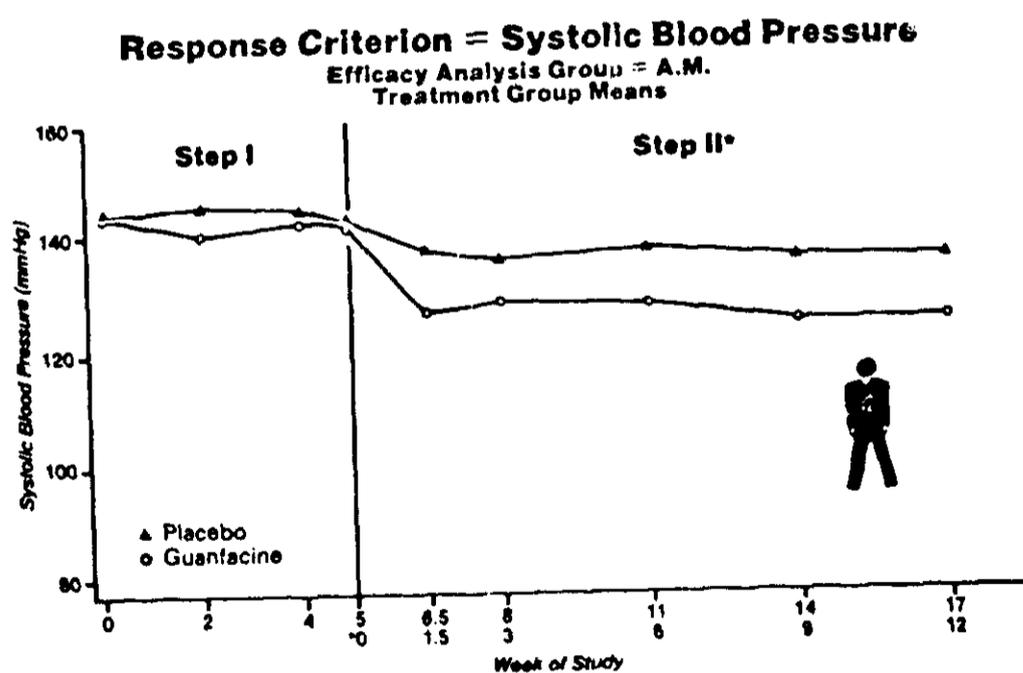


Table LIV

Response Criterion = Heart Rate
 Treatment Group Means by Week of Study
 Efficacy Analysis Group = A.M.
 Sitting Position

Week of Study	Statistic	Patients Randomized	Treatment Groups	
			Guanfacine	Placebo
Baseline	N	118	-	-
	Mean	80.2	-	-
1.5	N	-	60	58
	Mean	-	75.0	78.2
3	N	-	60	58
	Mean	-	75.8	78.6
6	N	-	60	57
	Mean	-	75.2	78.5
9	N	-	56	54
	Mean	-	73.1	78.3
12	N	-	56	52
	Mean	-	72.1	77.8

Figure 31

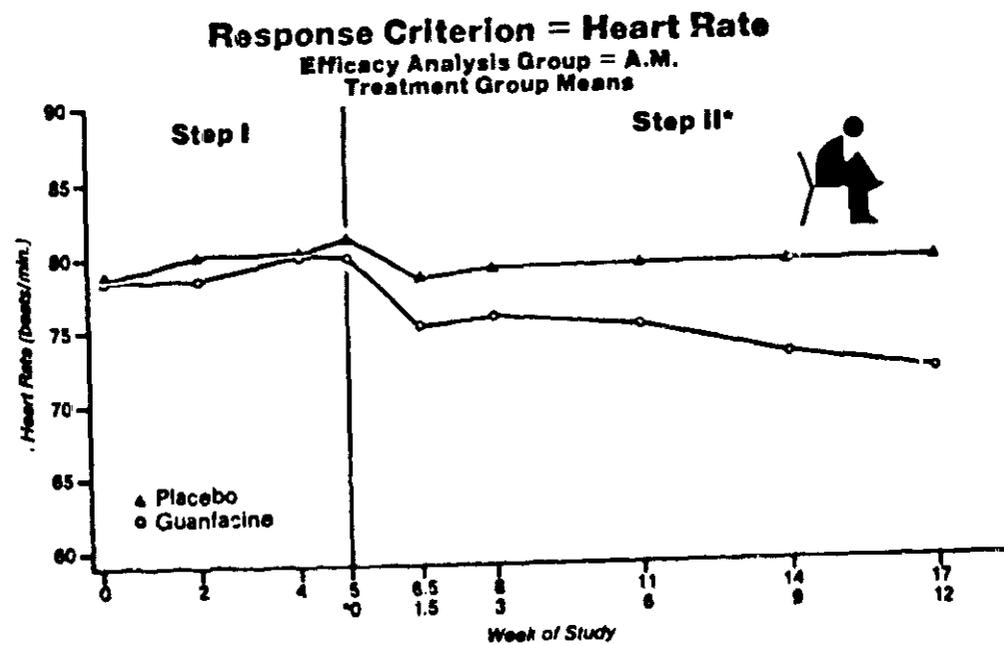
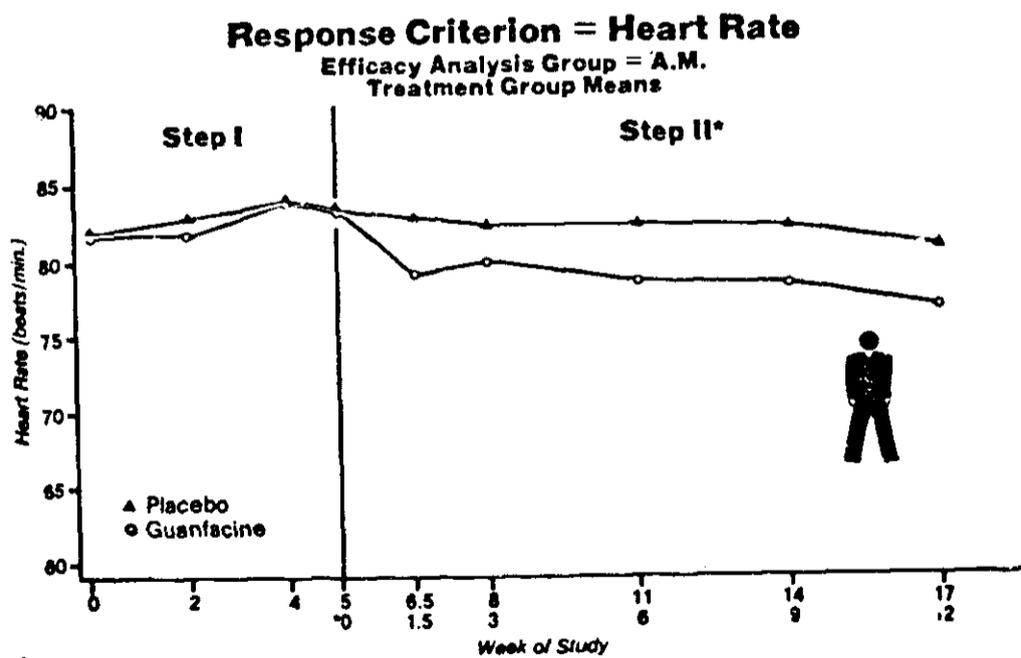


Table LV

Response Criterion = Heart Rate
 Treatment Group Means by Week of Study
 Efficacy Analysis Group = A.M.
 Standing Position

Week of Study	Statistic	Patients Randomized	Treatment Groups	
			Guanfacine	Placebo
Baseline	N	118	-	-
	Mean	83.5		
1.5	N	-	60	58
	Mean		79.0	82.1
3	N	-	60	58
	Mean		80.4	82.6
6	N	-	60	57
	Mean		78.8	82.8
9	N	-	56	54
	Mean		78.7	82.8
12	N	-	56	52
	Mean		77.0	80.6

Figure 32



P.M. Evaluation Groups. The baseline values of the blood pressure and heart rate of the patients who belonged in this category are shown in Table LVI. There were 128 patients; 65 had received guanfacine and 63 placebo. The groups were comparable regarding blood pressure and heart rate. These patients were evaluated 24 hours after they received their daily dose. During the 12-week treatment period, the mean diastolic blood pressure of the guanfacine group decreased by 11.4 mmHg from 99.8 to 88.4 mmHg in the sitting position (Table LVII, Fig. 33) and by 8.3 mmHg from 101.2 to 92.9 mmHg in the standing position (Table LVIII, Fig. 34). The respective changes in the mean systolic blood pressure were 15.1 (from 144.3 to 129.2) mmHg and 12.2 (from 143.7 to 131.5) mmHg. The placebo changes during the same period were 6.2, 4.4, 3.9, and 4.0 mmHg respectively (Tables LIX-LX; Figs. 35-36). The differences between the placebo and the guanfacine changes were all highly significant ($p < 0.01$). Heart rate was decreased by 6.5 (sitting) and 7.6 (standing) beats/min by guanfacine compared to 1.7 and 1.5 beats/min induced by placebo (Tables LXI and LXII; Figs. 37 and 38). The differences between the groups in any of these changes were not significant.

Thus, compared to placebo, guanfacine gave a fall in blood pressure of about 11/5 sitting and 8/4 standing, with a fall in heart rate of 5 beats per minute. This change is numerically somewhat smaller than in the A.M. group and could reflect some loss of effect at 24 hours, at least in some patients. Individual patients can be evaluated by their physicians for adequacy of control at 24 hours.

Table LXIII shows that 41 guanfacine and 40 placebo patients who were evaluated in the evening (PM) had a baseline diastolic pressure in the sitting position ranging from 95-99 mmHg. At the end of the treatment period the mean diastolic blood pressure of the guanfacine patients had dropped to 86.1 mmHg and 28 of them (68%) had become normotensive, i.e., their blood pressure was reduced to < 90 mmHg (Table LXIV). The respective blood pressure of the placebo patients was 90.7 mmHg and only 15 of them (37%) had become normotensive during the same period. Tables LXIII and LXIV show, in addition, that 24 guanfacine and 22 placebo patients of the P.M. group had a baseline diastolic pressure ranging from 100-114 mmHg. At the end of the treatment period (Week 12) the mean diastolic pressures of these patients had been lowered to 91.9 and 101.0 mmHg respectively, while 12 (50%) of the former and 2 (9%) of the latter had become normotensive. The lowering of the blood pressure was thus greater in patients with blood pressures in the 100-114 mmHg range (8-22 vs 9-13 mmHg), an observation seen with most antihypertensive drugs. Similar results were obtained with the A.M. groups (Tables LXV and LXVI). Analysis of the data by investigator indicated that there was no interaction.

Table LVI

Baseline Vital Signs - All Patients
Efficacy Analysis Group = P.M.

Vital Sign	Treatment Group	
	Guanfacine n=65	Placebo n=63
Diastolic Blood Pressure mean (s.d.) mmHg	99.3 (4.47)	100.3 (4.76)
Systolic Blood Pressure mean (s.d.) mmHg	141.6 (10.39)	146.9 (13.33)
Mean Arterial Pressure mean (s.d.) mmHg	113.4 (5.54)	115.8 (6.36)
Heart Rate mean (s.d.) beats/min.	80.5 (12.48)	83.8 (9.92)

Table LVII

Response Criterion = Diastolic Blood Pressure
 Observed Treatment Group Means by Week of Study
 Efficacy Analysis Group = P.M.
 Sitting Position

Week of Study	Statistic	Patients Randomized	Treatment Groups	
			Guanfacine	Placebo
Baseline	N	128	-	-
	Mean	99.8	-	-
1.5	N	-	65	62
	Mean	-	89.2	94.9
3	N	-	65	52
	Mean	-	89.4	93.9
6	N	-	62	61
	Mean	-	89.4	95.1
9	N	-	59	59
	Mean	-	87.2	93.1
12	N	-	58	56
	Mean	-	88.4	93.6

Figure 33

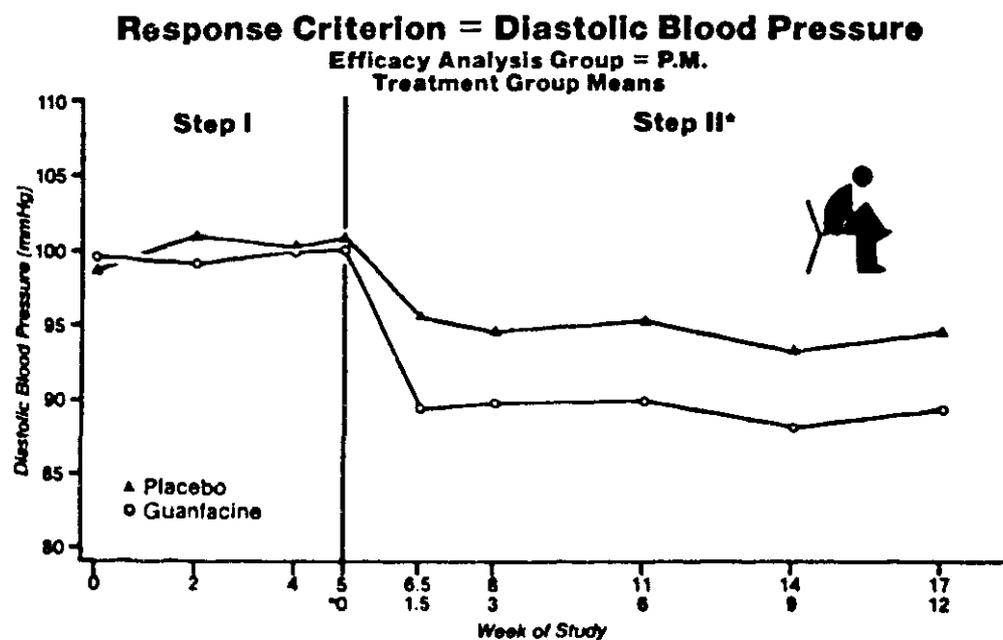


Table LVIII

Response Criterion = Diastolic Blood Pressure
 Observed Treatment Group Means by Week of Study
 Efficacy Analysis Group = P.M.
 Standing Position

Week of Study	Statistic	Patients Randomized	Treatment Groups	
			Guanfacine	Placebo
Baseline	N	128	-	-
	Mean	101.2	-	-
1.5	N	-	65	62
	Mean	-	94.0	98.2
3	N	-	65	62
	Mean	-	91.8	97.6
6	N	-	62	61
	Mean	-	92.5	97.7
9	N	-	59	59
	Mean	-	90.2	96.7
12	N	-	58	56
	Mean	-	92.9	96.8

Figure 34

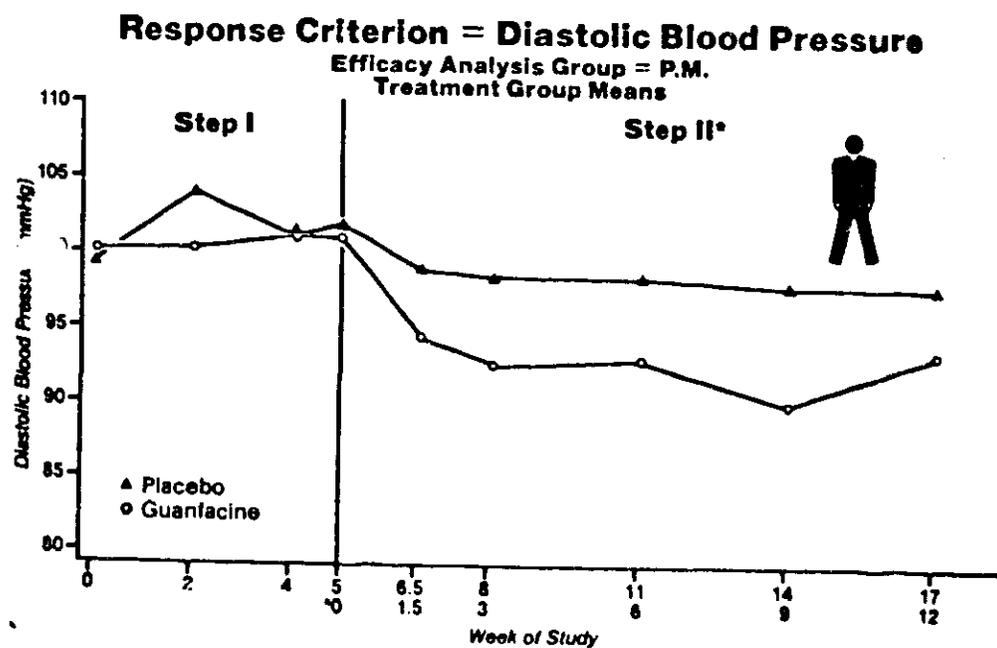


Table LIX

Response Criterion = Systolic Blood Pressure
 Observed Treatment Group Means by Week of Study
 Efficacy Analysis Group = P.M.
 Sitting Position

Week of Study	Statistic	Patients Randomized	Treatment Groups	
			Guanfacine	Placebo
Baseline	N	128	-	-
	Mean	144.3	-	-
1.5	N	-	65	62
	Mean	-	127.4	142.1
3	N	-	65	62
	Mean	-	129.1	140.0
6	N	-	62	61
	Mean	-	128.9	141.3
9	N	-	59	59
	Mean	-	126.9	138.6
12	N	-	58	56
	Mean	-	129.2	140.4

Figure 35

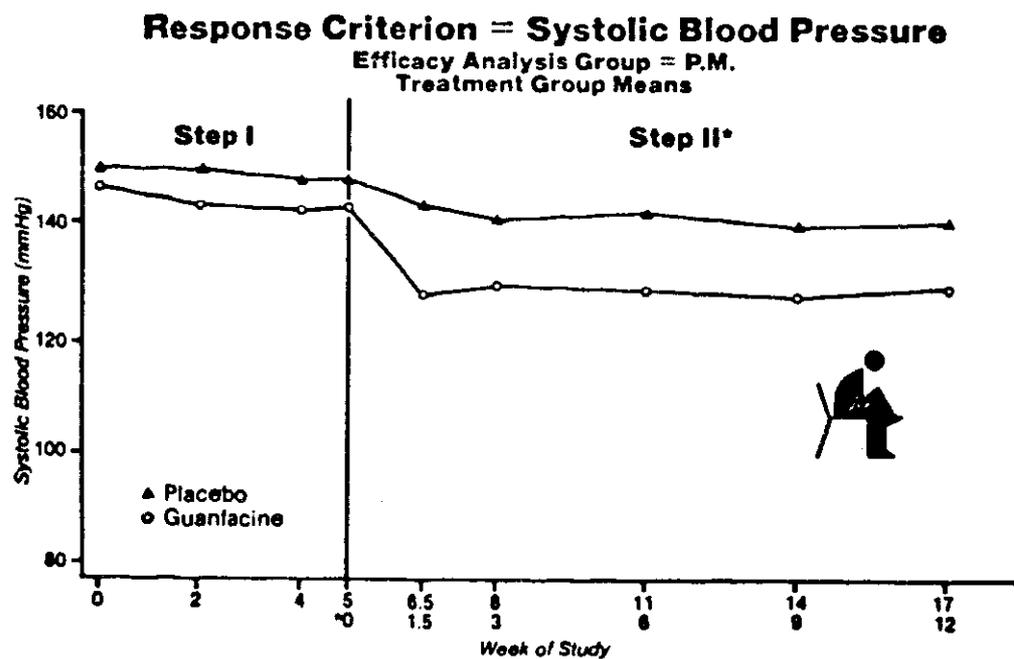


Table LX

Response Criterion = Systolic Blood Pressure
 Observed Treatment Group Means by Week of Study
 Efficacy Analysis Group = P.M.
 Standing Position

Week of Study	Statistic	Patients Randomized	Treatment Groups	
			Guanfacine	Placebo
Baseline	N	128	-	-
	Mean	143.7		
1.5	N	-	65	62
	Mean		129.9	141.2
3	N	-	65	62
	Mean		129.2	140.6
6	N	-	62	61
	Mean		131.0	140.8
9	N	-	59	59
	Mean		127.6	140.0
12	N	-	58	56
	Mean		131.5	139.7

Figure 36

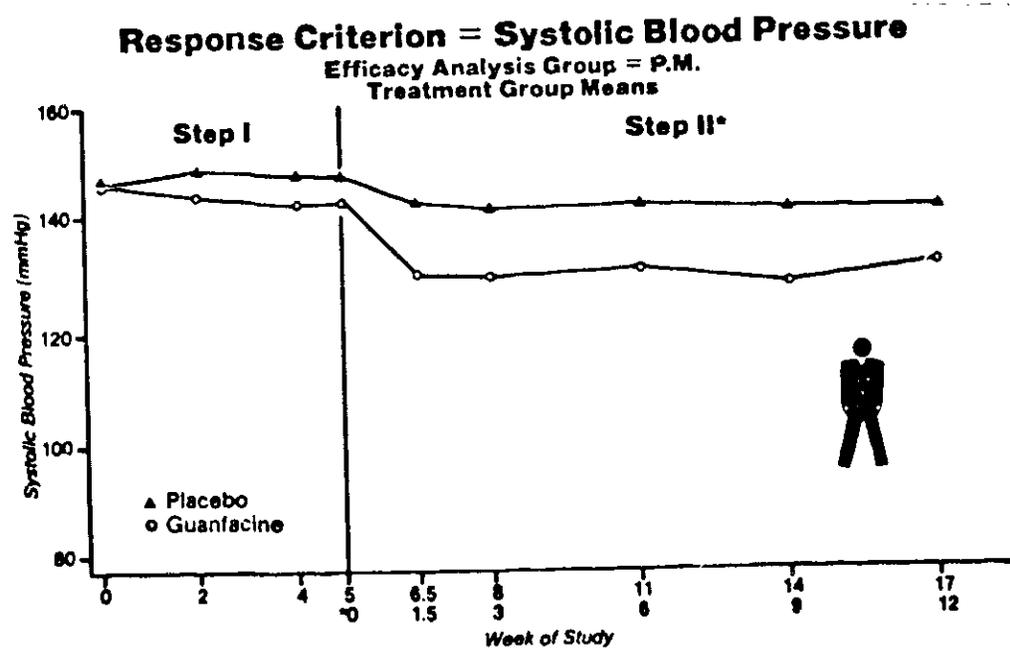


Table LXI

Response Criterion = Heart Rate
 Observed Treatment Group Means by Week of Study
 Efficacy Analysis Group = P.M.
 Sitting Position

Week of Study	Statistic	Patients Randomized	Treatment Groups	
			Guanfacine	Placebo
Baseline	N	128	-	-
	Mean	82.2		
1.5	N	-	65	62
	Mean		75.1	83.1
3	N	-	65	62
	Mean		77.0	81.5
6	N	-	61	61
	Mean		75.7	83.0
9	N	-	59	59
	Mean		75.7	82.7
12	N	-	58	56
	Mean		75.7	80.5

Figure 37

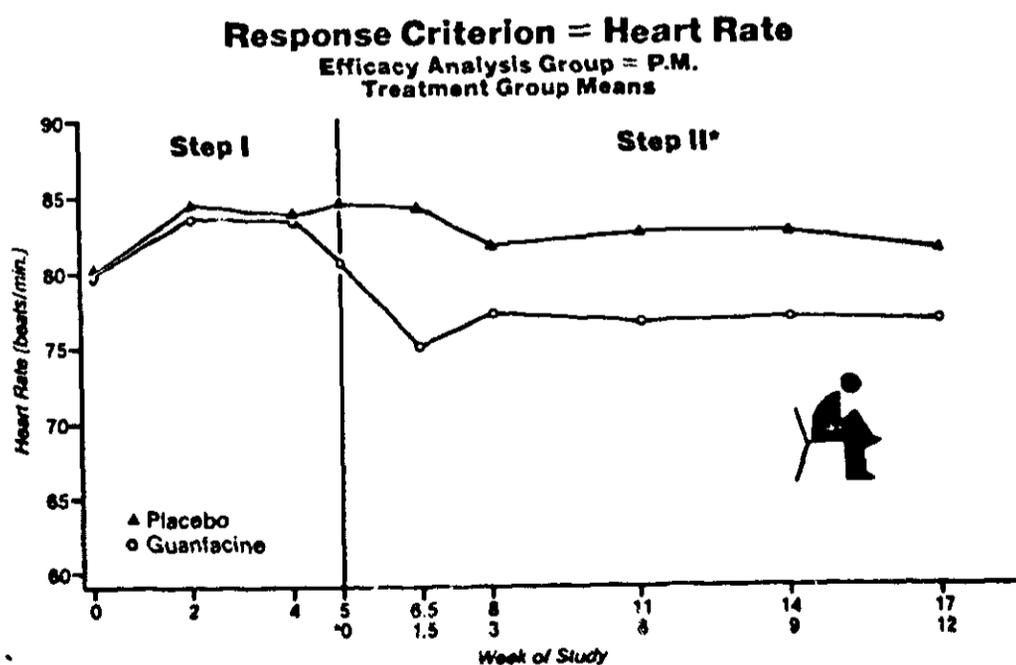


Table LXII

Response Criterion = Heart Rate
 Observed Treatment Group Means by Week of Study
 Efficacy Analysis Group = P.M.
 Standing Position

Week of Study	Statistic	Patients Randomized	Treatment Groups	
			Guanfacine	Placebo
Baseline	N	128	-	-
	Mean	87.4	-	-
1.5	N	-	65	62
	Mean	-	80.5	87.8
3	N	-	65	62
	Mean	-	80.0	85.7
6	N	-	61	61
	Mean	-	79.5	87.4
9	N	-	59	59
	Mean	-	80.5	87.7
12	N	-	58	56
	Mean	-	79.8	85.9

Figure 38

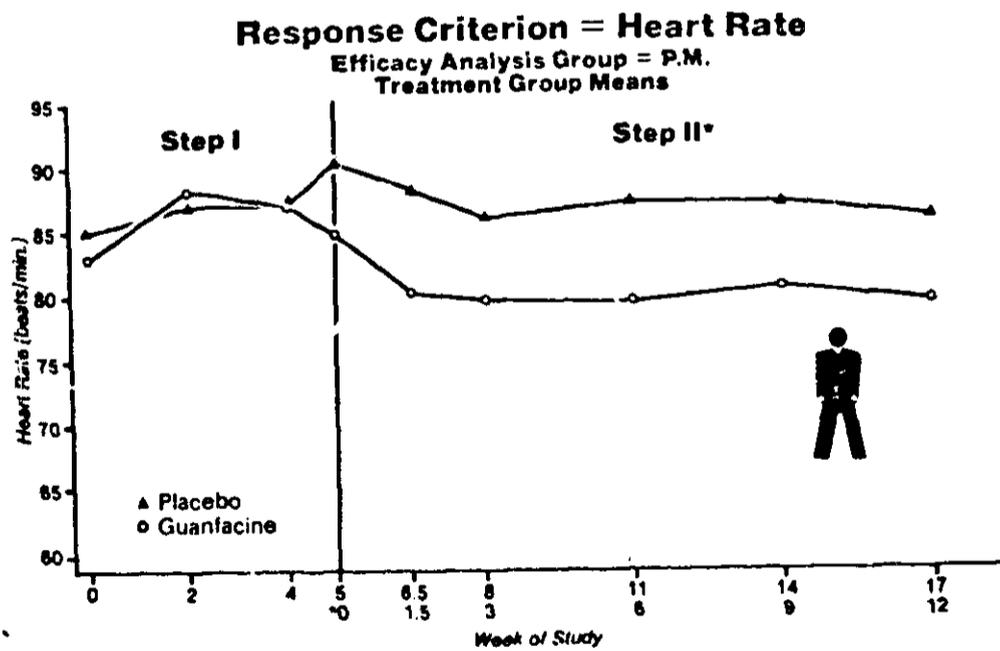


Table LXIII

Endpoint Means of Diastolic Blood Pressure
by Baseline Category
Efficacy Analysis Group = P.M.

Baseline DBP Category	Treatment Group	
	Guanfacine	Placebo
95-99 mmHg	86.1 N=41	90.7 N=40
100-114 mmHg	91.9 N=24	101.0 N=22

Table LXIV

Distribution of Patients Whose
Endpoint Diastolic Blood Pressure
was <90 mmHg By Baseline Category
Efficacy Analysis Group = P.M.

Baseline DBP Category	Treatment Group	
	Guanfacine	Placebo
95-99 mmHg	28/41 (68%)	15/41 (37%)
100-114 mmHg	12/24 (50%)	2/22 (9%)

Table LXV

Endpoint Means of Diastolic Blood Pressure
by Baseline Category
Efficacy Analysis Group = A.M.

Baseline DBP Category	Treatment Group	
	Guanfacine	Placebo
95-99 mmHg	84.7 N=46	91.6 N=40
100-114 mmHg	89.6 N=14	103.0 N=18

Table LXVI

Distribution of Patients Whose
Endpoint Diastolic Blood Pressure
Was <90 mmHg by Baseline Category
Efficacy Analysis Group = A.M.

Baseline DBP Category	Treatment Group	
	Guanfacine	Placebo
95-99 mmHg	35/46 (76%)	17/40 (42%)
100-114 mmHg	9/14 (64%)	1/18 (6%)

Guanfacine Dosage:

The average dose of guanfacine at week 17 was 1.41 mg/day for the P.M. group and 1.34 mg/day for the A.M. group. The dosage distribution and the respective mean changes in diastolic blood pressure in the sitting position are shown in Table LXVII. It can be seen that approximately one-half of the patients were controlled with 1 mg/day, one-fourth by 2 mg/day and the other one-fourth by 3 mg/day.

Table LXVII

Summary of Mean Changes in Diastolic Blood Pressure
by Endpoint Guanfacine Dose

Analysis Group	Dosage of Guanfacine at Endpoint		
	1.0 mg/day	2.0 mg/day	3.0 mg/day
A.M.	n=30 -12.4 mmHg	n=15 -10.4 mmHg	n=15 -14.9 mmHg
P.M.	n=29 -11.4 mmHg	n=19 -9.9 mmHg	n=18 -11.3 mmHg

Safety Analysis

Clinical Side Effects: One hundred and thirteen (113) of the 126 patients (90%) who received guanfacine complained of one or more side effects, mainly of dry mouth, constipation, and fatigue (Table LXVIII). In comparison only 28 of the 113 placebo patients (23%) complained of side effects during the same period. Dry mouth was the most common (11) complaint in these patients also. In 9 guanfacine and 2 placebo patients the side effects were serious enough to require discontinuation of treatment (Table LXIX). As in Study 01, the side effects associated with guanfacine are infrequently bothersome enough to warrant discontinuation. These side effects have been tabulated according to group and drug dosage in Tables LXX-LXXIII. Figure 39 shows that the number of adverse experiences decreased as patients continued treatment with guanfacine; this cannot be accounted for by loss of sensitive patients, as only 9 discontinued.

Side Effects Detected by Lab Tests: No drug-related changes were detected.

Conclusions: The results of this study confirm those of the previous study, showing that guanfacine has a modest antihypertensive effect. They also show that this effect lasts for 24 hours, which means that adequate control of hypertension can be obtained with a single daily dosage of guanfacine. The differences between the A.M. and the P.M. evaluations are not statistically significant, but could be real. Individual patients will need to be evaluated. It is likely that dose increase or divided dosing will yield a further effect in some patients.

Table LXVIII

Frequency Distribution of Patients
with Most Common Adverse Experiences
(Possibly or Probably Related to Treatment Only)

	Treatment Group	
	Guanfacine	Placebo
Number of Patients	126	123
Adverse Experience		
Dry Mouth	59 (47%)	11 (9%)
Constipation	20 (16%)	1 (1%)
Fatigue	15 (12%)	7 (6%)
Dizziness	8 (6%)	4 (3%)
Somnolence	5 (4%)	3 (2%)
Impotence	6 (5%)	2 (2%)

The frequency of side effects is outlined above. Most of these effects were not serious. It is surprising that the frequency of serious side effects necessitating discontinuation of treatment did not increase with dosage. Table LXIX shows that the frequency was virtually the same for all dosages. Five of the 58 patients (9%) who received 1 mg/day were discontinued because of side effects compared to 3 of the 34 patients (9%) who had received 2 mg/day and to 1 of the 33 patients (3%) who had received 3 mg/day. Similar conclusions were drawn from Study 01 (see also Table XL).

Table LXIX

Frequency Distribution of Patients Who
Prematurely Terminated From the Study Because
of Clinical Adverse Experiences

Week of Study	Treatment and Dosage at Time of Termination			
	Placebo	Guanfacine (mg/day)		
		1.0	2.0	3.0
1.5	0	0	0	0
3	0	3	0	0
6	0	2	2	0
9	2	0	1	1
12	0	0	0	0
Totals	<u>2</u>	<u>5</u>	<u>3</u>	<u>1</u>

Figure 39

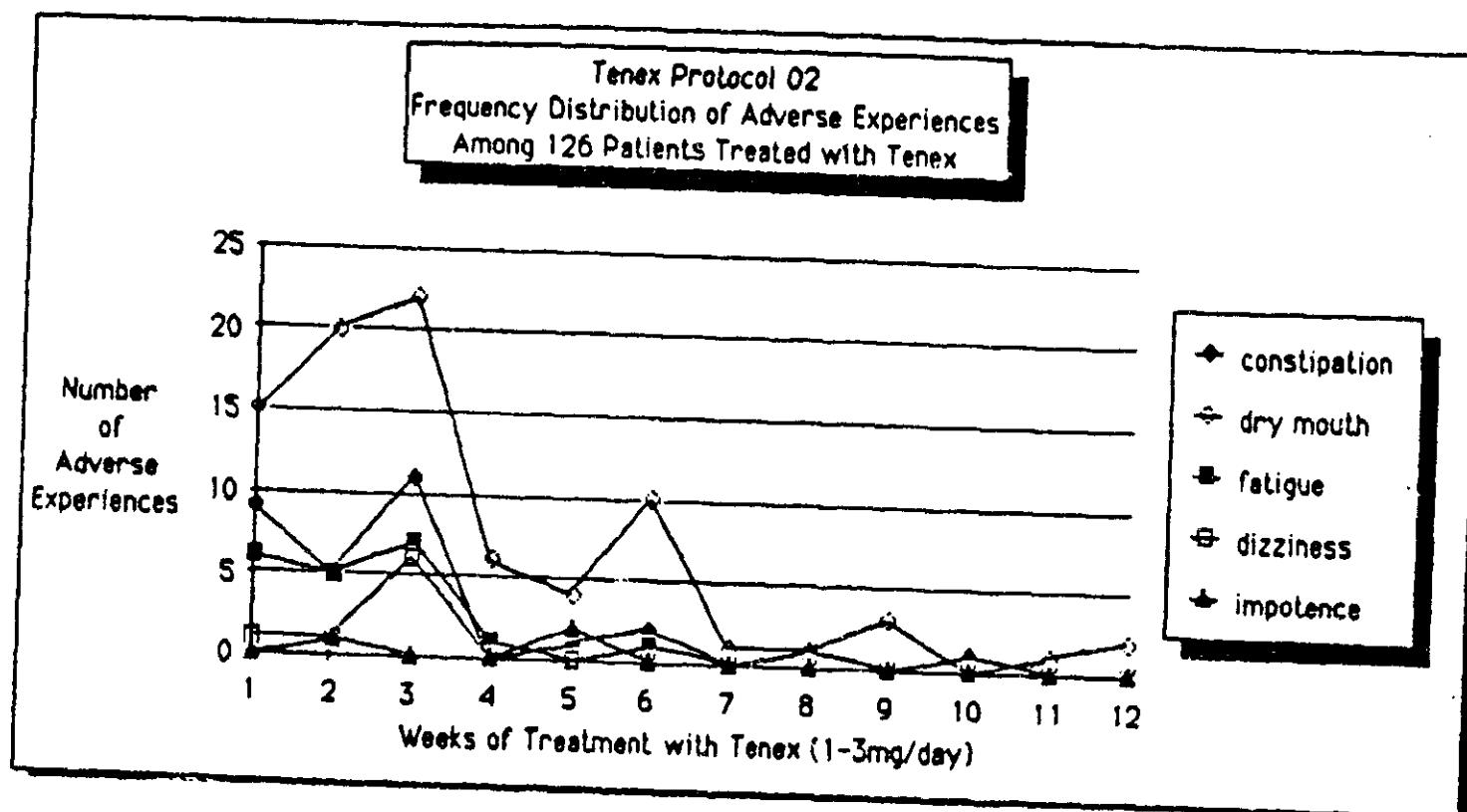


Table LXX

Adverse Drug Experiences as Reasons
for Discontinuation of Placebo

Number of Patients with Adverse Experiences: 2

Number of Adverse Experiences : 5

<u>Patient Identification</u>	<u>Adverse Experience</u>
27101	Syncope, headache
27214	Fatigue, vertigo, depression

Table LXXI

Adverse Drug Experiences as Reasons for Discontinuation
of Guanfacine at the 1.0 mg/day Dosage Level

Number of Patients with Adverse Experiences:	5
Number of Adverse Experiences	: 7

<u>Patient Identification</u>	<u>Adverse Experience</u>
21112	Confusion
21213	Dry mouth
24214	Dizziness, headache
26211	Depression
27210	Dry mouth, impotency

Table LXXII

Adverse Drug Experiences as Reasons for Discontinuation
of Guanfacine at the 2.0 mg/day Dosage Level

Number of Patients with Adverse Experiences:	3
Number of Adverse Experiences	: 9

<u>Patient Identification</u>	<u>Adverse Experience</u>
22113	Confusion, amnesia
26205	Constipation, dry mouth, fatigue, taste perversion
27202	Dry mouth, somnolence, testicu- discomfort

Table LXXIII

Adverse Drug Experiences as Reasons for Discontinuation
of Guanfacine at the 3.0 mg/day Dosage Level

Number of Patients with Adverse Experiences: 1	
Number of Adverse Experiences : 5	
<u>Patient Identification</u>	<u>Adverse Experience</u>
25102	Palpitation, dizziness, headache, tinnitus, abnormal vision

2. U.S. Trials: Stepped Care - Comparison with Clonidine

Comparison with Clonidine (Study 03)

This was a multi-investigator, double-blind, randomized comparison of guanfacine to clonidine as Step II treatment for mild to moderate essential hypertension. Duration of Step I was 5 weeks and patients whose sitting DBPs after 5 weeks of chlorthalidone, 25 mg/day, could be randomized to either guanfacine, 1 mg q.h.s. or clonidine 0.1 mg bid, a.m. + h.s. The duration of the Step II period was 6 months. During the last week of the Step I period and the week following the last week of the Step II period (the Drug Withdrawal Phase), patients were evaluated very closely (b.i.d. in the 9 outpatient studies and continuously in the 2 inpatient studies).

The 3 primary foci of the study were: 1) efficacy of the 2 drugs; 2) safety of the drugs with special emphasis on relative sedation properties, and 3) evaluation of the patterns of response after abrupt withdrawal of the drugs.

PATIENTS

Diagnosis. Patients with a history of essential hypertension or newly diagnosed patients with essential hypertension were eligible for admission to the Weaning/Screen Period of the study. The average (of 3 readings) sitting diastolic blood pressure must have been in the 95-114 mmHg (inclusive) range for a patient to be advanced to the Drug Evaluation Period.

Patient Sample. Patients of either sex or any race who were 21 years of age or older were included. Each investigator was supposed to complete at least 50 patients according to the protocol. Patients could be from private or clinic sources.

Inclusion/Exclusion Criteria. Patients who met the diagnosis and criteria specified above were eligible for admission to the Weaning/Screening Period of the study.

Patients excluded by the protocol were those: requiring certain concomitant medications (see protocol, p. 8, Appendix C); with known hypersensitivity to study medications; obese patients 50% over their ideal weight; with unstable diabetes; with hypertensive retinopathy Grade III or Grade IV (Keith-Wagener Scale); with a history of chronic alcoholism or drug addiction; with malignant disease or other serious disease including advanced renal disease and azotemia, cardiac disease, pulmonary disease, gastrointestinal disease, hepatic disease, congestive heart failure, angina pectoris, gout or clinically significant cerebrovascular disease; pregnant or lactating women; who received reserpine or guanethidine therapy immediately prior to entry into the study; who were on a diet intended to cause appreciable weight changes during the course of the study; with labile hypertension; with a myocardial infarction less than six months prior to entry into the study; or who were unable or refused to give written informed consent.

Patients were excluded from continuation in the Drug Evaluation phase of study if their average diastolic blood pressure was >114 mmHg for 2 consecutive visits during the Drug Evaluation Period or they missed 2 consecutive visits during the study.

DRUGS

The 2 drugs evaluated in this study were guanfacine and clonidine. All patients received 25 mg chlorthalidone daily for the duration of the study including a 5-week Step I period during which their blood pressure and diuresis were stabilized. During Step I, chlorthalidone was dosed in the morning. During Step II, chlorthalidone was dosed at bedtime. Guanfacine, the investigational drug, was given once daily at bedtime for 24 weeks (end of Week 5 through 29). Since clonidine was given according to the manufacturer's recommended b.i.d. dosage schedule, each patient in the guanfacine treatment group received a placebo capsule in the morning.

At scheduled visits every 4 weeks, the dosage of guanfacine, which started at 1 mg could be adjusted upward or downward by 1 mg increments to a maximum of 3 mg daily or a minimum of 1 mg daily depending upon the patient's response to the drug as determined by the investigator.

Patients in the clonidine treatment group started at a dosage of 0.1 mg b.i.d., and the dosage could have been adjusted based upon patient response to a maximum dosage of 0.3 mg b.i.d. at the same intervals as the guanfacine treatment group.

All Step II study medications were identical in appearance (orange capsules), and medications were blister-packed so that each patient received medication cards at each visit which would provide sufficient Step I and Step II medication were kept carefully by each investigator.

EVALUATIONS

Step I - Weaning/Screening Evaluation Period

All patients who had a history of essential hypertension and gave written informed consent were admitted to Step I during which their previous antihypertensive medications, if any, were discontinued gradually over the first 2 weeks. Clinical evaluations completed during Step I included: patient history, physical examination, electrocardiogram, chest x-ray, blood pressure (sitting and standing positions), heart rate, body weight, adverse drug experiences and patient response questionnaire which measured the degree of somnolence on a 100-mm visual analog scale. Laboratory evaluations included: complete blood count with differential, platelet count, SMAC-16 and urinalysis. All patients who completed the Step I period with a blood pressure average between 95-114 mmHg, inclusive, could be entered into Step II during which they were randomly assigned to receive either guanfacine or clonidine in addition to their chlorthalidone.

Step II - Drug Evaluation Period

Patients who entered Step II were evaluated at 4-weekly intervals for 6 months. Clinical evaluations performed at each evaluation included: blood pressure (sitting and standing positions), heart rate, body weight, patient response questionnaire and adverse drug experiences. Adverse drug experiences were elicited by asking each patient, in a general manner, "How do you feel today?" and "How have you been since your last visit?" Laboratory evaluations were made at the end of the second, fourth, and sixth month of Step I. These were the same as for Step I.

Drug Withdrawal Observation Periods

Inpatients. During Week 5 (last week of Step I therapy) and Week 30 (the week following abrupt discontinuation of Step II therapy), each patient was confined to either a hospital environment (Tulane Clinical Research Center) or a clinic (Arkansas Medical Research Testing Center) where evaluations were made every 2 hours during the day and every 4 hours at night. These evaluations included: determination of blood pressure and heart rate, symptoms of drug withdrawal, and 24

hour urinary catecholamine (epinephrine, norepinephrine and VMA) determinations. Symptoms of drug withdrawal were evaluated by asking each patient whether or not he/she has experienced any of 15 signs/symptoms of "rebound hypertension" on a checklist provided by the sponsor. Body weight was measured daily in the morning.

Outpatients. Patients returned to the investigator's office in the morning and evening during Week 5 and Week 30 for the same evaluations (except for catecholamine determinations) as given above for the inpatients.

At the end of Week 30 or when a patient prematurely terminated from the study, ECG and routine lab tests were done.

Step I therapy was continued during Week 30. After the last evaluation during Week 30, the patients were re-started on their previously effective antihypertensive therapy.

METHODS FOR EFFICACY ANALYSIS

The data available for efficacy were: systolic blood pressure, diastolic blood pressure and heart rate from both the sitting and standing positions. Sitting position measurements were obtained as the average of the last 3 of 5 measurements taken provided that the readings were within 5 mmHg of each other and standing measurements were recorded as the first of 2 evaluations. Patient efficacy data from all investigators were pooled for analysis.

Efficacy analyses were performed using an endpoint analysis and a categorical analysis.

Endpoint was defined as the last vital sign observation recorded prior to premature termination or completion of the study. In the endpoint analysis, change in vital signs was calculated as $\text{CHANGE} = \text{ENDPOINT} - \text{BASELINE}$ where baseline was the end of Week 4 observation. Week 4 was utilized because all patients were pooled for efficacy analysis across all investigators, and patients from two investigators were hospitalized for a Drug Withdrawal Observation Period baseline during Week 5 (end of Step I therapy). In order to qualify for endpoint analyses, patients had to have had at least one (4 weeks) follow-up visit.

Categorical analysis of efficacy data was performed by determination of the percentage of patients with an endpoint sitting diastolic blood pressure average less than or equal to 90 mmHg.

METHODS FOR SAFETY ANALYSES

Step I and Step II Evaluation Periods

Adverse Drug Experiences

After the initial visit, adverse drug experiences were reported at each evaluation. These spontaneously reported reactions may have been associated with the administration of chlorthalidone, guanfacine or clonidine, or the combination of the diuretic and the Step II agent. The percentage of patients who were prematurely terminated from the study due to adverse drug experiences was also compared between drugs.

Somnolence Rating Scale

The Patient Self-Evaluation Questionnaire on the case report form consisted of four questions that were answered by marking a 100-mm line at the point that most appropriately described the patients degree of somnolence at a particular time of day. This visual analog scale was used to establish a baseline measurement (at Week 4) and to evaluate the patient's change from baseline over the period of study drug administration, i.e., Step II. The change in degree of somnolence was calculated by taking the endpoint measurement and subtracting the baseline measurement for each patient.

Drug Withdrawal Observation Periods

Inpatient Studies

Vital Signs Changes

Average daily changes in blood pressure and heart rate were calculated by 1) subtracting the average daily vital sign values during the Drug Withdrawal Observation Period from vital signs measured at the end of the Step II Drug Evaluation Period (Week 29) and 2) subtracting the average daily vital sign values during the Drug Withdrawal Observation Period (Week 30) from vital signs measured in the comparable Week 5 period.

Symptoms of Drug Withdrawal

The frequency distribution of symptoms of drug withdrawal was calculated and compared for each treatment group.

Catecholamine Response

Urine specimens for catecholamine assay were pooled for each day of the Drug Withdrawal Observation Periods (Week 5 and 30), and the concentration of catecholamines at each day during each week was determined. The daily values for Week 30 were subtracted from the baseline values (Week 5), and the change in catecholamines over the last Drug Withdrawal Observation Period (Week 30) was compared between treatment groups.

Outpatients

The analyses for vital signs, symptoms of drug withdrawal and adverse drug experiences were made in the same manner as for the inpatient studies described above. There were no urine specimens collected for catecholamine analyses in the outpatient studies.

RESULTS

Table LXXIV
Overall Patient Accountability

<u>Entered</u>	<u>Step I</u>		<u>Eligible to Enter Step II</u>
	<u>Screen Failure</u>		
677	120		557

	<u>Step II</u>		
	<u>Guanfacine</u>	<u>Clonidine</u>	<u>Total</u>
Entered	279	278	557
Completed Step II	235	237	472
Prematurely Terminated	44	41	85
Reasons for Premature Termination:			
Adverse Effects	19 (6.8%)	22 (7.9%)	41
Death	1	1	2
Administrative	24	18	42
Eligible for Efficacy Analysis (Completed at least 4 weeks Step II)	270	276	546

	<u>Drug Withdrawal Phase</u>		
	<u>Guanfacine</u>	<u>Clonidine</u>	<u>Total</u>
Entered	235	237	472
Completed	229	226	455
Failure to Complete Withdrawal Phase (All Adverse Effects)	6	11	17

Demography

All Patients Who Received Step II Medications

The demographic characteristics of patients who entered Step II and were randomized to treatment are below. There were no significant differences between treatment groups for any demographic characteristic.

Table LXXV

	Step II Treatment Group	
	Guanfacine	Clonidine
Sitting DBP	101.4 ± 5.3	101.3 ± 5.2
Sitting SBP	147.6 ± 16.0	146.7 ± 15.3
Sitting HR	79.6 ± 10.3	80.2 ± 10.5
Standing DBP	103.3 ± 8.4	103.6 ± 8.2
Standing SBP	146.9 ± 17.7	146.8 ± 17.8
Standing HR	83.1 ± 11.0	83.8 ± 11.7
Age (year-)		
Mean	52.8	52.7
STD	11.4	10.7
Sex		
Female	138	148
Male	141	130
Race		
Black	113	119
Caucasian	159	159
Hispanic	4	0
Oriental	2	0
Other	1	0
Height (inches)		
Mean	67.3	67
STD	3.6	3.8
Weight (lbs.)		
Mean	183.6	185.5
STD	34.5	35.8

Efficacy Results

Blood Pressure and Heart Rate - Sitting Position

Endpoint Analysis

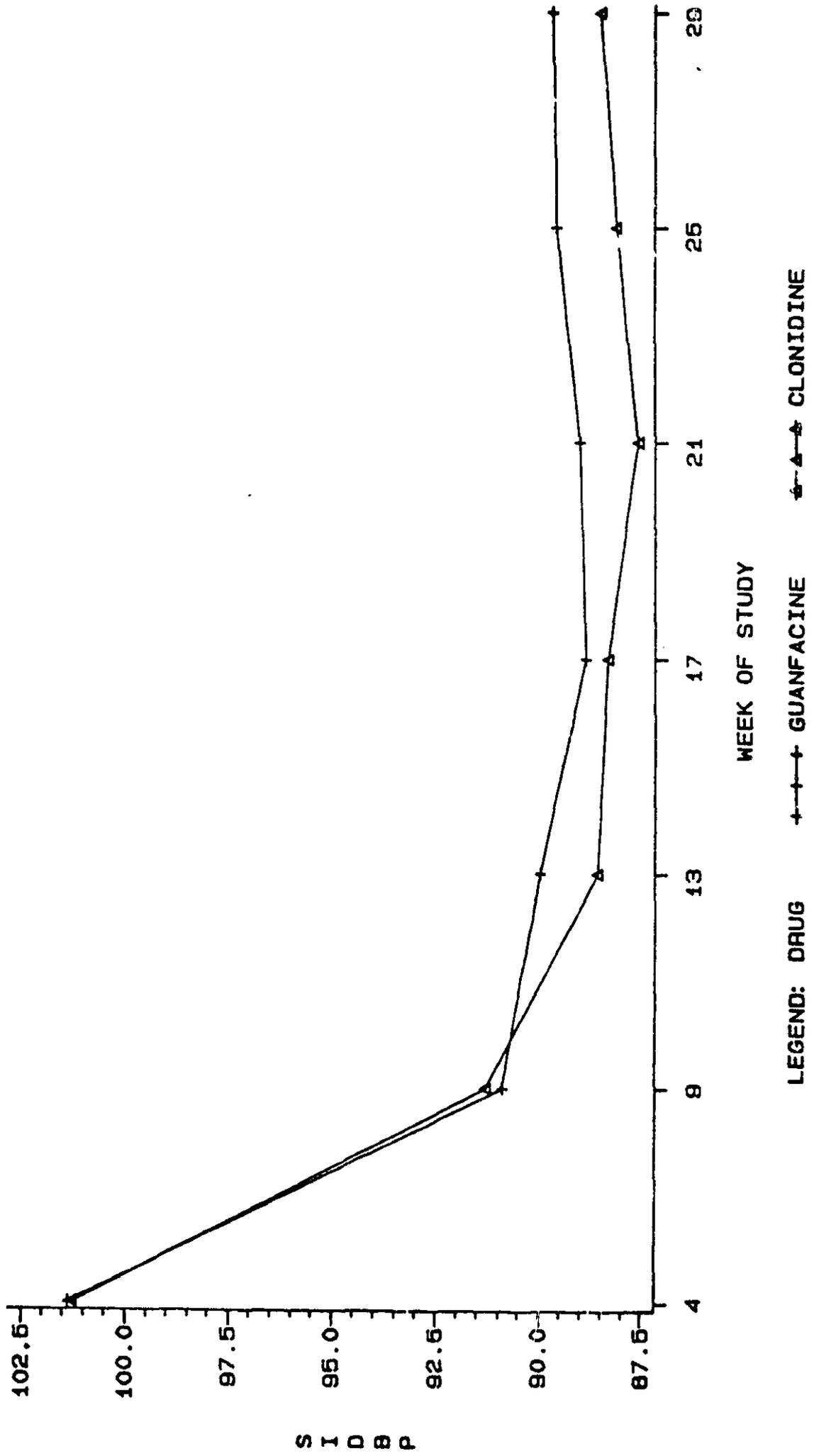
The efficacy data from all 11 investigators were pooled across studies for inclusion in the efficacy analysis. After 5 weeks of stabilization of blood pressure on 25 mg chlorthalidone daily, 557 patients were randomly assigned to receive either guanfacine or clonidine. Blood pressure and heart rate were measured at the end of each month of the Step II period for each of the 279 guanfacine patients and 278 clonidine patients.

Included in the endpoint analysis were 270 guanfacine patients and 276 clonidine patients. The mean change in DBP among patients treated with guanfacine was -11.3 mmHg and -12.1 mmHg for patients treated with clonidine. The observed decreases in DBP were clinically similar and were not different from one another ($p > 0.4$). The mean final daily dose of guanfacine was 1.9 mg/day and 0.4 mg/day for clonidine.

Although there were slight differences between treatment groups in mean changes of blood pressure or pulse, none of these differences was significant in the sitting ($p > 0.4$) or standing ($p > 0.7$) positions.

The figure below shows the mean diastolic blood pressure at each of the scheduled visits during Step II.

AHR 4459 PROTOCOL 03
MEAN SITTING DIASTOLIC BLOOD PRESSURE



S I D B P

The table below gives the frequency distribution of patients who either achieved or failed to achieve a goal diastolic blood pressure (sitting position) of ≤ 90 mmHg. Although 4% more of the clonidine treatment group achieved their goal, the difference between treatment groups is not statistically significant nor clinically relevant. Both treatments worked very well.

Table LXXVI

Endpoint Sitting Diastolic Blood Pressure

<u>Treatment Group</u>	<u>< 90</u>	<u>>90</u>	
Guanfacine	149 (55%)	121 (45%)	270
Clonidine	164 (59%)	112 (41%)	276

General Safety Analyses - Drug Evaluation Period (Step II)

The comparative number of patients with clinical adverse drug experiences during Step II is of primary importance.

The table below gives a summary of the most frequently occurring (>5%) clinical adverse drug experiences with each drug.

Table LXXVII

Frequency Distribution of Most Common Clinical ADEs
Drug Evaluation Period (Step II)

<u>Clinical Adverse Drug Experience</u>	<u>Guanfacine</u> <u>n = 279</u>	<u>Clonidine</u> <u>n = 278</u>
Dry mouth	84 (30%)	102 (37%)
Somnolence	59 (21%)	98 (35%)
Dizziness	30 (11%)	23 (8%)
Constipation	27 (10%)	13 (5%)
Fatigue	24 (9%)	23 (8%)

The table below shows the number of patients prematurely terminated from the study because of clinical adverse drug experiences. More patients were terminated at the first level than at the higher dose levels which may indicate that patients who did not tolerate either Step II drug at the lowest dose level did not proceed in the study, and therefore, these patients were not exposed to higher doses.

Table LXXVIII

Summary of Patients Prematurely Terminated from Study
Because of Clinical Adverse Drug Experiences
Drug Evaluation Period (Step II)

Treatment Group	Dose Level 1	Dose Level 2	Dose Level 3	Total
Guanfacine	1.0 mg/day 12 (4.3%)	2.0 mg/day 4	3.0 mg/day 2	18
Clonidine	0.2 mg/day 12 (4.3%)	0.4 mg/day 6	0.6 mg/day 2	20

The percentage of patients who prematurely terminated from the study because of an adverse drug experience was low and approximately the same for each treatment group (guanfacine, 6.5%; clonidine, 7.2%). A complete listing of the patients who prematurely terminated and their respective clinical adverse drug experiences can be found below.

Table LXXIX

Reasons for Patients Prematurely Terminated From Step II
Because of Adverse Drug Experiences

CLONIDINE GROUP

Patient Number	Week Discontinued	Dose	Reason
30117	17	0.2 mg	Hypotonia, anxiety, somnolence
30226	22	0.2 mg	Asthenia
30310	22	0.4 mg	Somnolence, polyuria, dry mouth
30314	9	0.2 mg	Somnolence
30315B	9	0.2 mg	Dry mouth and somnolence
30317	14	0.6 mg	Dizziness and somnolence
30345	17	0.4 mg	Edema
30350	9	0.2 mg	Dry mouth, somnolence, nausea
30910	9	0.2 mg	Nervousness, depersonalization, personality disorder
30923	13	0.4 mg	Somnolence, asthenia, constipation
30934	13	0.2 mg	Asthenia, dizziness, somnolence
30602	10	0.4 mg	Dry mouth and somnolence
30607	9	0.2 mg	Somnolence, fatigue, hypertonia
30610	9	0.2 mg	Anxiety
30614	17	0.6 mg	Somnolence
30730	13	0.2 mg	Somnolence
30829	9	0.2 mg	Dry mouth and dizziness
31011	17	0.2 mg	Impotence and somnolence
31030	17	0.4 mg	Constipation and dizziness
31138	19	0.4 mg	Alopecia, skin atrophy, nail disorder

Table LXXIX (continued)

Reasons for Patients Prematurely Terminated From Step II
Because of Adverse Drug Experiences

GUANFACINE GROUP

Patient Number	Week Discontinued	Dose	Reason
30205	10	1 mg	Dizziness
30222	9	1 mg	Somnolence
30238	16	1 mg	Ras'
30308	17	2 mg	Fatigue and constipation
30309	11	2 mg	Dizziness and somnolence
30313	9	1 mg	Dry mouth
30319	14	2 mg	Dry mouth, abnormal gait, edema
30342	18	3 mg	Dry mouth
30348	23	1 mg	Confusion, taste perversion, abnormal gait
30549	9	1 mg	Depression, constipation, insomnia
30909	9	1 mg	Nervousness, chest pain, asthenia
30946	17	2 mg	Constipation, asthenia, dry mouth, dizziness
30611	29	3 mg	Dry mouth and somnolence
30747	9	1 mg	Dizziness, fatigue, headache
31007	9	1 mg	Somnolence and abnormal vision
31015	9	1 mg	Dyspnea, chest pain, arrhythmia
31421	14	1 mg	Somnolence, dry mouth, paraesthesia
31133	16	1 mg	Pruritis

Two patients died while on Step II study medications. One patient (#30544) died while receiving 1 mg/day of guanfacine for 4 weeks. The patient was an 81 year old male with an 8 year history of essential hypertension, history of congestive heart failure and a left bundle branch block as indicated by ECG pretreatment. Concomitant medications at the time of death include: Lanoxin, Quinidex Extentabs, Dalmane, Hygroton, and Micro-K. The patient expired during sleep, and the presumed cause of death was a myocardial infarction. The patient's death was not attributed to guanfacine by the investigator.

The other patient who died was receiving clonidine. The death was not drug-related or study-related.

Somnolence Rating Scale

The percentage of patients with an increase in somnolence over baseline was calculated and the difference between treatment groups for the morning evaluation was statistically significant ($p=0.017$). All other evaluations approached but failed to reach statistical significance. These results suggest that guanfacine produces less somnolence than clonidine.

Laboratory Evaluations

Analyses of serum chemistry, hematology, and urinalysis data revealed no clinically important drug-related changes in test results for any patient in either treatment group. There were no patients in the guanfacine treatment group who were prematurely discontinued from the study solely because of a lab test abnormality. One patient (#31142) in the clonidine group was discontinued during Step II because of hypokalemia that began during Step I. This patient's serum potassium was low (3.4 mEq/L) at Day 0 and fell to a low of 1.8 mEq/L by Week 4. At the time of discontinuation from the study (Week 9), the patient's serum potassium had risen to 4.1 mEq/L.

Electrocardiogram Evaluations

There were no clinically important changes from baseline in electrocardiograms (ECGs) for any of the patients in the guanfacine or clonidine treatment groups. These results are summarized below. The results of all patients whose ECG changed from normal at baseline to abnormal were examined by the Medical Monitor and none of these was considered clinically important.

Table LXXX
Summary of Changes in ECG Evaluations
Drug Evaluation Period - Step II

Treatment Group	Patients with ECG Evaluations at Baseline/Termination from Study			
	Norm/Norm	Norm/Abnorm	Abnorm/Norm	Abnorm/Abnorm
Guanfacine	124, 52.1%	32, 13.5%	22, 9.2%	60, 25.2%
Clonidine	128, 53.1%	26, 10.8%	17, 7.1%	70, 29.1%

Drug Withdrawal Analyses

Abrupt withdrawal of clonidine and other centrally-acting, alpha-adrenergic agonists has resulted in a phenomenon referred to by various names: "rebound hypertension", "overshoot" or "drug withdrawal phenomenon". Most of the patients who have received clonidine and who have experienced this phenomenon have been reported anecdotally, and usually received doses of clonidine >0.6 mg/day for moderate to severe hypertension. This may be the first large-scale clinical trial ever to examine the "drug withdrawal phenomenon" with parallel treatment groups who received their Step II drugs in a double-blind fashion in patients with mild to moderate hypertension.

Thus, these data were analyzed by different methods to attempt to define the "drug withdrawal phenomenon". The principal difference in the methodology is related to the definition of "baseline". "Baseline measurements" were available from the end of Step I (Week 5) and the end of Step II (Week 29). Drug withdrawal analyses utilizing each of these "baselines" are given.

Inpatient Studies

Upon abrupt discontinuation of either guanfacine or clonidine at the end of Week 29, the mean blood pressure in both groups rose. The differences between treatment groups can be observed in the rate of change in diastolic and systolic pressure.

Using the end of treatment at Week 29 as a baseline week, the mean change in diastolic blood pressure is given in Figures 41 (Study 310) and 42 (Study 315). In Figure 41, the differences in the mean DBP on Days 2 and 3 of Week 30 were significantly greater ($p=.046$ and $p=.125$, respectively) in the clonidine treatment group. For study 315, the DBP curves were parallel between treatments, and inferential statistical analysis showed a statistically significant overall difference between treatment groups ($p=.008$) with regard to increase in DBP. In both studies, the DBP for the clonidine treated group rose at a faster rate than did the DBP for the guanfacine group.

Similar analyses were done for systolic blood pressure (SBP) and heart rate (HR), and these results were similar.

Figure 41

AHR 4458 PROTOCOL 03
MEAN CHANGE IN DIASTOLIC BLOOD PRESSURE
WEEK 30 - WEEK 29
STUDY 310

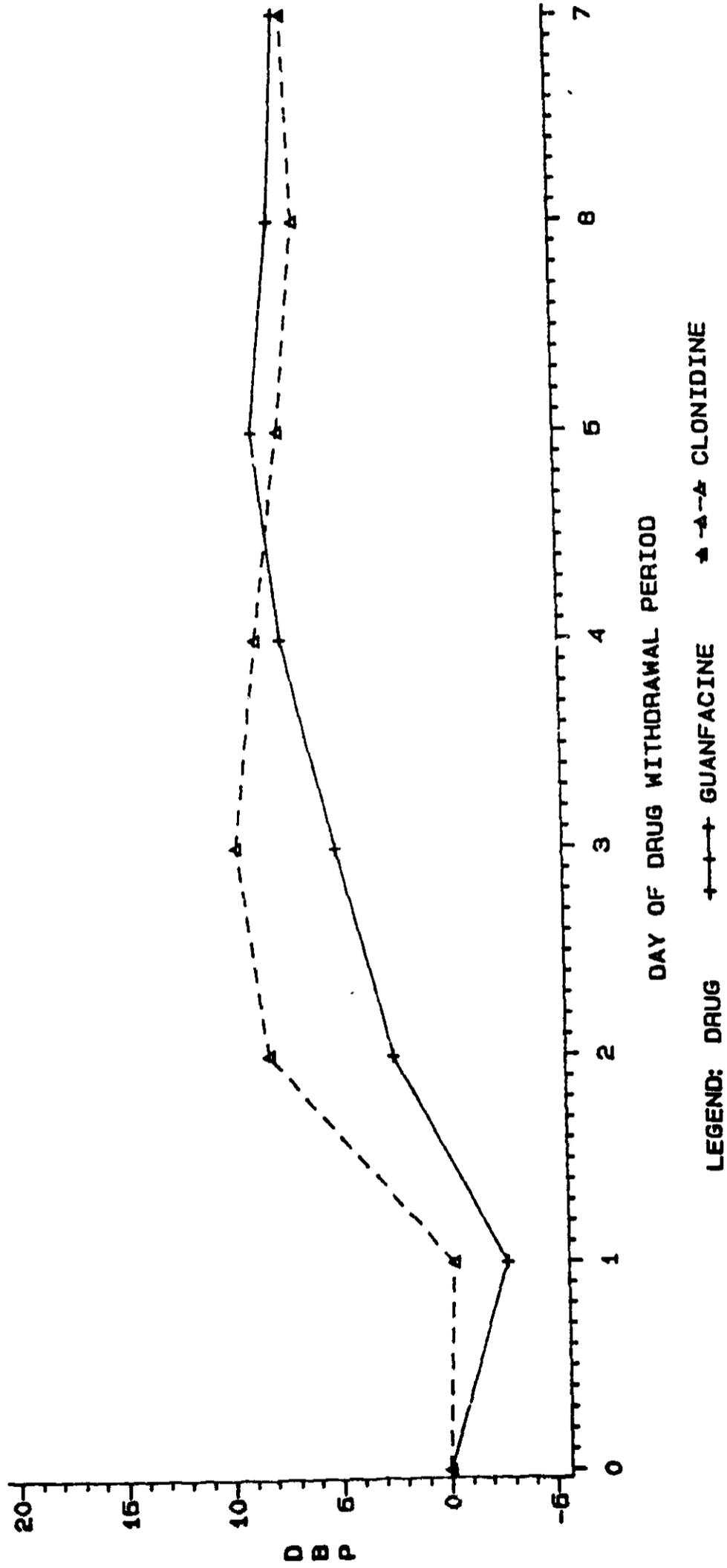
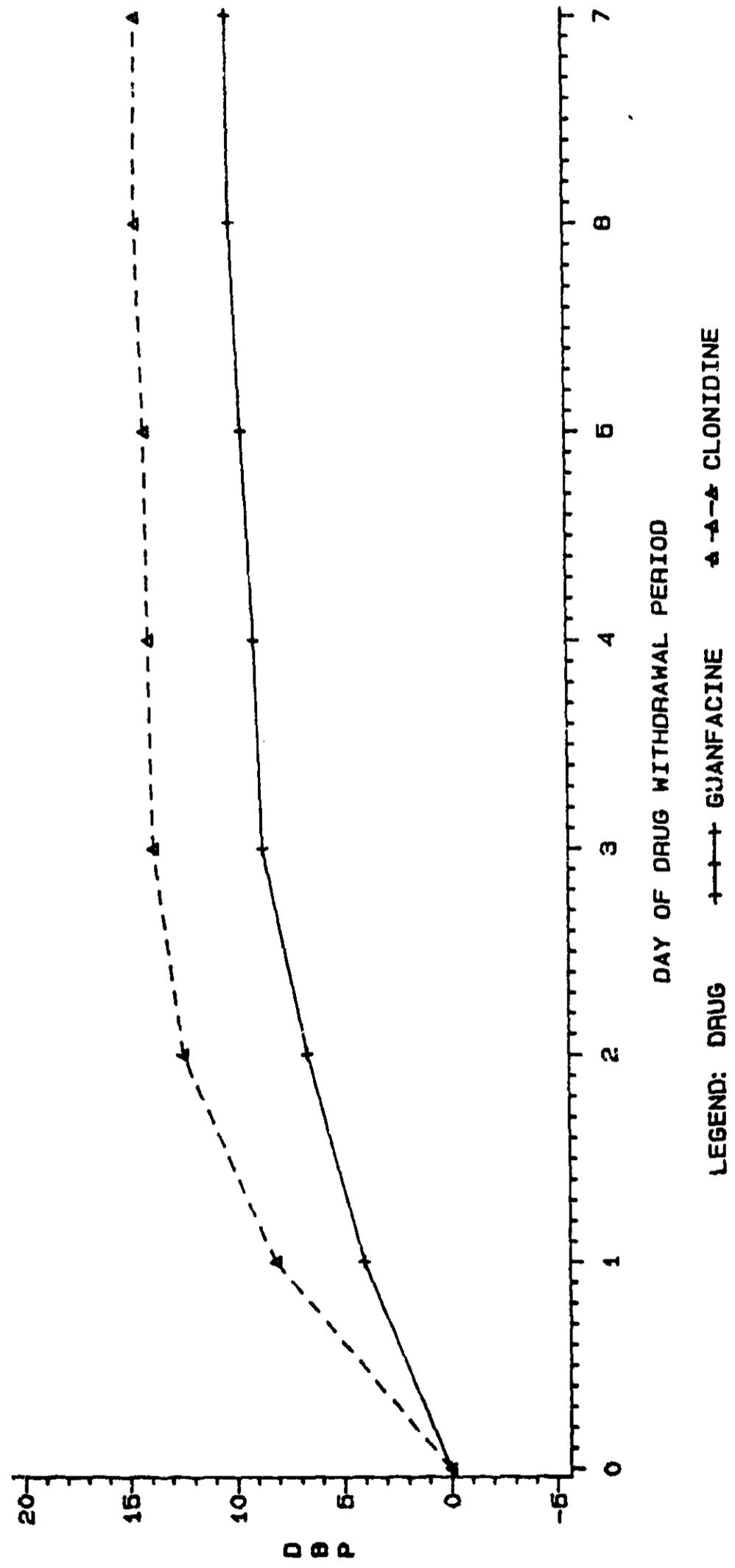


Figure 42

AHR 4458 PROTOCOL 03
MEAN CHANGE IN DIASTOLIC BLOOD PRESSURE
WEEK 30 - WEEK 29
STUDY 315



The frequency of patients who experienced an increase in DBP of >5 or >10 mmHg during each day of Week 30 is given in tables LXXXI and LXXXII. There were no significant differences in the frequency of patients who experienced an increase in DBP of >5 or >10 mmHg in Study 310. In Study 315, the percentage of patients who experienced an increase of >5 mmHg on Days 2 (guanfacine, 2% vs. clonidine, 14%), 3 (guanfacine, 5% vs. clonidine, 24%) and 4 (guanfacine, 4% vs. clonidine, 16%) of Week 30 was statistically significant ($p < 0.05$) and clinically relevant. These results confirm the observations with the mean change in DBP as given above.

Table LXXXI

Frequency of Patients Experiencing an Increase in Diastolic Blood Pressure
Increase = Max (Each Day) Week 30 - Overall Max Week E
AHR-4458, Protocol 03, Study 310

Treatment Increase	Group	Day						
		1	2	3	4	5	6	7
>5 (.331)	Guanfacine	1/20 (5%)	1/20 (5%)	4/20 (20%)	1/20 (5%)	6/20 (30%)	3/19 (16%)	3/19 (16%)
	Clonidine	2/22 (9%)	6/22 (27%)	6/22 (27%)	6/21 (29%)	4/21 (19%)	1/21 (5%)	1/21 (5%)
	*P-Value	(1.0)	(.096)	(.723)	(.093)	(.484)	(.331)	

>10	Guanfacine	0/20 (0%)	0/20 (0%)	1/20 (5%)	1/20 (5%)	1/20 (5%)	1/19 (5%)	0/19 (0%)
	Clonidine	1/22 (5%)	1/22 (5%)	2/22 (9%)	2/21 (10%)	1/21 (5%)	0/21 (0%)	0/21 (0%)
	*P-Value	(1.0)	(1.0)	(1.0)	(1.0)	(1.0)	(.475)	

*P-Values obtained via Fisher's Exact Test

Table LXXXII

Frequency of Patients Experiencing an Increase in Diastolic Blood Pressure
Increase = Max (Each Day) Week 30 - Overall Max Week 5
AHR-4458, Protocol 03, Study 315

Treatment Increase	Group	Day						
		1	2	3	4	5	6	7
>=5 (.114)	Guanfacine	0/55 (0%)	1/55 (2%)	3/55 (5%)	2/55 (4%)	1/55 (2%)	1/55 (2%)	1/55 (2%)
	Clonidine	5/59 (8%)	8/58 (14%)	14/58 (24%)	9/58 (16%)	5/57 (9%)	6/57 (11%)	6/57 (11%)
	*P-Value	(.058)	(.032)	(.007)	(.054)	(.206)	(.114)	
>=10 0/55	Guanfacine	0/55 (0%)	0/55 (0%)	0/55 (0%)	0/55 (0%)	0/55 (0%)	0/55 (0%)	0/55 (0%)
	Clonidine	2/59 (3%)	2/58 (3%)	4/58 (7%)	4/58 (7%)	2/57 (4%)	1/57 (2%)	1/57 (2%)
	*P-Value	(.496)	(.496)	(.119)	(.119)	(.496)	(1.0)	(1.0)

*P-Values obtained via Fisher's Exact Test

The mean diastolic pressure for each day during Week 5 and Week 30 and for each treatment group is given in figures 43 and 44. The mean DBP (Week 30) in Study 310 for the guanfacine treatment group plateaued by Day 5 of Week 30 at a level above the pretreat mean DBP (Week 5). In the clonidine treatment group, the mean DBP peaked at Day 3 of Week 30 at a level above the mean DBP at Week 5. During the last 3 days of week 30 the DBP in both groups was more or less the same. The results from Study 315 differ from those of Study 310 in that the mean DBP from neither group exceeded the pretreatment mean, but again, the rate of change in DBP was more rapid in the clonidine group than in the guanfacine group. The systolic blood pressure, however, increased above baseline levels in both groups during week 30 (Figure 45).

Figure 43

AHR 4458 PROTOCOL 03
MEAN DIASTOLIC BLOOD PRESSURE
OVER WEEKS 5 AND 30
STUDY 310

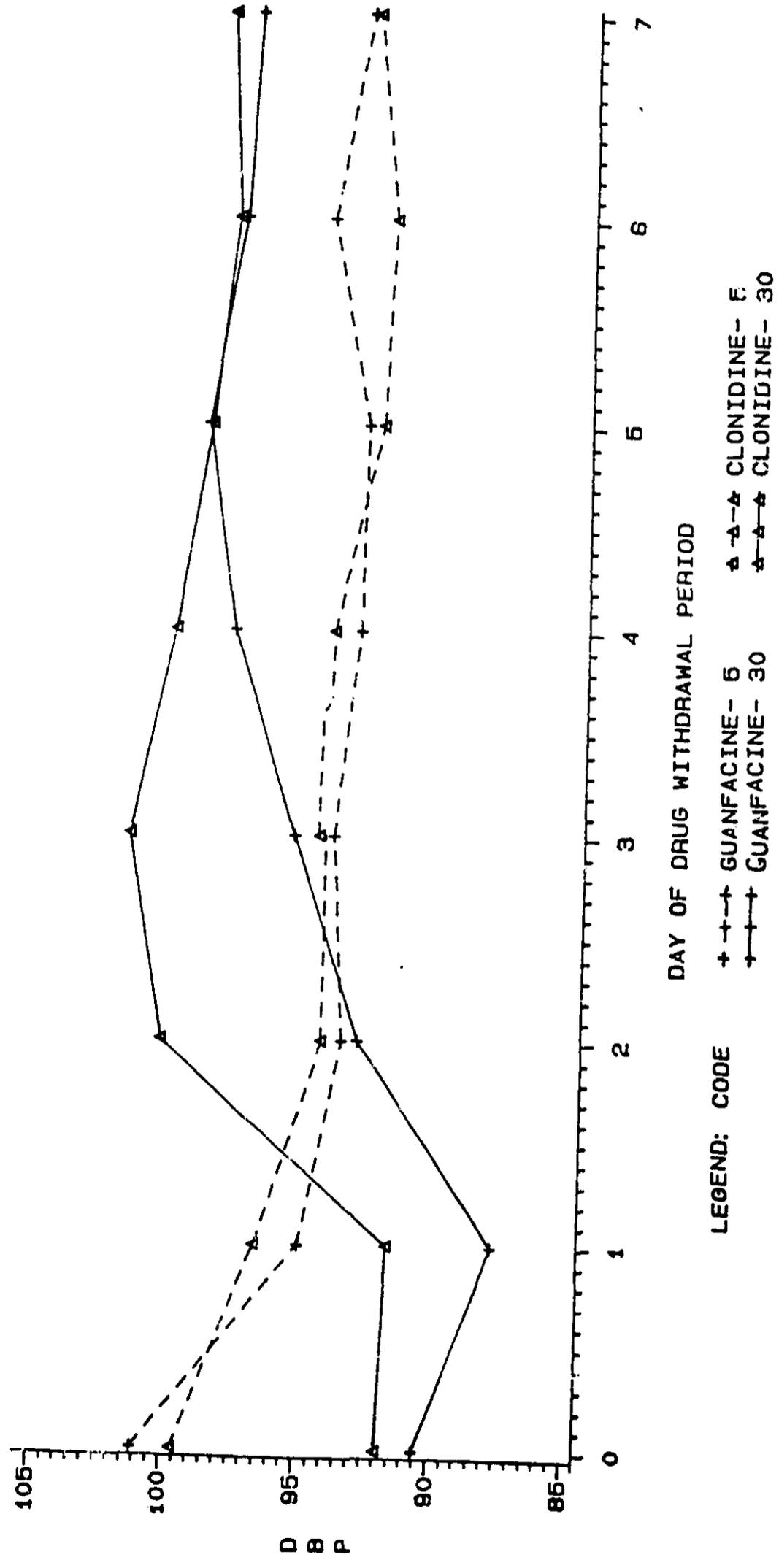


Figure 44

AMR 4458 PROTOCOL 03
MEAN DIASTOLIC BLOOD PRESSURE
OVER WEEKS 6 AND 30
STUDY 315

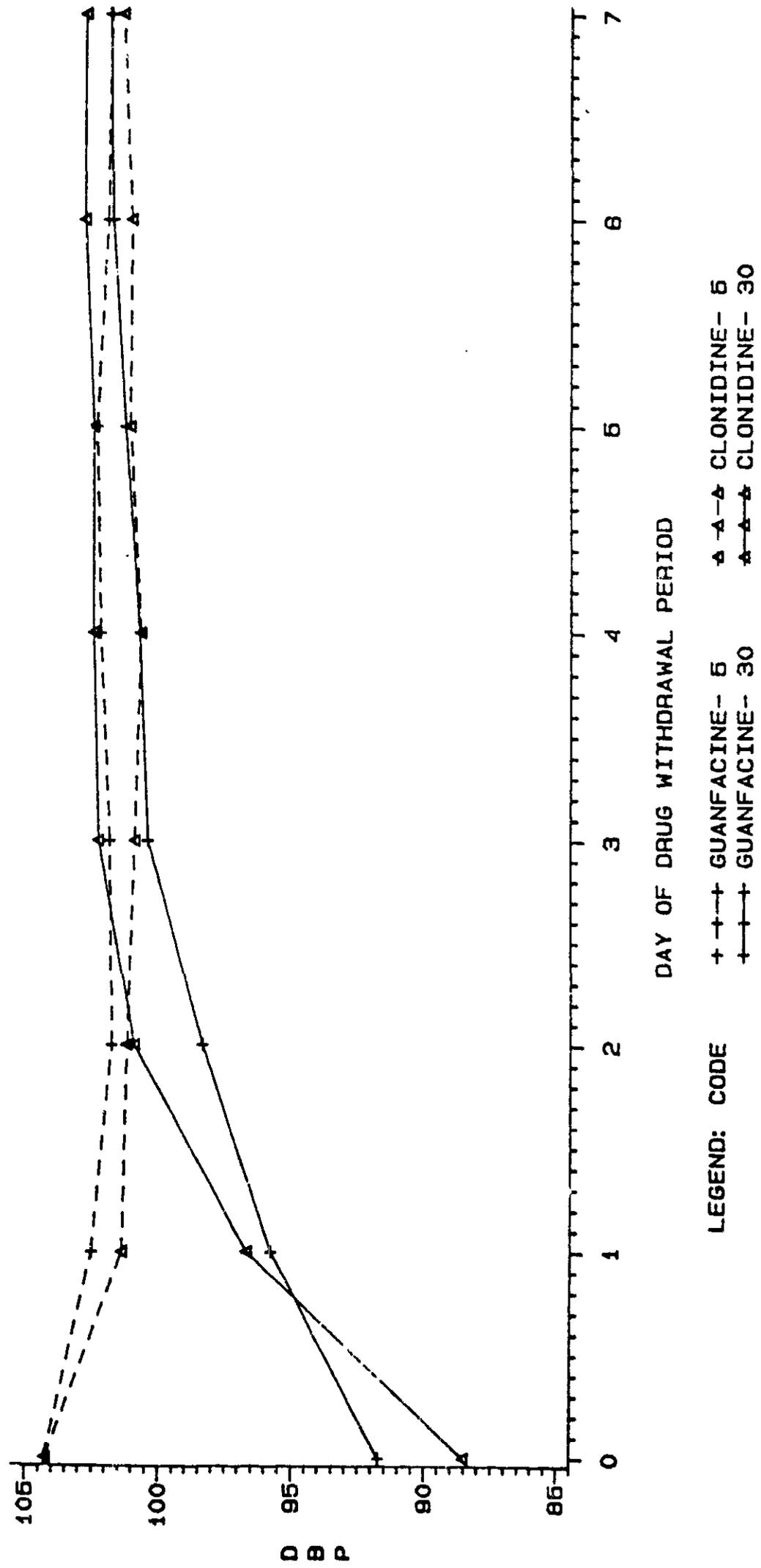
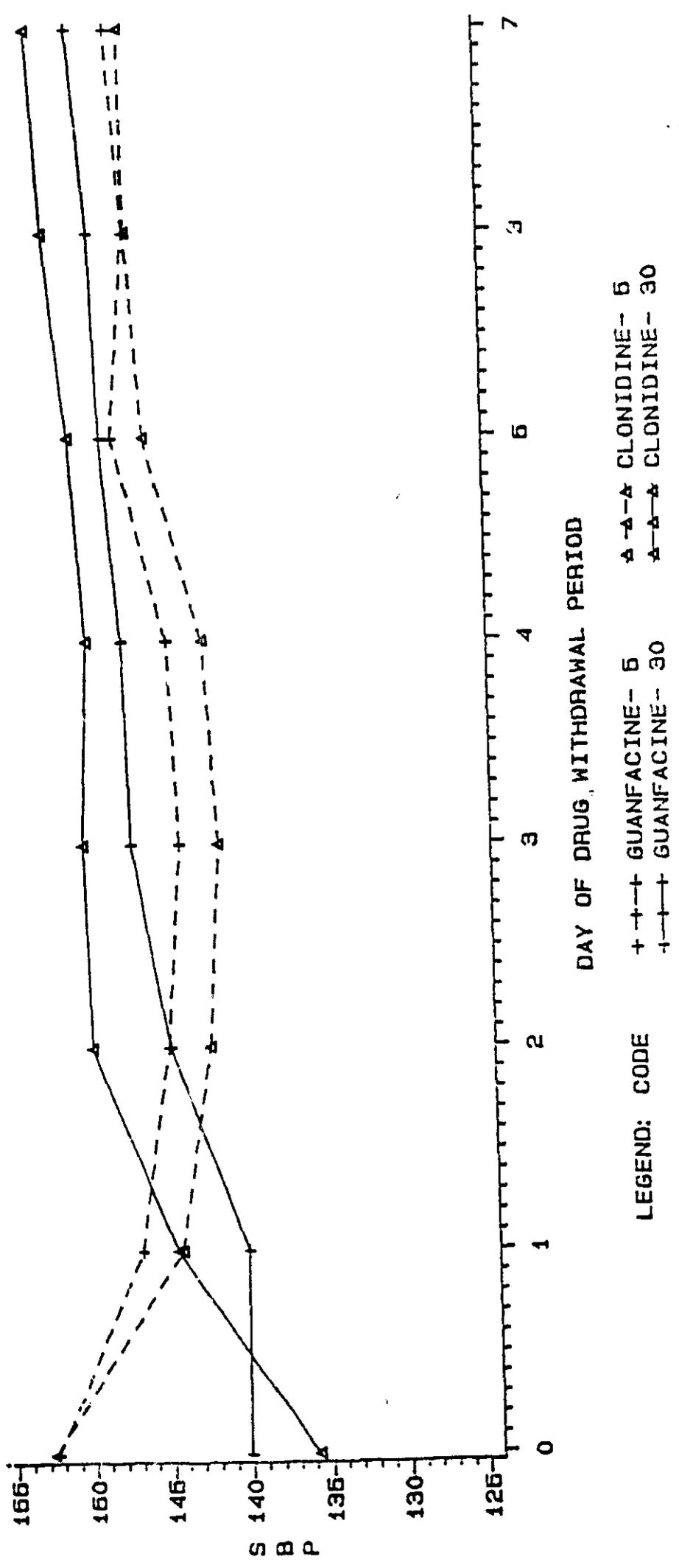


FIGURE 45
AIR 4458 PROTOCOL 03
MEAN SYSTOLIC BLOOD PRESSURE
OVER WEEKS 5 AND 30
STUDY 315



Symptoms of Drug Withdrawal

Every two hours during the day and every four hours at night during the Drug Withdrawal Observation Period (Week 30), each patient was asked whether or not they experienced any of the following symptoms which might be associated with abrupt withdrawal of centrally acting alpha adrenergic agonists: headache, palpitation, dizziness, tiredness, insomnia, fainting, nausea, vomiting, blurred vision, sweating, flushing, agitation/anxiety, apprehension, abdominal cramps, and chest pains.

Table LXXXIII

Summary of Drug Withdrawal Period Symptoms
Week 30
AHR-4458, Protocol 03, Study 310

		Guanfacine	Clonidine
Number of Patients Evaluated		20	22
Number Patients Experiencing 1 Symptom		2	1
Number Patients Experiencing 2 Symptoms		0	1
Number Patients Experiencing 3 Symptoms		0	0
Number Patients Experiencing ≥ 4 Symptoms		1	0

Symptom	Treatment Group	Number Patients Experiencing Symptom
Headache	Guanfacine	3 (15%)
	Clonidine	1 (5%)
Nausea	Guanfacine	1 (5%)
	Clonidine	0 (0%)
Vomiting	Guanfacine	1 (5%)
	Clonidine	0 (0%)
Abdominal Cramps	Guanfacine	1 (5%)
	Clonidine	0 (0%)
Palpitation	Guanfacine	0 (0%)
	Clonidine	1 (5%)
Dizziness	Guanfacine	0 (0%)
	Clonidine	1 (5%)

Table LXXXIV
 Summary of Drug Withdrawal Period Symptoms
 Week 30
 AHR-4458, Protocol 03, Study 315

		<u>Guanfacine</u>	<u>Clonidine</u>
Number of Patients Evaluated		55	59
Number Patients Experiencing 1 Symptom		15	14
Number Patients Experiencing 2 Symptoms		5	6
Number Patients Experiencing 3 Symptoms		1	3
Number Patients Experiencing >=4 Symtoms		0	6

<u>Symptom</u>	<u>Treatment Group</u>	<u>Number Patients Experiencing Symptom</u>
Headache	Guanfacine	19 (35%)
	Clonidine	24 (41%)
Dizziness	Guanfacine	4 (7%)
	Clonidine	5 (8%)
Nausea	Guanfacine	3 (5%)
	Clonidine	11 (19%)
Tiredness	Guanfacine	1 (2%)
	Clonidine	1 (2%)
Agitation/Anxiety	Guanfacine	1 (2%)
	Clonidine	1 (2%)
Insomnia	Guanfacine	0 (0%)
	Clonidine	5 (8%)
Apprehension	Guanfacine	0 (0%)
	Clonidine	5 (8%)
Vomiting	Guanfacine	0 (0%)
	Clonidine	4 (7%)
Flushing	Guanfacine	0 (0%)
	Clonidine	4 (7%)
Sweating	Guanfacine	0 (0%)
	Clonidine	1 (2%)
Chest Pains	Guanfacine	0 (0%)
	Clonidine	1 (2%)

Drug withdrawal symptoms, when reported, generally occurred during the first 4 days after abrupt discontinuation of either guanfacine or clonidine. The time course for appearance of drug withdrawal symptoms seemed to follow the rise in blood pressure, but there were no individual symptoms or groups of symptoms which preceded the increase in blood pressure such that these symptoms could be used as a harbinger of "rebound hypertension".

Catecholamine Response

The mean 24 urinary catecholamine output for each day of the Drug Withdrawal Observation Periods (Week 5 vs. Week 30) was calculated for epinephrine, norepinephrine, and VMA. However, attempts to correlate an increase in blood pressure with increase in any catecholamine were inconsistent across patients in both studies. Some patients showed large increases in urinary catecholamines with relatively little or no increase in blood pressure and others showed rather dramatic increases in blood pressure without concurrent increases in catecholamines. Thus, urinary catecholamine response does not appear to be a good predictor of "rebound hypertension".

Outpatient Studies

The results from 9 clinical investigators were evaluated for poolability and found to be poolable for all analyses. During Week 5 and at the beginning of Week 30, data from 160 guanfacine patients and 156 clonidine patients were available for analysis. These numbers fell to 155 and 148, respectively, by the end of the study.

Drug Withdrawal Reaction Results

Vital Sign Changes

Using the end of treatment at Week 29 as a baseline in figures 46, 47 and 48, the mean changes in diastolic blood pressure, systolic blood pressure and heart rate during Week 30 are shown. The increase in DBP among patients in the clonidine group was significantly greater than the increase observed in the guanfacine group on Days 1 ($p=0.002$), 2 ($p=0.051$), and 3 ($p=0.040$). Increases in SBP were greater and statistically significant on Day 1 ($p=0.003$) and 2 ($p=0.050$). These results paralleled the results observed in the inpatient studies with the increases in vital signs upon drug withdrawal being more rapid in the clonidine group than in the guanfacine group.

Figure 46

AHR 4458 PROTOCOL 03
MEAN CHANGE IN DIASTOLIC BLOOD PRESSURE
WEEK 30 - WEEK 29
OVERALL OUTPATIENT

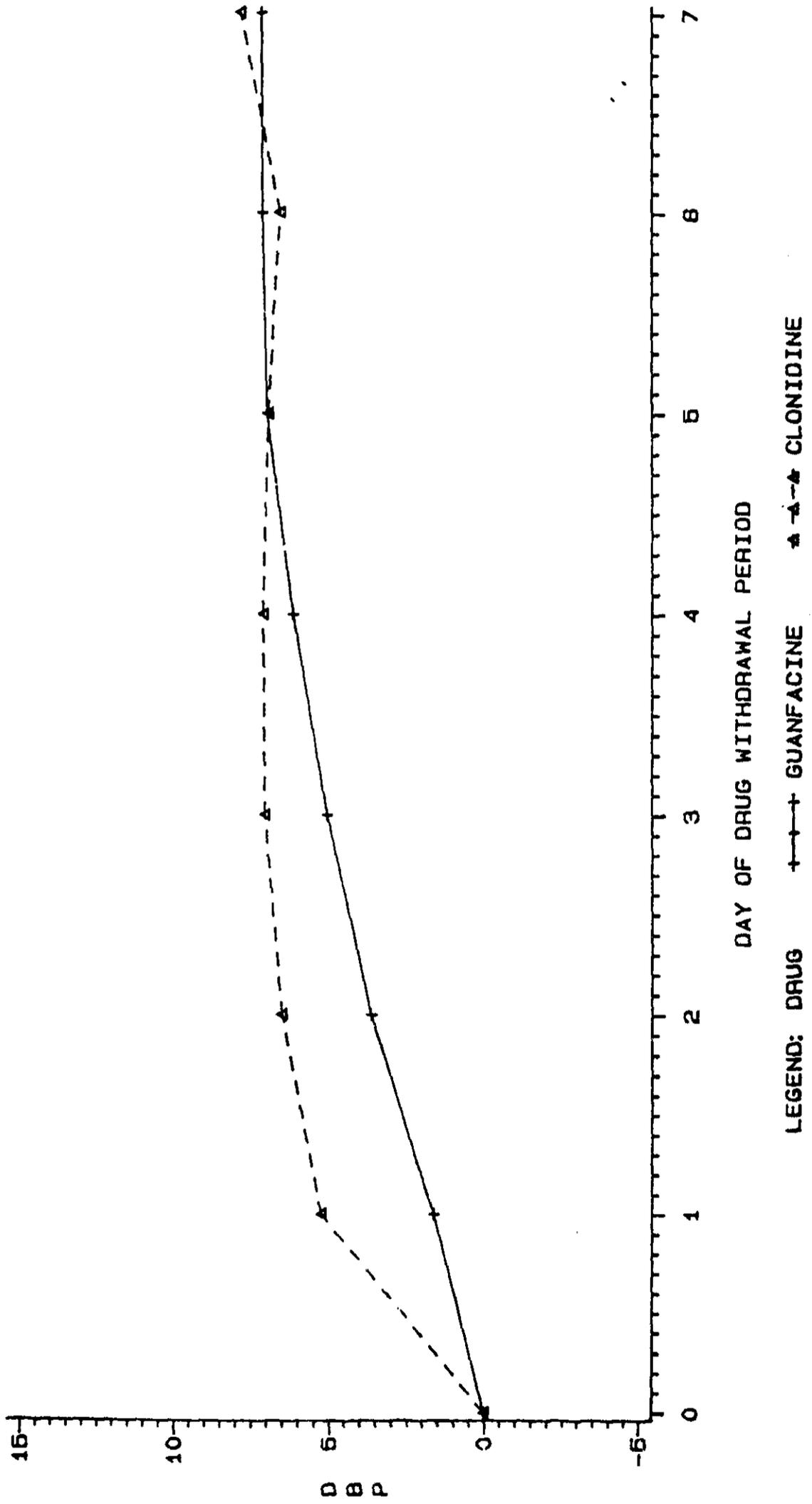
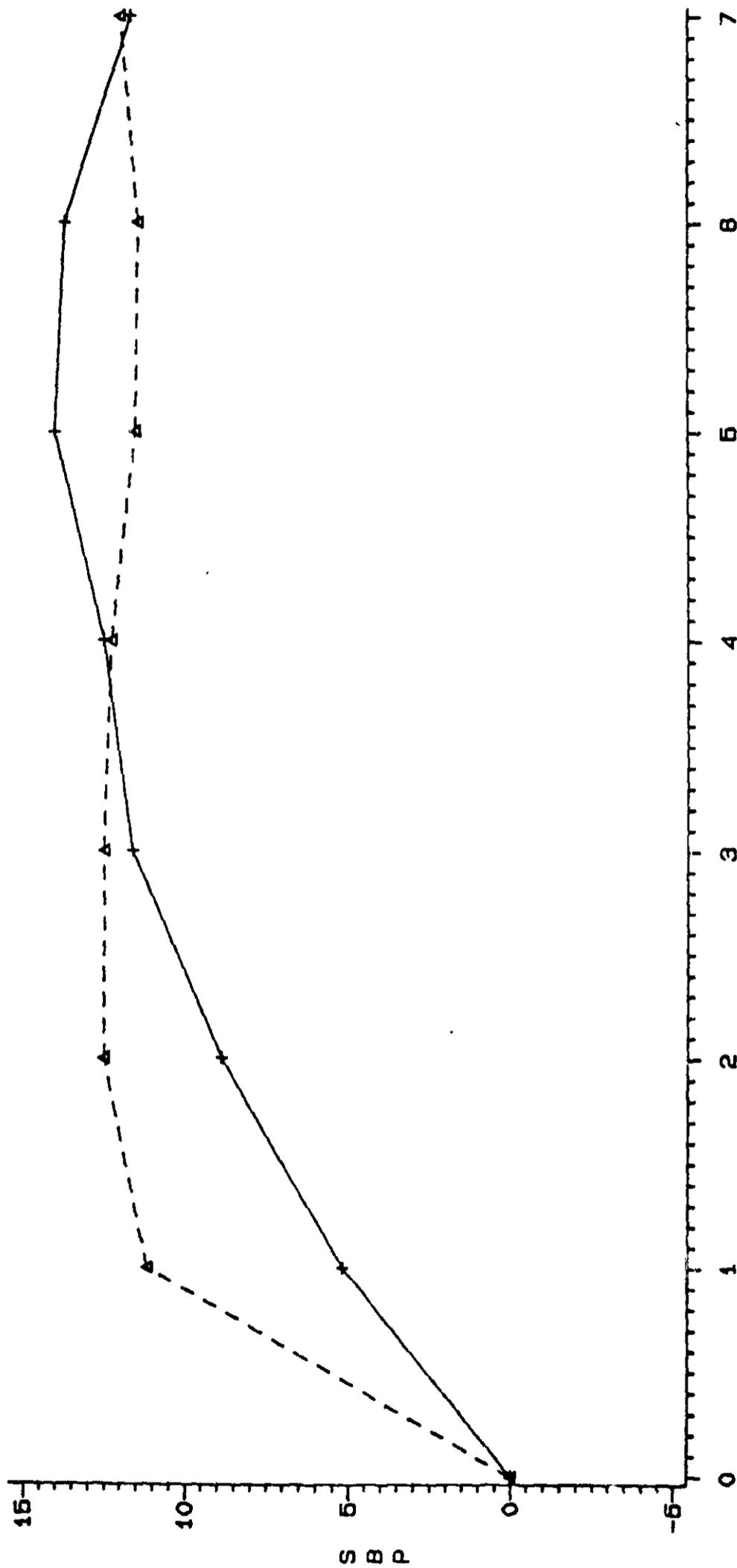


Figure 47

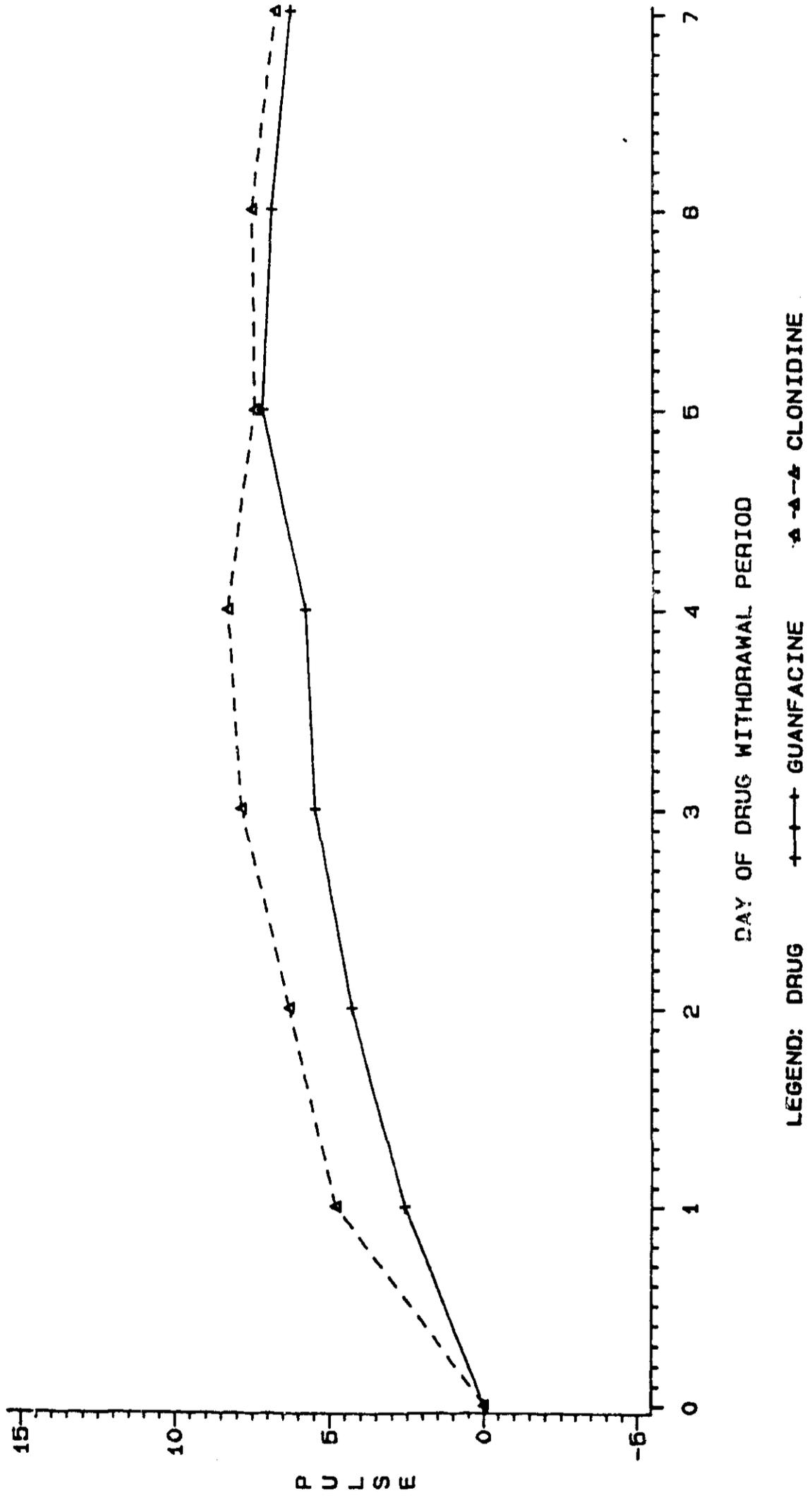
AHR 4468 PROTOCOL 03
MEAN CHANGE IN SYSTOLIC BLOOD PRESSURE
WEEK 30 - WEEK 29
OVERALL OUTPATIENT



LEGEND: DRUG +--+ GUANFACINE ▲-▲- CLONIDINE
DAY OF DRUG WITHDRAWAL PERIOD

Figure 48

AHR 445E PROTOCOL 03
MEAN CHANGE IN PULSE
WEEK 30 - WEEK 29
OVERALL OUTPATIENT



The mean DBP, SBP, and HR for each day during Weeks 5 and 30 are shown for each treatment group in figures 49-51. The mean DBP for both guanfacine and clonidine during Week 30 failed to "rebound" to the baseline mean DBP established during Week 5. The mean SBP during Week 30 for both treatment groups slightly exceeded the baseline mean SBP, and the mean SBP in the clonidine group rose at a much faster rate compared with the guanfacine group. Heart rate during Week 30 rose upon discontinuation of treatment, and the mean HRs at the end of Week 30 were slightly higher than at the end of Week 5. These results suggest that, on average, blood pressure and heart rate for patients treated with either guanfacine or clonidine on the doses and dosing schedule used in this study rise upon abrupt discontinuation of either drug, but the vital signs do not "overshoot" a control baseline.

The frequency distribution of patients with increases in diastolic blood pressure >5 or >10 mmHg were analyzed. There were no significant differences between treatment groups on any day of the Drug Withdrawal Period.

Figure 49

AHR 4458 PROTOCOL 03
MEAN DIASTOLIC BLOOD PRESSURE
OVER WEEKS 6 AND 30
OVERALL OUTPATIENT

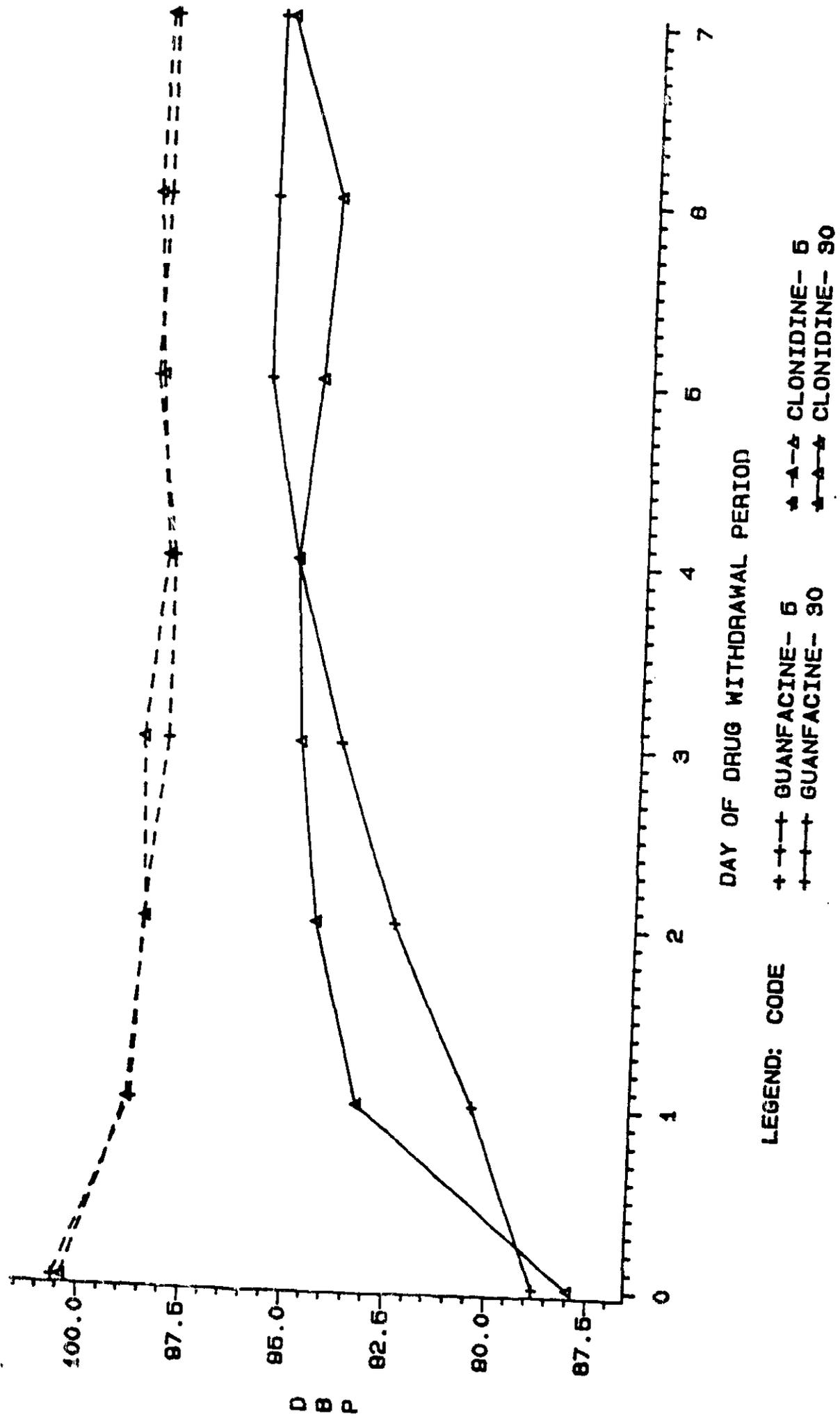


Figure 50

APR 4468 PROTOCOL 03
MEAN SYSTOLIC BLOOD PRESSURE
OVER WEEKS 5 AND 30
OVERALL OUTPATIENT

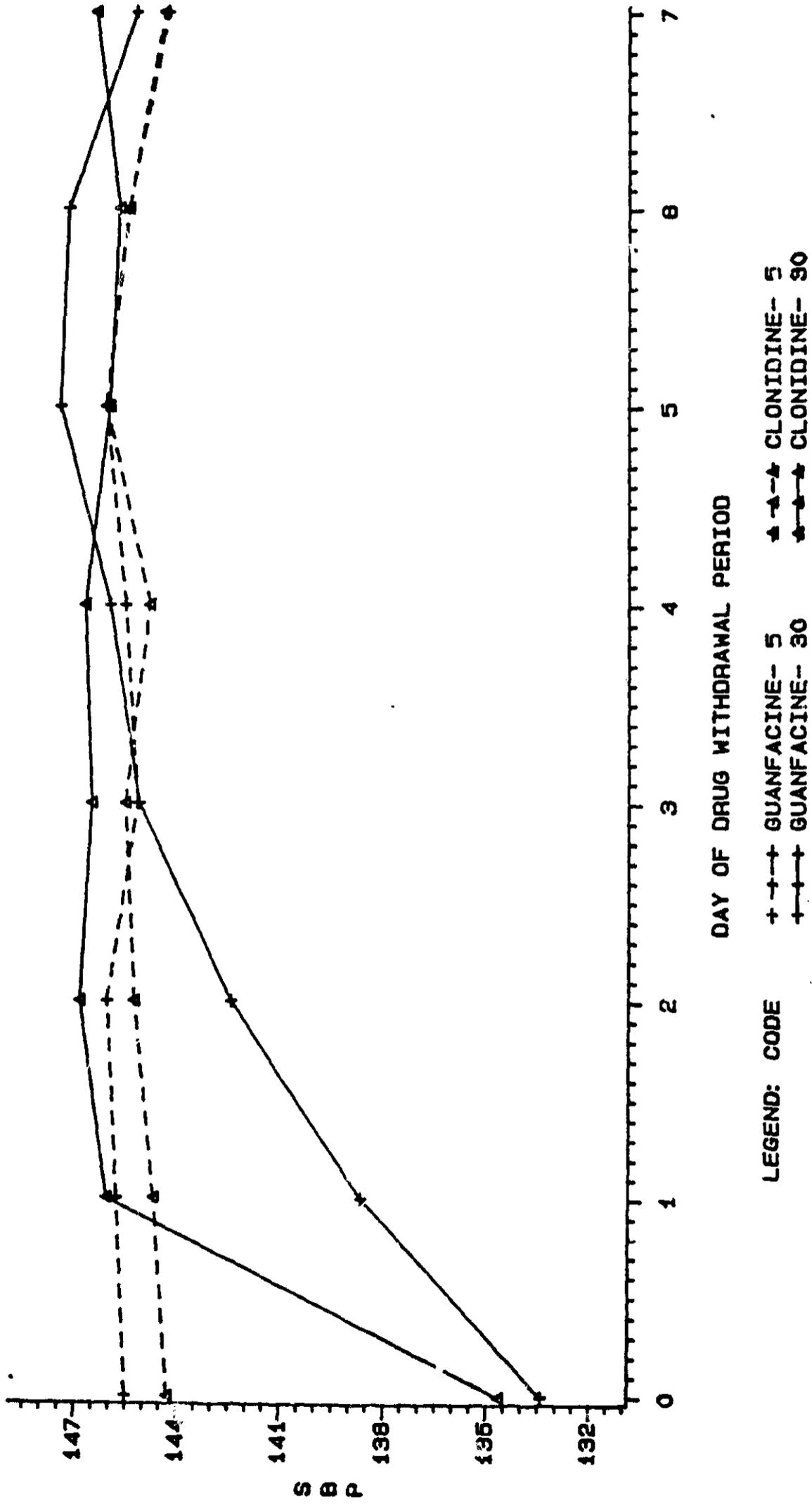
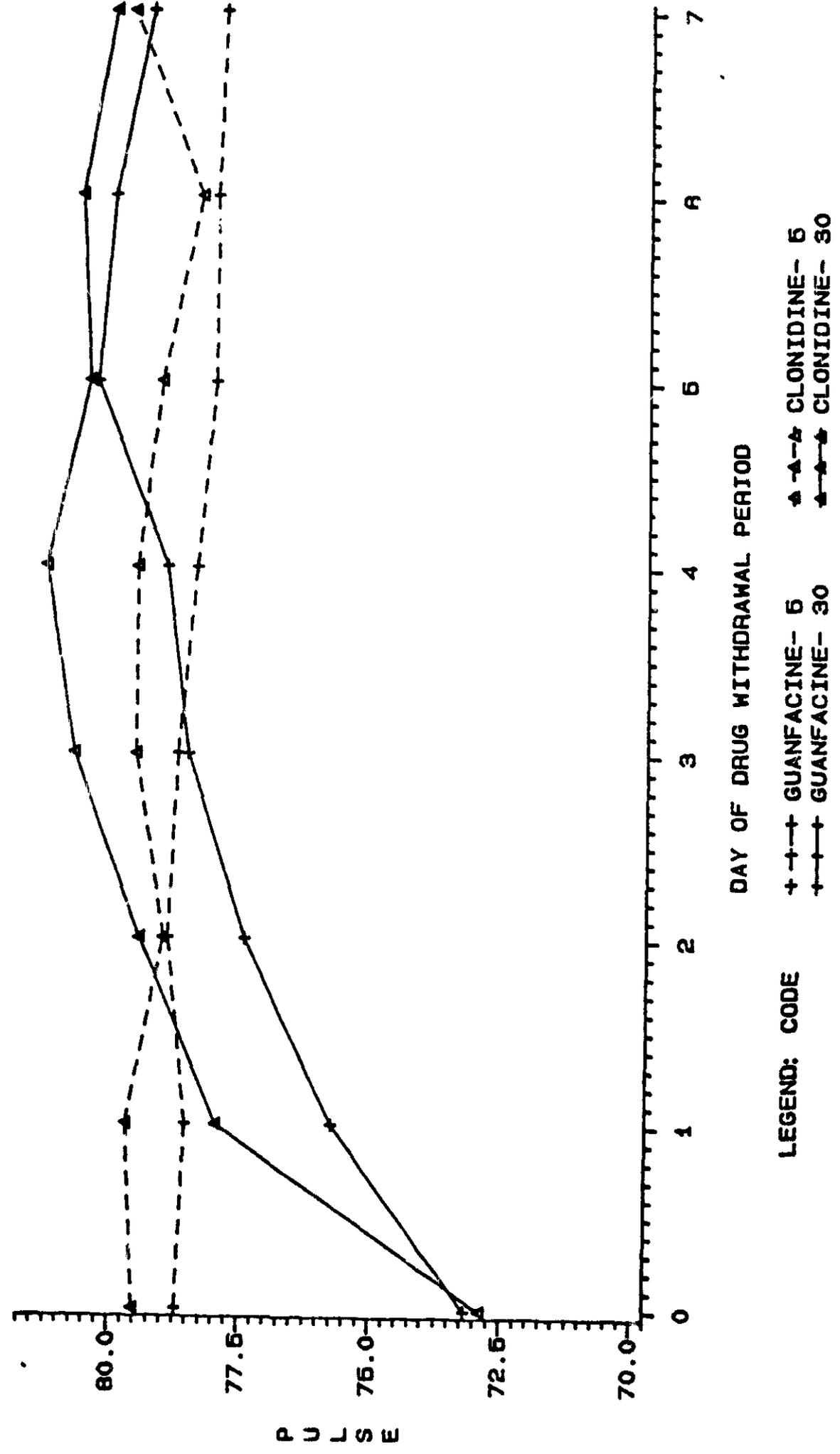


Figure 51

AHR 4458 PROTOCOL 03
MEAN PULSE
OVER WEEKS 6 AND 30
OVERALL OUTPATIENT



LEGEND: CODE +--+ GUANFACINE- 5 ▲-▲- CLONIDINE- 5
 +--+ GUANFACINE- 30 ▴-▴- CLONIDINE- 30

Symptoms of Drug Withdrawal

The frequency distribution of patients with 1, 2, 3, or >4 symptoms of drug withdrawal during Week 30 is given in Table LXXXV. The frequency distribution of patients who reported a particular symptom of drug withdrawal is also given.

Eight patients in the clonidine/chlorthalidone treatment group were discontinued from the study during the Drug Withdrawal Period (Week 30) because of symptoms of drug withdrawal and/or rapid elevation of blood pressure.

Five patients in the guanfacine/chlorthalidone treatment group were discontinued from the study during the Drug Withdrawal Period (Week 30) because of symptoms of drug withdrawal and/or rapid elevations of blood pressure.

Table LXXXV
 Summary of Drug Withdrawal Period Symptoms
 Week 30
 AHR-4458, Protocol 03
 Overall Outpatient

		<u>Guanfacine</u>	<u>Clonidine</u>
Number of Patients Evaluated		160	156
Number Patients Experiencing 1 Symptom		27	19
Number Patients Experiencing 2 Symptoms		18	15
Number Patients Experiencing 3 Symptoms		8	10
Number Patients Experiencing ≥ 4 Symptoms		20	28

<u>Symptom</u>	<u>Treatment Group</u>	<u>Number Patients Experiencing Symptom</u>
Headache	Guanfacine	44 (28%)
	Clonidine	51 (33%)
Tiredness	Guanfacine	26 (16%)
	Clonidine	33 (21%)
Dizziness	Guanfacine	23 (14%)
	Clonidine	19 (12%)
Nausea	Guanfacine	22 (14%)
	Clonidine	28 (18%)
Agitation/Anxiety	Guanfacine	20 (13%)
	Clonidine	20 (13%)
Flushing	Guanfacine	15 (9%)
	Clonidine	16 (10%)
Palpitation	Guanfacine	14 (9%)
	Clonidine	22 (14%)
Insomnia	Guanfacine	14 (9%)
	Clonidine	20 (13%)
Sweating	Guanfacine	12 (8%)
	Clonidine	15 (10%)
Apprehension	Guanfacine	11 (7%)
	Clonidine	9 (6%)

Table LXXXV (continued)
 Summary of Drug Withdrawal Period Symptoms
 Week 30
 AHR-4458, Protocol 03
 Overall Outpatient

Symptom	Treatment Group	Number Patients Experiencing Symptom
Abdominal Cramps	Guanfacine	9 (6%)
	Clonidine	10 (6%)
Chest Pains	Guanfacine	5 (3%)
	Clonidine	5 (3%)
Blurred Vision	Guanfacine	4 (3%)
	Clonidine	3 (2%)
Vomiting	Guanfacine	3 (2%)
	Clonidine	7 (4%)
Fainting	Guanfacine	3 (2%)
	Clonidine	3 (2%)

DISCUSSION

This was the first prospective, randomized, double-blind evaluation of the long-term use of guanfacine vs. clonidine that was ever done. Because it was a pioneer effort and involved a large number of patients, certain points demonstrated in the trial are quite important.

In this study, both drugs produced clinically significant reductions in blood pressure in patients with mild and moderate essential hypertension and, since titration was allowed, a good idea of the equipotent daily doses of the two agents can be discerned. In this trial, daily doses of guanfacine and clonidine in the ratio of 5:1 produced equal reductions in blood pressure.

Prior to the study it was postulated that, due to the long elimination half life of guanfacine relative to clonidine, the former could be effectively dosed once daily. In addition, it was felt that this long elimination half life would, upon sudden withdrawal of the drug, lengthen the time before the symptoms and/or signs of "rebound" hypertension appeared thus attenuating any risk to the patient should he miss a dose or two of the drug.

Yet another hypothesis based upon the long half life in humans and basic animal data, was that h.s. dosing of guanfacine would result in less sedation when compared to clonidine dosed b.i.d.

The 24-hour effectiveness was proven in Study 02.

The ability of guanfacine to produce a relatively benign rebound picture was shown in the present study. The number of patients with symptoms and/or signs of rebound was lower with guanfacine than with clonidine (although not significantly different) but was quite low with both agents thus supporting reports in the literature that suggest that rebound with clonidine is primarily seen after withdrawal of large daily doses and in patients with more severe hypertension.

Abrupt withdrawal of guanfacine produced, in this carefully controlled study, a slower return of blood pressure to pretreatment levels than did clonidine. After abrupt withdrawal of both alpha agonists, blood pressure and heart rate increases occurred earlier (days 1-3) with clonidine than with guanfacine (days 3-7). Since clonidine can provoke a withdrawal reaction within 24 hours, guanfacine is potentially advantageous, since should the patient miss a dose or two for any reason, the risk of rebound is less than with clonidine.

Due to the fact that guanfacine can be taken qd before bedtime, patients treated with it feel less somnolence during the day than patients treated with clonidine which is administered bid.

* * * * *

3. U.S. Trials: Monotherapy

Three well-controlled clinical studies (2 placebo-controlled and 1 positive-controlled) of guanfacine monotherapy were completed with 83 patients receiving guanfacine, 1 mg, at bedtime. These studies provided some evidence of the efficacy of guanfacine given as 1 mg/day monotherapy (Table LXXXVI).

Study 06 was designed to elucidate the effects of guanfacine on blood pressure, heart rate, plasma aldosterone and plasma volume in patients with mild to moderate essential hypertension (DBP = 90-114 mmHg). The study was double-blind, randomized, placebo-controlled with a parallel design. After a 4-week wash-out period, patients were randomized in a 2:1 (guanfacine: placebo) ratio to therapy. The treatment period lasted 4 weeks (Weeks 5-8). Plasma volume and plasma aldosterone were measured immediately prior to randomization and at the end of treatment. Blood pressure and heart rate were measured at entry into the screening period, Week 2, 4 (baseline, just prior to treatment), 6 and 8 (end of treatment). Blood pressure and heart rate were measured 12-18 hours after dosing. Seventeen patients received 1 mg of guanfacine and 9 received placebo. All patients took their medications at bedtime.

TABLE LXXXVI

Overall Summary of Results of Guanfacine Monotherapy Clinical Studies

Study No.	Investigator	n	Blood Pressures						Net Difference from Placebo					
			Baseline		Endpoint		Change							
			Guanf.	Place.	Guanf.	Place.	Guanf.	Place.		Guanab.				
06	M. Strauss	17	9	-	149/ 97	163/ 97	NA	140/ 84	156/ 99	NA	-9*/ -13	-7/ +2	NA	-2/ -15
11	J. Black-shear	21	21	-	150/ 97	159/ 97	NA	148/ 84	156/ 96	NA	-2*/ -13	-3/ -1	NA	+1/ -12
1401	J. Fillingim	27	-	28	145/ 97	NA	147/ 97	141/ 88	NA	142/ 87	-4**/ -9	NA	-5/ -7	-
1402	P. Boyles	18	-	18	151/ 95	NA	149/ 97	142/ 87	NA	135/ 84	-9**/ -8	NA	-14/ -13	-

*Compared to placebo $p < 0.05$.

**Compared with guanfacine = NS.

Guanfacine had no significant effect on either plasma volume or plasma aldosterone. Guanfacine significantly reduced diastolic blood pressure from a mean of 97 to 84 (-13 mmHg change) during the 1-month treatment period ($p < 0.0001$). Diastolic blood pressure in the 9 patients receiving placebo went up on average by 2 mmHg. The effect on systolic pressure was less clear pressure falling only 2.6 mmHg more than placebo. The mean decrease in diastolic blood pressure with 1 mg guanfacine over a 1-month treatment period was approximately equal to the mean decrease (-12.6 mmHg) observed in a dose-response study with 25 mg chlorthalidone (Study 01), but the systolic response was clearly smaller. No patients reported side effects in this study.

Blackshear (Study 11) investigated the effects of guanfacine on blood pressure, heart rate, blood glucose and plasma lipids using the same study design as Strauss with the exception of the treatment group sizes which were equal. Twenty-one patients received 1 mg guanfacine at bedtime for 4 weeks and 21 patients took placebo during the same period. Measurements of blood pressure, heart rate, and plasma lipids were done at the same time intervals as in Strauss' study. The baseline blood glucose samples were lysed during shipment to National Health Laboratories for analysis, and therefore, this variable could not be evaluated. Plasma lipids were not significantly altered by guanfacine treatment.

Diastolic blood pressure in guanfacine treatment group decreased (an average of 13 mmHg) by the end of treatment versus a mean decrease of 2 mmHg in the placebo group. These differences were highly significant ($p < 0.0001$). Systolic blood pressure, however, actually fell more in the placebo group (3.2 mmHg vs. 1.3 mmHg). The decrease in diastolic blood pressure with 1 mg of guanfacine was approximately the same as that observed in Study 01 (mean 12.6 mmHg). One patient reported dry mouth and 3 patients experienced drowsiness during treatment with guanfacine.

These two placebo controlled studies suggest the effectiveness of 1 mg/day guanfacine for the treatment of mild to moderate essential hypertension, but are limited in their interpretation by the absence of a clear effect on systolic pressure.

A third study of guanfacine as monotherapy (Studies 1401 and 1402) was conducted. The aim of this study was to compare the safety and efficacy of guanfacine versus guanabenz for the treatment of mild to moderate essential hypertension (seated DBP average of 90-114 mmHg). Of particular interest was the comparative incidence of somnolence.

The study was double-blind with a parallel design. The study was divided into a 2-week screening period during which placebo capsules (b.i.d.) were substituted for previously effective antihypertensive agents. Patients who completed this screening period, who met all other requirements for entry into the study, and whose average seated DBP was in the 90-114 mmHg range were randomized to either guanfacine or guanabenz. Guanfacine was given at bedtime as a 1-mg capsule, and a dummy placebo capsule was administered each morning to maintain the blind. Guanabenz was dosed at 4 mg, b.i.d. for the first 7 days followed by 8 mg b.i.d. for the remaining 7 weeks of treatment. All test medications (including placebo) were identical in appearance. Blood pressure and heart rate were measured 12-18 hours after the evening dose.

Ninety-one patients (45 guanfacine and 46 guanabenz) were randomized to treatment, and 89 patients (44 guanfacine and 45 guanabenz) completed the study. Comparative efficacy was measured by the percentage of patients normalized (DBP <90 mmHg) by the end of treatment. In the guanfacine treatment group, 62% were normalized versus 70% in the guanabenz group, but the differences were not statistically significant. The mean decrease in DBP in the guanfacine treatment group of both investigators was approximately the same (9 mmHg for Fillingim and 8 mmHg for Boyles). However, the mean decrease in DBP in Dr. Boyles' guanabenz treatment group were 13 mmHg versus 7 mmHg for Dr. Fillingim. These differences prevented the pooling of data for this type of efficacy analysis. It is possible that the differences between investigators could be explained because of Dr. Boyles' evaluation of patients during the morning versus Dr. Fillingim's evaluations which were generally done throughout the day. The guanabenz group in Dr. Boyles' study would have had their blood pressure measured closer to their last dose of guanabenz. If so, this could suggest some loss of effect of guanfacine toward the end of the 24-hour dose interval. The modest falls in BP in this active control study limit its persuasiveness as evidence of effectiveness. Note especially the very small change in systolic pressure.

The percentage of patients reporting an adverse experience was greater in the guanabenz group than in the guanfacine group (57% vs. 33%). The percentage of patient experiencing an increase in somnolence was also greater in the guanabenz group than in the guanfacine group (59% vs. 31%), and this difference was statistically significant ($p=0.008$).

Safety of Guanfacine Monotherapy

The frequency of the most common side effects with guanfacine monotherapy was low, lower than most of the studies in which guanfacine was combined with chlorthalidone. These results are given in Table LXXXVII. Different types of reported side effects were more numerous when guanfacine was given with chlorthalidone. Overall, the type of side effects reported with guanfacine are not unexpected for a centrally acting alpha-adrenergic agonist, and the frequency of selected bothersome side effects (somnolence) is less than that observed with guanabenz.

While these studies of 1 mg doses, as well as published studies of larger doses used in active control trials, indicate guanfacine is active as monotherapy, they do not yet show what the appropriate dose is, or, more precisely, do not describe dose-response and dose-adverse effect relationships.

Table LXXXVII

Comparison of Side Effects with Guanfacine as Monotherapy
or with Chlorthalidone

Frequency Distribution of Patients with Most Common Side Effects				
Side Effect	Study 01 n = 72	Study 06 n = 17	Study 11 n = 21	Study 14 n = 45
Dry mouth	6 (8.3%)	0	1 (4.8%)	6 (13.3%)
Dizziness	3 (4.2%)	0	0	2 (4.4%)
Headache	3 (4.2%)	0	0	2 (4.4%)
Somnolence	0	0	3 (14.3%)	*

*A special rating scale was used in this study to measure somnolence and the results cannot properly be compared with the other studies because information on somnolence was solicited from each patient by direct questioning.

Discussion

A single-rising dose tolerance study in normotensive volunteers (Study S-02, See Clinical Pharmacology Section of this document) suggested a dose-response relationship for the maximum effect of single doses of guanfacine (0.5, 1, 1.5, and 2 mg) given once daily and the evidence cited above suggests that a 1 mg dose as monotherapy has some effect in hypertensive patients. There are no well-controlled, dose-response studies in hypertensive patients on guanfacine monotherapy. Western European experience with guanfacine provides a historical perspective of the issues of proper dose. In Europe, the initially recommended dosage schedules resulted in doses 3-10 times higher than those now recommended as a result of the dose-response data now available. The recommended dose of guanfacine in Western Europe has been decreasing over the last 10 years, however, and investigators have shown excellent blood pressure response with 1-2 mg doses of guanfacine, given as a single, daily dose.

* * * * *

C. Supportive Controlled Studies

Protocol Number	Principal Investigator	Purpose of Study	No. Patients Receiving Tenex	No. Patients Receiving Placebo	No. Patients On Competitive Drug	Tenex Doses (mg/day)	Tenex Dosage Schedule
11	G. Csajkas, M.D.	Single-blind, crossover, efficacy/safety vs. placebo	10	10	NA	3-6	t.i.d.
12	I. Esch, M.D.	Single-blind, crossover, efficacy/safety vs. placebo	11	11	NA	3-6	t.i.d.
13	A. Heidland, M.D.	Single-blind, crossover, efficacy/safety vs. placebo	11	11	NA	3-9	t.i.d.
14	P. Peltola, M.D.	Single-blind, crossover, efficacy/safety vs. placebo	11	11	NA	3-6	t.i.d.
15	M. Radonic, M.D.	Single-blind, crossover, efficacy/safety vs. placebo	12	12	NA	3-6	t.i.d.
31	I. Esch, M.D.	Single-blind, crossover, efficacy/safety vs. methyl-dopa	20	20	20	1-5	b.i.d. or t.i.d.
32	A. Heidland, M.D.	Single-blind, crossover, efficacy/safety vs. methyl-dopa	20	20	20	1-6	t.i.d. or q.i.d.
33	O. Ripka, M.D.	Single-blind, crossover, efficacy/safety vs. methyl-dopa	14	14	14	1-15	b.i.d. to t.i.d.

C. Supportive Controlled Studies - Continued

Protocol Number	Principal Investigator	Purpose of Study	No. Patients Receiving Tenex	No. Patients Receiving Placebo	No. Patients On Competitive Drug	Tenex Doses (mg/day)	Tenex Dosage Schedule
37	A. Jäättelä, M.D.	Single-blind, crossover, efficacy/safety vs. clonidine	24	24	24	2-6	b.i.d. or t.i.d.
38	I. Persson, M.D.	Single-blind, crossover efficacy/safety vs. clonidine	20	20	20	2-15	b.i.d. or t.i.d.
39	A. Distler, M.D.	Single-blind, crossover, efficacy/safety vs. clonidine	16	16	16	2-6	b.i.d. or t.i.d.
Total No. of Studies 11			169	169	114	1-15	b.i.d. to t.i.d.

C. Supportive Controlled Studies

Investigators and Patient Accountability

Study Identification	Investigators	Location	No. Patients Studied
a.1. Baseline-controlled	G. Csajkas, M.D.	Versorgungskrankenhaus Berchtesgaden D-8240 <u>West Germany</u>	10
a.2. Baseline-controlled	I. Esch, M.D.	Senior Physician IIInd Med Department Hanusch-Krankenhaus A-1140 Vienna <u>Austria</u>	11
a.3. Baseline-controlled	A. Heidland, M.D.	Senior Physician University Medical Dept. D-8700 Würzburg <u>West Germany</u>	11
a.4. Baseline-controlled	P. Peltola, M.D.	University Hospital Department of Pharmacology Helsinki <u>Finland</u>	11
a.5. Baseline-controlled	M. Radonic, M.D.	Director, Department of Nephrology Rebro Hospital for Int. Diseases Faculty of Medicine Zagreb <u>Yugoslavia</u>	12
b.1. Methyl dopa-controlled	I. Esch, M.D.	IIInd Medical Dept. (Cardiac Unit) Hanusch Hospital Heinrich Collin-Strasse 30 A-1140 Vienna <u>Austria</u>	20

C. Supportive Controlled Studies
 Investigators and Patient Accountability - Continued

Study Identification	Investigators	Location	No. Patients Studied
b.2. Methyldopa-controlled	A. Heidland, M.D.	Head, Nephrology Dept. University, Med. Dept. Luitpold Hospital D-87 Würzburg <u>West Germany</u>	20
b.3. Methyldopa-controlled	O. Ripka, M.D.	2nd Clinic of Int. Medicine Charles University Prague <u>Czechoslovakia</u>	14
c.1. Clonidine-controlled	A. Jäätelä, M.D.	Dextra Oy, Munkkivuori Helsinki <u>Finland</u>	24
c.2. Clonidine-controlled	I. Persson, M.D.	Nørre Hospital Copenhagen <u>Denmark</u>	20
c.3. Clonidine-controlled	A. Distler, M.D.	OA und Leiter der Hochdruck- ambulanz Internal Medicine University-Klinik Joh. Gutenberg - Universität D-6500 Mainz <u>West Germany</u>	16

1. Baseline-Controlled Studies

Five small clinical studies, a baseline period as control, were performed. Results for all studies pooled are shown. After a placebo wash-out period of two weeks, a total of 55 patients were admitted to a hospital. Placebo was given for one week followed by two weeks of guanfacine, 1 mg t.i.d. for the first week and 2 mg t.i.d. for the second. Outpatient treatment was then continued for three to four weeks with dosage increases as required. The study design scheme is shown in Table LXXXVIII.

Table LXXXVIII

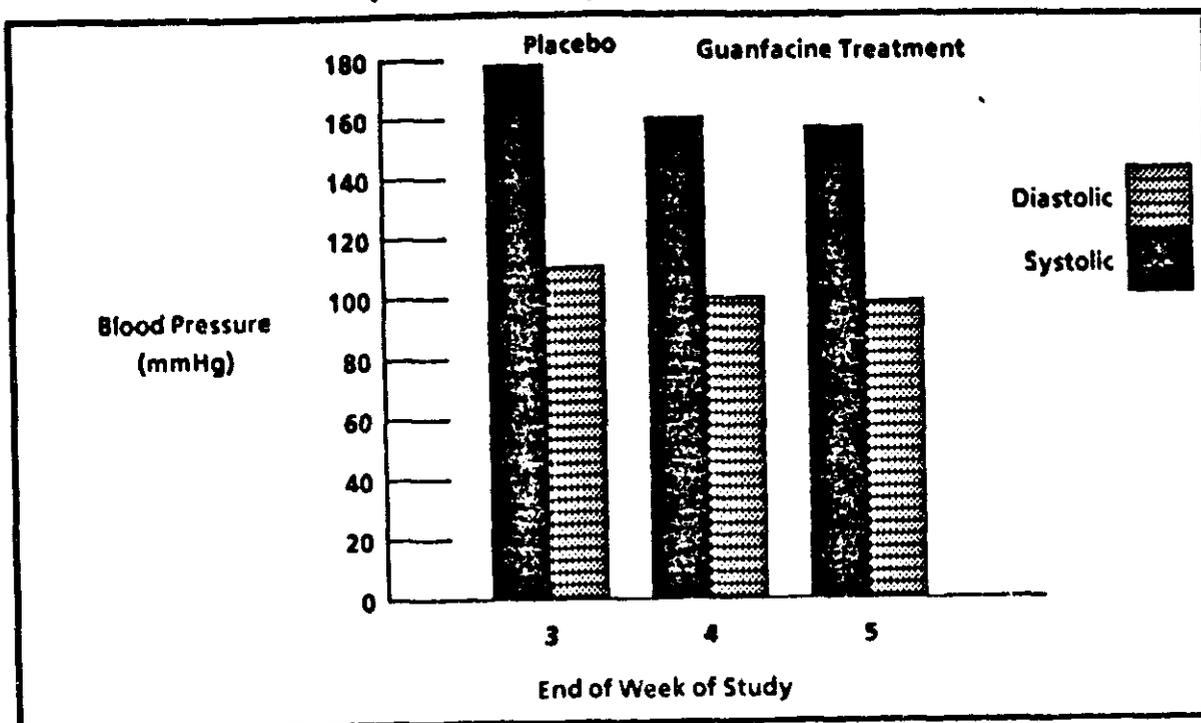
Placebo-Controlled Studies - Design Scheme

Time (weeks)	1	2	3	4	5	6	7	8	9
Study phase	Placebo wash-out period outpatients		Placebo hospitalization		guanfacine		ambulant treatment with guanfacine outpatients		
Dosage schedule	Placebo		Placebo t.i.d.	Guanfacine 1 mg t.i.d. 2 mg t.i.d.		Dosage increase as required			
BP		X	X	X	X	X	X	X	X
HR		X	X	X	X	X	X	X	X
Lab			X	Side effects			X		X

During the hospital treatment with guanfacine, the systolic blood pressure fell from 178 ± 17 mmHg to 157 ± 5 mmHg the diastolic pressure fell from 112 ± 10 mmHg to 99 ± 6 mmHg. There were no orthostatic reactions. These results are shown in Figure 51. The studies are presented only for completeness as their lack of any concurrent control and period of hospitalization makes their effectiveness results very difficult to interpret.

FIGURE 51

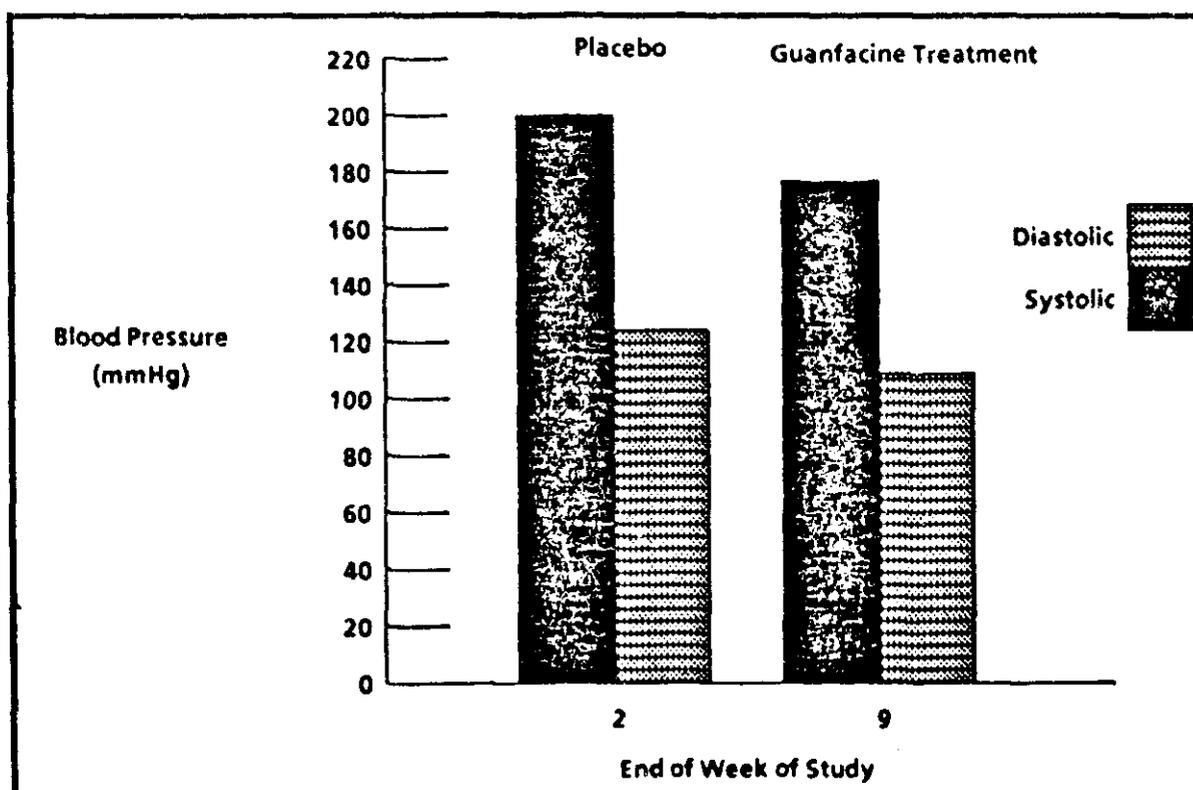
Placebo-Controlled Studies - Blood Pressure Results During Hospitalization
(Heidland study results excluded)



During the outpatient phase of these studies, comparing BP to the prehospitalization pressures, the mean systolic pressure fell from 204 = 22 mmHg to 176 = 17 mmHg, and the diastolic pressure decreased from 125 = 10 mmHg to 108 = 11 mmHg. These results are shown in Figure 52.

FIGURE 52

Placebo-Controlled Studies - Outpatient Blood Pressure Results



During these studies, 18 different side effects were recorded with guanfacine and 11 with placebo. The most common side effect was dryness of mouth (24%), followed by tiredness and dizziness (22% each). All side effects were transient, never very severe and frequently reported only at the beginning of treatment.

Hemograms, blood chemistries and urinalyses performed pre-treatment and on alternate weeks thereafter were within normal limits, and no drug-related trends were noted.

In conclusion, guanfacine appeared to be a safe antihypertensive agent when utilized as monotherapy at a mean daily dosage of 4.8 (range of 3 to 9 mg).

2. Methylodopa-Controlled Studies

Three, single-blind, crossover studies compared the efficacy and safety of guanfacine and methylodopa. The protocol design is shown in Figure 53.

FIGURE 53

Methylodopa-Controlled Study

GROUP A

Drug:	Placebo	Guanfacine	Placebo	Methylodopa	Placebo
Weeks:	2	6	2	6	2

GROUP B

Drug:	Placebo	Methylodopa	Placebo	Guanfacine	Placebo
Weeks:	2	6	2	6	2

Sixty-seven patients were randomly entered into either Group A or Group B. No other antihypertensive agents were allowed during the study. Only ambulant patients with stable, moderate to severe hypertension (essential or secondary) with previously untreated diastolic blood pressure of 100 to 120 mmHg were admitted. Exclusion criteria included labile hypertension of uncertain origin, organ complications, mental disorders, renal insufficiency, liver damage, severe diabetes mellitus, pregnancy and uncooperative patients. Concomitant treatments which may have an effect on blood pressure were prohibited.

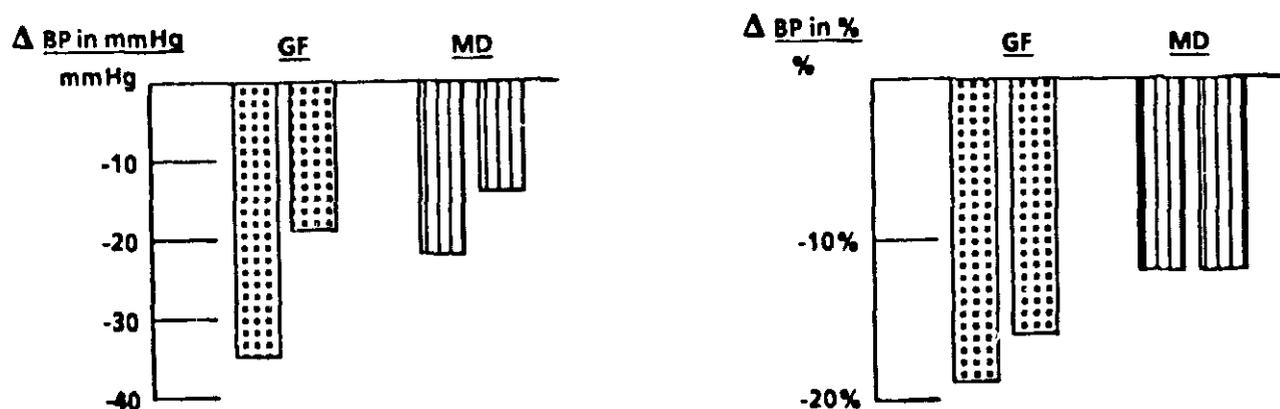
The principal evaluation parameters were recorded weekly or every other week. These parameters included blood pressure, pulse rate, dosage and side effects. Blood pressure was measured three times with the patient sitting down, and the mean of the last two readings was recorded. Laboratory tests and electrocardiograms were recorded before and after treatment.

The readings at the end of each treatment period were compared with the readings at the end of the previous placebo period. The results from the 54 patients evaluated in these three studies are given in Figure 54. Blood pressure was reduced with guanfacine (GF) by 36/20 mmHg and 22/14 mmHg with methyldopa.

The daily doses of the 2 drugs at the end of the study were 4.7 mg for guanfacine and 1290 mg for methyldopa.

FIGURE 54

Methyldopa-Controlled Study - Blood Pressure Changes



There was a slight reduction in heart rate with guanfacine but no clinically relevant bradycardia was observed.

Side effects appeared to be more common with guanfacine with 44/54, 81% patients reporting some side effect versus 31/54, 58% of patients treated with methyldopa. Orthostatic disturbances were more frequent and more severe with methyldopa (10 methyldopa patients versus 5 guanfacine patients). Additionally, methyldopa treatment was prematurely terminated in 7 patients because of side effects and lack of efficacy.

3. Clonidine-Controlled Studies

Three single-blind clinical studies were performed using the same methodology as described for the methyldopa-controlled studies. Sixty patients were evaluated in these studies.

Blood pressure was reduced with guanfacine by 31/13 mmHg versus 26/11 mmHg with clonidine. The mean daily dose of guanfacine at the end of the therapy was 5.3 mg; that of clonidine was 0.8 mg.

More side effects were noticed with clonidine (147) than with guanfacine (104). Side effects were reported among 46/60, (77%) of the guanfacine patients versus 54/60, (90%) of the patients who received clonidine. Asthenia and dizziness were observed in 42% of the patients treated with guanfacine and in 72% of the patients treated with clonidine. More importantly, 8 cases of rebound hypertension were observed after the withdrawal of clonidine. No rebound hypertension was observed with guanfacine withdrawal.

Overall Discussion and Conclusions

These 12 supportive, controlled, clinical trials involving 182 patients have design flaws that keep them from being considered well-controlled. They are, however, consistent with results of better-controlled trials and show that even high doses of guanfacine do not produce serious adverse effects.

* * * * *

D. Supportive Uncontrolled Studies

1. Long-Term Effectiveness and Safety (6-12 months duration of treatment)

Investigators and Patient Accountability

Study Identification	Investigators	Location	No. Patients Studied	Tenex Daily Dose (mg/day)
<u>6-12 Month Clinical Studies</u>				
Study No. 51	I. Esch, M.D.	Hanusch-Krankenhaus A-1140 Vienna, <u>AUSTRIA</u>	13	2-9
Study No. 52	A. Heidland, M.D.	Med. Universitätsklinik Abt. für Nephrologie 87 Wuerzburg, <u>GERMANY</u>	16	1.5-10.5
Study No. 53	L. Hennies, M.D.	Werderstr. 44 D-3150 Peine, <u>GERMANY</u>	9	1-17.5
Study No. 54	H. Kipping, M.D.	Facharzt für innere/Krankenhaus Süwestkoru 19 1 Berlin - 31, <u>GERMANY</u>	9	2-7.5
Study No. 55	N. Schaefer, M.D.	Dept. für Innere Mediz Hochdruckambulanz Steinhöferstr. 9 D-7900 ULM, <u>GERMANY</u>	15	1.5-20
Study No. 56	A. Jaaettelae, M.D.	Dept. of IInd Clinic of Medicine Helsingin Univ. Centr Hospital/Helsinki, <u>FINLAND</u>	13	1-7
Totals	Studies = 6			Patients = 75

D. Supportive Uncontrolled Studies

2. Long-Term Effectiveness (12 months)

Study Identification	Investigators	Location	No. Patients Studied	Tenex Daily Dose (mg/day)
<u>12-Month Clinical Studies</u>				
Study No. 101	W. Riebenbauer, M.D.	Praktischer Arzt Hans Sachs-Gasse 14 A-8010, Graz, <u>AUSTRIA</u>	15	1 - 7.5
Study No. 102	I. Esch, M.D.	II. Med. Abteilung Hanusch-Krankenhaus A-1140 Vienna, <u>AUSTRIA</u>	11	1 - 7.5
Study No. 103	A. Heidland, M.D.	Nephrol. Abteilung Med. Universitätsklinik Würzburg, <u>GERMANY</u>	20	1 - 15
Study No. 104	S. Toivonen, M.D.	Hämeentien Rääkäriasema Oy Helsinki, <u>FINLAND</u>		0.5 - 10
Study No. 105	W. Hofer, M.D.	Schillerstr. 65 Heilbronn a. N., <u>GERMANY</u>	8	2 - 7.5
Study No. 106	W. Klein, M.D.	Med. Univ.-Klink Auenburgerplatz 15 A-8036, Graz, <u>AUSTRIA</u>	9	2 - 15
Study No. 107	H. Kipping, M.D.	Facharzt für innere Erkrankungen Südwest-Korso 19 D-1000 Berlin-33, <u>GERMANY</u>	14	1 and 3

D. Supportive Uncontrolled Studies

2. Long-Term Effectiveness (12 months) - Continued

Study Identification	Investigators	Location	No. Patients Studied	Tenex Daily Dose (mg/day)
<u>12-Month Clinical Studies</u>				
Study No. 110	L. Hennies, M.D.	Facharzt fur innere Medizin Werderstr. 44 D-315 Peine, <u>GERMANY</u>	13	1 - 17.5
Study No. 112	M. Weisbrod, M.D.	Facharzt fur innere Medizin Bahnhofstr. 25 6733 Hassloch/Pfalz, <u>GERMANY</u>	18	1 - 10
Study No. 113	K. Rummelhardt, M.D.	Facharzt fur innere Medizin Reichstratsstrasse 11/4 A-1010 Wien, <u>AUSTRIA</u>	12	0.5 - 10.5
Study No. 115	S. Warmenius, M.D.	Med. Klin. Lasarettet 0701 01 Norrtaelje, <u>SWEDEN</u>	14	0.5 - 15
Study No. 116	H. von Frankenberg, M.D.	Facharzt fur innere Krankheite Sudl. Hilda promenade 10 75 Karlsruhe 1, <u>GERMANY</u>	16	1 - 10
Study No. 117	I. Nalbantgil, M.D.	II. Clin. des Maladies Int. Sect. de Cardiologie Fac. Méd. Univ. a Égie Izmin, <u>TURKEY</u>	13	0.5 - 10
Study No. 118	N. Schaefer, M.D.	Chefarztderinnern Abtei- lung des Kreisranken hauses D-7080 Aalen, <u>GERMANY</u>	27	2 - 20

D. Supportive Uncontrolled Studies

2. Long-Term Effectiveness (12 months) - Continued

Study Identification	Investigators	Location	No. Patients Studied	Tenex Daily Dose (mg/day)
<u>12-Month Clinical Studies</u>				
Study No. 119	H. Sonneveldt, M.D.	Internist Ziekenzorg Enschede, <u>NETHERLANDS</u>	9	1 - 15
Study No. 120	K. Binak, M.D. N. Siramaci, M.D.	Fac. med. de. Cerrahpasa Clinique des maladies internes Istanbul, <u>TURKEY</u>	13	1 - 4
Study No. 121	G. Frithz, M.D.	Medicinska Kliniken Centrallasarettet 63188 Eskilstuna, <u>SWEDEN</u>	11	2 - 10
Study No. 122	B. Linnestad, M.D.	Spesialist i indremedisin med. avd. Askim sykehus Askim, <u>NORWAY</u>	16	2 - 25
Study No. 123	K. Hayduk, M.D.	Medizinische Universitätsklinik Otfried-Müllerstrasse D-7400 Tuebingen, <u>GERMANY</u>	10	1 - 20

D. Supportive Uncontrolled Studies

2. Long-Term Effectiveness (12 months) - Continued

Study Identification	Investigators	Location	No. Patients Studied	Tenex Daily Dose (mg/day)
<u>12-Month Clinical Studies</u>				
Study No. 124	M. Radonic, M.D.	Klinik fur innere Erkrankungen Mediz. Fakultät Zagreb, <u>YUGOSLAVIA</u>	13	1 - 10
Study No. 125	D. Valis, M.D.	Renal Unit of the Diagnostic and Therapeutic Ctr. S.A. Athens, <u>GREECE</u>	7	1 - 7.5
Study No. 126	J. Rizzo-Naudi, M.D.	Consultant Physician St. Luke's Hospital Valetta, <u>MALTA</u>	10	0.5 - 6
Study No. 127	Th. J. J. Bloem, M.D.	Cardiology Maria Ziekenhuis Tilburg, <u>NETHERLANDS</u>	48	1 - 15
Study No. 128	F. Rhomberg, M.D.	innere Medizin FMH Tödistrasse 36 8002 Zürich, <u>SWITZERLAND</u>	13	2 - 7
Study No. 129	H. Wolf, M.D.	Medizinische Abteilung Allg. öffentl. Landeskrankenhaus 9400 Wolfsberg, Kärnten, <u>AUSTR</u>	10	1 - 7.5

D. Supportive Uncontrolled Studies

2. Long-Term Effectiveness (12 months) - Continued

Study Identification	Investigators	Location	No. Patients Studied	Tenex Daily Dose (mg/day)
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12-Month Clinical Studies

Study No. 130	E. Moritz, M.D.	Facharzt für innere Medizin i. med. Abteilung des Landes Krankenhausen Klagenfurt, <u>AUSTRIA</u>	15	0.5 - 15
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Study No. 131	A. Dodis, M.D.	Chief of the 1st Medical Clinic General Hospital 15 St. Andrew's Street Patras, <u>GREECE</u>	19	0.5 - 16
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Study No. 132	E. Kolb, M.D.	Facharzt für Chirurgie und Arzt für Allgemeinmedizin Haupt strasse 49 D-8752 Glattbach, <u>GERMANY</u>	26	0.5 - 15
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Study No. 133	N. Karatzas, M.D.	Cardiologist School of Medicine University of Athens Athens, <u>GREECE</u>	13	1 - 12.5
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D. Supportive Uncontrolled Studies

2. Long-Term Effectiveness (12 months) - Continued

Study Identification	Investigators	Location	No. Patients Studied	Tenex Daily Dose (mg/day)
<u>12-Month Clinical Studies</u>				
Study No. 134	G. Hanekopf, M.D.	Böhmerstrasse 37 D-3000 Hannover, <u>GERMANY</u>	15	2 - 4
Study No. 135	T. Stavnar, M.D.	Spes. Indremedisin Peter Gronsgt. 4, 3200 Sandefjord, <u>NORWAY</u>	15	1 - 20
Study No. 136	J. Furrer, M.D.	Med. Univ.-Poliklinik Kantonsspital Rämistrasse 100 8091 Zurich, <u>SWITZERLAND</u>	16	1 - 10
Study No. 138	H. Uhlemann, M.D.	Facharzt für innere Krankheit Aussigerstrasse 10 694 Weinheim/Bergstrasse <u>GERMANY</u>	15	0.5 - 15
Study No. 142	M. Karesoja, M.D.	Lauttasaaren lääkärikeskus Helsinki, <u>FINLAND</u>	8	1 - 5
Study No. 143	Y. Seedat, M.D.	Durban, <u>SOUTH AFRICA</u>	27	1 - 15

D. Supportive Uncontrolled Studies

2. Long-Term Effectiveness (12 months) - Continued

Study Identification	Investigators	Location	No. Patients Studied	Tenex Daily Dose (mg/day)
<u>12-Month Clinical Studies</u>				
Study No. 144	A. Efstratopoulos, M.D.	2nd Medical Dept. Med. School, Athens University Athens, <u>GREECE</u>	11	1 - 7.5
Study No. 146	R. Malta Carrasco, M.D.	Hospital central de I.A.S.E.R. Rio de Janeiro, <u>BRAZIL</u>	11	1 - 15
Study No. 148	A. Gelman, M.D.	Escola Pavlista de Medicine Sao Paulo, <u>BRAZIL</u>	16	1 - 20
Study No. 149	K. Stumpe, M.D.	Med. Universitatsspoliklinik Wilhelmstr. 35-37 53 Bonn, <u>GERMANY</u>	13	2 - 6
TOTALS	STUDIES = 39		PATIENTS = 580	

D. Supportive Uncontrolled Studies

3. Long-Term Effectiveness (24 months)

Study Identification	Investigator	Location	No. Patients Studied
<u>24-Month Clinical Studies</u>			
Study No. 101x	W. Riebenbauer, M.D.	GERMANY	11
Study No. 102x	G. Titscher, M.D.	AUSTRIA	7
Study No. 104x	S. Toivonen, M.D.	FINLAND	9
Study No. 107x	H. Kipping, M.D.	GERMANY	12
Study No. 113x	K. Rummelhardt, M.D.	AUSTRIA	6
Study No. 115x	S. Warmenius, M.D.	SWEDEN	14
Study No. 116x	H. von Frankenberg, M.D.	GERMANY	8
Study No. 118x	N. Schaefer, M.D.	GERMANY	17
Study No. 119x	H. Sonnerfeldt, M.D.	GERMANY	4
Study No. 121x	G. Frithz, M.D.	SWEDEN	6
Study No. 122x	B. Linnestad, M.D.	NORWAY	7
Study No. 124x	M. Radonic, M.D.	YUGOSLAVIA	5
Study No. 126x	J. Rizzo-Naudi, M.D.	MALTA	8
Study No. 127x	M. Bloem, M.D.	HOLLAND	12
Study No. 130x	E. Moritz, M.D.	AUSTRIA	8
Study No. 132x	E. Kolb, M.D.	GERMANY	12
Study No. 134x	G. Hanekopf, M.D.	GERMANY	12
Study No. 135x	T. Stavnar, M.D.	NORWAY	11

TOTALS STUDIES = 18

PATIENTS = 169

Two different types of clinical studies were performed to gain long-term experience:

- Six clinical studies of 6-12 months duration with hypertensive patients selected from previous studies (see Section C, Supportive Controlled Clinical Studies) and
- Thirty-nine studies of 1 year's duration involving new hypertensive patients, using added diuretics and/or beta-blockers and vasodilators if satisfactory results were not achieved with guanfacine as monotherapy. In a group of patients with severe hypertension treated with diuretics (and other antihypertensive agents), the diuretic therapy was continued and guanfacine was added. Of these 39 studies, 18 studies were continued on an open label basis for 12 additional months.

At the beginning of the trials, a wash-out period of at least 2 weeks was provided for and single-blind placebo was given. Also, in the 1 year studies, the drug was withheld after 6 and 12 months for a period of a week or a fortnight during which the blood pressure was recorded. Guanfacine daily doses ranged from 0.5-25 mg. For ethical reasons, this plan was not adhered to by some investigators for patients with severe hypertension.

6-12 Month Studies (Study Nos. 51-56)

Results

Seventy-five patients from previous studies continued their guanfacine treatment for up to 12 months. General patient data (demography) for these patients are given in Table LXXXIX. In general in those studies where a second placebo was given, blood pressures increased substantially and fell again when therapy was reintroduced. The single-blind nature of these placebo periods weaken the studies, but they provide evidence of persistent long-term effectiveness.

The blood pressure results from these studies are summarized in Table XC.

Side effects reported during these studies are given in Table XCI.

The clinical laboratory data did not reveal any adverse influence on serum chemistries or hematologies.

Table LXXXIX

Study Nos. 51-56: Demographic Characteristics

Study Number, Country	Number of Patients	Sex		Age (years)	Weight (kg)	Height (cm)
		Male	Female			
No. 51 (Austria)	13	1	12	36 - 61 (48)	56 - 93 (77.3)	155 - 186 (165)
No. 52 (Germany)	16	4	12	26 - 56 (43)	51 - 81 (69.6)	163 - 174 (168)
No. 53 (Germany)	9	3	6	46 - 70 (55.7)	67 - 92 (81.1)	158 - 183 (167)
No. 54 (Germany)	9	1	8	33 - 66 (58.4)	51 - 84 (66.2)	153 - 179 (162)
No. 55 (Germany)	15	5	10	22 - 66 (47.5)	51 - 84 (71.6)	160 - 174 (167)
No. 56 (Finland)	13	-	13	29 - 62 (51)	54 - 94 (68)	152 - 164 (160)
<u>Total:</u>	<u>75</u>	<u>14</u>	<u>61</u>			

() = Mean

Table XC
Study Nos. 51-56: Blood Pressure

Study No. Country	Placebo I	3 months	6 months	Placebo II	9 months	12 months	Reduction	
							mmHg	%
No. 51 (Austria) n = 13	165/106	150/90	150/92	166/103	145/92	146/92	19/14	11/13
No. 52 (Germany) n = 16	205/121	162/105	153/97	-	152/97	153/97	52/24	25/20
No. 53 (Germany) n = 9	193/115	166/95	150/90	180/111	163/100	160/100	33/15	17/13
No. 54 (Germany) n = 9	186/105	164/97	163/94	180/108	154/91	147/91	39/14	21/12
No. 55 (Germany) n = 15	190/112	145/93	153/93	-	148/90	151/94	39/18	20/18
No. 56 (Finland) n = 13	179/108	150/95	150/93	172/110	153/96	150/96	29/12	16/11

Table XCI
Study Nos. 51-56: Side Effects

Side Effects	Intensity					
	Guanfacine			Placebo		
	1	2	3	1	2	3
1. Dryness of the mouth	17	20	3			
2. Fatigue, tiredness	9	8		1		
3. Constipation	3	5				
4. Dizziness, postural hypotension	2	4				
5. Hypotonia		2				
6. Sweating	1	3		2		2
7. Retching, nausea, malaise		3				1
8. Increase in BP		1				1
9. Heartburn		1				
10. Loss of appetite		1				
11. Increase in pulse, palpitations				2	2	
12. Sleeplessness, disturbed sleep		2			1	1
13. Tinnitus				1		
14. Stomach ache				2	1	
15. Trembling	1	1				1
16. Bradycardia	2					
17. Hypoglycemia		1				
18. "milk thirst"	1					
19. Impotence	1					
20. Uremia						1
21. Urgency of micturition	1					
22. Itching pimples	1					
23. Pins and needles in the hands					1	
24. Dry hands		1				
25. Drowsiness		1				
26. Swelling of the eyelids	1					
27. Fever				1		
28. Depression					1	
29. Nervousness						1
Total	40	54	3	9	6	8
Grand Total		97			23	

Severity of the side effects:

- 1 = Mild
- 2 = Moderate
- 3 = Severe

12-Month Clinical Studies (Study Nos. 101-149)

Objective:

These studies examined usefulness of guanfacine in long-term treatment of all forms and stages of hypertension in routine clinical practice, i.e., without exclusion of patients with hypertensive or ischemic heart disease with or without signs of heart failure or of patients with other complicating conditions, e.g., renal insufficiency, cerebral, or peripheral vascular disease or diabetes.

After a wash-out period, provided the severity of the disease permitted this, guanfacine was administered and the dose successively increased until a satisfactory response was achieved. A diuretic was then added if necessary. If this combination was insufficient, a beta-blocker or vasodilator was added. The 12-month treatment was followed by a placebo period whenever possible.

Individual divergences from this general trial design were due to differences in therapy as practiced in different countries and by investigators, as well as to differences in the natural history of the disease in individual patients. In order to consider the possible influence of important endogenous and exogenous factors, complete case histories were taken. At the end of the study, all important objective parameters were evaluated and analyzed.

Patients:

Originally, 662 patients with elevated blood pressure were selected; 528 completed and 52 failed to complete due to adverse effects. There were 82 drop-outs unrelated to drug therapy (see Table XCII).

The patients can be characterized as follows:

Age: 51.8 years (mean; 52.1 in women, 51.7 in men)
Sex: 257 women, 323 men = total 580 patients

Etiology of hypertension:

essential	499 patients	(86%)
renal	55 patients	(9%)
renovascular	22 patients	(4%)
other (endocrine)	4 patients	(1%)

Degree of severity

mild	200 patients	(34%)
moderate	275 patients	(48%)
severe	101 patients	(18%)
not specified	4 patients	(1%)

Table XCII

Drop-outs (82 patients)

(Reason, Study Number, Total Number of Patients)

Normalization of BP During Placebo Phase	<u>Reason Patient Failed to Complete Study</u>				
	<u>Normalization of BP During Therapy</u>	<u>Administ- rative (e.g., moved away)</u>	<u>No Reason Given</u>	<u>Complications (Leading to Hospitalization) Death</u>	
104/11	106/3	117/2	102/3	101/2	102/1
119/1	116/1	124/3	106/1	110/1	110/1
121/1	119/1	127/1	110/3	113/2	123/1
122/1	122/1	128/2	127/3	119/1	127/3
124/1	123/4	131/1	129/1	121/1	129/2
	124/1	138/3	146/2	127/5	
		142/1		128/1	
		146/2		130/1	
		149/2		131/1	
				133/1*	
				134/1	
				135/1	
<hr/>					
Total:					
15	11	17	13	18	8

*Pregnancy

Pathology Noted at Onset

Positive signs of left ventricular hypertrophy:

- in ECG: 217 patients (37.4%)
- fluoroscopy: 223 patients (38.4%)

Signs of heart failure (objective): 105 patients (18%)

Pathological ocular fundus: 415 patients (71%)

Signs of impaired renal function: 71 patients (12%)

Concomitant disease: 324 patients (56%)

Dosage:

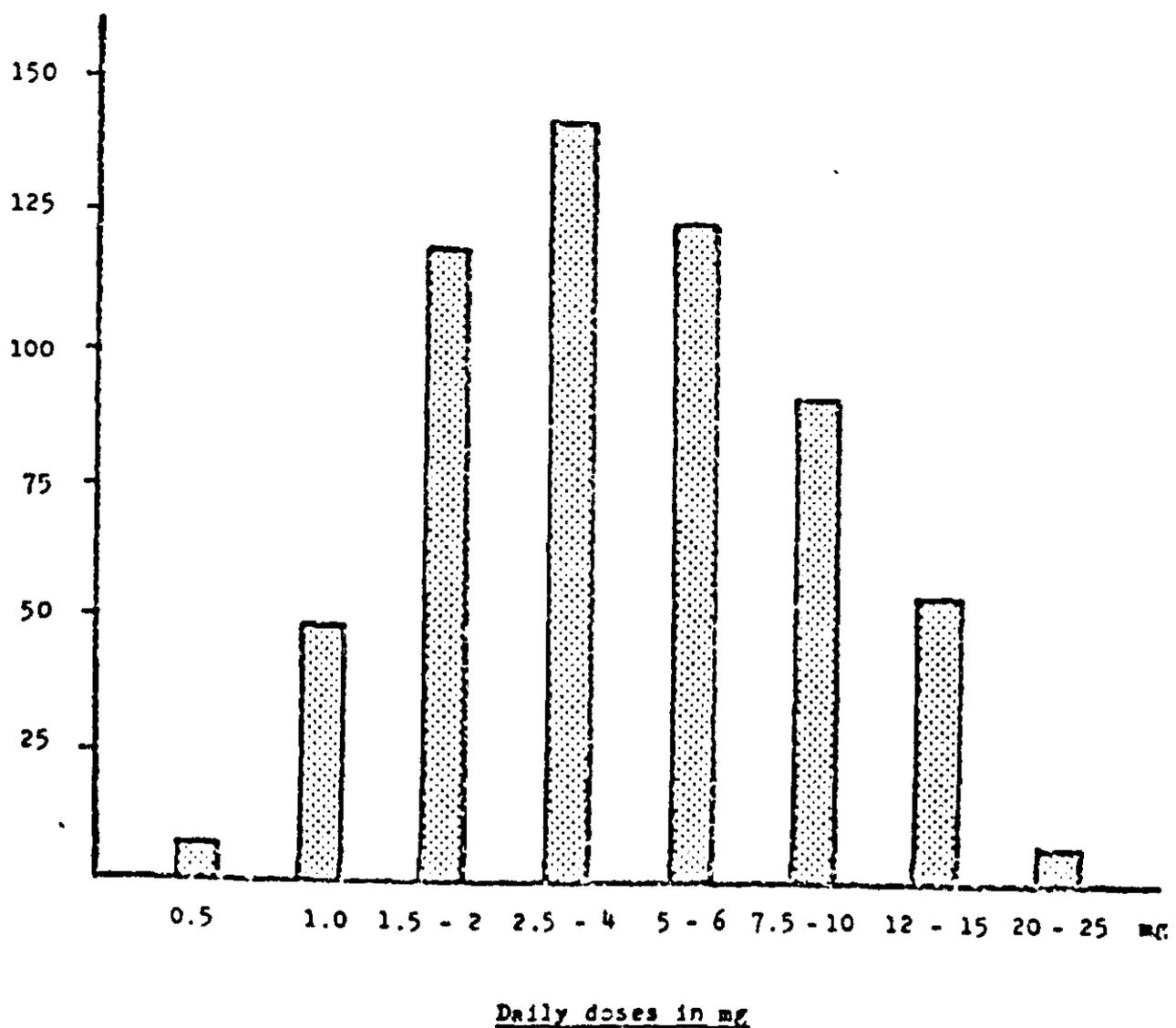
Analysis of the doses of guanfacine used in the 1-year studies on 580 patients revealed these results:

The mean dose was 4.7 mg.
 Doses up to 2 mg were adequate for 30% of the patients,
 doses up to 5 mg for 70%, and
 doses up to 6 mg for 75% of the patients.

In 16% of all patients, doses between over 6 to 10 mg, and in 9% of patients doses over 10 mg, were given. The highest dose used was 25 mg. Side effects were reported at quite high rates, reflecting the high doses used in an effort to gain adequate control in severely hypertensive patients. More recent evidence indicates those high doses have little or no added usefulness, although severely hypertensive patients were not included in formal, dose-response studies.

Figure 55 shows the range of the most frequently used daily doses.

Figure 55

Number of patients:

Dose schedule:

The majority of patients (269) was treated with 2 doses per day, 190 patients with 3 doses, and 82 patients were well controlled with a single daily dose. The rest received varying dosing schedules.

Mean values show that there is no difference between the effectiveness of these 3 different dosage schedules (see Table XCIII).

Table XCIII

Comparison of Once Daily vs. b.i.d. and t.i.d. Dosage Schedules

Blood Pressure:	Guanfacine Medication					
	Once Daily		Twice Daily		Three Times Daily	
	Before	After	Before	After	Before	After
n	82	82	269	269	190	190
Mean	186/111	149/91	183/110	151/92	191/114	162/98
Standard Dev.	27/13	26/15	26/12	20/11	25/14	24/14
Mean Reduction	-	37/20	-	32/18	-	29/16

SIDE EFFECTS:

Fifty-nine different side effects were seen during the study, the total being 966. By the end of the trials, 162 side effects (16.7%) were seen in only 20% of all patients treated. Sixty-six side effects were classified as "severe" throughout all the studies (6.8%). In 52 patients, therapy was discontinued because of side effects.

A complete list of side effects is given in Table XCIV. A list of those patients whose treatment was discontinued because of side effects is given in Table XCV.

*In the left upper corner: Total No. of Side Effects.
 **In the right lower corner: Side-effects at the end of the 1-year treatment.

Table XCIV
 Side Effects
 1-Year Studies - 580 Patients

Side Effects	Intensity*					
	1	1-2	2	2-3	3	X
1. Dryness of the mouth, dry mucous membranes	171 41	53 18	92 25	11 3	17 1	4* 1*
2. Tiredness, drowsiness, decrease of vitality, sleepiness, faintness	92 19	20 6	55 7	6 1	15	3
3. Weakness, feeling of weakness, muscular weakness, heavy arms and legs	13 1	2 1	11 2	2	2	1
4. Dizziness, orthostatic hypotension, vertigo, tinnitus	36 3	10	28 1	3	6	5 1
5. Collapse, syncope			1		1	1
6. Headache	13	2 1	5	1	1	1
7. Constipation	46 9	7 1	24 5	4 1	2	1
8. Sickness, nausea, queasiness	3 1		4	1	2	2
9. Loss of Appetite, anorexia	2 1		1			
10. Vomiting				1	1	
11. Insomnia, disturbed sleep	13	2	14		2	
12. Listlessness				1		

*Score:

- 1 = Mild
- 1-2 = Mild/moderate
- 2 = Moderate
- 2-3 = Moderate/severe
- 3 = Severe
- X = Not specified

Table XCIV - (Continued)

Side Effects
1-Year Studies - 580 Patients

Side Effects	Intensity*					
	1	1-2	2	2-3	3	X
13. Sweating, excessive sweating, night sweats, outbreaks of sweating	6 1	1	6		1	1
14. "Chest pain", "cardiac pain", "lancinating pain in the heart", perspiration	3 1					
15. Angina pectoris			1			1
16. Palpitations, tachycardia	3		1		2	1
17. Arrhythmia, extrasystoles	1					
18. Sinus bradycardia	2 1		1		1	8 3
19. Tremor, muscular tremors			1		1 1	
20. Restlessness, nervousness, etc.	3 2		1			3
21. Nightmares					1	
22. Incontinence					1	
23. Urinary frequency					1	
24. Dysuria						2
25. Polyuria	1					
26. Dry skin	1					
27. Epigastric pain, gastrointestinal complaints, pressure over the stomach	5 1		6 1		3	

*Score:

- 1 = Mild
- 1-2 = Mild/moderate
- 2 = Moderate
- 2-3 = Moderate/severe
- 3 = Severe
- X = Not specified

Studies No. 101-149

Table XCIV - (Continued)

Side Effects
1-Year Studies - 580 Patients

Side Effects	Intensity*					
	1	1-2	2	2-3	3	X
28. Depression	1			1	1	
29. "Sand" in the eyes	1		1			
30. Impotence	2	2	6	1		2
	1	1	2			
31. Paresthesia, numbness of fingers	5					1
32. Neck pain	1					
33. Leg pain	1					1
34. Migraine	1					
35. "Sensation in the head"	1				1	1
36. Shivering	3		1		1	
37. Chest sensation, oppression	1		2			
38. Dyspnoea			2		2	2
39. Furred tongue			1			
40. Glossitis, burning sensations in the tongue	2				1	
41. Immovable tongue, thick tongue			1	1	1	
42. Bitter taste, bad taste	3	2	1	1		
43. Bad breath			1			
44. Heartburn	1					

*Score:

- 1 = Mild
- 1-2 = Mild/moderate
- 2 = Moderate
- 2-3 = Moderate/severe
- 3 = Severe
- X = Not specified

Table XCIV - (Continued)
 Side Effects
 1-Year Studies - 580 Patients

Side Effects	Intensity*					
	1	1-2	2	2-3	3	X
45. Meteorism/fullness				1		
46. Weight gain			1			1 1
47. Small hemorrhage in finger/ eye lids					1	1
48. Exacerbation of psoriasis						1
49. Exanthema					1	
50. Rhagades	1		1			
51. Prickling in the hands	1					
52. Cold hands or fingers	2					
53. Anaesthesia	1					
54. Reduced libido			1			1
55. Scotomas	1					
56. "Nasal stenosis"						1
57. Weight loss	1					
58. Sialorrhea	1					
59. Diarrhea	1		1			
TOTAL	446	101	272	35	69	46
	82	28	43	5	2	6

*Score:

- 1 = Mild
 1-2 = Mild/moderate
 2 = Moderate
 2-3 = Moderate/severe
 3 = Severe
 X = Not specified

Studies No. 101-149

Table XCV

Discontinuation of Treatment for Adverse Effects
(Reason, Number of Patients, Study and Patient Number)

	Total No. of Patients	Number of Study and Patient Number
<u>Side Effects</u>		
Dryness of the mouth	20	101/5; 103/3; 112/6; 116/9; 119/12; 126/1; 127/45; 128/1,5,6,7; 129/1; 131/2; 132/16; 136/14; 138/4,14; 149/1,2,3
Sedation, sleepiness	3	125/4; 127/11; 135/1
Tiredness, weakness	12	104/3; 121/3,5; 128/12; 129/4; 131/1,5,6; 135/9,11; 136/15; 148/3
Depression	1	129/9
Headache	1	101/11
Nightmare	1	104/19
Nausea	3	130/8,12; 136/16
Constipation	7	116/5; 127/28,29,47; 138/14; 148/8,17
Orthostatic disturbances	2	121/2,11
Sleeplessness	1	119/4
Exanthema	1	123/3*

* = Visken and Lasix were given concomitantly.

The frequency of reporting of most side effects diminished with continued treatment. The overall frequency of dryness of the mouth was 60%, falling to 15% by the end of the treatment. Signs of sedation were seen in 33% of all patients and this dropped to 5.7% by the end of the study. Dizziness and other signs of orthostatic disturbances were seen in 15%, feeling of weakness in 5%, and constipation in 14% of all patients. At the end of the study, the incidence was under 1% for dizziness and 2.7% for constipation. Whether decreased reporting reflects a true decrease in occurrence cannot be determined from these data, but it is clear that adverse effects did not often cause discontinuation of treatment.

Sexual disturbances, such as loss of libido and impotence, were seen in 15 male patients (4.6%). All were of mild to moderate degree, and all but 4 were transient.

Establishing a drug cause for the other side effects is difficult as they were for the most part common complaints. It is noteworthy that 44/52 of the discontinuations reported dryness of the mouth, sedation, sleepiness, tiredness, weakness, constipation, and orthostatic problems as the reason.

Laboratory Findings:

Isolated changes occurring at different times throughout the studies were not considered to be of clinical relevance if the change was within the limit of methodological variation and was only transient (i.e., on single occasions).

All other variations are summarized in Tables XCVI-XCVIII. These changes can be explained either as symptomatic of the underlying disease (e.g., proteinuria, high creatinine, BUN, and pathological urine sediment for patients with renal hypertension, elevated blood sugar for patients with diabetes), or they may have been caused by intercurrent disease (elevated sedimentation rate, eosinophilia). As shown in Tables XCVI-XCVIII, more pathological values returned to normal than vice versa.

Table XCVI

Laboratory Data - Hematology

	Pretr. Value Path+Normal No. of Study/ Patient-No.	Total No. of Patients	Pathol. From Beginning to End	Total No. of Patients	Normal to Pathol.	Total No. of Patients	Inter- mitently Abnormal Value	Total No. of Patients	Not Evaluated (No. of Study)
Haemoglobin	130/1	1	101/1,10+	9	103/1,18*	8	112/2	1	113
			130/4,5,6,13;		112/5,9				119
			130/15,16,18		123/2,3,4,13				131
Erythrocytes			101/1,10+	12	103/1,18;*	5			113
			130/2,3,4,5;		123/2,4,13				119
			130/6,13,14;						131
			1340/15,16,18						135
Leukocytes	116/11	3	103/9,11	2	115/4,7+	2			113
	143/2,17								119
Eosinophils	148/1,5	2	148/11	1					131
									135
Sedimentation	102/1,3,12	28	110/13	33	134/8	3			112
	109		122/2,7,10		135/2,10				113
	104/8,22		123/2,3,4,13;						119
	110/5		123/14,15						131
	132/16		130						132/22
	134/10		134/5						133
		135/4,8						138/14	
		138/2,5,6,10						138/14	
		143/24						144	

*Severe renal hyp.

Table XCVII

Laboratory Data - Biochemistry

	Preter. Value Path+Normal No. of Study/ Patient-No.	Total No. of Patients	Pathol. From Beginning to End	Total No. of Patients	Normal to Pathol.	Total No. of Patients	Inter- mitently Abnormal Value	Total No. of Patients	Not Evaluate (No. of Study)
Creatinine	110/4,6,16	5	103/12 to 20	28	102/1	4		113	
	129/7		123		129/1			118*	
	144/1		130		142/6,9			119	
			144/8					127/26	
								131	
Urea	135/12	1	103/13 to 20	46	102/1	2		113	
			110/4		135/10			118*	
			112/16					119	
			123					131	
			130					146	
			132/2,10						
		135/3,4,14							
		144/2							
SGOT	105/3,5	3	110/14	6				113	
	143/3		116/11					119	
			132/6,25					127/3	
			143/1,2						
SGPT	105/3,5	5	102/4,10	7	104/9	3	130/28	113	
	143/3,5,22		104/18,25		142/3,6			115/13*	
			116/11					119	
			132/19					133	
		143/1							

*Various units used.

**Single artifactual result obtained.

Table XCVII (Continued)
Laboratory Data - Biochemistry

	Preter. Value Path→Normal No. of Study/ Patient-No.	Total No. of Patients	Pathol. From Beginning to End	Total No. of Patients	Normal to Pathol.	Total No. of Patients	Inter- mitently Abnormal Value	Total No. of Patients	Not Evaluated (No. of Study)
Blood Glucose	101/3 104/16 122/9 130/5 144/2	5	101/16 103/15 105/2 106/1 113/2 116/13 122/1,4 125/5,7 130/14,15,16 132/1,2,3,6,9 132/10,13,15 132/24+	27	104/9,13,18 121/9	4		119 123 127 131 135/1	
Bilirubin			143/1,2	2				115/7* error	
Cholesterol	104/24 110/5,7,8,12 110/13,15,16 110/17 117/2,14 122/1,4 132/4,16,24 135/2,12,14	19	101/2,4,8,12 101/16,17 104/8,14,27 106/1 110/4 113/2,5,11,13 122/2,6,7,19 125/2,3,6 133/2,3	24	132/11,17,19 132/20,21,26	6		115 119 138	
Triglycerides	123/2,9	2	123/11,12,15	3				115	

+Not fasting

Table XCVII (Continued)

Laboratory Data - Biochemistry

	Preter. Value Path+Normal No. of Study/ Patient-No.	Total No. of Patients	Pathol. From Beginning to End	Total No. of Patients	Normal to Pathol.	Total No. of Patients	Inter- mitently Abnormal Value	Total No. of Patients	Not Evaluated (No. of Study)
Alkaline Phosphatase	130/18	1	102/12 103/14 143/1,2,3	5					119
Sodium (in serum)									119 146
Potassium (in serum)				7					119 146
Chloride (in serum)									118 (incomplete) 119 133 146
Uric acid							121/6	1	133

Table XCVIII
Laboratory Data - Urinalysis

	Preter. Value Path-Normal No. of Study/ Patient-No.	Total No. of Patients	Pathol. From Beginning to End	Total No. of Patients	Normal to Pathol.	Total No. of Patients	Inter- mitently Abnormal Value	Total No. of Patients	Not Evaluat. (No. of Study)					
Protein	102/6,11	35	103/all (20)	63	102/15	11	101/4,7,10	5	112/-1					
	116/9		113/2,5,13		105/3		102/9		119/-9					
	118/4		116/2,5,10		116/1,3,6,8		113/3							
	132/1,6,9,17		116/11,13		116/14									
	132/20,22,23		123		132/7,13,15									
	132/25		130		132/24									
	133/1,11,13		131/1											
	138/11		132/3,12,14											
	143/2,4,6,8		132/26											
	143/10,12,14		138/1											
	143/15,16,17		143/23,24,25											
	143/18,19,20		143/26											
	143/21,22,27		144/8,9											
	144/1,2,7		146/1,5,8,10											
	Sugar		101/3		6		105/2		10	123/15	3	132/7	1	112/-15
			123/2,12,13				116/8			131/20		119/-9		
			131/3				132/2,3,13			132/16				
144/2		134/6												
		138/2												

Table XCVIII (Continued)
Laboratory Data - Urinalysis

	Preter. Value Path→Normal No. of Study/ Patient-No.	Total No. of Patients	Pathol. From Beginning to End	Total No. of Patients	Normal to Pathol.	Total No. of Patients	Inter- mitently Abnormal Value	Total No. of Patients	Not Evaluated (No. of Study)
Specific Gravity		15	130+					132	
Sediment	102/11 113/5 116/5 117/6 118/5, 11, 26 132/1, 9, 22, 25 134/1, 5, 6, 8, 9 134/15 143/1, 11, 16 143/18, 23, 27	23	103/a11 105/1, 2, 3, 5, 8 105/10 116/2 118/7, 13, 16 118/17, 25, 27 120 123 124/1, 9, 12 130 131/3 132/2, 3, 8, 10 132/15, 16, 17 132/20, 26 134/2, 3, 7, 11 134/13, 14	91	117/3 118/9, 10, 20 132/11, 12, 13 132/14 142/3, 9	10	101/4, 7 113/9 114/13	4	106/-9 112/-15 119/-9 144/-11
Urobilinogen	116/2	1	105/9	1					

There were no disturbances in water or electrolyte balance, no signs of liver damage, nor was any lasting impairment in sugar or fat metabolism found.

Normalization of proteinuria and pathological urine-sediment was relatively frequent in patients with severe essential and renal hypertension; the total number of normalizations of pathological laboratory findings was higher than the reverse.

Body weights

Body weight changes were recorded in 20 studies (276 patients). A decrease was observed in 10 (mean weight reduction 1.77 kg), and an increase in 7 studies (mean weight increase 1.58 kg). The latter was caused by a weight gain in 2 patients: an obese patient (+10 kg) and another treated with dihydralazine (+11 kg). Apart from these cases, no signs of water retention were observed. In 3 studies, no changes in body weight were seen after 1 year.

Therapy Discontinuations:

Ninety-one patients had their therapy discontinued. All cases in which the therapy was stopped but not defined as a drop-out by the investigator were analyzed. This applied to 91 patients.

The discontinuance was caused by side effects in 52 patients (see Table XCV). In 17 other patients, the cause was not well defined and in 3, it was due to normalization of blood pressure; in 8 patients, no adequate therapy response was achieved. Eleven patients suffered from either a concomitant disease or signs of progression of their illness: renal function deteriorated in 3 patients and one of them died, 2 suffered from severe angina, one patient with malignant hypertension was hospitalized for acute left heart failure and two for acute myocardial infarction (one died), 3 patients had acute cerebrovascular accidents, two of them being fatal. A total of 8 patients died.

- 1) Man, 50 years, obese, severe hypertension, cerebrovascular accident.
- 2) Man, 60 years, postoperative status for gastric ulcer, intestinal hemorrhage.
- 3) Man, 47 years, recent myocardial infarct, acute reinfarction.
- 4) Man, 47 years, acute cerebrovascular accident.
- 5) Man, 71 years, acute cerebrovascular accident.

- 6) Man, 53 years, sudden death - fibrillation (history of paroxysmal fibrillation).
- 7) Man, 49 years, sudden death - witnessing traffic accident, known to have severe coronary disease.
- 8) Man, 50 years, obese, severe hypertension, died during holiday abroad, cause unknown.

Concomitant Therapy - Interactions:

For combination therapy various antihypertensive drugs were administered. In more than 200 patients, diuretic agents of the thiazide type were given, e.g., hydrochlorothiazide, clopamide and chlorthalidone. In approximately 50 patients, beta-blockers such as pindolol, propranolol, etc. were administered and in approximately 50 patients vasodilators, hydralazine or dihydralazine were prescribed. Six patients received methyl dopa together with guanfacine and 2 patients (a reserpine-clopamide-dihydroergocristine combination). In isolated cases potassium-sparing diuretics such as spiro lactone were used. There was no evidence of interactions.

In addition, more than 370 different medicaments were used in 300 patients for the treatment of underlying diseases, such as coronary heart disease, cerebrovascular insufficiency and/or their complications, and for concomitant diseases, such as diabetes and gout. Some drugs, such as sedatives and analgesics, were also used quite often.

The following groups of medicaments were the most important ones and are discussed separately (Table XCIX).

Table XCIX

Drug/Indication	Number of Patients
Cardiac glycosides	115
Oral antidiabetic agents	5
Sedatives and hypnotics, including antidepressants and minor tranquilizers	103
Antihyperlipidemic agents	29
So-called antisclerotic agents and coronary vasodilators	52
Agents for digestive disorders	36
Analgesics - antirheumatic agents	38
Flu/common cold preparations	41
Vitamins and iron preparations	40
Anti-gout agents	24
Laxatives	16
Bronchodilators	13
Hormones	8
Oral contraceptives agents	18
Anticoagulants	7
Spasmolytics	10
Antibiotics	7
Sulfonamides	5
Preparations in urological indications	6
Preparations against venous insufficiency	11
Potassium supplements	10
Alkalinizing agents	2
Immunosuppressive drugs	2
Antimigraine drugs	2
Tuberculostatic drugs	2
Cholinergic agents	2
Insulin	10
Beta blockers	10

As can be seen, various drugs for approximately 30 indications were given. No signs of unexpected interactions were seen with any of these drugs.

Electrocardiogram:

The 12-lead ECG was recorded in nearly all patients (402) before and after therapy with guanfacine. ECG tracings before the start of treatment revealed the following: 202 patients had a normal ECG, 200 were pathological: 69 showed signs of left ventricular hypertrophy, 11 signs of left ventricular strain, and in 120 patients, changes typical for coronary heart disease were found: 95 showed ischemic or coronary ST-T wave changes, myocardial infarct was found in 5, and in 20 patients various other changes were seen (atrial fibrillation, LBBB, or RBBB and hemiblocks).

Table C

Electrocardiographic Changes

	N	%
Normal → Normal	291	73
Normal → Abnormal	46	11
Abnormal → Normal	65	16
Total	402	

Two-hundred ninety-one electrocardiograms remained unchanged; an improvement was seen in 65 cases and 46 cases showed signs of deterioration. In considering the therapeutic effect of an antihypertensive drug, the evolution of the ECG-pattern of left ventricular size is the most important finding.

In the above analysis, LVH-pattern showed a tendency to regress.

These results support the concept that therapy with guanfacine reduces left ventricular work, and they provide further support for the validity of the hemodynamic findings.

In many cases, sinus tachycardia was normalized, and bradycardia after treatment was observed in a few cases. In one patient, atrial fibrillation reverted back into sinus rhythm, in another, ventricular extrasystoles disappeared following treatment.

No signs of any cardiotoxic effect or alteration in myocardial cellular metabolism were seen. On the contrary, ECG improvement in many cases of myocardial ischemia was observed.

Ophthalmological Findings:

In the majority of patients, ophthalmological examination with special reference to the ocular fundus was performed before and after long-term treatment. The purpose was to support the diagnosis of established hypertension, to demonstrate any progress of the disease, and to prove the safety of the drug. In none of the studies could any direct or indirect unfavorable effect be observed.

24-Month Clinical Studies (Study No. 101X - 149X)

Investigators with patients who had completed 12 months of guanfacine in Study Nos. 101-149 were asked to continue treatment with follow-up of all willing and qualifying patients. Eighteen investigators studied a total of 169 patients in these 24-month clinical trials which are summarized below.

Open clinical therapeutic trial. Treatment with guanfacine alone or with additional medication.

- A wash-out period of 1-3 weeks duration was carried out at the beginning of the trial and at the end of the second year of treatment in those patients in whom this was acceptable from the medical point of view.
- Clinical progress was checked every second month and the laboratory investigations after months 18 and 24.
- At the end of the study, the values for blood pressure (BP) and heart rate (HR) at month 24 were compared with the initial values, with the values after one year and--where feasible--with the values after the washout period.
- BP and HR were checked before medication.

Number of patients: 169
Age: mean 51.6 years (range 21-79 years)
Sex: 71 females, 98 males

Etiology:

Essential hypertension	146 patients	(86%)
Renal hypertension	14 patients	(8%)
Renovascular hypertension	9 patients	(6%)

Severity of disease (WHO)

Mild	79 patients	(47%)
Moderate	72 patients	(43%)
Severe	16 patients	(9%)
Malignant	1 patient	(1%)
Not specified	1 patient	(1%)

The age of the patients and the distribution of the different types of hypertension correspond to the findings in the one-year study.

Results:

a) Overall results:

The overall results of the whole group after two years are shown in Table CI.

Table CI

Criteria	First Year	Second Year
Reduction of mean arterial pressure	16%	17%

Table CII shows the comparison of the initial values for blood pressure and heart rate with the values after one and two years of treatment. It is obvious that the blood pressure lowering effect was unchanged at the end of the second year.

Table CII

Blood Pressure (mmHg) and Heart Rate - 2 Years' Treatment, 169 Patients

	Pretreatment Value	End of 1st Year	End of 2nd Year	Mean Dose Guanfacine
<u>Monotherapy</u>				
BP \pm S.E.	184/106 (3/1)	152/90 (2/1)	152/89 (1/1)	
Mean art. pressure	132	111	110	3.2 mg
HR \pm S.E.	79 (1)	74.6 (1)	74 (1)	
<u>Combined Treatment</u>				
BP \pm S.E.	182/114 (3/1)	148/93 (2/1)	148/93 (2/1)	
Mean art. pressure	136	111	111	4.9 mg
HR \pm S.E.	79.7 (1)	72.6 (1)	73.7 (1)	

In more than half of the patients guanfacine was administered alone and in more than 50% of these patients in single doses. In the patients in whom guanfacine was combined with other drugs, multiple doses were more frequent than single doses.

b) Dosage and effect (success of therapy)

From Table CIII, it can be seen that the blood pressure lowering effect of all dosage schedules is approximately the same.

Table CIII

Guanfacine - Daily Doses (mg)					Blood Pressure (mmHg)		
Dosage	Mean	Median	Mode	Range	Before	End 1st	End 2nd y.
<u>Monotherapy</u>							
Once daily	2.2	2	2	0.5-5	183/105	149/90	149/86
b.i.d.	3.6	2	2	1-10	185/108	153/88	153/90
t.i.d.	3.7	3	3	1-7.5	188/107	158/93	160/98
<u>Combined Treatment</u>							
Once daily	3.2	2.5	2.5	1-6	181/112	144/90	145/90
b.i.d.	4.5	4	4	1-15	175/112	148/94	149/95
t.i.d.	7.1	6	3	1.5-25	192/116	152/94	149/94

c) Dosage in the first and second year of treatment

The comparison of the average daily doses at the end of the first and second year is shown in Table CIV. No increase in dosage was necessary (although it should be noted that the doses were probably excessive).

Table CIV

	n	Overall Mean Daily Dose	Monotherapy	Combined Treatment
End of 1st Year	580	4.7 mg	3.4 mg	6 mg
End of 2nd Year	169	3.6 mg	3.2 mg	4.9 mg

The comparison of the individual doses at the end of the first and second year of treatment in 169 patients elicited the following:

1)	Number of patients on same dose	93
2)	Number of patients on a higher dose	35
3)	Number of patients on a lower dose	41
	Total	<u>169</u>

Thus, no indication was found that tolerance to guanfacine develops within 2 years.

d) Single daily medication

The long duration of action of guanfacine permits a single daily administration of the drug. In 82 (14%) of 580 patients treated for one year the dose schedule was once-a-day. In the second year of treatment, this schedule was administered in 75 patients (44%).

The results of the 2 year studies confirm the results of the first year study.

Side Effects: (Table CV)

Sixteen different kinds of side-effects were observed in 51 patients, the global frequency during the year was 92 side effects in 169 patients (in the first year: 966 side effects in 580 patients). As in the one-year study, most side effects disappeared over time.

Table CV

Side Effects	Intensity ¹				
	1	1-2	2	2-3	3
1. Dryness of the mouth, dry mucous membranes	33* 23**	3 2	7 5	1 0	
2. Tiredness, drowsiness, decrease of vitality, sleepiness, faintness, lassitude	7 2	1 0	2 0		
3. Tired legs	1 0				
4. Dizziness, orthostatic hypotension, vertigo, tinnitus	7 2	1 0	2 0		1 0
5. Headache	1 1				
6. Constipation	5 2		1 0		1 0
7. Insomnia, bad sleeping	1 0		1 0		
8. Sweating, night sweats	2 0		1 0		
9. Nervousness	1 0				
10. Gastrointestinal disturbances	2 0				
11. Impotence	1 0				
12. Urticarial rash			1 0		

¹Score:

- 1 = Mild
 1-2 = Mild/moderate
 2 = Moderate
 2-3 = Moderate/severe
 3 = Severe

Total throughout the whole study: 92 s.e.
At the end of treatment only: 40 s.e.

*In the left upper corner: total no. of side-effects during the 2nd year.
 **In the right lower corner: side-effects at the end of the 2nd year.

Table CV (Continued)

Side Effects	Intensity ¹				
	1	1-2	2	2-3	3
13. Cold feet	1	0			
14. Sedation	1	2	0		
15. Arthritis urica					3
16. Stomatitis					1
					1
Total	63	7	15	1	6
	30	2	5	0	3

¹Score:

1 = Mild
 1-2 = Mild/moderate
 2 = Moderate
 2-3 = Moderate/severe
 3 = Severe

Total throughout the whole study: 92 s.e.
At the end of treatment only: 40 s.e.

*In the left upper corner: total no. of side-effects during the 2nd year.
 **In the right lower corner: side-effects at the end of the 2nd year.

Laboratory Findings

No electrolyte imbalance, pathological liver function or disorders of glucose and lipid metabolism were found in the second year, neither was any influence on the hematopoietic system as shown by the usual hematological tests.

Isolated changes occurring at different times throughout the studies were not considered to be of clinical relevance if the change was within the limit of methodological variation and was only transient (i.e., on single occasions).

Some deviations from the normal values can easily be explained as symptomatic for an underlying disease of the patient (diabetes, gout) or they were in connection with an intercurrent disorder.

Combination Antihypertensive Therapy

Combined therapy was used in 80 patients. The most frequent additional drug was a diuretic (thiazide), others were beta-blocking agents, vasodilators and other antihypertensives. The frequency was as follows:

<u>Preparations</u>	<u>Number of Patients</u>
Diuretics	61
Beta-blocking agents	1
Beta-blocking agents + diuretics	6
Vasodilators	5
Vasodilators + diuretics	3
Vasodilators + diuretics + beta-blockers	1
Others: Adelphan	1
prazosin	2

Concomitant Treatment

In addition, a series of other drugs was used for the treatment of underlying or intercurrent diseases.

The most important groups of medicaments were the following:

<u>Drug/Indication</u>	<u>Number of Patients</u>
Cardiac glycosides	41
Antidiabetic agents	4
Sedatives and hypnotics, including antidepressants and minor tranquilizers	5
Antihyperlipidemic agents	14
So-called antisclerotic agents and coronary vasodilators	18
Agents for digestive disorders	19
Analgesics - antirheumatic agents	7
Flu/common cold preparations	6
Vitamins and iron-preparations	7
Anti-gout agents	9
Bronchodilators	1
Hormones	1
Oral contraceptive agents	7
Anticoagulants	2
Spasmolytics	2
Antibiotics	4
Sulfonamides	2
Preparations against venous insufficiency	3
Potassium supplements	3
Alkalinizing agents	1

There were no signs or symptoms of interactions between guanfacine and any of these drugs.

Discontinuation of Therapy

In 5 patients, the treatment with guanfacine had to be discontinued. In 2 patients because of side effects--in 1 case because of a rash (study no. 126, patient no. 4), in one case because of dryness of the mouth (study no. 126, patient no. 9). In one patient (study no. 124, patient no. 8) a pre-existing ischemic heart disease worsened, angina pectoris and blood pressure increased. In the last 2 patients, complications of a concomitant disease occurred and they had to be treated surgically; one patient with a neuroglioma (study no. 132, patient no. 1); and the other one with a spinal tumor (study no. 132, patient no. 7).

There were no deaths in the 24-month study.

4. Post-Marketing Surveillance

Three multicenter national studies were carried out in Western Europe (Belgium, France, W. Germany) after marketing. A total of 11,270 patients, men and women, 16-91 years old (mean: 60 ± 12), were recruited. Guanfacine dosage varied from 0.5-15 mg/day and was administered t.i.d., b.i.d., or o.d. The patients' characteristics, the results, the dosages, and the side effects are tabulated in Tables CVI, CVII, CVIII, and CIX respectively.

All patients were started at 1 mg/day. Most of them had mild hypertension and their blood pressure was controlled with guanfacine alone at 1 or 2 mg/day. In 6-15% of the cases, however, the dosage was increased to more than 2 mg/day and in 7-29% of the cases additional antihypertensive medication was included.

Side effects were similar to those observed in the premarketing studies. No new or alarming adverse reactions were recorded.

Table CVI

Multicenter National Studies Patients' Characteristics

	Belgium	France	Germany
Number of patients:			
- started	1427	5039	4804
- evaluated	1234	3504	4627
Ratio: M:F (%)	45:55	46:54	44.6:55.4
Age (years, mean \pm SEM):	57 \pm 12 (16-91)	61 \pm 12.3 (20-86)	59.1
Therapy discontinued in: (intolerance, inefficacy)	8.9%	12.2%	6.6%
Duration of hypertension:	<1 year 17.2%	<1 year 20.4%	-
	1-2 y. 9.6%	1-4 y. 32%	
	2-7 y. 36.3%	5-10 y. 27%	
	>7 y. 25.7%	>10 y. 20%	

Table CVII
 Multicenter National Studies
 Duration, Mode, and Effects of the Treatment

	Belgium	France	Germany
Duration of Treatment	8 weeks	12 weeks	6 weeks
Start. Dose	1 mg (100%)	1 mg (80%)	1 mg (97%)
Monotherapy	71.5%	-*	93%
BP pretreatment (mmHg): lying: systolic diastolic	181 ± 21 106 ± 20	184.7 ± 18.8 104.2 ± 11.2	185 103
BP: end: systolic (lying) diastolic	151 ± 15 89 ± 9	154.4 ± 14.7 86.4 ± 9.2	156 90
Δ BP: systolic diastolic	-16.6% -16%	-16.4% -17.1%	-15.6% -14.5%
Heart rate (beats/min):	81 → 76	80 → 76	79 → 74

*Not specified

**As defined in: Jerie, 1980a

Table CVIII
 Multicenter National Studies
 Daily Doses Used at End of Study: (In % of Patients Treated)

	Belgium (week 8)	France (week ~12)	Germany (week 6)
1 mg	29%	18.9%	60%
2 mg	56%	73.6%	27.4%
3 mg	10%	3.8%	5.8%
4 mg + >	5%	3.6%	-
Concomitant Therapy	28.5%	10%	7.2%

Table CIX
 Frequency of Side Effects in National Multicenter Studies

	Belgium	France	Germany
Total number of patients with side effects	27.8%	41.5%	38.6%
Dry mouth	14.6	22	13.5
Drowsiness	4.7	9	-
Tiredness	3.1	5	11.7
Dizziness	4.1	4	9.4
Nausea	2.4	2	4.2
Constipation	1.8	4	2.6
Gastralgia	-	2	2.2
Headache	-	2	4.1
Loss of appetite	-	-	1.5
Insomnia	-	1	1.4
Orthostatic hypotension	-	1	-

Overall Discussion and Conclusion

Data from patients treated with guanfacine alone and in combination with other antihypertensive agents (diuretics, beta-blockers, vasodilators) for time periods up to 24 months provide adequate information on the long-term safety of the drug for treatment of essential hypertension. Dosages of guanfacine utilized in these studies were usually 2-25 times higher than the recommended starting dosage of 1 mg h.s. and side effects occurred more frequently with these higher doses. The frequency of reported side effects diminishes over time if a patient can tolerate the initial annoyance of a side effect.

The antihypertensive effect of guanfacine after 24 months was not different from the results obtained after 12 months of treatment. The dosage of guanfacine did not have to be increased during the 2nd year in order to maintain the hypotensive action. Thus, tolerance did not develop.

No undesirable interactions with concomitantly prescribed medications were noted.

E. The Safety of Guanfacine

1. Deaths. Guanfacine has been given to more than 1,690 patients in clinical trials in many parts of the world. In addition, 11,270 patients have been evaluated in a postmarketing surveillance program. Despite this large patient exposure, there has been no death reported that could be ascribed to the drug.

2. Adverse Effects

Incidence and Types

In open-labeled safety studies lasting from 6 to 12 months. There were 1,063 adverse effects reported in 655 patients (1.6 adverse effects/patients) taking a mean daily dose of 4.7 mg (range 0.5-25 mg). During the year 55 patients (8%) dropped out because of adverse effects:

Dry mouth	23
Sedation	15
Constipation	7
Nausea	3
Orthostatic Hypo.	2
Headache	1
Nightmare	1
Rash	1
Insomnia	1
Depression	1

When treatment was extended to 24 months in 169 patients, there were 92 adverse effects reported (0.54/patient). Mean daily dose of guanfacine was 3.6 mg. There were 2 dropouts during the second year, one with rash and the other with dry mouth.

Adverse effects were dose related. In a double-blind, placebo controlled evaluation, the following adverse effects were seen.

Table CX

Adverse Effect	Daily Doses		
	Placebo (n=73)	1.0 mg (n=72)	3.0 mg (n=72)
Dry mouth	5	6	20
Sedation	1	0	10
Weakness	0	0	7
Dizziness	2	3	3
Headache	3	3	2
Impotence	1	0	3

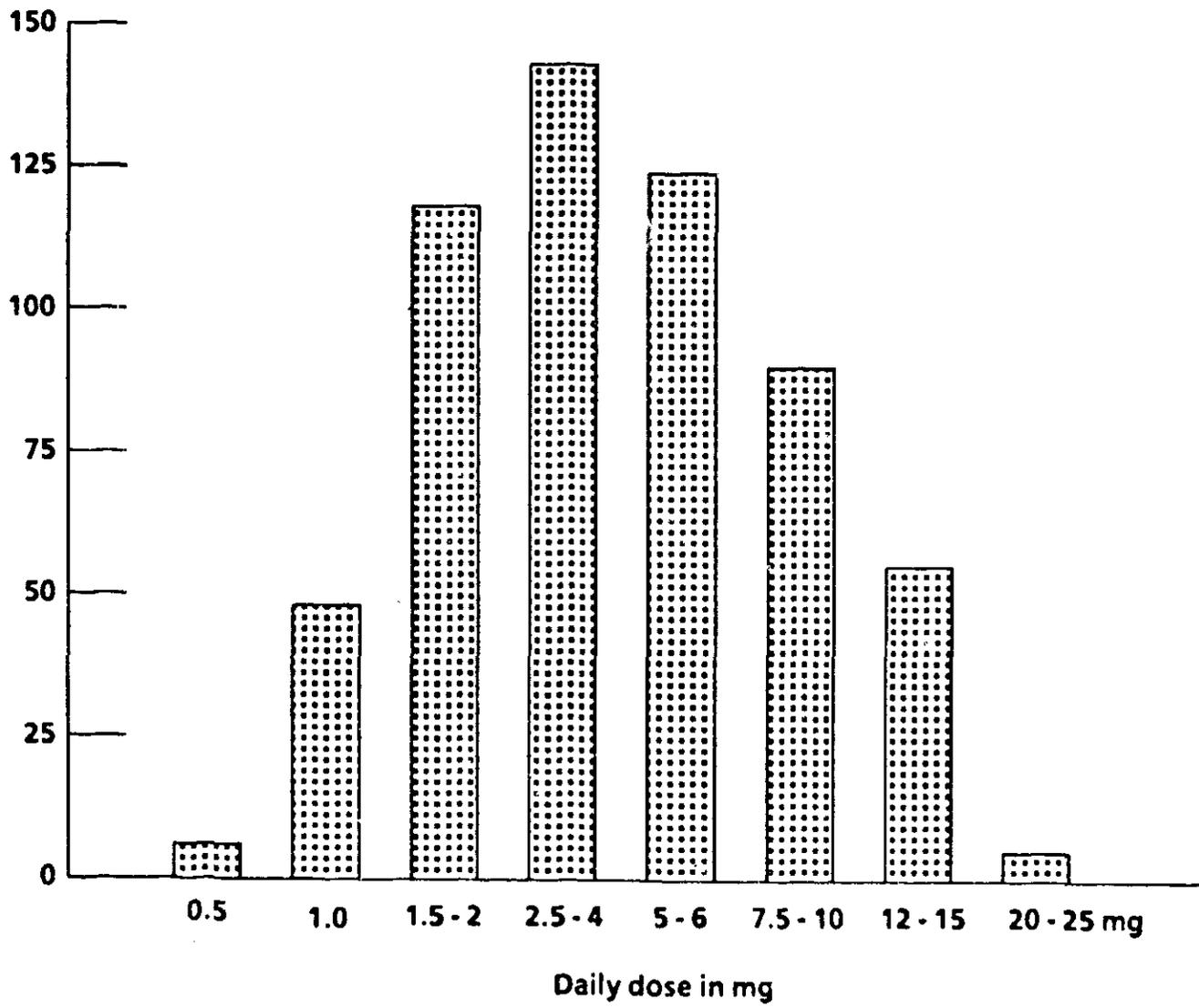
In another placebo-controlled study, side effects were evaluated over time to determine the course of these adverse effects with time. Adverse effects on drug, in completers, were as shown in Figure 56.

VI. Approved Package Insert

A copy of the package insert is attached.

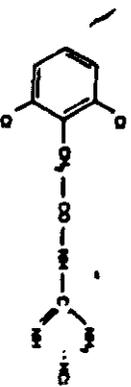
Figure 56

Number of Patients:



Package Insert

Description: Tenex (guanfacine hydrochloride) is a centrally acting anti-hypertensive with α_2 -adrenoceptor agonist properties. It is supplied as a light pink diamond shaped tablet for oral administration embossed with a 1 and engraved MPH on one side and engraved TENEX on the other side. Each tablet contains guanfacine base 1 mg (as the hydrochloride salt). The chemical name of Tenex (guanfacine hydrochloride) is N-amidino-2-(2,6-dichlorophenyl)acetamide hydrochloride and its molecular weight is 282.56. Its structural formula is:



Printed in U.S.A.

Guanfacine hydrochloride is a white to off-white powder, sparingly soluble in water and alcohol and slightly soluble in acetone. The tablets contain the following inactive ingredients: FD&C Red No. 40 aluminum lake, Lactose, Microcrystalline cellulose, Povidone, Stearic Acid.

Clinical Pharmacology: Tenex (guanfacine hydrochloride) is an orally active antihypertensive agent whose principal mechanism of action appears to be stimulation of central α_2 -adrenergic receptors. By stimulating these receptors, guanfacine reduces sympathetic nerve impulses from the vasomotor center to the heart and blood vessels. This results in a decrease in peripheral vascular resistance and a reduction in heart rate.

Controlled clinical trials in patients with mild to moderate hypertension who were receiving a thiazide-type diuretic have defined the dose-response relationship for blood pressure response and adverse reactions of guanfacine given at bedtime and have shown that the blood pressure response to guanfacine can persist for 24 hours after a single dose. In the dose-response

study, patients were randomized to placebo or to doses of 0.5, 1, 2, and 3 mg of guanfacine, each given at bedtime. The observed mean changes from baseline (tabulated below) indicate the similarity of response for placebo and the 0.5 mg dose. Doses of 1, 2, and 3 mg resulted in decreased blood pressure in the sitting position with no real differences among the three doses. In the standing position there was some increase in response with dose.

Mean Decrease in Seated and Standing Blood Pressure (BP) by Guanfacine Dosage Group

Vital Sign	n =				
	Placebo	0.5 mg	1 mg	2 mg	3 mg
Change in Systolic (seated) BP	-5	-5	-14	-12	-16
Change in Diastolic (seated) BP	-7	-6	-13	-13	-13
Change in Systolic (standing) BP	-3	-5	-11	-9	-15
Change in Diastolic (standing) BP	-5	-4	-9	-10	-12

Quinlacene hydrochloride is a white to off-white powder, sparingly soluble in water and alcohol or 3 slightly soluble in acetone. The tablets contain the following inactive ingredients: F&D&C Red No. 40 aluminum lake, Lactose, microcrystalline cellulose, Povidone, Stearic Acid.

Pharmacology: Tenex (quinlacene hydrochloride) is an orally active antihypertensive agent whose principal mechanism of action appears to be stimulation of central α_2 -adrenergic receptors. By stimulating these receptors, quinlacene reduces sympathetic nerve impulses from the vasomotor center to the heart and blood vessels. This results in a decrease in peripheral vascular resistance and a reduction in heart rate.

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study, patients were randomized to placebo or to doses of 0.5, 1, 2, and 3 mg of quinlacene, each given at bedtime. The observed mean changes from baseline, tabulated below, indicate the similarity of response for placebo and the 0.5 mg dose. Doses of 1, 2, and 3 mg resulted in decreased blood pressure in the sitting position with no real differences among the three doses. In the standing position there was some increase in response with dose.

Mean Decrease in Seated and Standing Blood Pressure (BP) by Quinlacene Dosage Group

Vital Sign	n = 63					
	Placebo	0.5 mg	1 mg	2 mg	3 mg	3 mg
Change in Systolic (seated) BP	-5	5	-14	-12	-12	-16
Change in Diastolic (seated) BP	-7	-6	-13	-13	-13	-13
Change in Systolic (standing) BP	-3	-5	-11	-9	-9	-15
Change in Diastolic (standing) BP	-5	-4	-9	-10	-10	-12

While most of the effectiveness of quinlacene was present at 1 mg, adverse reactions at this dose were not clearly distinguishable from those associated with placebo. Adverse reactions were clearly present at 2 and 3 mg (see Adverse Reactions).

In a placebo-controlled study of Tenex (quinlacene hydrochloride) a significant decrease in blood pressure was maintained for a full 24 hours after dosing. While there was no significant difference between the 12 and 24 hour blood pressure readings, the fall in blood pressure at 24 hours was numerically smaller, suggesting possible escape of blood pressure in some patients and the need for individualization of therapy.

In a double-blind, randomized trial, either quinlacene or clonidine was given at recommended doses with 25 mg chlorothalidone for 24 weeks and then abruptly discontinued. Results showed equal degrees of blood pressure reduction with the two drugs and there was no tendency for blood pressures to increase despite maintenance of the same daily dose of the two

drugs. Signs and symptoms of rebound phenomenon were not observed after discontinuation of either drug. Abrupt withdrawal resulted in a rapid return of diastolic and especially systolic blood pressure to pre-treatment levels, with occasional values greater than baseline. Whereas quinlacene withdrawal produced a greater increase in blood pressure than clonidine.

Pharmacodynamics: Hemodynamic studies in patients with hypertension treated with quinlacene showed a decrease in blood pressure accompanied by a decrease in peripheral resistance and a slight reduction in cardiac output under conditions of rest or exercise. Quinlacene (quinlacene hydrochloride) lowered eye and plasma catecholamine levels in hypertensive

was present at 1 mg, but was absent from 1000 mg. It was clearly present at 2 and 3 mg.

Signs and symptoms of rebound phenomena were infrequent upon abrupt withdrawal of clonidine produced a rapid return of classic and especially, systolic blood pressure to approximately pre-treatment levels, with occasional values significantly greater than baseline. whereas, quantitative withdrawal produced a more gradual increase in blood pressure, but also with occasional values significantly greater than baseline. Hemodynamic studies in man showed that the decrease in blood pressure was accompanied by a significant decrease in peripheral resistance and a slight reduction in heart rate (5 beats/min) during the treatment with clonidine. Cardiac output under conditions of rest and exercise was not affected by clonidine. Clonidine or clonidine was used for 24 weeks and no tendency for blood pressure to rise was observed. Plasma renin activity and plasma catecholamine levels in hypertensive patients, but this does not

correlate with individual blood pressure responses. Growth hormone secretion was stimulated with single oral doses of 2 and 4 mg of guanfacine. Long-term use of Tenex had no effect on growth hormone levels. Guanfacine had no effect on plasma aldosterone. A slight but insignificant decrease in plasma volume occurred after one month of guanfacine therapy. There were no changes in mean body weight or electrolytes. Pharmacokinetics: Relative to an intravenous dose of 2 mg, the absolute bioavailability of guanfacine is about 80%. Peak plasma concentrations occur from 1 to 4 hours with an average of 2.6 hours after single oral doses of 2 mg. The area under the concentration-time curve (AUC) increases linearly with the dose. In individuals with normal renal function, the average elimination half-life is approximately 17 hr (range 10-30 hr). Younger patients tend to have shorter

elimination half-lives (13-14 hr) while older patients tend to have half-lives at the upper end of the range. Steady state blood levels were attained within 4 days in most subjects. In individuals with normal renal function, guanfacine and its metabolites are excreted primarily in the urine. Approximately 50% (40-75%) of the dose is eliminated in the urine as unchanged drug, the remainder is eliminated is primarily as conjugates of metabolites produced by oxidative metabolism of the atomistic drug. The guanfacine-to-creatinine clearance ratio is greater than 1.0, which would suggest that tubular secretion of drug occurs. The drug is approximately 70% bound to plasma proteins, independent of drug concentration. The whole body volume of distribution is high (a mean of 6.3 L/kg), which suggests a high distribution of drug to the tissues.

The clearance of guanfacine in patients with varying degrees of renal insufficiency compared to patients with normal renal function has not been studied. Patients with renal insufficiency should be given lower doses. The manufacturer's literature and Administration and Administration: The drug is administered orally in the form of tablets. The recommended dose is 2 mg three times a day. The drug should be given with food. The drug should be given with food. The drug should be given with food.

Contraindications: The drug is contraindicated in patients with severe renal insufficiency. The drug is contraindicated in patients with severe renal insufficiency. The drug is contraindicated in patients with severe renal insufficiency.

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elimination half-lives (13-14 hr) while older patients tend to have half-lives at the upper end of the range. Steady state blood levels were attained within 4 days in most subjects.
In individuals with normal renal function, guanfacine and its metabolites are excreted primarily in the urine. Approximately 50% (40-75%) of the dose is eliminated in the urine as unchanged drug, the remainder is eliminated mostly as conjugates of metabolites produced by oxidative metabolism of the aromatic ring.
The guanfacine-to-creatinine clearance ratio is greater than 1.0, which would suggest that tubular secretion of drug occurs.
The drug is approximately 70% bound to plasma proteins, independent of drug concentration.
The whole body volume of distribution is high (a mean of 8.3 L/kg), which suggests a high distribution of drug to the tissues.
The clearance of guanfacine in patients with varying degrees of renal

insufficiency is reduced, but plasma levels of drug are only slightly increased compared to patients with normal renal function. When prescribing for patients with renal impairment, the low end of the dosing range should be used. Patients on dialysis also can be given usual doses of guanfacine hydrochloride as the drug is poorly dialyzed.
Indications and Usage: Tenex (guanfacine hydrochloride) is indicated in the management of hypertension. Since dosing information (see Dosage and Administration) has been established in the presence of a thiazide-type diuretic, Tenex should, therefore, be used in patients who are already receiving a thiazide-type diuretic.
Contraindications: Tenex is contraindicated in patients with known hypersensitivity to guanfacine hydrochloride.
Precautions: General: Like other antihypertensive agents, Tenex (guanfacine hydrochloride) should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular dis-

ease or chronic renal or hepatic failure.
Sedation: Tenex, like other orally active central alpha-2 adrenergic agonists, causes sedation or drowsiness, especially when beginning therapy. These symptoms are dose-related (see Adverse Reactions). When Tenex is used with other centrally active depressants (such as phenothiazines, barbiturates, or benzodiazepines), the potential for additive sedative effects should be considered.
Rebound: Abrupt cessation of therapy with orally active central alpha-2 adrenergic agonists may be associated with increases (from depressed to normal levels) in plasma and urinary catecholamines, symptoms of nervousness and anxiety, and less commonly, increases in blood pressure.
Information for Patients: Patients who receive Tenex should be advised to exercise caution when operating dangerous machinery or driving motor vehicles until it is determined that they do not become drowsy or dizzy from

the medication. Patients should be advised not to discontinue the medication abruptly. Laboratory tests: Abnormalities were identified in treatment with Tenex. Drug Interactions: The potential for additive CNS-depressant drug effects should be considered. Anticoagulants: Tenex was given guanfacine in several well-controlled studies with no

alpha-2 adrenergic agonist when beginning therapy (reactions) when taken as such as phenothiazines, barbiturates, or other sedative effects.

Patients should be warned that their tolerance for alcohol and other CNS depressants may be diminished. Patients should be advised not to discontinue therapy abruptly. In clinical trials, no clinically relevant laboratory test abnormalities were identified as causally related to drug during short-term treatment with lene (guanfacine hydrochloride). No specific adverse drug interactions have been identified. Drug interactions should be appreciated. But the potential for increased sedation when lene is given with other CNS depressant drugs should be appreciated. Anticoagulants: ten patients who were stabilized on oral anticoagulants were given guanfacine, 1.2 mg/day for 4 weeks. No changes were observed in the degree of anticoagulation. In several well-controlled studies, guanfacine was administered together with diuretics with no drug interactions reported. In the long-term safety studies, lene was given concomitantly with many drugs without evidence of

any interactions. The principal drugs given (number of patients in parentheses) were: cardiac glycosides (115), sedatives and hypnotics (103), coronary vasodilators (52), oral hypoglycemics (45), cough and cold preparations (45), NSAIDs (38), antihypertensives (29), antiparkinsonian drugs (24), oral contraceptives (18), tricyclic antidepressants (13), insulin (10), and beta blockers (10). Drug Laboratory Test Interactions: No laboratory test abnormalities related to the use of lene (guanfacine hydrochloride) have been identified. Carcinogenesis: Mutagenesis, Impairment of Fertility: No carcinogenic effect was observed in studies of 78 weeks in mice at doses more than 150 times the maximum recommended human dose and 10x weeks in rats at doses more than 100 times the maximum recommended human dose. In a variety of test models, guanfacine was not mutagenic. No adverse effects were observed in fertility studies in male and female rats. Pregnancy Category B: Administration of guanfacine to rats at 7x times the maximum recommended human dose and rabbits at 20 times the maximum

recommended human dose resulted in no evidence of impaired fertility or harm to the fetus. Higher doses (100 and 200 times the maximum recommended human dose in rabbits and rats respectively) were associated with reduced fetal survival and maternal toxicity. Rat experiments have shown that guanfacine crosses the placenta. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Labor and Delivery: Lene (guanfacine hydrochloride) is not recommended in the treatment of acute hypertension associated with toxemia of pregnancy. There is no information available on the effects of guanfacine on the course of labor and delivery. Nursing Mothers: It is not known whether lene (guanfacine hydrochloride) is excreted in human milk. Because many drugs are excreted in human milk,

caution should be exercised when Terex is administered to a nursing woman. Experiments with rats have shown that guanfacine is excreted in the milk. Pediatric Use: Safety and effectiveness in Children under 12 years of age have not been demonstrated. Therefore, the use of Terex in this age group is not recommended.

Adverse Reactions: Adverse reactions noted with Terex (Guanfacine hydrochloride) are similar to those of other drugs of the central α -2 adrenergic receptor class: dry mouth, sedation (lassitude), weakness (asthenia), dizziness, constipation, and impotence. While the reactions are common, most are mild and tend to disappear on continued dosing.

In a 12-week placebo-controlled, dose-response study the frequency of the most commonly observed adverse reactions showed a clear dose relationship from 0.5 to 3 mg, as follows:

Adverse Reaction	Assigned treatment, % of total				
	Placebo N=71	0.5 mg N=71	1.0 mg N=72	2.0 mg N=72	3.0 mg N=71
Dry Mouth	5 (7%)	4 (6%)	6 (8%)	8 (11%)	20 (28%)
Somnolence	1 (1%)	3 (4%)	0 (0%)	1 (1%)	7 (10%)
Asthenia	0 (0%)	2 (3%)	0 (0%)	2 (2%)	3 (4%)
Dizziness	2 (2%)	1 (1%)	3 (4%)	6 (8%)	3 (4%)
Headache	-3 (4%)	4 (5%)	3 (4%)	-1 (1%)	3 (4%)
Impotence	1 (1%)	1 (1%)	0 (0%)	1 (1%)	1 (1%)
Constipation	0 (0%)	0 (0%)	0 (0%)	5 (6%)	3 (4%)
Fatigue	3 (3%)	2 (3%)	2 (3%)	5 (6%)	3 (4%)

There were 41 premature terminations because of adverse reactions in this study. The percent of patients who terminated and the dose at which they terminated were as follows:

Dose	Placebo	0.5 mg	1 mg	2 mg	3 mg
Terminated	6.9%	4.2%	3.2%	6.9%	8.3%

Reasons for dropouts among patients who received guanfacine were: somnolence, headache, weakness, dry mouth, dizziness, impotence, asthenia, constipation, syncope, urinary incontinence, conjunctivitis, par-

esthesia, and dermatitis.

In a second placebo-controlled study in a second group of patients, the most common adverse reactions were dry mouth, dizziness, and depression. In the clonidine/guanfacine study, the most common adverse reactions were dry mouth, dizziness, and depression.

of adverse reactions in
and the dose at which they

2 mg	3 mg
6.9%	8.3%

received guanfacine were
dizziness, impotence, in-
fluenza, conjunctivitis, par-

esthesia and dermatitis.
In a second placebo-controlled study in which the dose could be adjusted
upward to 3 mg per day in 1-mg increments at 3-week intervals, i.e. a setting
more similar to ordinary clinical use, the most commonly recorded reactions
were dry mouth 4.7%, constipation 1.6%, fatigue 1.2%, somnolence 1.0%,
asthenia 0.6%, dizziness 0.6%, headache 0.4%, and insomnia 0.4%.
Reasons for dropouts among patients who received guanfacine were
somnolence, dry mouth, dizziness, impotence, constipation, confusion,
depression, and palpitations.
In the clonidine/guanfacine comparison described in Clinical Phar-
macology, the most common adverse reactions noted were:

	Guanfacine (n = 279)	Clonidine (n = 278)
Dry mouth	30%	37%
Somnolence	21%	35%
Dizziness	11%	8%
Constipation	10%	5%
Fatigue	9%	8%
Headache	4%	4%
Insomnia	4%	3%

Adverse reactions occurring in 3% or less of patients in the three controlled
trials were

System	Guanfacine	Clonidine
Cardiovascular	bradycardia, palpitations, substernal pain	
Gastrointestinal	abdominal pain, diarrhea, dyspepsia, dysphagia, nausea	
CNS	amnesia, confusion, depression, insomnia, libido decrease	

ENT disorders— rhinitis, taste perversion, tinnitus
Eye disorders— conjunctivitis, eye, vision disturbance
Musculoskeletal— leg cramps, hypokinesia
Respiratory— dyspnea
Dermatologic— dermatitis, pruritus, purpura, swelling
Urogenital— testicular disorder, urinary recurrence
Other— malaria, paresthesia, paresthesia

Adverse reaction reports tend to decrease over time. In an open-label trial
of one year's duration, 580 hypertensive subjects were given guanfacine,
titrated to achieve goal blood pressure, alone (51%), with diuretic (38%), with
beta blocker (3%), with diuretic plus beta blocker (6%), or with diuretic plus
vasodilator (2%). The mean daily dose of guanfacine reached was 4.7 mg.

Adverse Reaction	n
Dry mouth	
Dizziness	
Constipation	
Weakness	
Headache	
Insomnia	

bruits, taste perversion, tinnitus
 conjunctivitis, etc.; minor disturbances
 by cramps, hypokinesia
 dyspnea
 urticaria, purpura, purpura, sweating
 asthmalike disorder, urinary incontinence
 neuritis, parosmia, paresis

Reports tend to decrease over time. In an open-label trial
 in 580 hypertensive subjects were given guanfacine:
 with diuretic, alone (51%), with diuretic, 38%, with
 with diuretic plus beta blocker (5%), or with aortic plus
 the mean daily dose of guanfacine reached was 4.7 mg

Adverse Reaction	Incidence of adverse reactions at any time during the study	Incidence of adverse reactions at end of one year
Dry mouth	60%	15%
Drowsiness	33%	6%
Dizziness	15%	1%
Constipation	14%	3%
Weakness	5%	1%
Headache	4%	0.2%
Insomnia	5%	0%

There were 52 (8.9%) dropouts due to adverse effects in this 1-year trial. The causes were dry mouth (n = 20), weakness (n = 12), constipation (n = 7), somnolence (n = 3), nausea (n = 3), orthostatic hypotension (n = 2), insomnia (n = 1), rash (n = 1), migraines (n = 1), headache (n = 1), and depression (n = 1).
Drug Abuse and Dependence: No reported abuse or dependence has been associated with the administration of Tenex (guanfacine hydrochloride).
Overdosage: Signs and Symptoms: One case of guanfacine overdose has been reported. A 25-year-old female intentionally ingested 60 mg. She presented with severe drowsiness and bradycardia of 45 beats/minute. Gastric lavage was performed and an infusion of isoproterenol (0.8 mg in 12 hours) was administered. She recovered quickly and without sequelae.
Treatment of Overdosage: Gastric lavage and infusion of isoproterenol as appropriate.

Guanfacine is not dialyzable in clinically significant amounts (2.4 mg guanfacine hydrochloride is 1 mg daily given at bedtime to maintain serum hydrochloride) is 1 mg daily given at bedtime to maintain serum. Patients should already be receiving a thiazide type diuretic. If after 3 to 4 weeks of therapy, 1 mg does not give a satisfactory effect of Tenex is seen at 1 mg. (See Clinical Pharmacology). Some may show a rise in pressure toward the end of the dosing interval. Higher daily doses (rarely up to 40 mg/day in divided doses) have been used, but adverse reactions increase significantly with doses of 2 mg/day and there is no evidence of increased efficacy. No study established an appropriate dose or dosing interval when Tenex (guanfacine hydrochloride) is given as the sole antihypertensive agent. The frequency of rebound hypertension is low, but rebound can

There were 52 (8.9%) dropouts due to adverse effects in the 1-year trial. The most common causes were dry mouth (n = 20), weakness (n = 12), constipation (n = 7), dizziness (n = 3), nausea (n = 3), orthostatic hypotension (n = 2), insomnia (n = 1), rash (n = 1), migraines (n = 1), headache (n = 1), and depression (n = 1).

Abuse and Dependence: No reported abuse or dependence has been associated with the administration of lenex (guanfacine hydrochloride).

Signs and Symptoms: One case of guanfacine overdose has been reported. A 25-year-old female intentionally ingested 60 mg. She presented with severe grogginess and bradycardia of 45 beats/minute. Gastric lavage was performed and an infusion of atropine (0.6 mg in 12 mL of 5% dextrose) was administered. She recovered quickly and without sequelae.

Treatment of Overdose: Gastric lavage and infusion of atropine are the treatment of choice. Supportive care and monitoring of vital signs are appropriate.

Guanfacine is not dialyzable in clinically significant amounts (2.4%).

Dosage and Administration: The recommended dose of lenex (guanfacine hydrochloride) is 1 mg daily given at bedtime to minimize somnolence. Patients should already be receiving a laxative type diuretic.

If after 3 to 4 weeks of therapy, 1 mg does not give a satisfactory result, doses of 2 and then subsequently 3 mg may be given, although most of the effect of lenex is seen at 1 mg (See Clinical Pharmacology). Some patients may show a rise in pressure toward the end of the dosing interval; in this event a divided dose may be utilized.

Higher daily doses (rarely up to 40 mg/day in divided doses) have been used, but adverse reactions increase significantly with doses above 3 mg/day and there is no evidence of increased efficacy. No studies have established an appropriate dose or dosing interval when lenex (guanfacine hydrochloride) is given as the sole antihypertensive agent.

The frequency of rebound hypertension is low, but rebound can occur

When rebound occurs, it does so after 2-4 hours, which is delayed compared with clonidine hydrochloride. This is consistent with the longer half-life of guanfacine. In most cases, after abrupt withdrawal of guanfacine, blood pressure returns to pretreatment levels slowly (within 2-4 days) without ill effects.

How Supplied: Lenex tablets containing 1 mg guanfacine (as the hydrochloride salt) are available in bottles of 100 (NDC 0031-8901-63) and 500 (NDC 0031-8901-70) and in Dos-Cap Unit Dose Packs of 100 (NDC 0031-8901-64) and 500 (NDC 0031-8901-71).

Store at controlled room temperature (between 15°C and 30°C (59°F and 86°F)). Dispense in light-resistant container.

October 1986

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PHARMACEUTICAL DIVISION
A. H. ROBINS COMPANY
A. H. ROBINS MFG. COMPANY
RICHMOND, VA 23220

Tenex[®]
(Guanfacine)
1 mg Tablets

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October 1998

A.H. ROBINS

October 1998
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Tenex®
(Guanfacine Hydrochloride)

1 mg Tablets

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RICHMOND, VA 23220

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