

Study #307

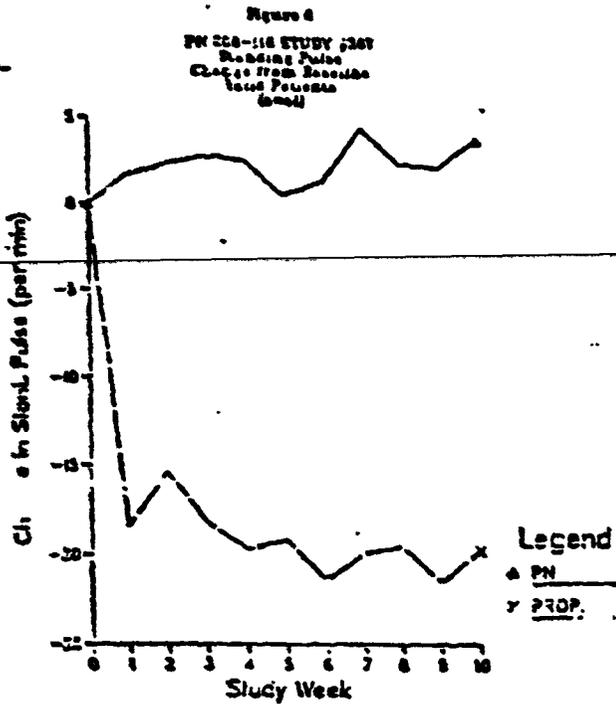


Fig. 6

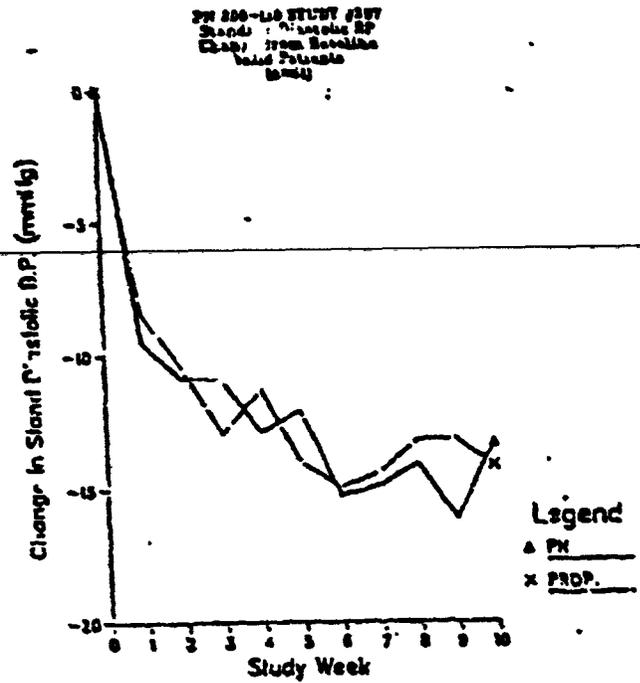


Fig. 5

Categorical comparisons show little difference in the two regimens.

Categorical Responses - Valid Patients
(Weeks 7-10)

Treatment Group	Total N	Number of Patients (%)			
		Category*			
		1	2	3	4
PN 200-110	33	8 (24)	21 (64)	4 (12)	0 (0)
Propranolol	29	8 (28)	16 (55)	4 (14)	1 (3)

*Category:

- (1) = supine diastolic ≤ 85 mm Hg with at least a 10 mm Hg decrease
- (2) = supine diastolic ≤ 85 mm Hg but still > 85 mm Hg
- (3) = supine diastolic > 85 mm Hg
- (4) = supine diastolic > 85 mm Hg with at least a 10 mm Hg decrease

5. Safety: There were 7 dropouts from the PN group, 9 from propranolol. Of the seven, five were due to adverse reaction. The roster of dropouts (partially valid patients) is shown in Table 4.

TABLE 4
PN 200-110 STUDY NO. 307
REASONS FOR PARTIAL VALIDITY FOR EFFICACY ANALYSIS

Patient No.	Treatment Group	Valid Thru Week	Discontinuation Week	Reasons
152	PN 200-110	2	2	Urticaria - Adverse Reaction
157	PN 200-110	3	3	Edema, Rash, GI Reflux - Adverse Reactions
206	PN 200-110	9	9	Subject Relocated
253	PN 200-110	9	10	Tachycardia - Adverse Reaction
302	PN 200-110	2	3	Noncompliant - 50% of Medication Taken in Wk 3
310	PN 200-110	6	6	Headaches, Shortness of Breath, Palpitations, Flushing - Adverse Reactions
314	PN 200-110	5	5	Tachycardia, Chest Pain Adverse Reactions
353	Propranolol	4	4	Study Drug Ineffective
304	Propranolol	8	8	Bradycardia - Adverse Reaction
208	Propranolol	4	5	Myocardial Infarction
312	Propranolol	3	3	Treatment Failure - Study Drug Ineffective
315	Propranolol	7	7	Treatment Failure - Study Drug Ineffective
351	Propranolol	5	5	Lost to Follow-Up
401	Propranolol	3	4	Upset Stomach - Adverse Reaction
406	Propranolol	6	6	Dizziness - Adverse Reaction
451	Propranolol	7	7	Stomach Discomfort - Adverse Reaction/Study Drug Ineffective

Urticaria is an unusual occurrence with this drug.

Safety was monitored by those means employed throughout the 6 major clinical trials besides examination of liver function. The liver enzymes were increased significantly in one patient who was discontinued from study after 3 weeks and gave a history of chronic alcohol abuse. Alkaline phosphatase LDH, SGOT and SGT were elevated in the follow up of another patient but not during the 10 weeks of the PN 200 administration. These elevations were also attributed to alcohol intake. A third patient showed slight elevation of enzymes which returned to normal. There was also aberration of liver function in 4 of the patients receiving propranolol.

6. Conclusion: There is no difference in the effect of propranolol and in ~~PN-200 in combination with hydrochlorotiazide~~ in control of mild to moderate hypertension. ~~PN-200 was safe in this combination.~~ Supporting evidence is offered that PN-200 is not hepatotoxic.

Long Term Study

I. Introduction objectives:

The primary purpose of this study is to assess safety of PN 200-110 in long term doses of 5-22.5 mg/day, with assessment of efficacy when appropriate.

One hundred and thirty-six (136) patients with mild hypertension, angina pectoris or CHF who had completed one of the double-blind trials were invited to participate in open label long term trial. Baselines for assessment of safety, while patients were receiving maintenance dose of medication were established before completion of controlled studies. Patients were evaluated weekly during earlier period of dose titration then monthly. Measures used to monitor safety were as outlined in the short term studies.

The mean doses of PN HCTZ for 3 month intervals are summarized in Tables 586. Safety was evaluated qualitatively so as to measure new and worsened findings (See Table 1).

Dropouts are classified in Table 40. New cardiovascular findings were most frequent early in the study. Edema, reported frequently, was usually mild and clearly unrelated to heart disease. Palpitations, pvc's and other cardiac abnormalities were mild and did not result in discontinuation. Cardiac function worsened by NYHA class in 7 and improved with PN Rx in 11/25 (Tables 12, 13). One patient left the study because of tachycardia pvc's; other ecg changes were minimal and transient.

There were no serious changes in blood counts or urine.

Table 25 displays laboratory data for the 12-month period. Blood sugar, uric acid elevation as expected occurred with HCTZ. Increase in hyperglycemia in diabetics receiving Pn is common and has produced no serious effects. Mild transient elevators of SGOT, SGPT, alkaline phosphatase do not suggest liver injury.

No abnormality attributable to the drug were found on repeated ophthalmologic examination.

Adverse reactions are listed in Table 16. Headache and dizziness are most frequent and there appears to be a dose response relationship.

TABLE 1
 PN 200-10 LONG-TERM STUDY
 EVALUATION SCHEDULE: OPEN-LABEL PHASE

	Initial Visit ¹	Weekly	q. 2 Weeks	q. 4 Weeks	q. 3 Months (12 Weeks)	q. 6 Months (24-26 Weeks)
Physical Exam OF PE*	X					X
Cardiovascular Evaluation OF CV	X		X ²	X		
Blood Pressure; Vital Signs OF VS	X	- EACH EVALUATION -				
Laboratory Evaluation (incl. urinalysis, CBC, blood chem.) OF LAB	X	X ³			X	
EKG Evaluation OF ECG	X	X ³		X		
Chest X-Ray OF CX	X					X
Ophthalmologic Examination OF OP	X ⁴					X
Concomitant Medication OF CM	- AS REQUIRED -					
Consent OF CD*	- AS REQUIRED -					
Medication Check OF MC	- EACH EVALUATION -					
Adverse Reactions OF AR	- EACH EVALUATION -					
End of Study Information OF ES	- UPON COMPLETION OR DISCONTINUATION -					

¹These evaluations were not repeated if performed at the end of the double-blind study. It was not necessary to re-record data on the OMF's used for this open-label, long-term phase if the data were recorded at the end of the double-blind study.

²Evaluation was performed q. 2 weeks while the patient was evaluated at weekly intervals until the dose and the patient were stabilized, then q. 4 weeks.

³Evaluation was performed weekly while the patient was evaluated at weekly intervals until the dose and the patient were stabilized, then q. 4 weeks.

⁴Evaluation was performed at the start of the open-label, long-term phase if not performed at the end of the initial double-blind study.

*Each visit, liver function tests (alkaline phosphatase, total bilirubin, LDH, SGOT, SGPT) were initiated during (cont'd) November, 1984, while the study was in progress.

*Can report form identifiers.

TABLE 16
PN 200-110 LONG-TERM STUDY
SUMMARY OF BODY WEIGHT DATA DURING ADMINISTRATION OF
PN 200-110 AS MONOTHERAPY AND FOLLOWING ADDITION OF NCTZ
ALL PATIENTS WITH PRE-PN 200-110 BASELINE DATA
BODY WEIGHT - LBS.

	Baseline Mean* (S.D.)	Mean Change from Baseline (S.D.)					
		Interval of PN 200-110 Treatment Duration					
		<1-3 wks.	4-6 wks.	7-9 wks.	10-12 wks.	Endpoint	Over All Intervals
PN 200-110 Monotherapy N	Pre-PN 200-110 189.3 (34.7) 125	+0.1 (3.1) 125	+0.1 (5.7) 87	+0.4 (6.4) 51	+1.9 (6.7) 18	-0.6 (6.6) 125	+0.1 (3.3) 125
PN 200-110 + NCTZ M	Pre-PN 200-110** + NCTZ 212.5 (42.3) 30	+0.5 (4.2) 22	-1.1 (4.9) 20	-1.8 (3.9) 5	-15.5 (21.9) 2	-1.2 (9.2) 30	-0.3 (4.4) 30

*although the number of patients included for each PN 200-110 interval decreases with time, the baseline for each group differs little from the baseline for the entire group. Therefore, the table contains the baseline mean for all patients with pre-PN 200-110 data.
 **The last visit during administration of PN 200-110 alone served as baseline for PN 200-110 + NCTZ.

Table 40
 PN 200-110 Long Term
 Summary of Patients' Reasons for
 Discontinuation of Long Term Therapy

Study No.	Pat No.	Weeks on Therapy	Total Daily Dose*	Coded Reason	Specific Reason for Discontinuation
5	102	54	22.5	Illness (NDR**)	
	103	9	15.0	Other	Chelation Therapy
	105	23	7.5	Drug Ineffective	Increased angina
	111	11	15.0	Other	Death (myocardial infarction)
	153	33	22.5	As per protocol	Completed 6 months
	154	25	22.5	Drug Ineffective	
	155	66	22.5	Other	Severe angina
206	1	28	22.5	Other	Hospitalized (chest pain at rest with ST seg depress)
	51	32	15.0	Other	Patient Choice
	53	25	22.5	Other	Patient Choice
	144	25	15.0	Adverse reaction	Patient Choice
301	304	33	5.0	Other	Arrhythmia not drug-related
	407	13	5.0	Uncooperative	
	410	6	20.0	Adverse reaction	Rash, edema
	604	10	20.0	Drug Ineffective	Lost to follow-up
	605	21	15.0	Other	Lost to follow-up
	609	9	15.0	Other	
	610	23	15.0	Other	Lost to follow-up
	616	12	20.0	Drug Ineffective	
	651	14	10.0	Other	Myocarditis; etiology unknown
	653	13	20.0	Drug Ineffective	
	656	12	15.0	Uncooperative	Lost to follow-up
302	302	11	12.5	Uncooperative	
	304	3	5.0	Adverse reaction	Headaches and palpitations
	307	13	5.0	Other	Lost to follow-up
	354	10	10.0	Adverse reaction (drug ineffective)	Elevated standing BP; headache
	355	14	20.0	Other	Lost to follow-up
	356	7	5.0	Drug Ineffective	
303	235	25	10.0	Uncooperative	
	274	1	5.0	Illness (NDR**)	Chest pain
	316	23	5.0	Illness (NDR**)	Low hemoglobin; angina
	322	24	5.0	Other	Paget's Disease
304	303	6	10.0	Adverse reaction	Tachycardia, PVC's
	305	18	10.0	Adverse reaction	GI complaints (bloating and joint pain)
	310	1	5.0	Adverse reaction	Vasodilatation symptoms
305	208	24	5.0	Illness (NDR**)	Small bowel obstruction

*Final prescribed daily dose (mg) of PN 200-110
 **Not Drug Related

European Studies:

Seven studies tested tolerance pharmacokinetics and bioavailability in healthy volunteers (Studies 2.1-2.7). These studies were supported by eight studies in hypertensive rats reviewed by pharmacology.

PHARMACOKINETICS

Study 2.1. In an open label study each of 16 healthy male subjects received single po doses of 0.5, 1.0, 2.5, 8.0, and 10 mg. Five of these subjects received 20 mg, two received 2 doses 2.5 and 20 and 5 and 10 mg. One received 3 doses 0.5, 5.0 and 10 mg.

There was no clear effect on b.p. in these groups but there was a dose related increase in heart rate. Headache and flushing were reported with higher doses.

Study 2.2 Thirteen normal males in open label study received single i.v. doses of .05 (n=3) 0.1(n=1), 0.2, 0.5, 1.0 (n=3) 2.0 mg (n=5) where n=number of subjects.

B.P., HR and side effects were observed for 24 hours. Plasma levels of PN were measured by gas chromatography (0.2 ng/ml sensitivity).

There was no dose dependent b.p. response; however heart rate increased proportionately. Doses of 1 and 2mg produced dose dependent tachycardia with dose. was seen ST segment flattening was seen in one receiving 0.5 and in 2 receiving 2mg.

One incidence of elevated liver enzymes was attributable to excess ethanol.

Plasma level and AUC were consistent with 1ST order kinetics calculations. A 1/2 life of 2 hours was found in this incomplete kinetic study.

Study 2.3 Single dose open label cross-over pharmacokinetic study with oral and sublingual dosing in 6 healthy males.

Drug was given in randomized order shown in table

<u>Dose</u>	<u>Administrator</u>
5	2 x caps of 2.5 mg
20	2 x caps of 10 mg
5	1 ml solution in 100 mg H ₂ O
20	4 ml solution in 100 mg H ₂ O
1	0.2 ml sublingual
5	1.0 ml syringe

Plasma levels of PN and its two metabolites were measured by gas chromatography. Plasma levels less than 2ng/ml had no effect on normal diastolic blood pressure. From 12-50 ng/ml the Log plasma level-blood pressure is linear.

Peak plasma level, reached in 0.6 ± 0.4 h, were 14 ± 9 and 43 ± 28 ng/ml for 5 and 20 mg respectively. Comparative kinetics of the two routes of administration demonstrates 1st pass liver metabolism.

BIOAVAILABILITY

Study 2.4 Each of 6 healthy males randomly received 5 mg PN PO, 1 mg ^{13}C PN IV or both doses simultaneously with a week between each dose. The PN and metabolites were measured in the plasma over 26 hours and in the urine up to 24 hours.

Mean plasma levels of parent drug and metabolites for separate or simultaneous administration indicate bioavailability to be independent of route of administration. Absorption from the gut was nearly 100%. Unchanged drug in the urine was zero and clearance was independent of route. The bioavailability of p.o. dose was 18%.

Study 2.5 Steady state kinetic study mean plasma levels were measured from a single, 5 mg dose. Seven days later subjects received 5 mg b.i.d. and after 14 days of treatment plasma levels were measured in steady state.

Plasma levels of PN were similar after single and multiple dose treatment. There was minimum drug accumulation and elimination half lives were similar except for prolongation of terminal half life with multiple doses.

Headaches and flushing were the commonest adverse reactions. One subject was eliminated because of elevated liver enzymes after a single dose and another withdrew because of headache.

Study 2.6. Six healthy men each received p.o. simultaneously 5 mg PN200 (2.5 mg cap x 2) and 5 mg ^{13}C PN in 100 ml up water. Plasma levels were monitored for 24 hour.

The Table displays the more rapid absorption of the solution is more rapid, but the similar AUC's for the capsule and solution indicate the capsules as almost completely absorbed.

Study 2.7 A test in 6 men for isotope effect of labelled PN showed almost identical plasma conc each time point. There was no isotope effect on the kinetic properties of the drug.

HYPERTENSION STUDIES

Study 3.1 Single PO doses were given in an open label study to patients with moderate to severe hypertension. Seventeen (17) had renal and 4 essential hypertension. Three had CNS disease and two had heart block II or III Open study in pts with moderate to severe hypertension.

The first 11 patients received 20 and the dose subsequently reduced initially and the dose subsequently so that 15 received the 10 mg dose. The larger dose was shown to have a greater effect on systolic b.p. and for longer time. The responder rate (the number of patients with a fall of systolic to 160 or diastolic to 95 torr within 4 hours.) was greater with 20 mg than for 10 mg. There were no symptoms reported to have resulted from hypotension.

The plasma levels from 2 patients with renal failure were compared with levels from 6 volunteers from a previous study. PN was more slowly excreted and 1ST this but plasma level was ca = the control at 8 hours. Metabolites 203-831 and 204-144 were eliminated more slowly by patients with renal failure than by normal controls. Headache and tachycardia were observed with the 10 mg dose, dizziness with 20mg.

Study 3.2 Single and multiple dose effect in hypertensive patients. Three patients with untreated DBP of 120 mm Hg each received a single dose 5 mg of PN. B.P. was taken supine standing arrest supine and standing 1 and 3 m after hand grip exercise.

~~Single dose of 5 mg lowered B.P. fell significantly both at rest and after exercise in all 3 patients. The study was continued with freely adjusted dose finishing at 10 day 2.5 mg b.i.d. followed by 3 days 5 mg b.i.d. There was a significant fall blood pressures and no instance of postural hypotension. One patient stopped treatment after 5 days because of headache.~~

Study 3.3 Single Blind Short term effect study in hypertensive patients. Twelve patients with systolic pressures over 180 or diastolic pressures over 100 each received placebo for 2-7 days then PN in freely titrated doses of 2.5-20mg bid for 5-19 days so as to achieve desired blood pressure. Tachycardia and dizziness were the commonest side effect the subjects receiving 20mg t.i.d. (sic) discontinued medication because of these symptoms. Symptoms were most prominent and onset of treatment or rapid increase in dose.

Trans aminase levels were elevated in 2 patients receiving cumulative doses of 75 and 50 mg. Details of follow-up are lacking. There were no other significant abnormal values reported.

The patients receiving 20 mg t.i.d. stopped p. 2-3 days because of dizziness associated with orthostatic hypotension and reflex tachycardia.

Study 3.4. Single Blind Short-term effect study with placebo post treatment period in hypertensive patients.

Ten hospitalized patients fulfilling the above criteria were given placebo 3-6 days prior to 6-10 days active drug. Initial doses of 2.5 mg b.i.d. were doubled q3 days as necessary to normalize BP. Five placebo responders were eliminated.

Lowering of blood pressure was apparent 2hr after A.M doses and was still present to lesser degree at the end of the inter-dosing interval. Liver enzymes were elevated in 2 patients although high transaminase levels appeared likely to have resulted from concomitant diclofenac. Two stopped because of side-effects.

Study 3.5. Open label treatment of hypertensive patients previously treated with PY 108-068 (a calcium channel blocker). Nine male patients with blood pressure under good control with PY 108-068 were given NP in doses which were adjusted during a titration period of 56 \pm 29 days. Doses as high as 60 mg were required. Relative potency of PN to PY was estimated to be ca 5 to 1.

Study 3.6. Comparative IV Dose-effect study with PN and PY:

A group of twenty hypertensive patients received PN IV bolus in doses of 0.001, 0.02, 0.05, 0.10, 2.5 and 1.2. An other group of 15 received PY 0.1, 0.2, 0.5, 1.2, 5 mg.

In addition to heart rate and blood pressure, Parameter CO SVR PAP, PCP were determined by heart cath. in 6 of PN, and in 7 of the PY group. As clear dose response for all parameters with both drugs was shown. PN was estimated to have 6 times the potency of PY. Headache and palpitation occurred and cumulative doses and PN from 0.2 to 2.0 mg. ST segment depression in one patient accompanied by precordial pressure was attributed to coronary steal. In another angina was not associated ECG change. Increase heart rate was similar with the two drugs.

Study 3.7 Long term effect study in hypertensive patients. Ten patients with diastolic pressures above 100 torr were treated with single blind placebo for 2-6 weeks then actively titrated with PN

5 mg 1 week.

5 mg 2 week

10 mg 1 week

until achieving a target of 95 mmHg Diastolic pressure. One patient stopped on the fourteenth day because of facial flush.

The response, clearly superior to the placebo baseline, appeared to last long enough for bid dosing.

Study 3.8 Double blind cross-over comparison of PN-100 to PY Active treatment of 6 patients with benign essential hypertension 4-5 weeks after 2 weeks placebo washout showed the drugs to have nearly identical effects on blood pressure.

Summary and Conclusions: In the relatively small European trials Pharmacokinetics, bioavailability, and pharmacodynamics were measured and there were no findings inconsistent with domestic studies. Small clinical efficacy studies indicate PN will be effective when given twice daily. Adverse hypotensive effects may be anticipated when a dose of 20 mg bid is necessary for blood pressure control in patients with more severe hypertension. Side effects are those attributable vasodilation.

Study #10

Study #12

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Study #15

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SAFETY

The most frequently occurring adverse reactions arranged in the following table are attributable to the physiologic effects of vasodilation. A long list of symptoms classified as ADR includes many incidental afflictions having no bearing on the drug's actions. There have been six deaths reported during the course of the studies. None is related to the drug. A case of sudden death occurring in a patient taking placebo (Study #15) is not included in this group.

A listing of dropouts from each study without consideration of adverse reactions follows:

1. Pharmacokinetic Studies

- | | | |
|----|------------|----------------|
| 1) | Study #3 | No dropouts |
| 2) | Study #310 | See Study #398 |
| 3) | Study #311 | No dropouts |
| 4) | Study #318 | 3 dropouts |
| 5) | Study #319 | 3 dropouts |
| 6) | Study #321 | No dropouts |
| 7) | Study #322 | No dropouts |
| 8) | Study #313 | 3 dropouts |
| 9) | Study #315 | 1 dropout |

2. Pharmacodynamic Studies: There were no dropouts in Studies 7, 9, and 11.

3. Clinical Efficacy Studies

- | | | |
|----|------------|--------------------------------------|
| 1) | Study #301 | 14 dropouts |
| 2) | Study #302 | 11 dropouts |
| 3) | Study #303 | 11 dropouts (PN 200, 11 HCTZ) |
| 4) | Study #304 | 5 dropouts (PN 200, 12 propranolol) |
| 5) | Study #305 | 20 dropouts |
| 6) | Study #307 | 16(7 PN-200, 9 Propranolol dropouts) |

4. Other Studies

1) Study #14	0
2) Study #15	4
3) Study #101	6
4) Study #10	1
5) Study # 12	4
6) Study #5	3
7) Study #6	14
8) Study #203	0
9) Study #206	2
10) European Studies	9
11) Long-Term Study	34 (In progress)

Dropouts from the major efficacy studies do not appear so numerous as to influence the efficacy data. The mortalities were thoroughly explored and were demonstrably unrelated to medication. Two suicides occurred in gravely ill and disturbed patients. There is no evidence that isradipine has a depressing effect on the CNS. Dropouts are enumerated by the study below. Headache, a side effect CA channel blockers attributable to vasodilation and as acceptable or accompaniment to treatment as is NTG. In one study of Nifedipine there was hardly any difference in the incidence with the drug compared with placebo. Similarities with passage of time is shown in the sketch abstracted from data tabulated in Safety Update.

Hypotension is less frequent than with Nifedipine and for all intents and purposes is not a problem in patients with mild to moderate hypertension. The reflex increase in heart arising from vasodilation by isradipine is entirely within physiologic limits in almost all cases. The symptom of palpitation can be interpreted as subject awareness of the heart due to increased cardiac output resulting from the desired reduction in systemic vascular resistance, arguably the most physiologic means of treating hypertension. The exaggeration of the pharmacologic effects should be of no consequence.

The sponsor repeatedly states that increase in heart rate is of no clinical significance and in support of this contention observes that isradipine is without anti-arrhythmic effect. This observation, consistent with the effects on the conduction system and the principle that anti-arrhythmic activity carries with it the risk of arrhythmia is further evidence of the drug's safety. Physiologic as it may be isradipine consistently increases heart rate.

Joint pain is mentioned next in frequency after these symptoms which are accounted for by vasodilation. The symptoms are not described in detail and there is no mention of associated systemic symptoms. Rash which has been described rarely has not been seen in association with arthralgia. There were no laboratory findings e.g. hemolytic anemia, proteinuria to suggest the autoimmune phenomena of a drug reaction. The clinical conditions were not found to be such as to indicate investigation by ANA titer.

The most serious question of safety to arise during the course of the studies was hepatotoxicity, which arose in Study #310 with the finding of abnormal liver function following an otherwise uneventful pharmacokinetic study. The question of hepatotoxicity is examined in the rechallenge study #398.

The long term reports a case of abnormal liver function arose on a patient after one month's treatment. A sixty year old man was found to have elevated liver enzymes and the drug was stopped. Some weeks later, the enzymes returned to normal levels. This experience is similar to that encountered with nifedipine. With both the drugs, abnormal liver function is a rare occurrence and evidence does not indicate that either drug is hepatotoxic although it was recommended that possibility exists in the labelling of nifedipine. In the European Studies, isolated case of hepatic disturbances could be related to alcohol or other offending agent.

Safety evaluations carefully monitored throughout the studies indicate the drug is safe in patients with mild to moderate hypertension. The meager experience of the European trials suggests that the side effect of hypotension may become a problem if isradipine is used to treat the more severe forms of the disease. The contention repeatedly stated that rise in pulse is not clinically significant appears correct.

The evidence from animal and human studies indicates that the effect which isradipine has on SVR is greater than its negative inotropic effect. In a failing heart this effect on myocardial contractility may assume greater importance.

The two studies devoted to this subject were of limited scope and in one hypotension was a serious complication. This experience is similar to that in the European Study in which postural hypotension developed in two patients with severe hypertension. These two patients, both responsive to treatment, dropped from the study had history of serious heart disease.

The most serious question of safety may be considered has been resolved by rechallenge for drug induced liver dysfunction and by careful monitoring of patients under study. Isradipine can be called safe for treatment of mild hypertension.

Study #398

Of the 54 subjects meeting the criteria for normals in the pharmacokinetic studies, 310, 313, and 18, thirteen were found to have abnormalities of liver function. While there were no adverse reactions or abnormal lab studies during the studies to draw attention the liver, one month after the completion of Study 310, an elevated transaminase was found in the plasma of one of these subjects in preparation for another study. Subsequently, similar findings appeared in another subject. To determine whether the abnormalities in liver function resulted from the drug, as many of the volunteers as possible were gathered for rechallenge study.

Seven of the subjects had transaminase levels between 200 and 1600 U, four exhibited levels less than 200U. Hepatitis antibodies were demonstrated in six of the men. See Table 8 (see page 111). All the subjects had been clinically well since the last study save for four who had been ill briefly, two with jaundice. These subjects had been gathered from professional drug study volunteers that included alcoholics, addicts, and others prone to liver disease. Something of the background of these subjects is shown in Table 3 on the next page.

Study plan called for finding of liver enzyme with 15% normal before undergoing rechallenge. Eleven men were admitted to the study. Nine of these received 10 mg PN 200/3-4 days after the liver screening. Blood samples were taken an hour later, then daily for eight days and subsequently every other day for the duration of the study. Two subjects did not receive because of persistent elevation of enzymes. One of these received placebo, the other no treatment.

Results:

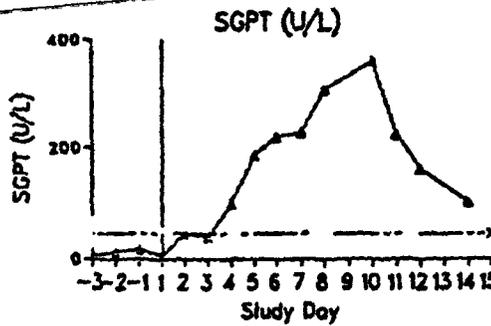
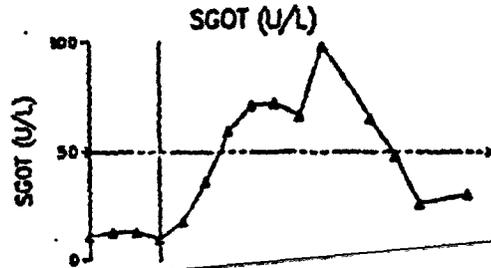
Two of the subjects showed a rise in enzymes following rechallenge. It is pointed out that the rise in the response to rechallenge is less than expected with hypersensitivity. See Figure (see page 110). Subject #3 as well as the two subjects not rechallenged underwent biopsy of the liver. In two of these cases the evidence against drug is definite. The other showing rise in enzyme following challenge refused to undergo biopsy. There thus remains a shadow of doubt cast by two subjects.

Conclusions:

Evidence both direct and indirect argue convincingly against implication of PN 200 in liver toxicity. The choice of the subjects from the chaotic background in which malnutrition and ill health are the norm, a high incidence of diseased livers is almost a certainty. It could, moreover, be expected that toxic influence e.g. alcohol would be worsened by a drug's placing a heavy metabolic burden on the liver.

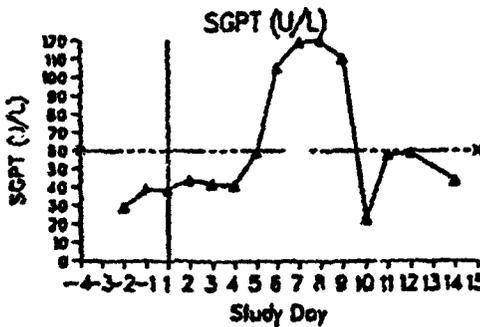
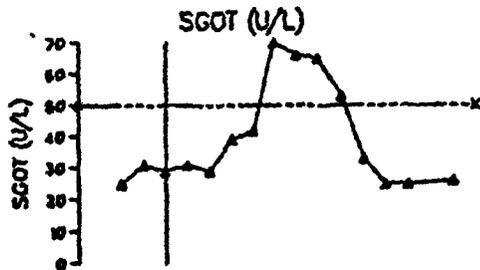
This meticulous and demanding study make it appear that the drug is not toxic to the normal liver.

PN 200-110 STUDY #398
Rechallenge of Subject #3



Previous Maximum Value: SGOT - 545, SGPT - 1230

PN 200-110 STUDY #398
Rechallenge of Subject #11



Previous Maximum Value: SGOT - 855, SGPT - 1280

The rise in enzymes in response to hypersensitivity reaction would be expected to be higher than that to the original insult.

TABLE 8

PN 230-110 STUDY NO. 310
 BLOOD CHEMISTRY VALUES: 4-6 WEEKS
 FOLLOWING COMPLETION OF THE TRIAL

NAME	DATE	LDB	ALK PHOS	T-BILI	SGOT+	SGPT+
1. RR	5/17 (S ¹)	214	95	0.5	15	34
	6/3 (PD ²)	150	100	0.4	18	37
	8/9		97.4 ³	0.7 ³	20.4 ³	30.0 ³
	DATE	Hb _a Ag	H _a Ab	Hb _c Ab	monospot	
	8/11	neg	neg		neg	
NAME	DATE	LDB	ALK PHOS	T-BILI	SGOT+	SGPT+
2. AL	5/11 (S ¹)	241	64	0.7	17	22
	6/3 (PD ²)	310	65	0.4	51	54
	8/5		202	2.0	815	1625
	8/14		125	0.9	69	394
	DATE	Hb _a Ag	H _a Ab	Hb _c Ab	monospot	
	8/11	neg	neg	-	-	
NAME	DATE	LDB	ALK PHOS	T-BILI	SGOT+	SGPT+
3. DMS	5/11 (S ¹)	215	101	0.3	55	55
	6/3 (PD ²)	185	108	0.3	34	36
	8/13		82	0.3	53	79
	DATE	Hb _a Ag	H _a Ab	Hb _c Ab	monospot	
	8/11	neg	neg	-	-	
	8/13	neg		pos		
NAME	DATE	LDB	ALK PHOS	T-BILI	SGOT+	SGPT+
4. CW	5/17 (S ¹)	176	85	0.5	22	20
	6/3 (PD ²)	154	113	0.5	59	50
	6/29		32	1.0	29	40
	DATE	Hb _a Ag	H _a Ab	Hb _c Ab	monospot	
	8/11		neg			
	8/13					

See last page of this table for explanation of footnotes.

TABLE 8 (CON'T)

NAME	DATE	LDB	ALK PHOS	T-BILI	SGOT+	SGPT+
5. DN	5/11 (S ¹)	184	117	0.9	19	17
	6/3 (PD ²)	148	114	0.9	13	23
	7/5		272	0.3	600	1070
	8/9		114	0.2	47	26
	DATE	Hb ₂ Ag	HaAb	Hb _c Ab	monospot	
	8/9	neg	neg	-	neg	
	8/11	neg	neg	pos		
NAME	DATE	LDB	ALK PHOS	T-BILI	SGOT+	SGPT+
6. RP	5/11 (S ¹)	199	79	0.4	17	12
	6/3 (PD ²)	188	85	1.0	38	38
	7/16		74	0.7	25	16
	DATE	Hb ₂ Ag	HaAb	Hb _c Ab	monospot	
		8/11	neg	neg		
NAME	DATE	LDB	ALK PHOS	T-BILI	SGOT+	SGPT+
7. JK	5/11 (S ¹)	177	117	0.6		
	6/3 (PD ²)	150	1			
	8/14		1			204 ⁴
	DATE	Hb ₂ Ag	HaAb		monospot	
		8/11	-		pos	
	8/14	neg	-	-		
NAME	DATE	LDB	ALK PHOS	T-BILI	SGOT+	SGPT+
8. BT	5/11 (S ¹)	204	65	0.8	26	30
	6/3 (PD ²)	163	75	0.5	19	17
	7/24	-	155	1.3	610	990
	8/2	-	-	0.8	52	-
	8/14		85	0.8	39	55
	DATE	Hb ₂ Ag	HaAb	Hb _c Ab	monospot	
		8/2	-	neg IgM	-	
			pos IgG			
	8/14	neg		pos		

See last page of this table for explanation of footnotes.

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TABLE 8 (CON'T)

NAME	DATE	LDB	ALK PBOS	T-BILI	SGOT+	SGPT+
9. DS	5/17 (S ¹)	264	74	0.3	35	22
	6/3 (PD ²)	211	80	1.0	16	52
	8/13	-	107	0.3	41	50
	8/14	-	90	0.5	68	142
	DATE	Hb ₂ Ag	H _a Ab	Hb _c Ab	monospot	
8/11	neg	neg	-			
NAME	DATE	LDB	ALK PBOS	T-BILI	SGOT+	SGPT+
10. HP	5/16 (S ¹)	147	140	1.0	11	42
	6/3 (PD ²)	127	123	1.1	17	30
	8/6 data OK					
	DATE	Hb ₂ Ag	H _a Ab	Hb _c Ab	monospot	
	8/11	neg	neg	-		
8/14			neg			
NAME	DATE	LDB	ALK PBOS	T-BILI	SGOT+	SGPT+
11. SP	5/11 (S ¹)	186	67	0.7	32	17
	6/3 (PD ²)	164	82	0.5	27	37
	7/17	-	88	0.4	120	182
	8/8	-	128	0.9	244	350
	8/14	-	131	0.4	128	304
	DATE	Hb ₂ Ag	H _a Ab	Hb _c Ab	monospot	
	8/8	neg	neg	neg	neg	
8/11	neg	-	-			
NAME	DATE	LDB	ALK PBOS	T-BILI	SGOT+	SGPT+
12. JG	5/16 (S ¹)	115	80	0.3	27	36
	6/7 (PD ²)	138	73	0.4	26	46
	DATE	Hb ₂ Ag	H _a Ab	Hb _c Ab	monospot	
	8/11	neg	-	-		

See last page of this table for explanation of footnotes.

TABLE 8 (CON'T)

NAME	DATE	LDB	ALK PHOS	T-BILI	SGOT+	SGPT+
13. SM	5/11 (S ¹)	357	78	0.4	15	20
	5/16	244	-	-	12	40
	6/3 (PD ²)	162	81	0.3	12	40
	8/15	-	67	0.4	17	15
	DATE	Hb _s Ag	HaAb	Hb _c Ab	monospot	
	8/11	neg	neg	-	-	
NAME	DATE	LDB	ALK PHOS	T-BILI	SGOT+	SGPT+
14. EM	5/16 (S ¹)	179	75	0.3	16	8
	6/3 (PD ²)	180	67	0.3	14	25
	8/15	-	66	0.3	17	12
	DATE	Hb _s Ag	HaAb	Hb _c Ab	monospot	
		8/11	-	neg	-	-
NAME	DATE	LDB	ALK PHOS	T-BILI	SGOT+	SGPT+
15. LG	5/16 (S ¹)	153	65	0.2	13	12
	6/3 (PD ²)	147	62	0.3	12	12
	8/6	-	105	0.6	212	686
	8/13	-	83	0.6	82	236
	DATE	Hb _s Ag	HaAb	Hb _c Ab	monospot	
	8/11	neg	neg	neg		
	8/13	neg				
NAME	DATE	LDB	ALK PHOS	T-BILI	SGOT+	SGPT+
16. PG	5/11 (S ¹)	183	59	0.8	16	17
	6/3 (PD ²)	138	81	0.4	18	25
	8/15	-	160	1.2	545	1230
	8/14	-	-	1.5	-	-
	DATE	Hb _s Ag	HaAb	Hb _c Ab	monospot	
	8/11	neg	neg			

See last page of this table for explanation of footnotes.

TABLE 8 (CON'T)

NAME	DATE	LDB	ALK PCOC	T-BILI	SGOT+	SGPT+
17. WB	5/23 (S ¹)	207	105	0.4	23	14
	6/7 (PD ²)	163	96	0.3	24	21
	8/13		142	0.3	32	70
	DATE	Hb ₂ A _g	H _a Ab	Hb _c Ab	monospot	
	8/11	neg	neg	neg		
	8/13	neg				
NAME	DATE	LDB	ALK PCOC	T-BILI	SGOT+	SGPT+
18 AP	5/23 (S ¹)	225	117	0.8	46	34
	6/7 (PD ²)	210	118	0.6	18	27
	6/15	180	122	1.4	855	1260
	8/9		218	3.2	142	544
	8/13		154	2.2		
	DATE	Hb ₂ A _g	H _a Ab	Hb _c Ab	monospot	
	8/9	neg	neg	neg		
8/13						

See last page of this table for explanation of footnote.

TABLE 8 (CON'T)

LABORATORY VALUES - RESULTS AS OF 8/15/84

NORMAL VALUES (UNLESS OTHERWISE NOTED)

ALKALINE PHOSPHATASE (ALK PHOS)	36-126 IU/L
TOTAL BILIRUBIN (T. BILI)	0.2 - 1.2 MG/DL
LDH	60-200 IU/L
SGOT	0-40 IU/L
SGPT	0-45 IU/L
HEMOGLOBIN (H _g)	13.0 - 16.7 GM/DL
HEMATOCRIT (HCT)	40.0 - 51.0%
WBC COUNT	4.2 - 10.8 TH/CUMM
MCV	80 - 90 CU MIC
PLATELET COUNT	27.5 - 33.5 UUG
	150,000 - 300,000 (NO. NOTED MUST BE MULTIPLIED BY 20,000)

OTHER NOTATIONS

+ SGOT and SGPT determinations described for May and June were performed on samples frozen and sent to Sandoz for assay of plasma drug concentrations. The assays were performed 8/14/84 to 8/15/84, at MetPath, Teterboro, NJ. See Table 9 for normal ranges. All other determinations for SGOT and SGPT were performed on freshly obtained samples at a lab in Vermont.

¹ Samples for LDH, Alkaline Phosphatase, and Total Bilirubin drawn between 5/11/84 and 5/23/84 at the Screening Evaluation.

² Samples for LDH, Alkaline Phosphatase, and Total Bilirubin drawn between 6/2/84 and 6/7/84 at the Post-Study Evaluation.

³ Normal values done in outside laboratory

ALK PHOS	30-100 IU/L
T-BILI	0-1.0 MG/DL
SGOT	7-24 IU/L
SGPT	4-25 IU/L

⁴ Done outside laboratory. Normal ranges not given. T-BILI, SGPT, SGOT were considered elevated.

⁵ Done outside laboratory. Values reported as normal.

The liver enzymes of the 18 subjects from frozen plasma samples

Subject No.	Sex	Age	Race	Height (cm)	Weight (kg)	Laboratory Results for Reference				Date of Exam
						ALT (U/L)	AST (U/L)	ALP (U/L)	Gamma-GT (U/L)	
1	M	35	W	175	70	45	120	15	10/15/68	
2	F	42	W	160	55	35	100	12	10/15/68	
3	M	28	W	180	80	55	130	18	10/15/68	
4	F	38	W	155	60	40	110	14	10/15/68	
5	M	45	W	170	75	50	125	16	10/15/68	
6	F	30	W	165	65	45	115	13	10/15/68	
7	M	40	W	185	85	60	140	20	10/15/68	
8	F	35	W	160	60	40	110	14	10/15/68	
9	M	25	W	175	70	50	125	16	10/15/68	
10	F	48	W	155	65	45	115	13	10/15/68	
11	M	32	W	180	80	55	130	18	10/15/68	
12	F	37	W	165	65	45	115	13	10/15/68	
13	M	43	W	175	75	50	125	16	10/15/68	
14	F	29	W	160	60	40	110	14	10/15/68	
15	M	47	W	185	85	60	140	20	10/15/68	
16	F	33	W	165	65	45	115	13	10/15/68	
17	M	39	W	180	80	55	130	18	10/15/68	
18	F	41	W	160	60	40	110	14	10/15/68	

Subject No.	Sex	Age	Race	Height (cm)	Weight (kg)	Laboratory Results for Reference				Date of Exam
						ALT (U/L)	AST (U/L)	ALP (U/L)	Gamma-GT (U/L)	
19	M	35	W	175	70	45	120	15	10/15/68	
20	F	42	W	160	55	35	100	12	10/15/68	
21	M	28	W	180	80	55	130	18	10/15/68	
22	F	38	W	155	60	40	110	14	10/15/68	
23	M	45	W	170	75	50	125	16	10/15/68	
24	F	30	W	165	65	45	115	13	10/15/68	
25	M	40	W	185	85	60	140	20	10/15/68	
26	F	35	W	160	60	40	110	14	10/15/68	
27	M	25	W	175	70	50	125	16	10/15/68	
28	F	48	W	155	65	45	115	13	10/15/68	
29	M	32	W	180	80	55	130	18	10/15/68	
30	F	37	W	165	65	45	115	13	10/15/68	
31	M	43	W	175	75	50	125	16	10/15/68	
32	F	29	W	160	60	40	110	14	10/15/68	
33	M	47	W	185	85	60	140	20	10/15/68	
34	F	33	W	165	65	45	115	13	10/15/68	
35	M	39	W	180	80	55	130	18	10/15/68	
36	F	41	W	160	60	40	110	14	10/15/68	

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TABLE 8
 PM 200-110 STUDY #398
 RESULTS OF THE HEPATITIS SCREEN

Subjects Re-Challenged with PM 200-110

Test	Subject Number							
	3	4	5	7	8	10	11	
Hepatitis A: Antibody IGM	Neg	Neg	Neg	Neg	Neg	Neg	Neg	
IGG	Neg	Pos	Pos	Neg	Neg	Neg	Neg	
Hepatitis B: Surface Antigen: Ratio	0.7	0.8	0.6	1.5	0.8	0.5	0.9	
Surface Antibody: Ratio	1.0	4.5	79	0.9	4.0	0.6	0.2	
Core Antibody	Pos	Pos	Pos	Pos	Pos	Neg	Neg	
E _s Antigen	Neg	Neg	Neg	Neg	Neg	Neg	Neg	
E _e Antibody	Neg	Neg	Pos	Neg	Pos	Neg	Neg	
Cytomegalovirus Titer: Antibody	<1/2	1/2	1/16	1/4	<1/2	ND	ND	
IFA (IGM)	<1/8	<1/8	<1/8	<1/8	<1/8	ND	ND	
Leptospira Agglutins	Neg	Neg	ND	Neg	Neg	ND	ND	

Subjects NOT Re-Challenged with PM 200-110

Test	Subject Number	
	6	9
Hepatitis A: Antibody IGM	Neg	Neg
IGG	Neg	Neg
Hepatitis B: Surface Antigen: Ratio	0.8	1.0
Surface Antibody: Ratio	1.0	2.0
Core Antibody	Neg	Pos
E _s Antigen	Neg	Neg
E _e Antibody	Neg	Neg
Cytomegalovirus Titer: Antibody	<1/2	ND
IFA (IGM)	<1/8	ND
Leptospira Agglutins	Neg	ND

*Normal Range:

CMV Antibody = <1/2
 CMV, IFA (IGM) = <1/8
 ND - Not Done

Reproductive Male Hormone StudyStudy #321

Introduction and Objective: Interstitial cell tumors in the rat have undergone extensive study. In this animal, tumors have been produced with enormous doses of PN 200. Genotoxic effects have not been found and the tumors are thought to result from hormonal stimulation. To test whether such an effect may arise in humans, this study was undertaken to assess effects of PN 200 on male reproductive hormone levels. Effects on urinary FSH & LH; serum testosterone, prolactin, FSH & LH were evaluated.

Design: Study is a randomized parallel group placebo controlled trial.

Results: Healthy male volunteers aged 21-35 were selected and evaluated in the manner described in other studies.

Table 1

PN 2-5-7.5 mg o.i.d.

Placebo
Washout

Randomization

PLACEBO

TABLE 1
PN 200-110 STUDY NO. 32a
DOSAGE SCHEDULE*

Treatment Group	PERIOD I	PERIOD II							Final Evaluation Day 15
	Placebo Phase (Single-Blind)	Active Treatment (Double-Blind)**							
	Study Days 1-7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14***	
Group A (PN 200-110)	One (1) placebo capsule tid	PN 2.5 mg tid	PN 2.5 mg tid	PN 5.0 mg tid	PN 5.0 mg tid	PN 7.5 mg tid	PN 7.5 mg tid	PN 7.5 mg tid	No study medication administered
Group B (Placebo)	One (1) placebo capsule tid	Pcb tid	Pcb tid	Pcb tid	Pcb tid	Pcb tid	Pcb tid	Pcb tid	No study medication administered

← Single-Blind → Double-Blind →

PN = PN 200-110 Capsule
Pcb = Placebo Capsule

*Study medication administered tid at 7:00 AM, 12 noon, and 3:00 PM at least one (1) hour prior to the respective meals. Any subject who could not tolerate the dosage regimen of study medication was to be discontinued from the study at that time; no alteration in the prescribed dosage regimen was permitted.

**Dose indicated was according to a t.i.d. dose regimen (i.e., respective daily doses required for PN 200-110 were 2.5 mg tid = 7.5 mg, 5.0 mg tid = 15 mg, and 7.5 mg tid = 22.5 mg).

***The final dose (3:00 PM) was not scheduled for administration on Study Day 14.

Median age 25, 60% white in each group. A slight disparity of height found between the two groups was dismissed as inconsequential.

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There were no significant changes in hormone levels as indicated in the table.

TABLE 9
 PN 200-110 STAIN NO. 304
 ANALYSIS OF HORMONE LEVELS DETERMINED BY SERUM (BLIND) SAMPLES
 AVERAGE OF DAY 7 BASELINE (9 HOUR AUC) COMPARED TO DAY 14 (EACH HOUR POST-DOSE)

Variable	Treatment Group	n	Baseline mean	Mean Change on Day 14 - Hour Post Dose								
				1	2	3	4	5	6	7	8	9
PRL (u/ml)	PN 200-110	9	8.33	-0.46	-0.23	0.32	-0.26	-0.37	-0.79(*)	-0.12	-0.68	0.34
	Placebo	8	8.31	-1.00*	-1.10*	-0.06	-0.68	-1.00*	-0.68	-0.31	-0.68	0.07
LH (u/ml)	PN 200-110	9	4.66	0.75	1.01	0.42	0.09	2.16**	-0.47	1.01	-1.91(*)	0.09
	Placebo	8	4.66	-1.26	-0.17	-1.04	-1.26	0.37	1.09	1.37	-0.30	-0.30
FSH (u/ml)	PN 200-110	9	616.22	72.41	14.91	-3.29	-22.64	-75.061(*)	-34.64	-120.42**	-130.64**	-43.42
	Placebo	8	616.22	275.19*	77.57	0.82	48.96	-25.2*	1.70	-48.96	-66.81*	-38.56
PGE (ng/ml)	PN 200-110	9	7.82	-0.43	-1.04	-0.13	-1.72**	-3.72**	-4.21**	-0.88	0.01	-0.04
	Placebo	8	8.72	-2.63**	-3.60**	-1.72**	-3.10**	-3.70**	-4.60**	-1.41	-1.28	-0.70

(*p<.05, **p<.01, ***p<.001)

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Abnormalities of liver function are clearly established by serologic findings in 4 subjects. The others whose levels are not explained were equally distributed between Rx and placebo groups. Repeated examination indicates likelihood of lab error, and it is entirely reasonable to conclude that liver disease was not induced by PN 200 in these men.

Conclusion:

PN-200 is without effect on reproductive hormones and other side effects are not of a serious nature. Further data supporting this conclusion is under pharmacology's review.

ISRADIPINE
PN 200 SANDOZ

Discussion and Conclusions:

Two well designed multi-center studies demonstrates that Isradipine is effective in reducing mild to moderate hypertension. The drug was clearly superior to placebo in these large studies and in 4 other studies compared favorably with HCTZ and propranolol. The drug was also effective in combination with HCTZ.

Pharmacokinetics and two clinical studies established dose responsiveness and suitability of b.i.d. dosage. Consideration of single daily dose was dismissed after a short trial.

The dose ranging as well as the larger studies show that the drug is best given in the smallest dose and not increased for a week; then gradually increased to desired level for maintenance or maximum safe dose is reached. In this manner not only is optimal efficiency of dosage achieved, but the severity of side effects diminished. The daily dose ranges from 5-20 mg.

Efficacy is claimed only for the milder forms of hypertension uncomplicated by renal, cardiac, or cerebral disease. In this situation with doses 20 mg the unpleasant and hazardous effects of orthostatic hypotension and reflex tachycardia are not a problem. In smaller less rigidly controlled European studies these effects were encountered several times. Systematic investigation of this adverse reaction has not been pursued and it can be conjectured that the difference in European experience results from inclusion of individuals with more severe hypertension and reduction of b.p. in these patients production of a reflex response not stimulated in the healthy mild hypertensive. Moreover in these sicker patients there may be compromise of

the homeostatic mechanisms so as to make the responsiveness to b.p. drop more sensitive. Regardless of the mechanism potential hazard from orthostatic hypotension is a consideration in treatment of more severe hypertension.

Safety: preclinical evaluation of carcinogenicity, teratogenicity, acute and chronic toxicity indicated no potential hazard from Isradipine other than Leydig cell hyperplasia found in the rat. Testicular tumor occurs: no; uncommonly in the rat and cellular hyperplasia seems afraid certain to result from prolonged hormonal stimulation. One clinical study demonstrated no disturbance of the reproductive hormones resulting from therapeutic doses of Isradipine.

~~During the course of study 3 pts have died from a myocardial infarct one of which was taking the medication. There is no evidence to indicate that Isradipine produced the fatal lesion. The most serious question regarding safety arose in pharmacokinetic study volunteers unfortunately selected from a population endemic with hepatitis. Individuals from this study were reexamined, rechallenged where feasible, and all but one shown to have hepatitis. In those rechallenged there was no drug reaction. Subsequent dose monitoring of liver function has shown only an occasional rise in enzyme level consistent with moderate ethanol intake. The drug is, beyond reasonable doubt, not hepatotoxic. The rapid metabolism of this drug places a burden on the liver which may be manifest by enzyme elevation when a load of ethanol or other agent is presented to the liver. Effects of interaction with drugs e.g. erythromycin should be anticipated.~~

The commonest side effects headaches, flushing, edema, can be explained by the effect of vasodilation. Headache is the most frequent of these side effects and though listed throughout the study under nervous system, there were no instances of encephalopathy or neuropathy with the possible exception of diabetes. These side effects were usually mild to moderate and only rarely interrupted treatment. Heart rate was consistently increased but not to a physiologically significant extent. It is repeatedly emphasized by that the unpleasant symptoms diminish with time and are mitigated by gradually increased dosage. Dosing instructions could well be copied from the protocol of Study #7.

There were occasional instances of worsening of diabetes and rare instances of impotence. Neither is fully explained and may conceivably have a common origin. Bioavailability is unaffected by food though absorption is delayed a half hour. Bioavailability is enhanced in the elderly presumably the result of slowing hepatic and renal function with age. Efficacy and safety of the drug are under study in the elderly.

Recommendation is for approval.

LABELING

The most serious question of safety arising from Study #310 is dealt after properly and is the claim that Isradipine is safe is consistent with the observations. The rechallenge study failed to demonstrate that Isradipine produced liver damage. It could be argued whether this evidence is positive proof.

There are no apparent defects in the account of the drug's pharmacologic actions. The representation of the therapeutic effects to be expected in hypertension is reasonable.

Effect on Diabetes is similar to that of nifedipine. No mention is made of the possible additive effects of PN-200 and HCTZ on diabetes. Edema formation, a commonplace is readily explained by relaxation of arteries without reduction in venous pressure. The drug does not cause progressive fluid retention.

Afterload reduction is a sound basis for treatment of CHF, though studies to date have not established the safety of this drug in this condition. Severe hypertensives may respond differently than do pts with mild to moderate hypertension.

Mild diuresis encountered during clinical trials left unexplained is attributable to nature which appear to be an effect of Ca entry blockers in general. Whether this effect is particularly important after Isradipine or is more prominent than other agents of this class is unknown. It is thought that long term hypertensive response may depend on this renal effect. Data gathered thus far do not support efficacy of Isradipine in angina through relaxation of large coronary arteries by CA entry blockers is well established.

Asthma is benefited little if all by isradipine's effect on bronchial smooth muscle. However, the drug can be used safely in asthmatic patients.

Drug interaction with agents likely to be used concurrently is no problem, but the added burden of other agents metabolized by the liver may significantly increase bioavailability of one or the other agent. This consideration has not been mentioned in the clinical trials.


Robert Kimball, M.D.

cc
Orig.
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