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N18-873 1 of 3

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NDA 18-873

Drug Generic Name:
Mexiletine Hydrochloride

Applicant:
Boehringer Ingelheim Ltd.
90 East Ridge Road
P.O. Box 368
Ridgefield, Ct 06877

Drug Trade Name:
Mexitil

I. Indications for Use:

Mexitil is indicated for the suppression of symptomatic ventricular arrhythmias, including frequent premature ventricular contractions, unifocal or multifocal, couplets and ventricular tachycardia. Like other antiarrhythmics, mexiletine has not been shown to prevent sudden death in patients with serious ventricular ectopic activity, and also, like other antiarrhythmics, it has potentially serious adverse effects, including the ability to worsen arrhythmias. It is therefore essential that each patient given mexiletine be evaluated electrocardiographically and clinically prior to and during mexiletine therapy to determine whether the response to mexiletine supports continued treatment.

II. Dosage form, route of administration and recommended dosage:

A. Dosage Form:

Mexitil is available as hard gelatin capsules containing 150 mg, 200 mg and 250 mg of mexiletine hydrochloride.

B. Dosage and Administration:

The dosage of Mexitil must be individualized on the basis of response and tolerance. Administration with food is strongly recommended. Initiate Mexitil therapy with 200 mg every eight hours when rapid control of arrhythmia is not essential. A minimum of two-three days between dose adjustments is recommended. Dose may be adjusted up or down by 50 or 100 mg. Satisfactory control can be achieved in most patients by 200 to 300 mg given every eight hours with food. If satisfactory response has not been achieved at 300 mg q8h, and the patient tolerates Mexitil well, a dose of 400 mg q8h may be tried. The dose should not exceed 1200 mg/day as the severity of CNS side effects increases with the total daily dose.

Loading Dose: When rapid control of ventricular arrhythmias is essential, an initial loading dose of 400 mg of Mexitil may be administered, followed by a 200 mg dose in eight hours. Onset of therapeutic effect is usually observed within 30 minutes to two hours.

Q12H Dosage Schedule: If adequate suppression is achieved on a Mexitil dose of 300 mg or less every eight hours, a 12-hour schedule may be employed to improve patient compliance or convenience.

This may be started by giving the q8h dose every 12 hours while carefully monitoring the degree of suppression of ventricular ectopy and then, if necessary, the dose may be adjusted to maintain the desired response.

Transferring to Mexitil: The following dosage schedule, based on theoretical considerations rather than experimental data, is suggested for transferring patients from other Class I oral antiarrhythmic agents to Mexitil. Mexitil treatment may be initiated with a 200 mg dose, and titrated to response as described above, 6-12 hours after the last dose of quinidine sulfate, 3-6 hours after the last dose of procainamide, or 6-12 hours after the last dose of disopyramide.

In patients for whom withdrawal of the previous antiarrhythmic agent is likely to produce life-threatening arrhythmias, hospitalization of the patient is recommended.

When transferring from lidocaine to Mexitil, the lidocaine infusion should be stopped when the first oral dose of Mexitil is administered, but the infusion line should be left open until suppression of the arrhythmia appears to be satisfactorily maintained. Consideration should be given to the similarity of the adverse effects of lidocaine and Mexitil and the possibility that they may be additive.

III. Manufacturing and Controls:

A. Manufacturing and Controls

Mexiletine hydrochloride is prepared by a synthetic process that has been described in sufficient detail to permit a determination of the validity of the assigned chemical structure and the suitability of the specifications and test methods for the bulk new drug substance. The compound is a racemic mixture. Raw materials and intermediates are satisfactorily characterized, and sufficient attention is given to isolation and purification of the new drug substance.

The controls over the manufacturing procedures which include specifications and test methods for the new drug substance, the inactive ingredients, and the finished dosage form give sufficient assurance of the identity, strength, quality and purity of the drug.

B. Stability

Stability studies have been conducted on the new drug substance, the dosage forms in the proposed market container (opaque HDPE bottles and blister packages). The data submitted adequately support the 36 month expiration date for the drug product.

The applicant has made the commitment to place initial production lots on stability study when they become available.

C. Methods Validation

The analytical methods for control of the new drug substance and drug product are being validated by FDA Laboratories. The methods are considered suitable for control and regulatory purposes after incorporation of minor changes.

D. Labeling

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

Insofar as could be determined from a thorough search of available references, the trade name Mexitil is not in conflict with the name of any other drug.

E. Establishment Inspection

Inspection of Boehringer Ingelheim KG, Boehringer Ingelheim Ltd., and other facilities that do the contract packing of the drug product has been performed to determine their compliance with "Current Good Manufacturing Practice Regulations." A satisfactory report was received from the Office of Compliance which states there is no reason to withhold approval of the NDA.

F. Environmental Impact Analysis Report

The Environmental Impact Analysis Report states that the manufacture of Nexetil is expected to have little or no impact on the environment.

IV. Pharmacology:

A. Pharmacodynamics

Mexiletine hydrochloride is a new Class IB antiarrhythmic agent whose chemical structure and electrophysiological properties resemble those of lidocaine, although its anticonvulsant and pharmacokinetic properties differ from that drug. Unlike lidocaine, it is effective following oral administration and possesses a long plasma half-life.

The efficacy of mexiletine hydrochloride was determined in various animal screening models and was compared with that of other known antiarrhythmic agents. In isolated guinea pig and rabbit atrial tissues, therapeutically relevant concentrations of mexiletine hydrochloride (1-5 ug/ml) reduced the maximal rate of depolarization of the action potential so that the conduction velocity was slowed, the excitability threshold was increased and the effective refractory period was lengthened without a significant change in the resting membrane potential or the spontaneous frequency of the sinoatrial node. In the isolated canine Purkinje fiber system the effective refractory period was shortened but not as much as the action potential duration, so that the ratio of the effective period to the action potential duration was increased by mexiletine.

In intact animals mexiletine hydrochloride increased the fibrillation threshold of the ischemic myocardium and reversed ventricular tachyarrhythmias resulting from ouabain intoxication or coronary ligation.

Generally, in terms of dose (mg/kg), the activity of mexiletine hydrochloride was found to be superior to quinidine, lidocaine, phenytoin and procainamide in the various antiarrhythmic and antifibrillatory screening studies conducted.

The secondary pharmacological effects of mexiletine hydrochloride include local anesthetic and anticonvulsive activity. The anticonvulsive activity was demonstrated in a number of animal models and may be due to its inhibitory effect on the uptake and release of gamma aminobutyric acid. The compound has no effect on the autonomic nervous system and does not interfere with the function of biogenic amines. It has neither antihistaminic activity nor alpha- or beta-adrenergic blocking properties.

B. Pharmacokinetics

The pharmacokinetic profile of mexiletine hydrochloride is characterized by high systemic availability (83%) following oral administration, with peak levels attained in 1-1.5 hours; plasma half-lives in rats and dogs ranged from 8 to 23 hours.

Following both oral and intravenous administration, renal excretion of metabolites and parent drug accounted for 80-90% of the administered substance regardless of the species studied; fecal excretion was always less than 10%. Renal clearance of the compound was increased by urinary acidosis. The excretion pattern in rats, dogs and monkeys was not altered by chronic dosing.

Tissue distribution studies conducted in rats and rabbits after oral and intravenous dosing, showed the highest concentrations of the radio-labeled substance within 30 minutes of administration. Radioactivity decreased rapidly, and by 6 hours significant levels could only be found in gastrointestinal tract tissue; by 24 hours, only minimal residual levels were seen. The drug was found to penetrate the blood/brain barrier and placental barrier in trace amounts.

Mexiletine hydrochloride was extensively metabolized in all species studied. In rats, 90% of the radioactivity in urine was due to polar nonextractable conjugates of the hydroxy-metabolites, predominantly glucuronides. The two major metabolites in human urine were a parahydroxy-derivative, which was present as a glucuronide, and a hydroxymethyl derivative which was present in both free and conjugate forms. Multiple dosing studies in rats, dogs and monkeys indicated that accumulation of the compound did not occur.

C. Toxicology

The toxicity of mexiletine hydrochloride was evaluated in a variety of animal species, both rodent and non-rodent, following acute, subchronic and chronic administration. Carcinogenicity, reproduction and mutagenicity studies were also performed. Acute oral and intravenous administration studies in mice, rats, rabbits (p.o. only) and dogs, revealed LD₅₀'s ranging from 112 (dog) to 630 (rat) mg/kg p.o. (which is approximately 5 to 26 times the maximum [24 mg/kg] recommended daily dose in a 50kg human) and 19 to 60 mg/kg i.v. The major signs and symptoms of toxicity were related to the effect of the drug on the central nervous system.

Subchronic oral toxicity studies included the following: mouse, 4 weeks at doses of 40, 80 and 160 mg/kg; rat, 4 weeks at doses of 40, 100 and 250 mg/kg; rat, 13 weeks at doses of 15, 30, 60 and 150-200 mg/kg; and dog, 13 weeks at doses of 3, 9 and 15-30 mg/kg. In the 4-week mouse and rat studies, doses of 80 and 100 mg/kg, respectively, produced slight transient ataxia, whereas the higher doses caused ataxia and convulsions. In male mice, myocardial necrosis (3/25) and deaths (4/25) were recorded at the highest dose level. In rats, a reversible decrease in total protein, increase in cholesterol and a slight increase in liver weights (females only) were noted in the high-dose group; however, no significant pathological findings were observed. In the 13-week rat study, no clinical signs of intolerance other than a slight reduction in mean food consumption in the high-dose males were observed. Histopathological examination revealed fatty changes in the livers of animals in the two highest dosage groups, which appeared to be largely reversible in recovery animals. In the 13-week dog study, diarrhea and emesis were the only symptoms noted. Histopathological examination showed a fatty degeneration of myocardial fibers in 2/6 middle-dose and 4/6 high-dose animals, and peripheral fatty degeneration of the liver in 1/6 high-dose animals.

Subchronic intravenous studies of 4 weeks duration were also conducted in dogs (at doses of 1.5, 3.0 and 13.5 mg/kg), monkeys (at doses of 1.5, 4.5 and 12.0 mg/kg) and rats (at doses of 5, 10 and 20 mg/kg). In the dog and monkey, doses of 12.0 and 13.5 mg/kg produced muscular incoordination, ataxia and convulsions. A transient increase in heart rate was also noted in dogs. In rats, dosages of 10 and 20 mg/kg caused ataxia, tonic spasms, hyperventilation and mortalities (two deaths occurred at 10 mg/kg and 17 [57%] at 20 mg/kg). However, in all three species histopathological examination failed to indicate any treatment-related findings.

Chronic oral toxicity studies were conducted in rats and dogs. Three studies were performed in rats: two of 26-weeks duration at doses of 20, 40, 80 and 120 mg/kg (gavage) and 40, 90 and 200 mg/kg (diet), respectively; and one of 78-weeks duration at doses of 20, 40 and 240 mg/kg (diet). Following oral administration to rats at doses of 80 mg/kg and higher, effects on the central nervous system were observed which included ataxia and convulsions. Other effects included decreased food consumption, weight loss, fatty livers and mortalities. Reversible increases in organ weights (i.e., adrenals, males; ovaries and thyroids, females) were also noted. In the 78-week study, elevations in SGPT and serum alkaline phosphatase values were observed in the high-dose group, but were not associated with any histopathological findings.

In the dog, oral studies of 27 and 52 weeks duration were conducted at dose levels of 5, 10, 20 and 40 mg/kg. Except for an increased incidence of emesis, the 20 mg/kg dose level was well tolerated in both the 27 and 52 week studies. At the high-dose (40 mg/kg), ataxia, tremors, salivation and tonic-clonic convulsions were observed. In the 52-week study, a transient increase in heart rate was also noted and three of the six high-dose animals died (after 36 weeks). Histopathological examination of animals in the 27-week study revealed fatty changes in the heart in the two low-dose groups (2/6 animals at 5 mg/kg, 1/6 at 10 mg/kg) and in the liver in the two high-dose groups (1/6 animals at 20 mg/kg and in 4/6 at 40 mg/kg). In the 52-week study, fatty changes were observed in the livers of 1/6 controls, 2/6 low and 2/6 mid-dose dogs. These changes were not observed in the high-dose group.

In summary, in the subchronic and chronic studies in mice, rats and dogs, some fatty changes have been seen microscopically in the liver but specific liver enzyme levels were unimpressive. Alkaline phosphatase (AP) and SGPT levels were raised in moderate degree and apparently treatment-related only in high-dose animals in the 78-week rat study and were not associated with significant morphologic changes in the liver. Although this compound may be capable of producing minor changes in liver fat content at high doses in rats and dogs, these changes appear to be of little clinical significance.

An 18-month oral carcinogenicity study in mice and a two-year study in rats did not establish a carcinogenic potential for mexiletine hydrochloride at doses up to 160 and 240 mg/kg, respectively, (via dietary admixture) which is 7 to 10 times the maximum recommended human daily dose. Anemias and abnormally low WBC levels were seen sporadically in treated rats. High dose male rats exhibited fatty liver changes at twice the rate of controls.

All three segments of the reproduction studies were performed. Effects of mexiletine on fertility and general reproductive performance were determined in rats; teratogenic potential was evaluated in mice, rats and rabbits; and peri/postnatal effects were studied in rats. Following oral administration of up to 200 mg/kg (approximately 8 times the maximum recommended human daily dose), no effect on fertility was noted; however, drug-treated animals exhibited slight ataxic movements, tremors and weakness immediately post-dosing. Although high dose levels produced side effects in dams, there were no effects on litter parameters or on the

development, behavior, function or reproductive capability of F_{1a}, fetuses of a second litter (F_{1b}) or second generation (F₂). Similarly, oral doses of up to 60 mg/kg administered during gestation and throughout lactation were without effect on litter parameters or progeny. Although segment II studies via the oral route of administration in 3 species failed to reveal a teratogenic potential at doses of up to 80 mg/kg/day, these studies suggested an increased sensitivity to the convulsant action of mexiletine with pregnancy. Rat and rabbit intravenous administration studies at doses up to 10 mg/kg also did not result in any teratogenic effects, although the increased numbers of dead implants observed only in rabbits in the middle dose group (7 dead implants among 14 pregnant animals in the control group, 8/13 at 2.5 mg/kg, 15/15 at 5 mg/kg, 4/15 at 10 mg/kg) suggested a reduced viability at these levels.

Mexiletine hydrochloride did not induce any mutagenic effects in the Ames test, with or without microsomal enzyme activation, at concentrations of 3.2 - 3000 mcg/plate.

V. Medical:

A. Clinical Pharmacology

Eleven phase I and II studies (See Table I) have defined the bioavailability and pharmacokinetics of mexiletine, provided evidence of effectiveness in two dosage regimens and explored drug-drug and drug-disease interactions. In addition, a substantial body of published literature is available reflecting experience with mexiletine in the United Kingdom and Europe. (Mexiletine was marketed in the U.K. in 1975 and subsequently in 31 other countries).

Table 1: Clinical Pharmacology of Mexiletine

Type of Study	Investigator	Enrolled/ Analyzed	Patient Characteristics	Dose of mexiletine	Duration of Treatment	Summary
Bioavailability (open label)	Zimney, M.	4/4	Healthy males 18-50 yrs.	200 mg solution 100 mg capsules 200 mg capsules 400 mg capsules	single dose single dose single dose single dose	Bioavailability of capsule approximately 80% of oral solution
Bioavailability (open label)	Zimney, M.	26/24	Healthy males 18-50 yrs	200 mg solution 200 mg capsules with food 200 mg capsules without food	single dose single dose single dose	No significant difference among treatments.
Pharmacokinetics/ Pharmacodynamics (open label)	Vozech, S. Follath, F.	58/58	Ventricular ar- rhythmias; CHF (27) 50M/8F	200-250 mg q8h 400-600 mg loading dose	variable single dose	Dose-plasma level relationship found to be linear. Loading dose suppressed ectopy. Therapeutic plasma levels sustained six hours post dose.
Pharmacokinetics/ Pharmacodynamics (open label)	Podrid, P. Lown, B.	137/122	Symptomatic VE resistant to conventional drug therapy.	400 mg (loading)	Assessment of single dose	The 400 mg loading dose produced plasma levels within the therapeutic range, and suppressed ventricular ectopy.
Single-blind multiple rising dose response and tolerance also dose-related	Ruskin, J. Steen, S. Thompson, W.	50/35	Inpatients with 130 PVC/hr; 29M/21F	placebo q8h 200 mg q8h 300 mg q8h 400 mg q8h placebo q8h	Day 1 Days 2-4 Days 5-7 Days 8-10 Days 11-12	Reduction in PVC's was dose-related: 64% at 200 mg, 89% at 300 mg and 90% at 400 mg. Frequency of adverse events was also dose-related.
Multiple rising dose-response and tolerance. (open label)	Podrid, P. Lown, P.	15/15	130 PVC/hr at rest or 12 PVC/ minute during exercise testing	200-400 mg q8h	4-7 days	Mexiletine significantly reduced PVC, couplet and VT frequency at rest and during exercise. Tolerance was dose- related.
Comparison of Dosage Intervals (open label)	Ruskin, J. Steen, S.	31/28	19M/12F patients with chronic VE. Median PVC/hr: 199.	100-400 mg q8h 200-450 mg q12h	1-7 days 4-60 days	19 of 28 patients were controlled on q8h dosing. 17 of 19 patients were also controlled on q12h dosing

Table 1: Clinical Pharmacology of Mexiletine
(Continued)

Type of Study	Investigator	Enrolled/ Analyzed	Patient Characteristics	Dose of mexiletine	Duration of Treatment	Summary
Non-invasive hemodynamic assessment (open label)	Podrid, P. Lown, B.	15/14	10M/6F MI:7; VT:6; CHF:6;Cardiomy- opathy:4	400 mg loading dose 300-400 mg q8h	single dose 3-5 days	Mexiletine did not impair right or left ventricular ejection fractions, and significantly reduced PVC's, couplets and VT.
Non-invasive hemodynamic	Saml, M.	20/18	CHF + ventricular ectopy	400 mg loading dose 300 mg q8h	single dose 7-10 days	Mexiletine did not significantly change stroke volume, end diastolic volume, ejection fraction/rate or cardiac output, and significantly reduced ventricular ectopy.
Pharmacokinetics and Safety in Renal Failure (open label)	Moosley, R.	16/16	Creatinine clear- ance: 0-10: 6 11-40: 6 41-70: 4	200 mg	1-2 single doses	There were no significant differences across the creatinine clearance groups in AUC, peak plasma concentrations or time-to-peak.
Digitalis-Inter- action (open label)	Lowenthal, D.	10/9	Healthy males	Digoxin 0.5mg/day mexiletine 200mg q8h	Days 1-14 Days 8-14	Mexiletine did not alter serum digoxin levels.

1. Bioavailability and Pharmacokinetics

a. Bioavailability and Absorption:

Unlike lidocaine, mexiletine is well-absorbed from the gastrointestinal tract. Plasma mexiletine levels can be reliably quantitated using a gas-liquid chromatographic method. Plasma concentrations after intravenous (100 mg over four minutes) and oral (3mg/kg in solution) administration of mexiletine were obtained in four healthy volunteers (See Figure 1). The area under the mean curve was 2.06 mcg.hr/ml following intravenous administration and 1.81 mcg.hr/ml with oral solution (88% systemic availability). [Prescott, et al: Postgrad Med J 53 (Suppl 1):50-55, 1977]

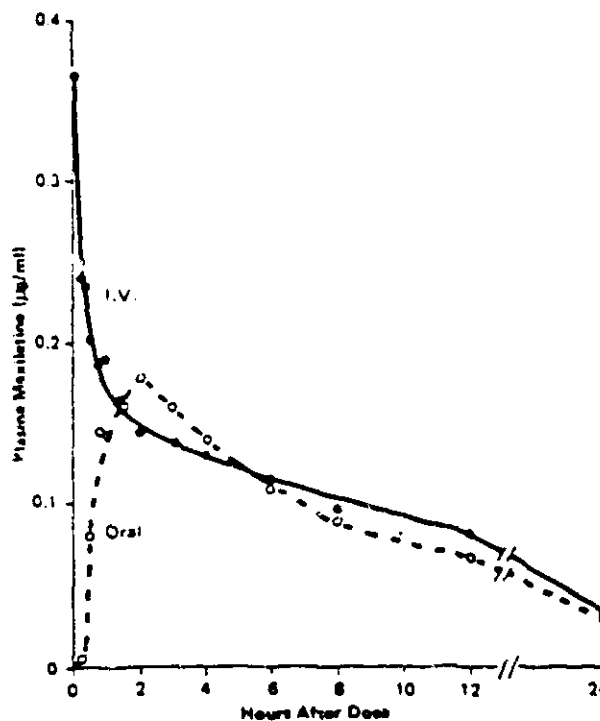


FIGURE 1

Mean plasma mexiletine concentrations in four healthy volunteers given 100 mg intravenously (●—●) and the concentrations corresponding to an equivalent oral dose (○—○). See text.

Two studies (Zinney) compared the bioavailability of mexiletine capsules to oral solution in healthy male volunteers. In the first, a pilot study involving four healthy subjects, plasma concentrations and urinary excretion of mexiletine were evaluated after administration of single oral doses of 200 mg in solution and 100, 200 and 400 mg as capsules. Each volunteer received all four doses; a washout period of seven days separated each dose. The bioavailability of the capsule was approximately 80% of oral solution; for four subjects, this did not differ significantly from 100%. Plasma levels were proportional to dose. Urinary excretion of unchanged mexiletine was low (2-10%) and variable.

The second study by Zinney compared the oral absorption of two 200 mg mexiletine capsules administered with or without food to 400 mg of oral solution in 24 healthy male patients. Treatments were separated by a five-day washout period. As shown in Table 2, areas under the curve for mexiletine taken with or without food did not differ significantly from one another or from the AUC of solution. There was a slight (0.1 hr) but significant increase in the time to peak when mexiletine was given with food.

Table 2

<u>Mexiletine 400 mg</u>	<u>AUC(48 hrs, mcg. hrs/ml)</u>	<u>Peak concen- tration(mcg/ml)</u>	<u>Time-to-peak (hours)</u>
reference solution	12.8 $\pm$ 0.70	0.82 $\pm$ 0.02	2.8 $\pm$ 0.2
capsules without food (% solution)	11.4 $\pm$ 0.5 (89.1)	0.72 $\pm$ 0.02 (87.8)	2.8 $\pm$ 0.2 (100.0)
capsules with food (% solution)	12.2 $\pm$ 0.7 (95.3)	0.77 (93.9)	2.9 $\pm$ 0.2 (103.6)

b. Dose linearity

Plasma concentrations were proportional to dose in the four-subject bioavailability study, but the number of subjects is too small for the study to serve as primary evidence of dose proportionality. Plasma concentrations were also available on the third day of each dose for twenty patients in the single-blind, multiple rising dose response and tolerance study. An analysis of the mean plasma levels of mexiletine after 200, 300 and 400 mg q8h showed the concentrations to be proportional to dose and linear. However, interpatient variation was too great to permit this analysis alone to be accepted as definitive proof of dose proportionality.

Dr. S. Vozech et al included an assessment of dose linearity in their analysis of pharmacokinetic parameters of mexiletine in 58 patients with ventricular arrhythmias [Eur. J. Clin. Pharmacol. 23, 445-451, 1982]. The analysis was based on 452 plasma mexiletine determinations. Individual results as well as group averages were available. Approximately 80% of the individual plasma mexiletine concentrations were between 0.5 and 2.0 mcg/ml, consistent with concentrations commonly reported during chronic therapy.

Vozech and his colleagues used NONMEM, a data analysis approach developed and tested by Sheiner and Beal [Beal S, Sheiner LB(1979) NONMEM Users Guide] to develop population pharmacokinetic parameters for mexiletine. NONMEM has previously been shown to be capable of detecting the difference between linear and non-linear kinetics (as in the case of phenytoin). As shown in Table 3, Vozech's estimates of mexiletine pharmacokinetics are similar to results obtained at other centers in both patients and normals, and by both oral and intravenous routes of administration.

Table 3

Pharmacokinetic Parameters of Mexiletine

<u>Population</u>	<u>N</u>	<u>Treat- ment</u>	<u>ka (hr⁻¹)</u>	<u>z (hr⁻¹)</u>	<u>t_{1/2} (hr)</u>	<u>Vd (l/kg)</u>	<u>Ke1 (1/hr/kg)</u>	<u>t_{lag} (hr)</u>
Patients [Vozech et al 1982]	58	p.o.	3.1 ± 0.5	0.072	9.7	5.3 ± 0.2	0.38	0.3
Patients [Campbell et al 1978]	10	i.v.	-	0.060	11.6*	6.6 ± 0.9	0.39	-
Normals [Zinney]	24	p.o.	0.9 ± 0.3	0.067	10.3	6.8 ± 1.6	0.45	0.1

* Harmonic mean calculation from Campbell [Br. J. Clin. Pharmacol 6: 103-108]

NONMEM analysis demonstrated that the data fit a one-compartment linear pharmacokinetic model. The assumption of linearity was rigorously tested with respect to time dependence, which was possible because data points were well distributed among a loading dose phase, a nonsteady-state maintenance dose, and a steady-state phase. The data were consistent with linear pharmacokinetics for mexiletine in the recommended dose range. Furthermore, in this representative, stable, patient population, there was no indication of changing pharmacokinetic parameters over the course of treatment with a fixed maintenance dose of mexiletine.

Vozech et al also verified the reliability of the mexiletine analysis by comparing the NONMEM parameter estimates with results reported by others, evaluating the goodness of fit and predicting the serum concentrations of patients not included in the analysis. As shown above, the NONMEM results are consistent with findings in normals and intravenously dosed patients.

Goodness of fit was indicated by the small standard errors of parameter estimates and good agreement between measured data and predicted values and their respective standard deviations. Moreover, estimates of values for mexiletine patients not included in the analysis corresponded closely to those predicted by NONMEM.

Among the patients studied by Vozech et al, there were 27 with congestive heart failure and 8 with abnormal liver function. In this study, the pharmacokinetic parameters of mexiletine were not affected by congestive heart failure or liver disease. According to the authors, the lack of effect of liver disease was probably due to the small number of patients with severe hepatic impairment and the large interpatient variability of mexiletine clearance.

A relevant study by Prescott et al determined the average oral clearance of mexiletine in 101 patients on chronic therapy to be 0.34 l/h/kg, which agrees closely with the Vozech estimate of 0.38 l/h/kg.

Additional evidence of dose linearity was provided by Pottage et al, who reported a significant linear relationship between mean steady-state plasma mexiletine concentration and daily dose in 101 patients on chronic oral therapy [Postgrad Med J 53 (Suppl 1): 155-157, 1977]. Average mexiletine concentration was approximately 2.0 mcg/ml for patients dosed with 1200 mg/day and approximately 1.0 mcg/ml for patients receiving 600 mg/day.

Thus, the available data, most of it obtained from patients in typical therapeutic settings, shows that mexiletine possesses linear pharmacokinetic characteristics in the recommended dose range (up to 1200 mg/day).

c. Metabolism

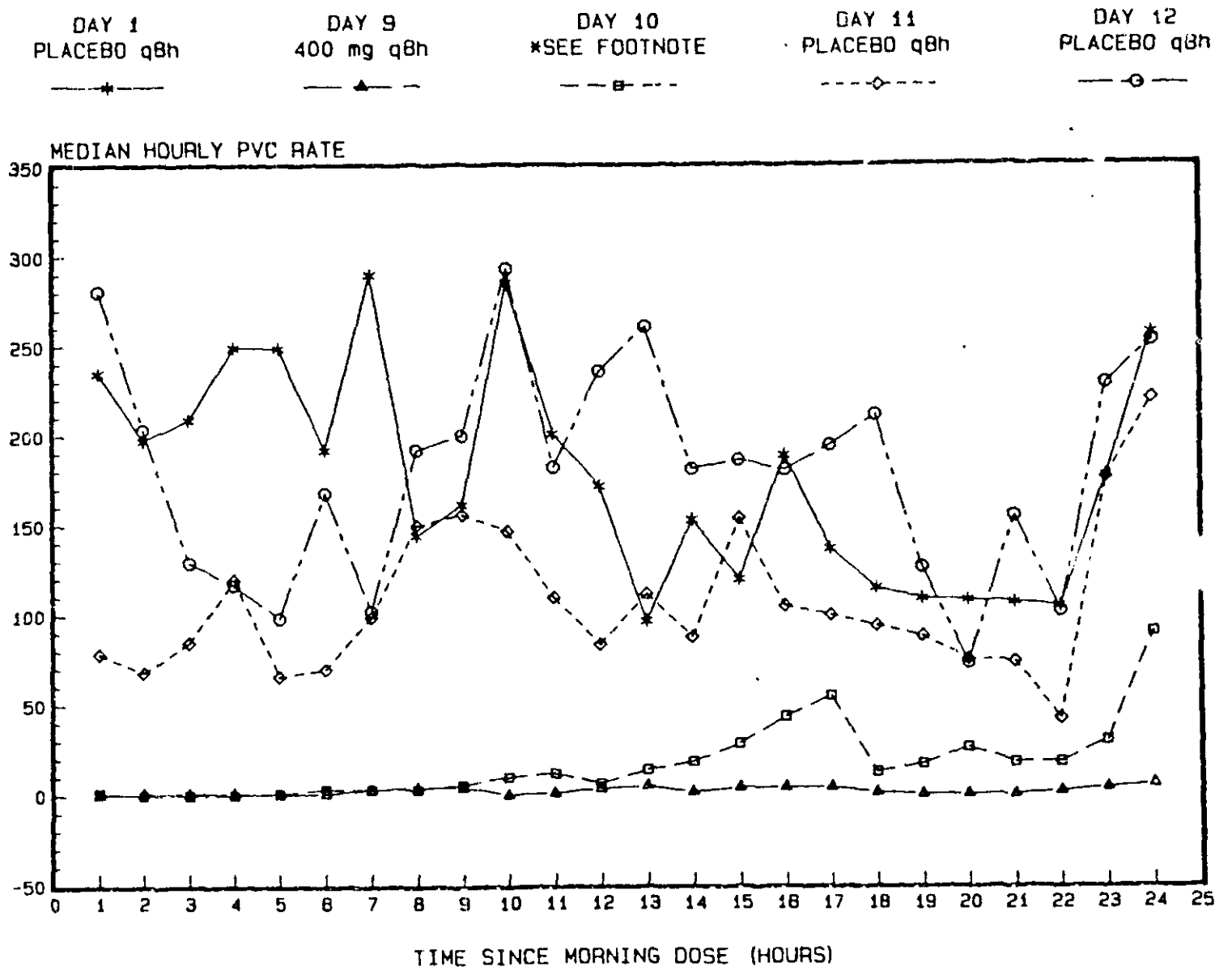
Mexiletine is extensively metabolized in the liver. Further information on metabolism is given in Section 4 (Drug-Disease and Drug-Drug Interaction.)

Several metabolites of mexiletine have shown minimal antiarrhythmic activity in animal models. The most active is the minor metabolite N-methylmexiletine, which is less than 20% as potent as mexiletine. The urinary excretion of N-methylmexiletine in man is less than 0.5%. Thus, the therapeutic activity of MEXITIL is due to the parent compound.

Figure 2 presents the median hourly PVC rates for 15 patients who received the full ten days of prescribed therapy in the dose-ranging study and achieved at least a 70% reduction in PVCs from baseline. Patients received their last full dose of mexiletine therapy on Day 9 and on Day 10 received a single morning dose of 400 mg mexiletine. They then entered the placebo washout phase. The median PVC rates began to increase slightly within 12 hours after the last mexiletine dose. By Day 11, the median frequency was approaching baseline levels and by Day 12 it had essentially returned to baseline. This time course for the return of ectopy is consistent with the plasma half-life of mexiletine (10-12 hours) observed in patients and shows there is no clinically significant plasma level of an active metabolite present whose half-life is longer than that of mexiletine.

FIGURE 2

RETURN OF ECTOPY AFTER DISCONTINUATION OF MEXILETINE THERAPY IN 15 PATIENTS WHO RESPONDED (70% REDUCTION) IN THE DOSE RANGING STUDIES



* AM DOSE OF 400 mg FOLLOWED BY PLACEBO q8h

d. Excretion

Less than 10% is excreted unchanged by the kidney. While urinary pH does not normally have much influence on elimination, marked changes in urinary pH influence the rate of excretion: acidification accelerates excretion while alkalinization retards it. Further information is given in section 4. There is a single report [Lewis, Postgrad. Med J. 57 (671):546-7, Sept. 1981] indicating that mexiletine appears in breast milk in concentrations similar to those in plasma.

2. Pharmacodynamics of Loading and Maintenance Doses of Mexiletine

The recommended dosage of mexiletine, 200 to 400 mg every eight hours, initiated with a 400 mg loading dose where rapid control of arrhythmia is desired, was based on early experience with mexiletine in the United Kingdom and further assessed in the sponsor's program of U.S. studies.

The loading dose is intended to more rapidly yield the therapeutic plasma concentrations of 0.50-2.0 mcg/ml. This range is based on some early British studies and on more recent dose-response information (see section b below).

N.P.S. Campbell et al [(Postgrad Med J 53 (Suppl 1): 114-117, 1977] studied both intravenous and oral administration of mexiletine in 156 patients, most of whom had recent myocardial infarction. Treatment was prophylactic in 33 patients with persistent ST depression, but 123 patients had ventricular ectopy so that effectiveness could be evaluated. At plasma concentrations of 0.5-0.74 mcg/ml, 51% of observations were associated with satisfactory suppression of ventricular ectopy; when plasma levels were between 0.75-2.0 mcg/ml, 79% of observations denoted efficacy and 5.5% were associated with adverse effects. Above 2.0 mcg/ml, there was no increase in effectiveness, while the frequency of adverse effects rose to 30%; the incidence of severe adverse effects (e.g. bradycardia, hypotension) was 19%.

Table 4

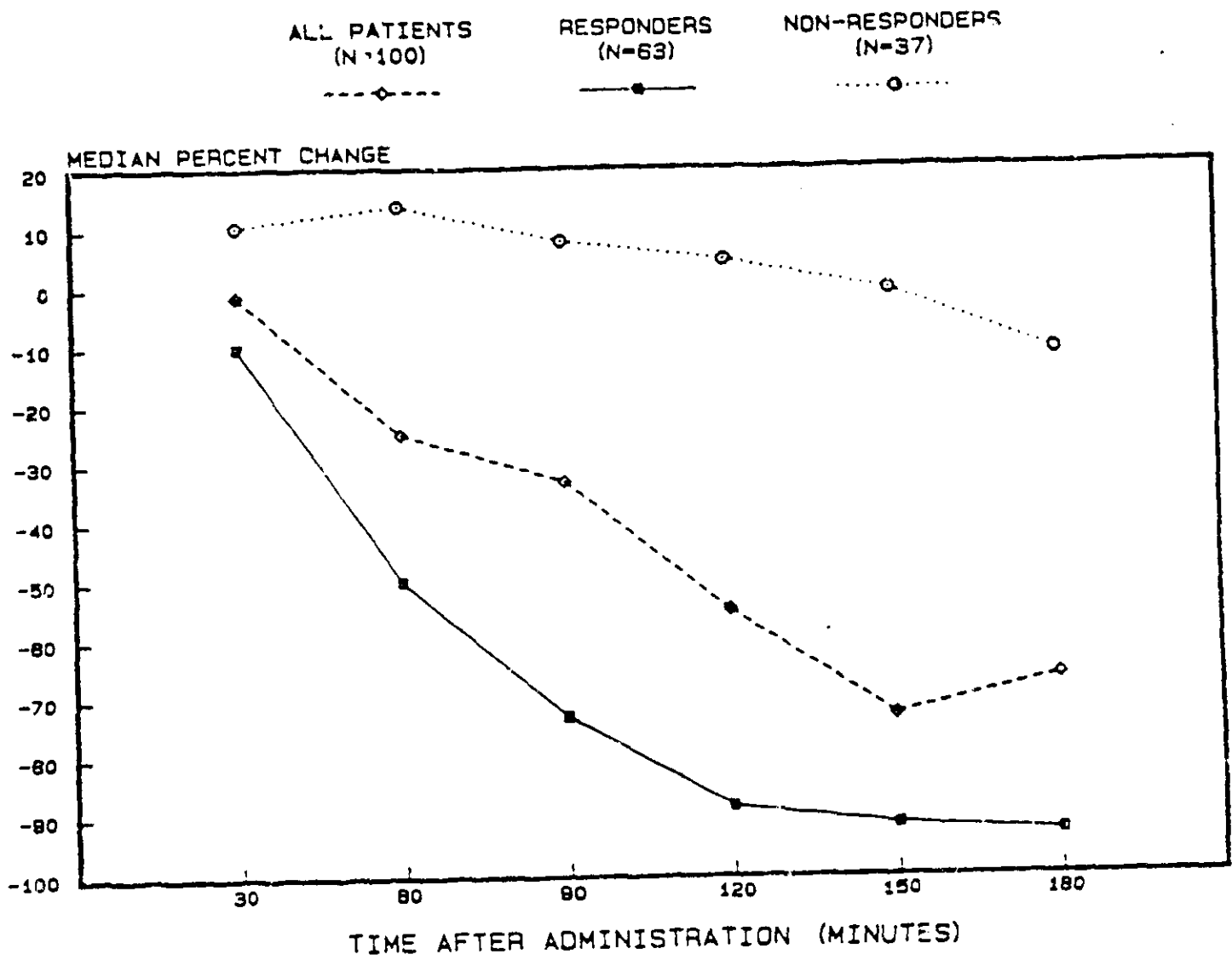
Median % Change
in PVC's During Exercise

<u>Time after 400 mg Dose</u>	<u>All patients (N=122)</u>		<u>Responders* (N=59)</u>		<u>Non-responders (N=53)</u>	
	<u>Median</u>	<u>%Change</u>	<u>Median</u>	<u>%Change</u>	<u>Median</u>	<u>%Change</u>
Control(-30min)	101.0	-	111.0		90	
1 hour	74.0	-36.5	33.0	-61.5	86.0	-12.7
2 hours	38.0	-56.3	11.5	-88.5	82.0	-14.8
3 hours	24.0	-68.5	6.5	-88.5	82.0	-19.6

*At least 70% reduction in PVC's during exercise

FIGURE 3

PERCENT CHANGE IN PVCs/30 MINUTES IN 100 PATIENTS
FOLLOWING A 400 MG LOADING DOSE OF MEXITIL

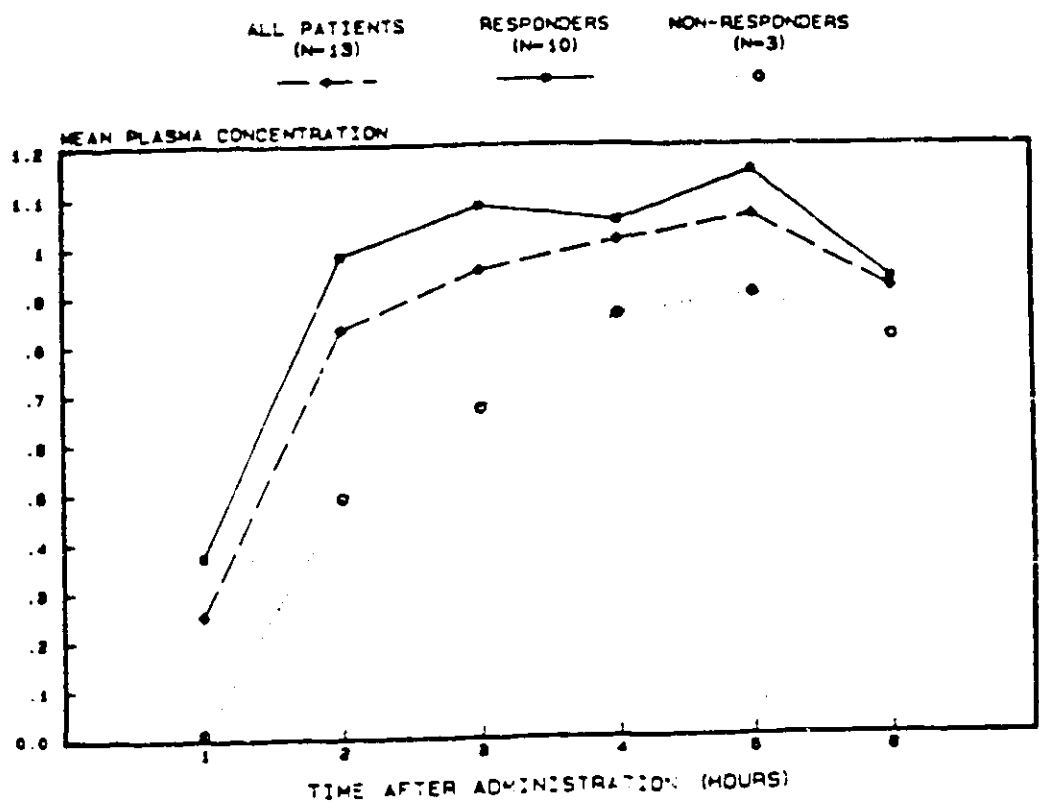


Plasma concentrations were obtained for 57 of the patients in this study, and were similar in responders and non-responders. Mean plasma levels were within the therapeutic range (0.5-2.0 mcg/ml) one hour after dosing and continued to rise at the second and third hour, consistent with the improved response seen by Campbell as plasma concentrations above 0.75 mcg/ml are reached.

<u>Time after Dose</u>	<u>Mean mexiletine plasma level (mcg/ml) (n=57)</u>
1 hr	0.74 $\pm$ 0.11
2 hr	0.96 $\pm$ 0.10
3 hr.	1.15 $\pm$ 0.10

Vozen and Follath (1982) assessed the 400 mg mexiletine loading dose in 13 patients with chronic ventricular ectopy. As shown in Figure 4, the 400 mg dose suppressed ventricular ectopy and maintained therapeutic plasma concentrations throughout the six hour observation period.

MEXITIL PLASMA LEVELS OVER SIX HOURS IN 13 PATIENTS FOLLOWING A 400 MG LOADING DOSE



HOURLY PERCENT CHANGE IN PVC RATE IN 13 PATIENTS
FOR SIX HOURS FOLLOWING A 400 MG LOADING DOSE OF MEXITIL

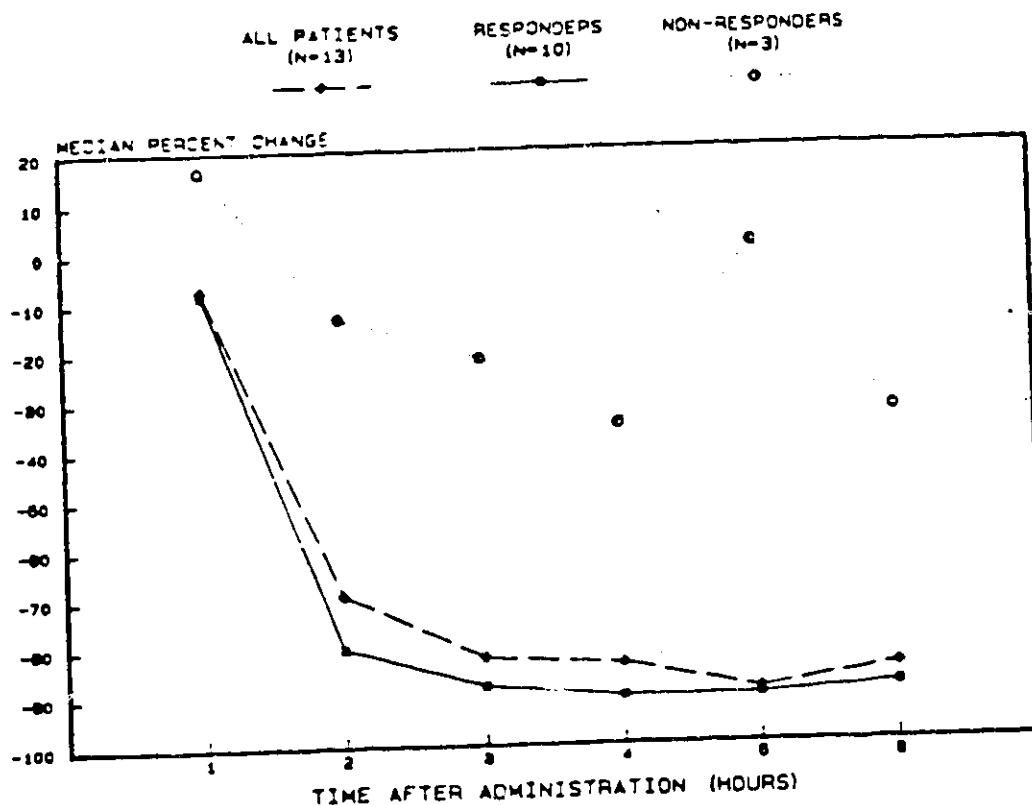


FIGURE 4

b. Dose Response

Dose response to mexiletine was investigated in a multi-center single-blind dose-ranging study. This study was designed to assess the efficacy and tolerability of mexiletine in patients with chronic ventricular ectopy (at least 30 PVC's/hour) by comparing three dose levels to placebo lead-in and run-out periods. The schedule of treatments was:

Day 1	Placebo
Days 2-4	200 mg q8h
Days 5-6	300 mg q8h
Days 7-9	400 mg q8h
Days 10-12	Placebo

Twenty-four hour Holter ECG monitoring was performed on each day of the study; efficacy at each dose was assessed by comparing PVC frequencies on the last day of each dose regimen (when steady state should have been reached) to baseline. When a patient had adverse effects at the 300 mg or 400 mg dose level, the dose was reduced to the previous level.

Fifty patients entered the study at three centers, but 15 could not be analyzed for efficacy because of: medication errors (5); failure to obtain a placebo Holter recording (5); insufficient PVC rate at entry (2); intercurrent non-cardiac illness (2); or concurrent administration of lidocaine (1).

As shown in Table 5, all 35 analyzable patients completed 200 mg q8h; 20 completed all three dose levels.

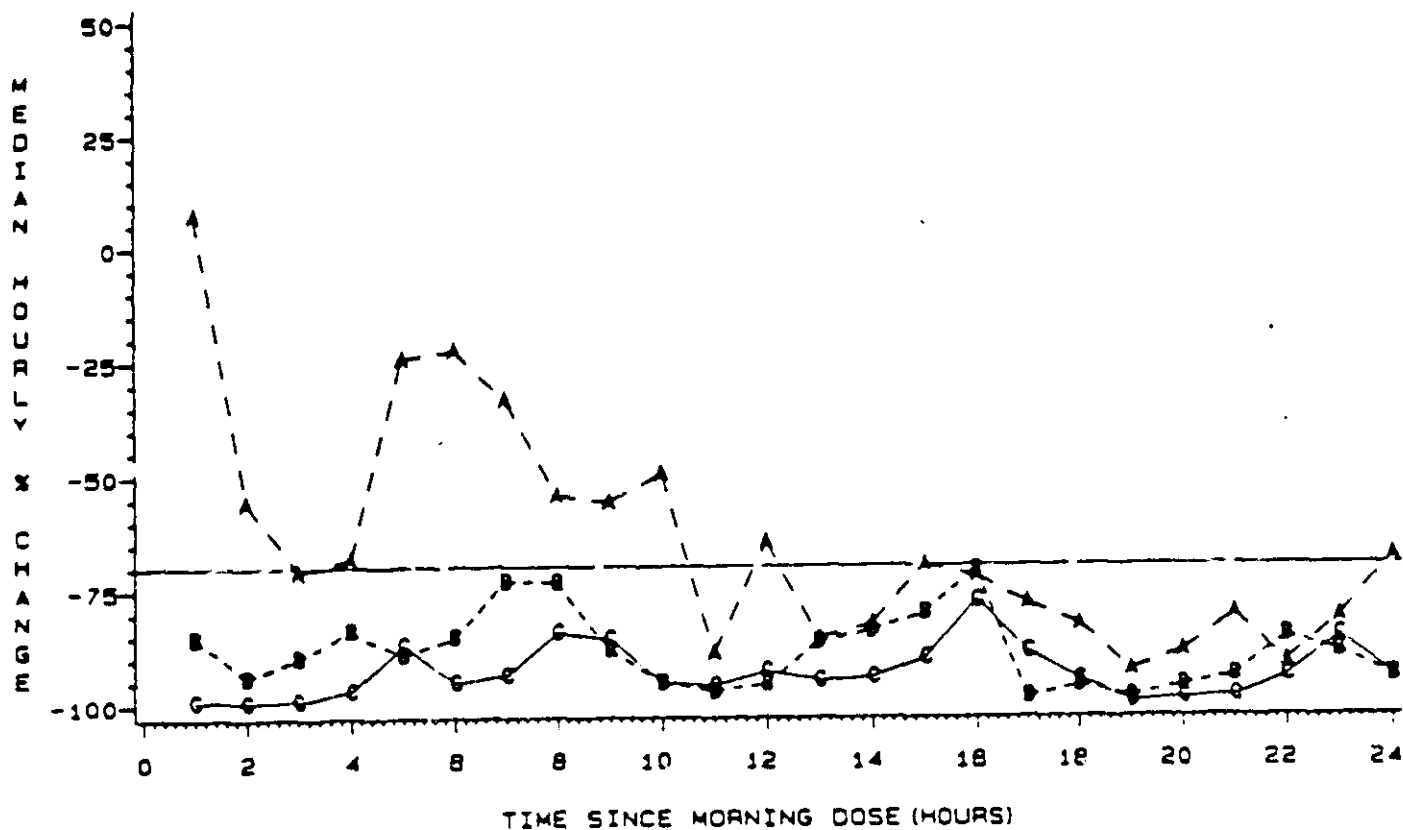
Table 5

PVC Reduction in Mexiletine Dose-Ranging Trial

	<u>200 mg q8h</u>	<u>300 mg q8h</u>	<u>400 mg q8h</u>
Number of Pts. completing dose level	35	31	20
No. of Pts. with ≥70% PVC reduction (% of Pts.)	14 (40%)	20 (65%)	15 (75%)
Median % reduction PVC's all pts.	64%	89%	95%

In this study, which did not include a loading dose, there was a marked drop (+ 55%) in PVC rate in patients who responded to mexiletine within two hours after the first 200 mg dose. During the first day, PVC's increased somewhat near the end of the eight hour dose interval. By the second day of active therapy, the PVC rate was reduced by at least 70% from the baseline obtained during placebo therapy throughout the dose interval. See Figure 5. Presumably, peak concentrations on day 1 entered the therapeutic range but trough values did not stay in that range. With accumulation on days 3 and 4, the therapeutic range was maintained throughout the day.

MEDIAN PERCENT CHANGE FROM BASELINE IN PVC'S/HOUR
FOR 14 PATIENTS WHO RESPONDED (70% REDUCTION)
TO 200MG MEXITIL IN THE DOSE RANGING STUDIES



LEGEND:
A=DAY 2
B=DAY 3
C=DAY 4

FIGURE 5

In the twenty patients who completed all three dose levels, the reduction in PVC's, proportion of responders and plasma levels of mexiletine were clearly dose related, at least up to 300 mg. (See Figures 6 and 7). The increase from 300 to 400 mg, with a resulting increase of plasma concentrations from peaks of 2.2 to 2.8 and troughs of 1.0 to 1.3, did not have much effect.

Lown and Podrid evaluated 15 patients for response to mexiletine by means of 24-hour Holter monitoring and treadmill exercise testing before and on the last day of mexiletine therapy. Patients were treated for up to seven days. On Day 1, they received a 400 mg loading dose of mexiletine followed by 200 mg at eight hour intervals. On days 2, 3 and 4, the dose was increased daily by 100 mg increments up to a maximum of 400 mg q8h. Treatment at the lower dose was resumed if side effects occurred when the dose was increased.

Holter findings revealed a statistically significant reduction in the median PVC rate from a baseline of 166/hour to 29/hour at the end of treatment ($p = 0.0008$). The median percentage of hours in which couplets or ventricular tachycardia occurred dropped from 39% to 6% for couplets ($p = 0.0008$) and from 5% to 0% for VT ($p = 0.04$).

On exercise testing at the end of treatment, median PVCs/minute were significantly reduced as compared to baseline from 5.0 to 0 during the pre-exercise period ($p = 0.0118$), from 5.4 to 0.2 during exercise ($p = 0.002$) and from 10.0 to 0.5 ($p = 0.008$) during the post-exercise period.

DOSE-RESPONSE RELATIONSHIP IN 20 PATIENTS
 COMPLETING ALL THREE DOSE LEVELS IN THE DOSE-RANGING STUDY

Page 26 - NDA 18-873

MEDIAN %
 REDUCTION

NUMBER OF
 RESPONDERS

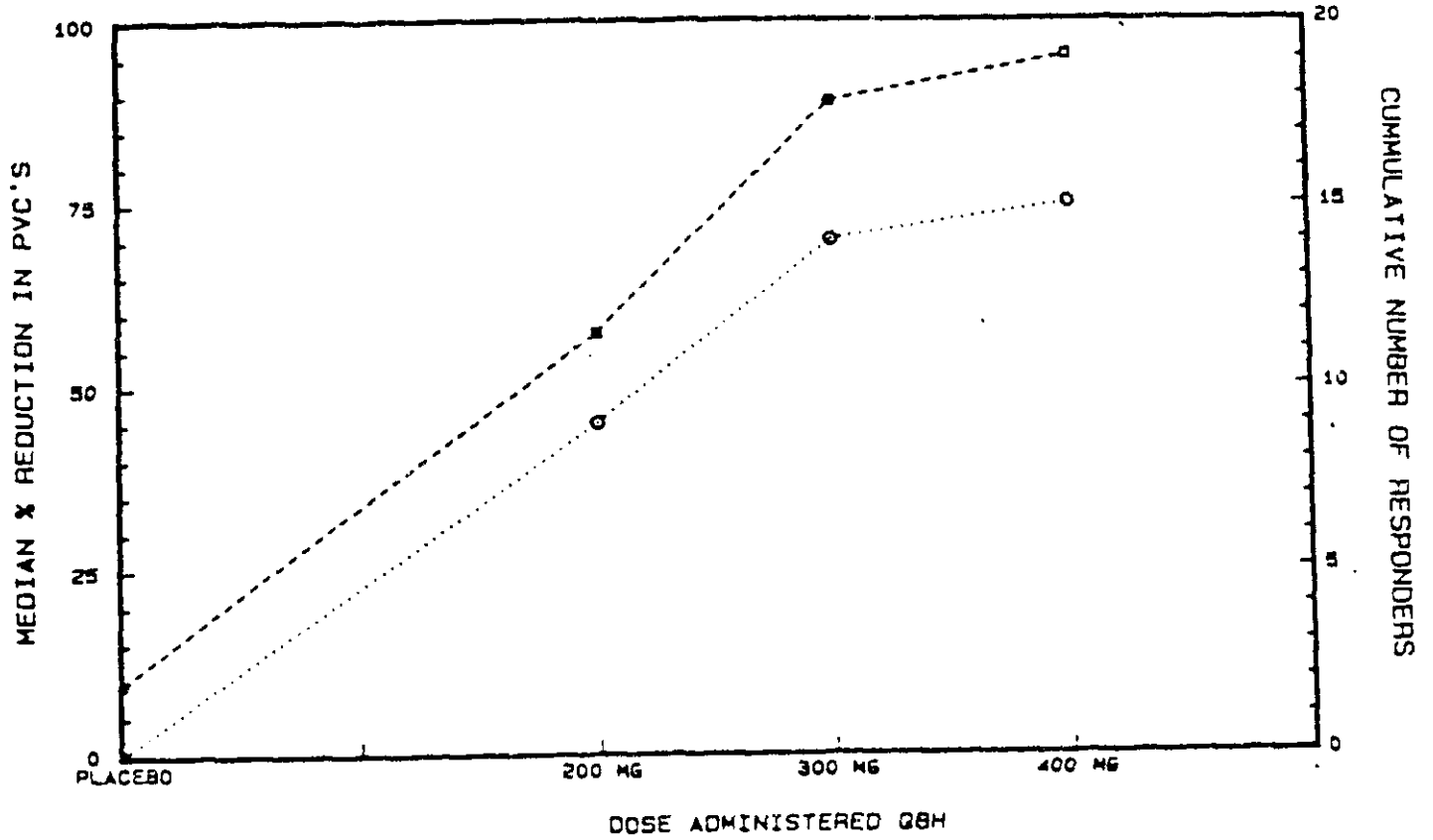


FIGURE 6

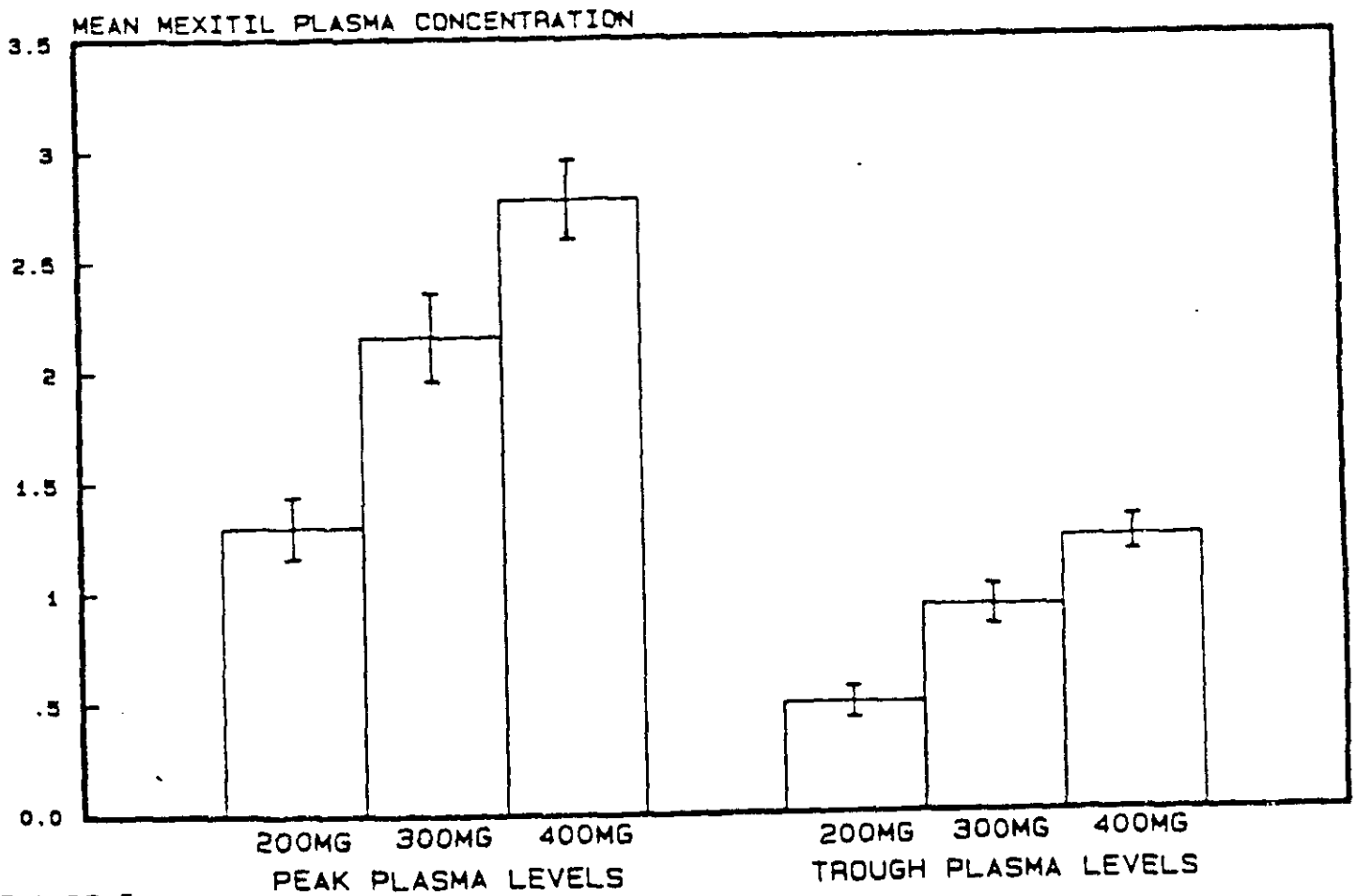


FIGURE 7
 ±STANDARD ERROR

c. Q12H Dose Regimen

Mexiletine's half-life of 10-12 hours suggests that twice daily administration may be effective, at least in some patients. A single-blind study compared the q8h and q12h regimens in 31 patients at two centers. Patients with chronic ventricular ectopy (at least 30 PVC's/hr) were evaluated by 24-hour Holter recordings on both dosage regimens. After two 24-hour baseline Holter recordings, patients were given a 400 mg loading dose of mexiletine, followed by 200 mg q8h. The dose was increased by 100 mg q8h to a maximum of 400 mg if subsequent Holter recordings did not show total suppression of ventricular tachycardia and at least 50% reduction in PVC rate. A confirming Holter recording was obtained one week later.

If satisfactory control was observed and confirmed during q8h dosing, the patient was switched to the q12h regimen. Dosage was again titrated until a 24-hour Holter ECG showed total suppression of VT and greater than 50% reduction in PVC's.

Three patients could not be evaluated; two had insufficient PVC's at study entry (less than 30/hr) and one was given disopyramide and mexiletine during the baseline evaluations.

Nineteen of the 28 analyzable patients (68%) were controlled on the q8h dose regimen; 17 of these 19 patients (89%) were successfully controlled on q12h dosing as well.

As shown in Figure 8, PVC suppression was consistent throughout the dose interval for both 8 and 12 hour dosing schedules. The mean daily dose of mexiletine was 600 mg when given q8h and 655 mg q12h.

Mexiletine plasma levels were available at the end of the dose interval and two hours post dose for seven patients:

Mean Mexiletine Plasma Levels (N=7 pts.)

	<u>end of dose interval</u>	<u>2 hours post-dose</u>
q8h	1.00 mcg/ml	1.29 mcg/ml
q12h	0.93 mcg/ml	1.79 mcg/ml

The trough levels were comparable on both regimens; the higher two-hour value for the q12h schedule can be attributed to the higher individual dose (mean 327 mg q12h vs 200 mg q8h). However, on each dose regimen, both peak and trough plasma levels were well within the target range of 0.5 to 2.0 mcg/ml. The data suggest that it will be possible to maintain some patients on a q12hr schedule, but that other patients more sensitive to the side effects of mexiletine or resistant to its effectiveness will do better with the smaller peak-trough differences attainable with q8hr dosing.

MEDIAN NUMBER OF PVC'S/HOUR
FOR 19 ANALYZED PATIENTS

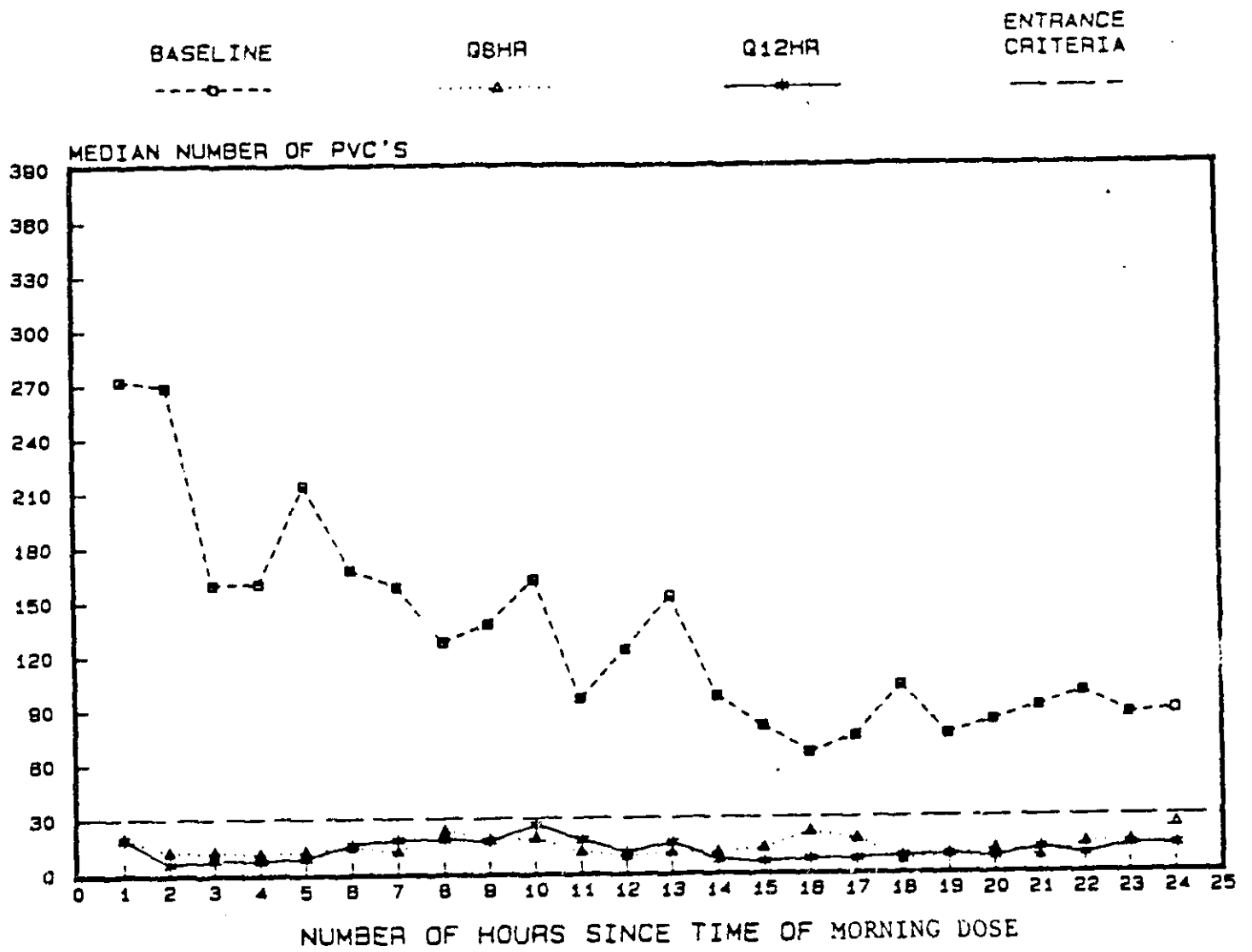


FIGURE 8

3. Hemodynamic effects of Mexiletine

Non-Invasive

Chronic oral mexiletine therapy had no effect on radionuclide ejection fractions in 35 patients with moderate to severe left ventricular ejection fractions in the studies conducted by Podrid and Sami (see Table 1).

Invasive studies

There have been eight reports of invasive measurement of hemodynamic parameters during mexiletine (see following reference list). The 123 patients studied had a variety of cardiac problems:

<u>Cardiac Status</u>	<u>No. of Patients</u>
Acute MI	52
Old MI	31
Valvular HD	16
ASHD	13
Digitalis Recipients	6
Myocarditis	2
Other	3
	<u>123</u>

Mexiletine was administered orally in two studies and intravenously in six.

Kuhn et al studied the effects of a single oral dose of 600 mg of mexiletine in 13 patients with chronic ventricular ectopy. Hemodynamic data were obtained for at least 30 minutes prior to drug administration and for six hours thereafter. Three hours after dosing the mean pulmonary artery diastolic pressure (PADP) increased from 12.1 ± 3.2 to 13.8 ± 3.5 mmHg and the mean cardiac output decreased from 7.4 ± 0.93 to 6.44 ± 0.79 l/min (see Figure 9). These changes were not statistically significant.

Merx et al studied 57 patients on the first and second days of acute myocardial infarction; 29 were randomized to mexiletine treatment and 28 to a nontreatment control group. Mexiletine was given as an intravenous loading dose of 2mg/kg body weight. This was followed two hours later and then every six hours by 200 mg orally for a total of 48 hours. Hemodynamic monitoring was performed in 22 patients in the mexiletine group and 21 patients in the control group. Pulmonary artery end diastolic pressure, cardiac index, systemic blood pressure and

heart rate were measured before mexiletine therapy and 3 to 6 times per 24 hours according to the clinical situation during mexiletine administration. Although differences were not statistically significant, PADP decreased less in the mexiletine group (6% day 1 and 2% increase day 2) than the control group (14% day 1 and 24% day 2). Over the same observation period, cardiac index decreased more in the mexiletine group (10% day 1 and 6% day 2) than the control group (3% day 1 and 6% day 2). See Figure 9.

KUHN, 1977 (single 600 mg dose)				
	Mean PADP*		Mean Cardiac Output	
Baseline	12.1 ± 3.2 mm Hg		7.4 ± 0.9 l/min	
3 hours post dose	13.8 ± 3.5 mm Hg		6.4 ± 0.8 l/min	

MERX, 1978 ^a (200 mg q6h)				
	Mean PAEDP**		Mean Cardiac Index	
	Mexiletine	Control ^b	Mexiletine	Control ^b
Baseline	12.8 (n=21)	14.4 (n=16)	3.1 (n=21)	3.2 (n=16)
Day 1	12.0 (n=22)	12.4 (n=16)	2.8 (n=22)	3.1 (n=16)
Day 2	13.0 (n=17)	11.0 (n=15)	2.9 (n=17)	3.0 (n=15)

*PADP - pulmonary artery diastolic pressure
 **PAEDP - pulmonary artery end-diastolic pressure
^aValues are approximated from graphs
^bControl group received no treatment

FIGURE 9: Mean Values for Hemodynamic Parameters Following Oral Administration of Mexiletine

The differences between the groups were not statistically significant. The findings of Kuhn and Merx suggest oral mexiletine may have a mild myocardial depressant effect.

Intravenous doses ranging from 1.0-3.6 mg/kg were administered at the other six centers. Pulmonary artery pressure appeared to rise with increased dosing while cardiac output was reduced slightly or not at all. No consistent change was seen in arterial pressure.

At the highest doses used (3.6mg/kg), two patients treated by Bernard et al in the acute stage of myocardial infarction developed an adverse cardiovascular reaction of hypotension and bradycardia after rapid intravenous infusion. This responded to treatment with i.v. atropine. Otherwise no symptomatic, clinically evident deterioration was seen in any of the patients.

The invasive hemodynamic studies suggest that mexiletine has a mild myocardial depressant effect and a mild vasoconstrictive effect. With oral mexiletine therapy, only mild, statistically insignificant, increases in pulmonary artery pressures occurred. Table 6 presents the mexiletine infusion rates, peak plasma levels, and both significant and insignificant changes in hemodynamic parameters observed in these studies.

TABLE 6

Author/ Number of Patients	MEXITILLO: IV Dose and Rate	Peak Plasma Level	Mean Baseline, Peak & Time of Peak PAP	Hemodynamic Parameters	
				Change Statistically Significant	Change Not Statistically Significant
Barnum/10	1.5mg/kg over 30 sec.	NR	NR	At Rest: ↑ HR, ↑ PASP, ↑ LVEDP During 2nd minute of atrial pacing at 100 bpm: None	At Rest: ↑ CO, ↓ SV, ↑ MPAP, and ↑ LVdP/dt During 2nd minute of atrial pacing at 100 bpm: CO, SV and MPAP unchanged, ↑ PASP & LVEDP, ↓ PLVdP/dt
Bernard/10	25 mg/min	NR	11.9 mm Hg at baseline, 15.5 mm Hg at 60 min (p < 0.01)	During 2nd minute of handclap exercise: ↓ CO, ↓ PLVdP/dt At 10 + 20 min post dose (mean of two observations): ↑ HR, ↓ CO, ↓ SV, ↑ HBP & DBP, ↑ PASP, ↑ MPAP, ↑ PCWP At 60 min post dose: ↑ HBP & ↑ DBP, ↑ SR, ↑ PASP, ↑ MPAP, ↑ PCWP	During 2nd minute of handclap exercise: ↓ HR, ↓ SV, ↓ PASP, ↑ MPAP, ↑ LVEDP, ↓ LVSP At 10 + 20 min post dose (mean of two observations): ↑ SBP, ↑ SR At 60 min post dose: ↓ HR, CO no change, ↓ SV, ↑ SBP
Campbell/16	6/16: 150 mg bolus	NR	13 mm Hg at baseline, 15 mm Hg at 5 min (p < 0.02)	At 5 min post injection: ↑ MPAP At 10 + 20 min post injection: None	At 5 min post injection: ↑ HR, ↑ HFAP, ↑ LVEDP, CI no change, ↓ SWI, ↑ PVR, ↑ SVR At 10 + 20 min post injection: At 20 mins no change in HR, MPAP, LVEDP and CI, ↑ HFAP, ↑ SWI, ↑ PVR & ↑ SVR

TABLE 6
(Continued)

Author/ Number of Patients	HEXITIL®: IV Dose and Rate	Peak Plasma Level	Mean Baseline, Peak & Time of Peak PAP	Hemodynamic Parameters	
				Change Statistically Significant	Change Not Statistically Significant
Campbell cont'd	5/16: 2.7 mg/kg over 2.5 min	NR	16 mm Hg at baseline, 19 mm Hg at 2 min (p < 0.05)	At 2 min post injection: ↑ MPAP	At 2 min post injection: All factors (except mean PAP) at 2, 5 and 10 mins post injection. At 10 mins: ↑ HR, MFAP no change, ↓ LVSP, ↓ LVEDP, ↑ CI, ↑ SWI, ↓ PVR & ↓ SVR
Hencard/15	1.5 mg/kg at 25 mg/min	NR	23.0 at baseline, 23.7 at 15 min (n.s.)	5 mins post injection: ↑ HAPS, ↑ HAPW & ↑ SVR	5 mins post injection: ↑ HAPD, ↓ HR, ↓ CI, ↓ SV, ↑ RAP, ↑ PAP, ↑ PCWP & ↑ PVR
				15 mins post injection: ↑ SVR	15 mins post injection: ↑ HAPS, ↑ HAPD, ↑ HR, ↓ CI, ↓ SV, ↓ RAP, ↑ PAP, ↑ PCP, ↑ SVR & ↑ PVR
				30 mins post injection: ↓ SV & ↑ SVR	30 mins post injection: ↑ HR, ↓ CI, ↓ SV, ↑ HAP, ↑ RAP, ↑ PAP, ↑ PCP, ↑ SVR & ↑ PVR
Pozernel/24	1-2 mg/kg bolus then 350-500 mg over 20-50 min	NR	16.1 mm Hg at baseline, 15.9 mm Hg post infusion (n.s.)	Post-Infusion None	Post-Infusion ↓ SBP, ↓ DBP, ↓ MBP, ↓ HR, ↓ CI, ↑ SVI, ↓ LVSW, ↓ TPR ↓ PXR/100, ↓ TTI, ↓ MPAP & ↓ EDPAP

TABLE 6
(Continued)

Author/ Number of Patients	MEXITIL®: IV Dose and Rate	Peak Plasma Level	Near Baseline, Peak & Time of Peak PAP	Hemodynamic Parameters	
				Change Statistically Significant	Change Not Statistically Significant
Saunamaki/6	10 mg/min for 10 mins. ↓ 6.5 mg/min during testing	2.70 ug/ml ± 0.68 at 10 min after initiation of infusion, 1.68 ± 0.73 at 15 min.	31.7 at baseline 37.2 post infusion	13-22 min after initiation of infusion	
				Statistical significance for mean values not given ↑ HR, CO, PASP, PADP, MPAP, PCWP ↓ SV, BASP, BADP, BAMP, LVSU, PVR, PEVR	

Abbreviations

- CO Cardiac Output
- SV Stroke Volume
- HR Heart Rate
- PASP Pulmonary Artery Systolic Pressure
- PADP Pulmonary Artery Diastolic Pressure
- MPAP Mean Pulmonary Artery Pressure
- LVSDP Left Ventricular End-Diastolic Pressure
- LVSP Left Ventricular Systolic Pressure
- PLV dp/dt Peak Left Ventricular dp/dt
- MBP Mean Blood Pressure
- DBP Diastolic Blood Pressure
- PCWP Pulmonary Capillary Wedge Pressure
- SR Systemic Resistance
- MFAP Mean Femoral Artery Pressure
- SMI Stroke Work Index
- PVR Pulmonary Vascular Resistance
- PEVR Peripheral Vascular Resistance
- HAP Humeral Artery Pressure (S=Systolic, D=Diastolic, M=Mean)
- RAP Right Arterial Pressure
- LVSU Left Ventricular Stroke Work
- TPR Total Peripheral Resistance
- TTI Tension Time Index
- EDVAP End Diastolic Pulmonary Artery Pressure
- PXIR/100 Pressure x Rate Product Divided by 100
- BAP Brachial Artery Pressure (S=Systolic, D=Diastolic, M=Mean)

TABLE 6
(Continued)

Author/ Number of Patients	HEXITILLO: IV Dose and Rate	Peak Plasma Level	Hemodynamic Parameters	
			Mean Baseline, Peak & Time of Peak PAP	Change Statistically Significant
Saunamaki/6	10 mg/min for 10 mins.	2.70 ug/ml ± 0.68 at	31.7 at baseline	13-22 min after initiation of infusion Statistical significance for mean values not given
	1 6.5 mg/min during testing	10 min after initiation of infusion, 1.68 ± 0.73 at 15 min.	37.2 post infusion	

Abbreviations

- CO Cardiac Output
- SV Stroke Volume
- HR Heart Rate
- PASP Pulmonary Artery Systolic Pressure
- PADP Pulmonary Artery Diastolic Pressure
- MPAP Mean Pulmonary Artery Pressure
- LVEDP Left Ventricular End-Diastolic Pressure
- LVSP Left Ventricular Systolic Pressure
- PLV dp/dt Peak Left Ventricular dp/dt
- MBP Mean Blood Pressure
- DBP Diastolic Blood Pressure
- PCWP Pulmonary Capillary Wedge Pressure
- SR Systemic Resistance
- MFAP Mean Femoral Artery Pressure
- SWI Stroke Work Index
- PVR Pulmonary Vascular Resistance
- PEVR Peripheral Vascular Resistance
- HAP Humeral Artery Pressure (S=Systolic, D=Diastolic, M=Mean)
- RAP Right Arterial Pressure
- LVSM Left Ventricular Stroke Work
- TPR Total Peripheral Resistance
- TTI Tension Time Index
- EDPAP End Diastolic Pulmonary Artery Pressure
- PAPHR/100 Pressure x Heart Rate Product Divided by 100
- BAP Brachial Artery Pressure (S=Systolic, D=Diastolic, M=Mean)

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4. Drug-Disease and Drug-Drug Interactions of Clinical Significance

Information on a number of drug-disease and drug-drug interactions involving mexiletine has appeared in the medical literature. Two studies (see Table 1) were conducted by the sponsor: one investigated mexiletine pharmacokinetics and safety in 16 patients with varying degrees of renal failure; the other assessed the effect of concurrent mexiletine administration on serum digoxin levels in healthy volunteers.

a. Drug-Disease Interactions

Hepatic Disease

The plasma elimination half-life of mexiletine was significantly increased to 25.3 ± 6.4 hours in eight cirrhotic patients compared to 17.4 ± 1.8 in seven healthy subjects [El Allaf et al (1982a)]. Similar results were described by Nitsch et al (1982) who found an elevated mean peak plasma concentration of 2.21 ± 0.94 mcg/ml in nine patients with severe hepatic disease compared with 0.63 ± 0.22 mcg/ml in 24 control patients with cardiac disease. In contrast Vozen et al (1982) found no change in mexiletine kinetics in eight patients with abnormal liver function. Transaminases were elevated in all 8 of these patients and in 4 of the 8, serum bilirubin was greater than 1.3 mg% and the prothrombin time was less than 60% of normal. The authors attributed the lack of change to the small number of patients with severe hepatic impairment and the large interpatient variability of mexiletine clearance.

Thus, smaller doses of mexiletine may be required to maintain therapeutic plasma levels in patients with moderate to severe hepatic disease. These patients should be monitored carefully, particularly during dose adjustments.

Congestive Heart Failure

Leahey (1980b) found a mexiletine mean elimination half-life of 15.4 ± 5.8 hours in 14 patients with left ventricular failure compared to 8.1 ± 1.8 hours in normal volunteers. However, Campbell et al (1978) found no significant prolongation of elimination half-life in six patients with clinical evidence of congestive heart failure. Similarly, in patients with cardiac insufficiency, Pottage et al (1978; 13 patients) and Nitsch et al (1982a; eight patients) found no change in mexiletine plasma levels. El Allaf et al (1982a) investigated the kinetics of mexiletine in nine patients with clinical and hemodynamic manifestations of advanced right-sided heart failure. The mean plasma half-life in these patients was increased to 23.2 ± 11.2 hours compared to 11.4 ± 1.8 hours in seven normal subjects.

Therefore, smaller doses of mexiletine may be required to maintain therapeutic plasma concentrations in patients with severe congestive heart failure and secondary hepatic dysfunction. These patients should be monitored carefully during therapy.

Renal Disease

Renal excretion accounts for only a small portion of mexiletine elimination (about 10% is excreted unchanged in the urine). Consistent with this, studies in patients with renal impairment have shown little or no change in the pharmacokinetics of mexiletine. In a study conducted by Woosley, 16 patients with creatine clearances of 5-55 ml/min received single doses of 200 mg of mexiletine. Areas under the curve were similar for patients with creatinine clearances of less than 10, 10-30 and 30-70 ml/min. In six patients a second dose of 200 mg was given during hemodialysis. Mean mexiletine plasma concentrations during dialysis were very close to those obtained on a non-dialysis day. El Allaf et al (1982b) found no significant change in the elimination half-life of mexiletine after chronic oral administration of 50 mg t.i.d. in patients with renal impairment and creatinine clearances of 10-30 ml/min. Patients with creatinine clearances less than 10 ml/min, however, showed an increase from 10.4 hr in normals to 15.7 hr. Nitsch et al (1982a) found no increase in peak and trough blood levels in 14 patients with serum creatinines of 1.8 to 6.3 mg%.

Thus, patients with severe renal impairment, i.e., with creatinine clearances less than 10 ml/min, may require slightly lower doses of mexiletine to maintain therapeutic concentrations. These patients should be carefully monitored during therapy.

Acute Myocardial Infarction

Delayed and possibly incomplete absorption of mexiletine has been described in patients with acute myocardial infarction [Prescott et al, (1977); Pottage, et al (1978)]. Administration of narcotics further delayed absorption, prolonging the time from initial dosing to peak concentration from approximately 2-3 hours to 6 hours. The delay in absorption associated with acute myocardial infarction may be related to an increase in gastric emptying time; narcotics exacerbate this process.

Pentikainen et al (1983) likewise found delayed absorption of mexiletine in 7 patients with acute myocardial infarction, 6 of whom had received oxycodone. The patients were studied first within 24 hours after the onset of symptoms of acute myocardial infarction and then re-studied 7-14 days later. A single dose of 400 mg of mexiletine was administered orally. Samples of venous blood were collected at specified intervals through 48 hours after dosing and all urine was collected through 72 hours after dosing. During the acute phase of myocardial infarction the mean time from dose administration to peak concentration was 4.68 ± 2.04 hours and during the chronic phase, 1.45 ± 0.17 hours (N.S.). Areas under the plasma concentration-time curves and plasma protein binding of mexiletine were similar during the acute and chronic phases of myocardial infarction. The elimination half-life, however, was 15.03 ± 0.61 hours during the acute phase and 11.75 ± 0.80 hours (p less than 0.01) in the chronic phase.

Pentikainen et al (1984) also studied the kinetics of intravenous mexiletine during acute myocardial infarction in 11 patients using a study design similar to that described above for oral mexiletine. Patients were studied within 24 hours of the onset of myocardial infarction and again 7 - 14 days later. An intravenous dose of 200 mg mexiletine was infused over a 30 minute period. Samples of venous blood were drawn at intervals through 48 hours after dosing and all urine was collected through 72 hours after dosing. During the acute phase of myocardial infarction the mean plasma terminal half-life was 14.7 ± 3.4 hours and 11.3 ± 2.4 hours (p less than 0.05) during the chronic phase. The mean steady-state volume of distribution was 578 ± 97 liters during the acute phase and 405 ± 33 liters during the chronic phase (p less than 0.05). Plasma protein binding was similar for the acute and chronic phase as was total plasma clearance.

Thus, during the first 12-24 hours of acute myocardial infarction the absorption of mexiletine may be delayed and incomplete. Administration of narcotics during this time exacerbates the absorption delay. Plasma elimination half-life is mildly prolonged to approximately 15 hours during the first 12-24 hours of acute myocardial infarction.

d. Drug-Drug Interactions

Absorption

Several pharmacokinetic drug interactions have been described that affect the absorption of mexiletine. Mexiletine, a weak base (pK_a 8.4), is poorly absorbed in the stomach. Therefore, drugs that affect gastric emptying time alter the absorption kinetics of mexiletine without altering the extent of bioavailability.

Narcotics such as morphine and diamorphine have been found to prolong the absorption half-life of mexiletine; myocardial infarction itself may produce this effect [Pottage et al (1978)]. Gelusil [$Al(OH)_3 + Mg(OH)_2$] [Herzog et al (1982)] and atropine [Wing et al (1980)] have also been shown to prolong the time-to-peak of mexiletine. Conversely, metoclopramide accelerates gastric emptying and decreases the time-to-peak [Wing et al (1980)].

Since narcotics, antacids, and myocardial infarction prolong absorption, the onset of mexiletine's therapeutic action may be somewhat delayed.

Metabolism

Drugs that affect the hepatic mixed function oxidase system can influence the metabolism of mexiletine. Co-administration of liver enzyme inducers such as phenytoin [Begg et al (1982)] and rifampin [Pentikainen et al (1982)] cause a decrease in mexiletine elimination half-life and plasma concentrations. Conversely, concomitant administration of cimetidine increases mexiletine plasma levels [Nitsch and Luderitz (1982)].

Thus, when liver enzyme inducers are administered concurrently with mexiletine, the dosage of mexiletine may have to be increased to maintain therapeutic blood levels. When an inhibitor of hepatic enzymes is co-administered, dose reduction may be necessary. In either case, careful monitoring of efficacy and tolerance should guide dose adjustment.

Concurrent Drug Administration

Mexiletine has been administered concomitantly with warfarin without evidence of interaction [Esser and Kikis (1978), Esser (unpublished report, Appendix E), Pottage et al (1978)].

Digoxin blood levels were unchanged by concomitant mexiletine therapy [Leahey and Reiffel (1980)] or slightly but not significantly lowered [Saris, Lowenthal et al (1983); Day and Hunt (1983)]. In the latter studies, magnesium-aluminum hydroxide, which was administered concurrently to alleviate gastrointestinal upset, accounts for the reduction in digoxin blood levels.

Concurrent administration of mexiletine and amiodarone has generally been well tolerated [Waleffe et al (1980); Koonlawee et al (1983); Heger et al (1983); Hoffman et al (1983)]. There is one report of atypical ventricular tachyarrhythmia with this combination [Tartini et al (1982)]. In some patients combination therapy may have increased efficacy [Waleffe et al (1980)].

Duff and coworkers (1983) have described a beneficial pharmacodynamic interaction between mexiletine and quinidine. In this patient group, combination therapy increased efficacy over either drug alone. Greater efficacy was achieved even though lower doses of both drugs were used. Toxicity with the combination was less than with single therapy. Similarly, a beneficial effect on efficacy has been seen with the combination of mexiletine and propranolol [Leahey (1980)].

No interaction was found between mexiletine and diazepam or nitrazepam [Pottage et al (1978)].

In general, both response and tolerance should be carefully monitored during concurrent administration of mexiletine and other drugs.

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Wing, L.M.H., et al: The effect of metoclopramide and atropine on the absorption of orally administered mexiletine. *Br J Clin Pharmacol* 9(5):505-509, May 1980.

*Published report of study conducted by D. Lowenthal.

8. Efficacy in Clinical Trials

1. Controlled Trials

The antiarrhythmic efficacy of mexiletine was compared to that of placebo and the conventional oral antiarrhythmic agents, procainamide, quinidine and disopyramide, in five multicenter, double-blind trials. A total of 884 patients, males and females ranging in age from 18 to 77 years, with baseline PVC rates exceeding 30 per hour, participated in these trials. Additionally, many patients had complex arrhythmia forms - couplets, ventricular tachycardia and R on T. Both idiopathic ventricular arrhythmias and ventricular arrhythmias secondary to underlying cardiovascular disease were represented. The design and results of these trials are summarized in Table 1 and a more detailed discussion of each multicenter trial follows.

TABLE 1
U.S. Controlled Clinical Trials with Mexiletine

Trial	Trial Design	Dose and Duration	Number of Patients Entered	Number of Patients Analyzed	Treatment Failures				Dropouts (other than treatment failures)	Results
					Lack of Efficacy	Adverse Event	Death	Total		
Multicenter Placebo Trial (4 centers)	Double-blind, randomized, crossover study evaluating antiarrhythmic efficacy & safety of mexiletine as compared to placebo in patients with ≥ 30 PVCs/hour.	Single loading dose: 400 mg q8h or placebo 4 capsules. Mexiletine 100-400 mg q8h; Placebo 1-4 capsules q8h. Dose titrated to efficacy or maximum tolerated dose. Duration: 4 weeks/treatment.	53	Mexiletine 46 Placebo 48	See Results				5	>70% reduction in PVCs in 24 patients on mexiletine, 6 patients on placebo. Median reduction in PVCs 70% in mexiletine group, 10% in placebo group (significantly different, $p < 0.0001$). Mexiletine significantly better than placebo in reducing median frequency of couplets ($p < 0.001$) and VT ($p = 0.019$).
Multicenter Procaïnamide Trial (5 centers)	Double-blind, randomized, parallel-group study comparing efficacy & safety of mexiletine vs. procaïnamide in controlling ventricular arrhythmias in patients with ≥ 20 PVCs/hr.	Single loading dose: mexiletine 400 mg or procaïnamide 1000 mg. Mexiletine 200-400 mg q8h or procaïnamide 500-1000 mg q6h. Dose titrated to efficacy or maximum tolerated dose. Duration: 12 weeks.	80	76	19	27	1	47	4	Significantly more ($p=0.02$) treatment successes* with mexiletine (38%) than with procaïnamide (20%). Frequency of couplets and VT reduced by both drugs in majority of patients with these forms at baseline.
					(25%)	(36%)	(1%)	(62%)	(5%)	
			78	76	37	22	2	61	2	
					(49%)	(29%)	(3%)	(80%)	(3%)	

TABLE 1 (Cont'd)
U.S. Controlled Clinical Trials with Mexiletine

Trial	Trial Design	Dose and Duration	Number of Patients		Treatment Failures				Dropouts (other than treatment failures)	Results
			Entered	Analyzed	Lack of Efficacy	Adverse Event	Death	Total		
Multicenter Disopyramide Trial (11 centers)	Double-blind, randomized, parallel-group study comparing efficacy & safety of mexiletine vs. disopyramide in the management of ventricular arrhythmias in patients with ≥ 30 PVCs/hour.	Mexiletine 200-400 mg q8h or disopyramide 100-200 mg q6h. Dose titrated to efficacy or maximum tolerated dose. Duration: 12 weeks.	Mexiletine							Treatment success* achieved in 29% on mexiletine, 44% on disopyramide (not significantly different). Couplets and VT reduced by both drugs in majority of patients with these forms at baseline.
			74	63	19 (30%)	26 (41%)	0 (0%)	45 (71%)	6 (10%)	
			Disopyramide							
			69	54	19 (35%)	11 (20%)	0 (0%)	30 (56%)	10 (19%)	

* Treatment success was defined as $\geq 70\%$ reduction from baseline in PVCs.

a. Mexiletine vs. Placebo

Study Design

The purpose of this double-blind, crossover study was to compare the antiarrhythmic efficacy and safety of mexiletine and placebo. The effects of concomitant digitalis administration on response to treatment were also evaluated. Fifty-three patients from four centers participated in this study. The investigators and the number of patients enrolled at each center are listed below.

<u>Investigator/Address</u>	<u>Number of Patients</u>
C. Richard Conti, M.D. University of Florida JHM Health Center, Box J-277 Gainesville, FL 32610	12
Rolf Gunnar, M.D. Loyola University Stritch School of Medicine 2160 South First Avenue Maywood, IL 60153	17
G. Douglas Moir, M.D. 210 South Juniper Street Escondido, CA 92025	12
Joel Morganroth, M.D. Lankenau Hospital City Line & Lancaster Avenues Philadelphia, PA 19151	12

Mexiletine and placebo were each administered for 4 weeks in randomly assigned sequence. Patients had the following cardiovascular diseases.

<u>Diagnosis</u>	<u>Number of Patients</u>
Atherosclerotic heart disease	26
Idiopathic ventricular arrhythmia	11
Hypertensive heart disease	3
Other	13

In order to enter the study, patients had to have an average PVC rate greater than 30 per hour, documented by two 24-hour Holter recordings. The median frequency of PVCs at baseline was 289/hour.

Following a loading dose of 400 mg mexiletine or 4 placebo capsules, patients took 100 mg mexiletine or 1 placebo capsule q8h. The dose was titrated, if necessary, at weekly intervals in increments of 100 mg mexiletine q8h (maximum 400 mg q8h) or 1 placebo capsule q8h (maximum 4 capsules q8h) until greater than 50% suppression of PVCs was achieved or the maximum dose was reached. Reduction of dosage was permitted if intolerable side effects occurred. After four weeks on one treatment, patients immediately crossed over to the other treatment.

Two 24-hour Holter recordings were done at baseline. Holter monitoring was done weekly throughout the study to assess the response to treatment.

The protocol and original statistical analysis defined a treatment response as greater than or equal to 50% reduction from baseline in PVCs on the Holter evaluation obtained at the completion of 4 weeks of treatment. The data were reanalyzed using 70% suppression of PVCs as the criterion for response. The results presented here reflect the revised analysis.

Results

Of the 53 patients enrolled in the study, 48 completed four weeks on mexiletine and 49 completed four weeks on placebo. Five patients were dropped during the study: two because of adverse reactions to mexiletine (both gastrointestinal distress), one because of a myocardial infarction (not related to the study drug), and one because the Holter tape was unreadable. Each of these four patients was excluded from both the mexiletine and placebo analyses. In the fifth patient (who completed the placebo treatment period), the Holter recording after the second week of mexiletine therapy showed one 13-beat run of ventricular tachycardia associated with dizziness. The patient was admitted to the hospital and mexiletine was discontinued. This patient was included only in the placebo efficacy analysis. In addition, two patients were excluded from the mexiletine efficacy analysis and one from the placebo analysis because their Holter recordings could not be interpreted. Thus, 46 patients were analyzed after mexiletine and 48 after placebo. A 70% or greater reduction from baseline in PVCs was achieved by 24 patients on mexiletine and 6 patients on placebo (Table 2). The majority of mexiletine responders were taking 200 to 400 mg q8h. The response to mexiletine 100 mg q8h was indistinguishable from the response to placebo.

Following a loading dose of 400 mg mexiletine or 4 placebo capsules, patients took 100 mg mexiletine or 1 placebo capsule q8h. The dose was titrated, if necessary, at weekly intervals in increments of 100 mg mexiletine q8h (maximum 400 mg q8h) or 1 placebo capsule q8h (maximum 4 capsules q8h) until greater than 50% suppression of PVCs was achieved or the maximum dose was reached. Reduction of dosage was permitted if intolerable side effects occurred. After four weeks on one treatment, patients immediately crossed over to the other treatment.

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TABLE 2

Response to 4 Weeks of Treatment
(Mexiletine vs. Placebo)

Treatment	Final Dose (q8h)	Number of Patients	
		Responders ($\geq$ 70% reduction)	Non-responders
Mexiletine (n=46)	100 mg	2	2
	200 mg	6	1
	300 mg	9	8
	400 mg	<u>7</u>	<u>11</u>
	Total	24	22
Placebo (n=43)	1 cap	1	2
	2 caps	2	3
	3 caps	1	9
	4 caps	<u>2</u>	<u>28</u>
	Total	6	42

The degree of reduction from baseline for all patients completing 4 weeks of treatment (Table 3) was greater with mexiletine (70.3%) than with placebo (10.3%). This difference was statistically significant (p less than 0.0001). The study design, which called for maintaining any dose that yielded at least a 50% reduction in PVCs may have led to underestimating the maximum effect of mexiletine as only 18 patients reached the 400 mg dose; larger doses might have given a larger than 50% response.

TABLE 3

Percent Reduction from Baseline in PVCs/Hour
After Four Weeks of Treatment
(Mexiletine vs. Placebo)

	Number of Patients	
	Mexiletine	Placebo
Total analyzed	46	48
<u>Percent Reduction from Baseline</u>		
Increased	10	21
0 - 25	1	9
26 - 50	5	7
51 - 70	6	5
71 - 80	7	4
81 - 90	9	1
91 - 100	8	1

Mean Reduction:	44.8%	11.6% increase
Median Reduction:	70.3%*	10.3%

* Difference between treatments statistically significant, p less than 0.0001

Among all patients who received treatment with mexiletine (53) or placebo (49), one patient in each treatment group had a fourfold or greater increase from baseline in PVC rate on the final treatment Holter.

The reduction in PVCs was further evaluated to determine whether concomitant administration of digitalis altered the response to treatment. There was no appreciable difference in response between digitalis users and non-users. The median percent reduction in PVCs was 66.2% in 13 patients using digitalis and 75.2% in 33 patients not using digitalis.

Forty-one patients had couplets at baseline. Couplet frequency was reduced in 36/41 patients (88%) after mexiletine and 20/41 (49%) after placebo. Mexiletine produced a median decrease from baseline of 94.9%, while a median increase of 17.7% was seen with placebo.

TABLE 4

Percent Reduction from Baseline in Couplets/Hour
(Mexiletine vs. Placebo)

	Number of Patients	
	<u>Mexiletine</u>	<u>Placebo</u>
Patients with couplets at baseline	41	41
<u>% Percent Reduction from Baseline</u>		
Increased	5	21
0 - 25	0	2
26 - 50	3	3
51 - 75	3	4
76 - 100	30	11

Mean change
from baseline: 45.2% increase 160.3% increase

Median change
from baseline: 94.9% decrease 17.7% increase

Median couplet frequency at baseline was 21.8/day. This decreased to 1.4/day following mexiletine treatment and was essentially unchanged following placebo (22.1). The difference between treatments was statistically significant, p less than 0.0001.

Among all patients (including those excluded from the efficacy analysis) who had couplets at baseline (48 patients treated with mexiletine, 44 with placebo), a tenfold or greater increase from baseline in couplets on the final treatment Holter was seen in 1 patient on mexiletine and in 2 on placebo.

Four patients had no couplets at baseline. Couplets were seen on the final treatment Holter in one of these patients during mexiletine treatment (rate 0.04/hour) and in two patients during placebo (rates 0.04 and 0.09/hour).

The rate of ventricular tachycardia (beats/hour) was reduced from baseline in 25/26 patients (96%) on mexiletine and 18/27 patients (67%) on placebo. The median percent reduction from baseline in the mexiletine group was 100%.

TABLE 5

Percent Reduction in VT (Beats/Hour)
(Mexiletine vs. Placebo)

	Number of Patients	
	<u>Mexiletine</u>	<u>Placebo</u>
Number of patients with VT at baseline	26	27
<u>Percent Reduction</u>		
Increased	1	9
0 - 25	2	0
26 - 50	3	3
51 - 75	3	2
76 -100	17	13
Mean % reduction	5.2%*	146.7% (increase)
Median % reduction	100.0%	60.0%

* This mean is due to an outlier who had an increase in VT from a baseline of 0.12 beats per hour to 2.36 beats per hour at 4 weeks, an increase of 1889%.

The median rate of ventricular tachycardia at baseline was 5.4 beats/day. This decreased to 0 after mexiletine treatment and to 3.1 beats/day after placebo. The difference between treatments was statistically significant, $p = 0.019$.

Among all patients (including those excluded from the efficacy analysis) who had ventricular tachycardia at baseline (33 patients treated with mexiletine, 29 with placebo), a tenfold or greater increase from baseline in VT on the final treatment Holter was seen in 2 patients on mexiletine and in 3 on placebo.

Twenty patients had no evidence of ventricular tachycardia at baseline. None of these patients had VT on the final mexiletine treatment Holter, while 3 had VT (maximum rate 0.51 beats/hour) on the final placebo Holter.

There were no clinically significant changes in mean blood pressure or pulse rate after treatment with either mexiletine or placebo.

All patients had a 12-lead electrocardiogram at baseline and at the end of the 8-week study (or at the time of discontinuation from the study). Mexiletine did not produce any significant changes from baseline in the mean PR, QRS or QT intervals, regardless of whether patients were receiving concomitant digitalis therapy.

b. Mexiletine vs. Procainamide

Study Design

This double-blind, parallel-group study compared mexiletine and procainamide in the treatment of ventricular arrhythmias. This study also evaluated the effects of the study drugs, alone or with concomitant digitalis, diuretic or beta blocker therapy, on electrocardiogram intervals. One hundred and fifty-eight patients from the five centers listed were randomly assigned to 12 weeks of treatment with either mexiletine (80) or procainamide (78).

<u>Investigator/Address</u>	<u>Number of Patients</u>
Michael Bilitch M.D. Parkview Medical Building 1420 San Pablo Street, C-201 Los Angeles, CA 90033	33
Patrick C., Breaux, M.D. Cardiology Department East New Orleans Medical Center 5640 Read Boulevard New Orleans, LA 70127	34
Robert H. Eich, M.D. Professor of Medicine Chief, Cardiology Section State University of New York Upstate Medical Center 750 East Adams Street Syracuse, NY 13210	28
Sidney Goldstein, M.D. Henry Ford Hospital 2799 West Grand Boulevard Detroit, MI 48202	32
Bramah N. Singh, M.D., Ph.D. Department of Cardiology Wadsworth VA Hospital Wilshire and Sawtelle Boulevards Los Angeles, CA 90073	31

Patients had one or more of the following cardiovascular diagnoses:

<u>Diagnosis</u>	<u>Number of Patients</u>
Atherosclerotic heart disease	91
Idiopathic ventricular arrhythmia	48
Hypertensive heart disease	32
Other	33

To qualify for entry into the study, patients were required to have a baseline PVC rate greater than or equal to 20 per hour (average of two 24-hour Holter recordings).* The median hourly frequency of PVCs at baseline was 242.4 in the mexiletine group and 208.1 in the procainamide group.

Following a loading dose of 400 mg mexiletine or 1000 mg procainamide, patients received mexiletine 200 mg q8h or procainamide 500 mg q6h**. Because of the different dosing schedules, the medications were dispensed by a third party in order to preserve blinding, but in fact the whole procedure casts doubt upon the blinding as casual contacts among patients or discussions with physicians could reveal the differences in therapy. As the Holters were read by third parties, this defect in blinding is not critical.

The dose was titrated, if necessary, at biweekly intervals in increments of 100 mg mexiletine (maximum 400 mg q8h) or 250 mg procainamide (maximum 1000 mg q6h), until greater than or equal to 50% suppression of PVCs was achieved (assessed by 24-hour Holter monitoring as described below) or intolerable side effects occurred. If 50% reduction in PVCs was achieved at any dose level (as confirmed by Holter done two weeks after initial dose and 48 hours to 8 days after each dosage adjustment) and at least 40% suppression was maintained on subsequent Holters, no further dosage adjustment was made. However, if this degree of PVC suppression was attained and the patient was not yet at the maximum dose, titration could be continued if one or more of the following were present: R on T phenomenon; persistence or appearance of significant numbers of multiform PVCs, couplets, or ventricular tachycardia. Patients were treated for a total of 12 weeks. As noted for the placebo study, this design could lead to an underestimate of the effect of mexiletine; patients achieving a modest response (50% reduction) would not be given larger doses in most cases.

* Although the criterion for entry was a baseline PVC rate greater than or equal to 20 per hour, all but two patients had baseline PVC rates exceeding 30 per hour.

** The recommended dosing schedule for procainamide is 250 - 500 mg q3h. The 500 - 1000 mg q6h dose selected for the protocol corresponds to the investigators' usual clinical practice and was chosen to improve patient compliance.

Response to treatment was evaluated by means of 24-hour Holter monitoring. Two consecutive 24-hour Holters were done at baseline and at the end of 12 weeks of treatment. Holter monitoring was routinely done during the study at weeks 2, 4 and 8, and more frequently if dose titration was necessary.

In the original statistical analysis, treatment success was defined as greater than or equal to 50% reduction in PVCs on one Holter, with continued suppression of at least 40% through the final Holter at 12 weeks. The data were reanalyzed, however, using 70% suppression of PVCs through the final Holter as the criterion for success. The findings presented here reflect the revised analysis. Patients who did not achieve and maintain this level of suppression were considered efficacy failures. Patients who were discontinued because of intolerable side effects were considered side effect failures, regardless of the degree of PVC suppression achieved.

Results

One hundred and fifty-eight patients (80 mexiletine, 78 procainamide) were enrolled in the trial. All patients except those dropped for administrative reasons (4 mexiletine and 2 procainamide patients who had protocol violations or were lost to follow-up) were included in the analysis of treatment success or failure (Table 6). All patients (including administrative failures) who had a baseline and a treatment Holter (69 mexiletine, 72 procainamide) were included in the remaining efficacy analysis, using their last treatment Holter to evaluate suppression of ectopy.

Table 6 presents the treatment successes and failures in each treatment group. More patients were controlled with mexiletine (38.2%) than with procainamide (19.7%); this difference was statistically significant ($p = 0.02$). The majority of mexiletine responders (greater than or equal to 70% suppression of PVCs) were controlled at the 200 and 300 mg q2h dose levels.

N18-873 2 of 3

TABLE 6

Treatment Successes and Failures by Final Dose
Following Treatment with Mexiletine or Procainamide

Treatment	Final Dose	Treatment Success*	Treatment Failures		
			Efficacy	Side Effects	Deaths
Mexiletine (76 patients) ^a	200 mg	12	3	13	1
	300 mg	13	1	8	0
	400 mg	4	15	6	0
		<u>29</u> (38.2%)**	<u>19</u> (25.0%)	<u>27</u> (35.5%)	<u>1</u> (1.3%)
Procainamide (76 patients) ^a	500 mg	6	2	12	1
	750 mg	5	5	4	1
	1000 mg	4	30	6	0
		<u>15</u> (19.7%)	<u>37</u> (48.7%)	<u>22</u> (28.9%)	<u>2</u> (2.5%)

^a Excluding administrative failures (4 mexiletine, 2 procainamide)

* greater than or equal to 70% reduction from baseline in PVCs

** Difference between treatments statistically significant (p = 0.02)

Of the treatment failures (Table 6), all those with side effects or death (except for 1 side effect failure in the procainamide group) failed to complete the 12 weeks of study while 10 of the 19 mexiletine and 26 of the 37 procainamide efficacy failures failed to complete the 12 weeks.

Gastrointestinal and central nervous system side effects were the most common with both mexiletine and procainamide. The percentage of treatment failures due to side effects was similar in both groups. Death was due to myocardial infarction in one patient in each treatment group and to cardiac arrest in one patient in the procainamide group. None of the deaths were believed to be related to the study medications. A detailed discussion of adverse experiences and deaths will be found in Section C, Safety.

There are many possible measures of the reduction from baseline in PVC rates, depending on the patient population. An "all patient" analysis involves the least patient selection but could be biased against a drug with more drop-outs due to side effects, as the optimally effective dose might not be reached. An analysis of all patients except those dropped for side effects would overcome that problem. An analysis of 12 week completers would tend, in this case, to favor procainamide as many of the procainamide non-responders were not allowed to complete the 12 weeks. Table 7 shows all three of these analyses.

TABLE 7

Median Percent Reduction from Baseline in Hourly
PVC Rate on Final Treatment Holter
(Mexiletine vs. Procainamide)

	<u>Mexiletine (n)</u>	<u>Procainamide (n)</u>
All patients*	69.9 ^a (69)	34.4 (72)
All patients except side effect failures	77.8 ^b (53)	34.1 (56)
Patients completing 12 weeks	85.4 (38)	75.4 (27)

-
- ^a Difference between treatments statistically significant, P = 0.006.
^b Difference between treatments statistically significant, P = 0.002.
* Baseline but no treatment Holter evaluation was available for an additional 11 mexiletine and 6 procainamide patients.

The range of reduction from baseline in PVCs for all patients with baseline and treatment Holters is presented in Table 7A. Thirty-four patients (49%) in the mexiletine group and 23 (32%) in the procainamide group had reductions greater than 70% on their final treatment Holter.

TABLE 7A

Range of Reduction from Baseline in Hourly PVC Rate
on Final Treatment Holter for All Patients
with Baseline and Treatment Holters
(Mexiletine vs. Procainamide)

<u>Percent Reduction</u>	<u>Number of Patients</u>	
	<u>Mexiletine (n = 69)</u>	<u>Procainamide (n = 72)</u>
Increased*	15	30
0 - 25	3	4
26 - 50	6	10
51 - 70	11	5
71 - 80	8	8
81 - 90	10	4
91 - 100	16	11

* Three (4.3%) patients in the mexiletine group and 1 (1.4%) in the procainamide group had a fourfold or greater increase in PVCs on the final treatment Holter.

Table 8 presents the median percent reduction from baseline in couplets and ventricular tachycardia on the final treatment Holter for the three patient groups (all patients with baseline and treatment Holters; all patients except side effect failures; and 12-week completers) for those patients who had couplets or VT at baseline. Mexiletine produced median decreases ranging from 83 to 96% in couplets and 97 to 100% in VT. Procainamide produced median decreases of 40 to 77% in couplets and 88 to 93% in VT.

TABLE 8

Median Percent Reduction from Baseline in Couplets (Events/Hour) and VT (Beats/Hour) on Final Treatment Holter for Patients with Couplets or VT at Baseline (Mexiletine vs. Procainamide)

	Couplets		VT	
	Mex (n)	Proc (n)	Mex (n)	Proc (n)
All patients*	83.0 ^a (62)	44.9 (64)	96.5 (47)	93.1 (45)
All patients except side effect failures	86.8 ^b (46)	40.0 (49)	100.0 (36)	37.9 (35)
Patients completing 12 weeks	96.4 (33)	77.0 (25)	100.0 (23)	90.5 (16)

* Ten additional mexiletine patients and 5 additional procainamide patients had couplets at baseline but were missing treatment couplet evaluation, while an additional 7 mexiletine and 3 procainamide patients who had VT at baseline were missing treatment VT evaluation. One patient in the mexiletine group had no baseline couplet or VT data.

a Difference between treatments statistically significant, $P = 0.03$.

b Difference between treatments statistically significant, $p = 0.05$.

Table 8A presents the range of reduction from baseline in couplets and VT on the final treatment Holter for all patients. Reductions in couplets of 76% or greater were seen in 61% of the mexiletine patients and 41% of the procainamide patients. For VT, 72 and 62% of mexiletine and procainamide treated patients, respectively, had reductions greater than or equal to 76%.

TABLE 8A

Range of Reduction from Baseline in Couplets (Events/Hour) and VT (Beats/Hour) on Final Treatment Holter for All Patients with Couplets or VT at Baseline* (Mexiletine vs. Procainamide)

% Reduction	Couplets		VT	
	Mex (n=62)	Proc (n=64)	Mex (n=47)	Proc (n=45)
Increased*	13	25	10	15
0-25	3	4	0	0
26-50	4	4	1	1
51-75	4	5	2	1
76-100	38	26	34	28

* A tenfold or greater increase in couplet rate on the final treatment Holter was seen in 3 mexiletine patients (4.8%) and 1 procainamide patient (1.6%). For VT, 1 mexiletine patient (2.1%) and 2 procainamide patients (4.4%) had a tenfold or greater increase.

A small number of patients who had no evidence of complex forms at baseline had couplets or ventricular tachycardia on the final treatment Holter. In the mexiletine group, 2/7 patients had couplets (0.04, 0.21 events/hour) and 2/25 had VT (0.06, 0.85 beats/hour). In the procainamide group, 1/9 patients had couplets (2.58 events/hour) and 2/30 had VT (0.25 and 0.13 beats/hour) on the final Holter.

Mexiletine did not significantly alter mean EKG intervals (PR, QRS, QT_C) as compared to baseline, regardless of whether patients were concomitantly taking digitalis and/or diuretics. Procainamide significantly increased all three intervals for the group as a whole and for the subgroup of patients not using digitalis. Procainamide also significantly increased the PR and QT_C intervals for diuretic users and the QRS and QT_C intervals for diuretic non-users.

Mean systolic and diastolic blood pressure showed an increase of 4.5 mm Hg after mexiletine, a statistically significant difference. Mexiletine had no significant effect on mean pulse rate.

c. Mexiletine vs. Quinidine

Study Design

Two multicentered, double-blind, parallel group trials - Study A and Study B - compared mexiletine and quinidine in the management of ventricular arrhythmias. The trials also assessed whether adverse effects on EKG intervals occurred with the study drugs alone or in combination with digitalis, diuretic or beta blocker therapy.

Two hundred and ninety-eight patients from fifteen centers participated in Study A and were randomly assigned to 12 weeks of treatment with mexiletine (150) or quinidine (148). Two hundred and thirty-two patients from fourteen centers were enrolled in Study B (118 mexiletine, 114 quinidine). The investigators and the number of patients enrolled at each center are listed below.

<u>Mexitil vs. Quinidine - Study A</u>	<u>Number of Patients</u>
Reuben Berman, M.D. Marvin Segal, M.D. Mount Sinai Hospital 2215 Park Avenue Minneapolis, MN 55404	22
Patrick C. Breaux, M.D. Cardiology Department East New Orleans Medical Center 5640 Read Boulevard New Orleans, LA 70127	29
Paul E. Fenster, M.D. Assistant Professor Cardiology Section Arizona Health Sciences Center Tucson, AZ 85724	27

Mexitil vs. Quinidine - Study A

Number of Patients

Thomas Glatter, M.D.
Robert Conn, M.D.
Thomas Terry, M.D.
Charles Ray Webb, M.D.
University of Missouri
Kansas City School of Medicine
2411 Holmes Street
Kansas City, MO 64108

10

Morrison Hodges, M.D.
Director, Cardiology Section
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701 Park Avenue
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20

Richard C. Klein, M.D.
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27

Norman Krasnow, M.D.
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18

Syed Mohiuddin, M.D.
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16

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27

William A. Pitt, M.D.
Associate Director
Cardiopulmonary Department
Mercy Hospital and Medical Center
4077 Fifth Avenue
San Diego, CA 92103

20

<u>Mexitil vs. Quinidine - Study A</u>	<u>Number of Patients</u>
Philip R. Reid, M.D. Assistant Professor of Medicine Division of Cardiology & Clinical Pharmacology The John Hopkins Hospital 600 North Wolfe Street Baltimore, MD 21205	15
Rodolpne Ruffy, M.D. Cardiology Division The Jewish Hospital of St. Louis 216 South Kingshighway P.O. Box 14109 St. Louis, MO 63178	19
Jang B. Singh, M.D. Director Cardiac Catheterization Laboratory St. Vincent Hospital 25 Winthrop Street Worcester, MA 01604	23
Douglas K. Stewart, M.D. Director, Cardiac Catheterization Laboratory University of Washington Division of Cardiology, RG-20 Cardiovascular Research & Training Center Seattle, WA 98195	20
Albert L. Waldo, M.D. University of Alabama Medical Center University Station Birmingham, AL 35294	5

<u>Mexitil vs. Quinidine - Study B</u>	<u>Number of Patients</u>
Michael E. Assey, M.D. Assistant Professor of Medicine Division of Cardiology 81F C Clinical Science Building Medical University of South Carolina 171 Ashley Avenue Charleston, SC 29403	22
Kul Deep Chadda, M.D. Long Island Jewish Hospital Hillside Medical Center, Room 2135 New Hyde Park, NY 11040	10
R. Charles Curry Jr., M.D. 2400 Bedford Road Orlando, FL 32803	22
Henry DeMots, M.D. Chief, Cardiology Veterans Administration Medical Center 3710 Southwest U.S. Veterans Hospital Road Portland, OR 97201	21
Joel Kupersmith, M.D. Mount Sinai Medical Center One Gustave L. Levy Place New York, NY 10029	30
Anthony M. Marlon, M.D. Southwest Heart Associates 2040 W. Charleston Boulevard Suite 400 Las Vegas, NV 89102	23
David McCall, M.D. Director, Adult Cardiology University of Nebraska Medical Center 42nd and Dewey Avenue Omaha, NE 68105	4
Joel Morganroth, M.D. Chief, Cardiac Research & Education Cardiovascular Division The Lankenau Hospital Lancaster Avenue West of City Line Philadelphia, PA 19151	20

Mexitil vs. Quinidine - Study B

Number of Patients

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10

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6

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10

Patients had been diagnosed as having one or more of the following cardiovascular diseases:

Diagnosis	Number of Patients	
	Study A	Study B
Atherosclerotic heart disease	128	110
Idiopathic ventricular arrhythmia	76	68
Hypertensive heart disease	72	58
Other	75	73
Not reported	2	0

To qualify for entry into the study, patients were required to have a minimum of 30 PVCs per hour (average of two 24-hour Holter recordings). In Study A, the median hourly frequency of PVCs at baseline was 196 in the mexiletine group and 271 in the quinidine group. In Study B, it was 349 and 341 in the mexiletine and quinidine groups, respectively. The difference between treatment groups was not statistically significant in either study.

Patients began treatment with mexiletine 200 mg q8h or quinidine 200 mg q6h. Because of the different dosing intervals, the medications were administered by a third party in order to preserve blinding. As noted above, third party blinding may not always preserve the blind, but that is not critical here, as the Holters were read by a third party. The dose was titrated, if necessary, in 100 mg increments (to a maximum of 400 mg mexiletine q8h or 400 mg quinidine q6h) until 70% suppression of PVCs was achieved or intolerable side effects occurred. Once a patient achieved 70% reduction from baseline, no further dosage adjustment was made so long as the patient maintained at least 55% suppression on subsequent Holters. Patients were treated for a total of 12 weeks.

Two consecutive 24-hour Holter recordings were done at baseline. Holter monitoring to evaluate the therapeutic response was done one week after initiation of treatment and a confirming Holter 48 hours to 8 days later. If titration was necessary, Holter analysis was done at these same intervals after each dosage adjustment. A final Holter evaluation was done at 12 weeks.

The protocol and original statistical analysis defined treatment successes as patients who achieved 70% suppression of PVCs on one Holter and subsequently maintained at least 55% suppression through the final Holter at 12 weeks. The data were reanalyzed, however, using a more stringent standard that defined treatment successes as those patients who, after reaching 70% reduction in PVCs, maintained that degree of suppression through the final Holter. Patients who did not maintain 70% suppression were considered efficacy failures. Patients who were dropped because of intolerable side effects were considered side effect failures, regardless of the degree of PVC control they achieved.

Results - Study A

Two hundred and ninety-eight patients were enrolled in this trial (150 mexiletine, 148 quinidine). Fifteen mexiletine and eight quinidine patients who were still in progress at the time the study was analyzed for the NDA were excluded from the efficacy analysis. Of the remaining patients (135 mexiletine, 140 quinidine), all except administrative failures (8 mexiletine and 12 quinidine patients with protocol violations, missing data or lost to follow-up) were included in the analysis of treatment success or failure (Table 9). All patients (including administrative failures) who had a baseline and a treatment Holter (117 mexiletine, 122 quinidine) were included in the remaining efficacy analysis; using the last treatment Holter to evaluate arrhythmia suppression.

Table 9 presents the treatment successes and failures in both treatment groups. Treatment success (greater than or equal to 70% reduction in PVCs) was achieved in 39 patients (30.7%) on mexiletine and 48 patients (37.5%) on quinidine; this difference was not statistically significant. The majority of mexiletine treatment successes (33/39) occurred at the 200 and 300 mg q8h dose levels. The percentages of efficacy and side effect failures were similar for both treatment groups.

TABLE 9

Treatment Successes and Failures by Final Dose
(Mexiletine vs. Quinidine Study A)

Treatment	Final Dose	Treatment Success*	Treatment Failure		
			Lack of Efficacy	Side Effects	Deaths
Mexiletine (127 patients) ^a	100 mg ^b	0	0	1	0
	200 mg	22	6	26	1
	300 mg	11	9	13	0
	400 mg	6	23	9	0
	<u>Total</u>	39 (30.7%)**	38 (29.9%)	49 (38.6%)	1 (0.8%)
Quinidine (128 patients) ^a	200 mg	25	14	29	2
	300 mg	14	6	6	1
	400 mg	9	16	5	1
	<u>Total</u>	48 (37.5%)	36 (28.1%)	40 (31.3%)	4 (3.1%)

^a Administrative failures (8 mexiletine, 12 quinidine) excluded.

^b One patient had his dose reduced to 100 mg because of an adverse event and was subsequently discontinued as a side effect failure

* greater than or equal to 70% reduction from baseline in PVCs

** Not significantly different from quinidine (p = 0.27)

Of the treatment failures (Table 9), all of the side effect failures and deaths failed to complete the 12 weeks of the study, while 23 of the 38 mexiletine and 19 of the 36 quinidine efficacy failures failed to complete 12 weeks.

The most common side effects were gastrointestinal or central nervous system in nature. One patient in the mexiletine group died of ventricular tachycardia. In the quinidine group, the causes of death were ventricular fibrillation (1 patient), arteriosclerotic heart disease (1 patient) and sudden death (2 patients). In no case was death attributed to the study medication. Side effects and deaths are discussed in detail in Section C, Safety.

As in the previous study, the median percent reductions from baseline PVC rate on the final treatment Holter were examined in three ways: for all patients who had a baseline and treatment Holter; for all patients except side effect failures; and for those patients who completed the 12-week study (Table 10). Median reductions ranged from 60 to 92% for mexiletine and 81 to 92% for quinidine.

TABLE 10

Median Percent Reduction from Baseline in Hourly PVC Rate on Final Treatment Holter (Mexiletine vs. Quinidine Study A)

	<u>Mexiletine (n)</u>	<u>Quinidine (n)</u>
All patients*	59.6 ^a (117)	81.0 (122)
All patients except side effect failures**	69.5 (83)	86.4 (94)
Patients completing 12 weeks	92.3 (54)	91.8 (65)

-
- * An additional 18 patients in each treatment group were missing treatment Holter evaluation
 - ** Treatment Holter evaluation was not available for 2 additional mexiletine and 6 quinidine patients. One mexiletine patient had no Holter data.
 - ^a Difference between treatments marginally statistically significant, p = 0.06.

The range of reduction from baseline in PVCs for all patients with baseline and treatment Holters is presented below (Table 10A). Forty-four percent of the mexiletine patients and 57% of the quinidine patients had reductions greater than 70%.

TABLE 10A

Range of Reduction from Baseline in Hourly PVC Rate
on Final Treatment Holter for All Patients
(Mexiletine vs. Quinidine Study A)

<u>% Reduction</u>	<u>Number of Patients</u>	
	<u>Mexiletine</u> <u>(n = 117)</u>	<u>Quinidine</u> <u>(n = 122)</u>
Increased*	24	20
0 - 25	9	6
26 - 50	19	10
51 - 70	13	17
71 - 80	5	8
81 - 90	12	14
91 - 100	35	47

* A fourfold or greater increase in PVCs on the final treatment Holter was seen in 1 mexiletine patient, (0.9%) and 5 quinidine patients, (4.1%).

For the three patient groups, median reductions from baseline in couplets ranged from 93 - 99% with mexiletine and 98 - 100% with quinidine, while median reductions of 100% in ventricular tachycardia and R on T were seen with both treatments, as shown in Table 11.

TABLE 11

Median Percent Reduction from Baseline in Couplets, VT and R on T (Events/Hour) on Final Treatment Holter for Patients with Complex Forms at Baseline (Mexiletine vs. Quinidine Study A)

	Couplets		VT		R on T	
	Mex (n)	Quin (n)	Mex (n)	Quin (n)	Mex (n)	Quin (n)
All patients*	92.5 (107)	98.3 (102)	100.0 (73)	100.0 (64)	100.0 (78)	100.0 (81)
All patients except side effect failures**	93.4 ^a (76)	99.3 (78)	100.0 (50)	100.0 (48)	100.0 (52)	100.0 (64)
Patients completing 12 weeks	99.1 (51)	100.0 (56)	100.0 (33)	100.0 (34)	100.0 (36)	100.0 (44)

* In addition, baseline but no treatment evaluation was available for couplets in 14 mexiletine and 15 quinidine patients; for VT in 9 mexiletine and 14 quinidine patients; and for R on T in 12 mexiletine and 14 quinidine patients. Four mexiletine patients and 1 quinidine patient were missing baseline couplet and VT data.

** In addition, baseline but no treatment evaluation was available for 1 mexiletine and 3 quinidine patients with baseline couplets, 1 mexiletine and 4 quinidine patients with baseline VT and 6 quinidine patients with baseline R on T.

^a Difference between treatments statistically significant, $p = 0.05$

Table 11A presents the range of reduction from baseline in couplets, ventricular tachycardia and R on T on the final treatment Holter for all patients who had these forms at baseline. Reductions greater than 75% were seen in the majority of patients in both treatment groups.

TABLE 11A

Range of Reduction from Baseline in Couplets, VT and R on T (Events/Hour) on Final Treatment Holter for All Patients with Complex Forms at Baseline (Mexiletine vs. Quinidine Study A)

% Reduction	Couplets		VT		R on T	
	Mex (n=107)	Quin (n=102)	Mex (n=73)	Quin (n=54)	Mex (n=78)	Quin (n=81)
Increased*	16	14	8	11	9	14
0 - 25	3	2	2	2	1	2
26 - 50	4	4	2	0	0	1
51 - 75	14	7	1	3	5	2
76 - 100	70	75	60	48	63	62

* A tenfold or greater increase from baseline in couplet rate on the final Holter was seen in 1 mexiletine patient (0.9%) and 3 quinidine patients (2.9%). For VT, 1 mexiletine patient (1.4%) and 6 quinidine patients (9.4%) had a tenfold or greater increase.

Of those patients who had no evidence of complex arrhythmias at baseline, 5 patients out of 22 in the quinidine group had couplets (maximum rate, 17.21 events/hour); 3 patients out of 49 in the mexiletine group and 6 out of 61 in the quinidine group had ventricular tachycardia on the final Holter (maximum rate 0.06 events/hour with mexiletine, 0.88 with quinidine). None of the 10 patients in the mexiletine group who had no couplets at baseline had couplets on the final Holter.

Mexiletine did not significantly affect mean EKG intervals (PR, QRS, QT_C), regardless of whether patients were receiving concomitant treatment with digitalis, diuretics or beta blockers, with the exception of a statistically significant (p less than 0.05) prolongation of the PR interval by 0.0058 second in patients not using beta blockers. Quinidine statistically significantly prolonged the QT_C interval for the group as a whole (p less than 0.01) and for patients who were not concomitantly using digitalis (p less than 0.01), beta blockers (p less than 0.01), or diuretics (p less than 0.05).

Neither treatment produced any significant change from baseline in mean pulse rate.

Results - Study B

Of the 232 patients enrolled in this trial (118 mexiletine, 114 quinidine), fifteen (7 mexiletine, 8 quinidine) were still in progress when the study was analyzed for the NDA and were excluded from the efficacy analysis. Of the remaining patients (111 mexiletine, 106 quinidine), all except administrative failures (6 mexiletine and 9 quinidine patients with protocol violations, missing data or lost to follow-up) were evaluated for treatment success or failure (Table 12). All patients (including administrative failures) who had a baseline and a treatment Holter (100 mexiletine, 89 quinidine) were included in the remaining efficacy analysis, using the last treatment Holter to assess suppression of ectopy.

Treatment successes and failures are tabulated below. Treatment success (greater than or equal to 70% reduction in PVCs) was achieved in 32 patients (30.5%) on mexiletine and 25 patients (25.8%) on quinidine; this difference was not statistically significant. Most of the mexiletine treatment successes (27/32) reached control at the 200 and 300 mg q8h dose levels. The frequency of efficacy and side effect failures was similar for both drugs.

TABLE 12

Treatment Successes and Failures by Final Dose
(Mexiletine vs. Quinidine Study B)

Treatment	Final Dose	Treatment Success*	Treatment Failure		
			Lack of Efficacy	Side Effects	Deaths
Mexiletine (105 patients) ^a	200 mg	16	7	19	1
	300 mg	11	7	13	0
	400 mg	5	14	12	0
	<u>Total</u>	<u>32 (30.5%)**</u>	<u>28 (26.7%)</u>	<u>44 (41.9%)</u>	<u>1 (1.0%)</u>
Quinidine (97 patients) ^a	200 mg	15	12	29	1
	300 mg	7	6	3	2
	400 mg	3	16	3	0
	<u>Total</u>	<u>25 (25.8%)</u>	<u>34 (35.1%)</u>	<u>35 (36.1%)</u>	<u>3 (3.1%)</u>

- ^a Administrative failures (6 mexiletine, 9 quinidine) excluded
* greater than or equal to 70% reduction from baseline in PVCs
** Not significantly different from quinidine (p = 0.48)

Of the treatment failures (Table 12), all of the side effect failures and deaths failed to complete the 12 week study, while 16 of the 28 mexiletine and 16 of the 34 quinidine efficacy failures failed to complete 12 weeks.

Gastrointestinal and central nervous system side effects were the most frequently reported. The causes of death for the four patients who died during the study were sudden death (1 mexiletine, 2 quinidine) and myocardial infarction (1 quinidine). A fifth patient died in ventricular fibrillation four days after being discontinued from the study as a mexiletine efficacy failure. None of these deaths were believed to be related to the study medications. Side effects and deaths are discussed in greater detail in Section C, Safety.

Table 13 presents the median reductions from baseline PVC rate on the final treatment Holter for three patient groups: all patients with a baseline and treatment Holter, all patients excluding side effect failures; and patients who completed the 12 week study. The median reductions ranged from 63 to 87% in the mexiletine treatment group and from 50 to 77% in the quinidine group. The differences between treatments in median percent reductions were not statistically significant.

TABLE 13

Median Percent Reduction from Baseline in Hourly
PVC Rate on Final Treatment Holter
(Mexiletine vs. Quinidine Study B)

	<u>Mexiletine (n)</u>	<u>Quinidine (n)</u>
All patients*	63.4 (100)	60.4 (89)
All patients except side effect failures**	75.3 (65)	64.5 (69)
Patients completing 12 weeks	87.2 (44)	77.4 (43)

-
- * Baseline but no treatment Holter evaluation was available for an additional 11 mexiletine and 17 quinidine patients.
 - ** Baseline but no treatment Holter evaluation was available for an additional 2 mexiletine and 2 quinidine patients.

The range of reduction from baseline in PVC rate on the final treatment Holter for all patients with baseline and treatment Holters is presented in Table 13A. Forty percent of patients in the mexiletine group and 42% in the quinidine group had reductions greater than 70%.

TABLE 13A

Range of Reduction from Baseline in Hourly PVC Rate on
Final Treatment Holter for All Patients
(Mexiletine vs. Quinidine Study B)

% Reduction	Number of Patients	
	Mexiletine (n = 100)	Quinidine (n = 89)
Increased*	17	18
0 - 25	11	4
26 - 50	11	13
51 - 70	17	17
71 - 80	5	6
81 - 90	8	12
91 - 100	27	19

* A fourfold or greater increase from baseline in PVC rate was seen on the final Holter in 1 mexiletine patient (1.0%) and 3 quinidine patients (3.4%).

For couplets, VT and R on T, the median percent reductions from baseline for the three patient groups are shown in Table 14. The median reductions in couplets ranged from 94 to 100% with mexiletine and 93 to 99% with quinidine. For VT and R on T median reductions of 99 - 100% were seen in all patient groups with both study drugs. The differences between treatments in median percent reductions were not statistically significant.

TABLE 14

Median Percent Reduction from Baseline in Couplets, VT and R on T
(Events/Hour) on Final Treatment Holter for Patients
with Complex Forms at Baseline
(Mexiletine vs. Quinidine Study B)

	Couplets		VT		R on T	
	Mex (n)	Quin (n)	Mex (n)	Quin (n)	Mex (n)	Quin (n)
All patients*	93.7 (92)	92.7 (80)	100.0 (69)	99.6 (63)	100.0 (79)	100.0 (74)
All patients except side effect failures**	96.2 (61)	95.0 (61)	100.0 (45)	99.8 (48)	100.0 (51)	100.0 (58)
Patients completing 12 weeks	99.4 (41)	98.7 (37)	100.0 (29)	100.0 (25)	100.0 (32)	100.0 (35)

* In addition, baseline but no treatment evaluation was available for 9 mexiletine and 17 quinidine patients with baseline couplets; 6 mexiletine and 13 quinidine patients with baseline VT; and 8 mexiletine and 8 quinidine patients with baseline R on T. One quinidine patient was missing baseline couplet data.

** Baseline but no treatment evaluation was available for 1 mexiletine and 2 quinidine patients with couplets, 1 mexiletine and 1 quinidine patient with VT and 1 quinidine patient with R on T.

As shown in Table 14A, the majority of patients in both treatment groups had reductions of more than 75% from baseline in couplets, VT and R on T.

TABLE 14A

Range of Reduction from Baseline in Couplets, VT and R on T (Events/Hour) on Final Treatment Holter for All Patients with Complex Forms at Baseline (Mexiletine vs. Quinidine Study B)

% Reduction	Couplets		VT		R on T	
	Mex (n=92)	Quin (n=80)	Mex (n=69)	Quin (n=63)	Mex (n=79)	Quin (n=74)
Increased*	18	15	12	15	13	11
0 - 25	4	2	1	1	4	2
26 - 50	3	6	4	1	3	3
51 - 75	10	7	6	4	4	4
76 - 100	57	50	46	42	55	54

- * A tenfold or greater increase from baseline on the final Holter was observed in couplets in 3 mexiletine (3.3%) and 2 quinidine patients (2.5%) and in VT in 3 mexiletine (4.3%) and 1 quinidine patient (1.6%).

Of those patients who had no evidence of complex arrhythmia forms at baseline, couplets were seen on the final Holter in 1/8 quinidine patients (rate 0.04) and VT was seen in 1/36 mexiletine (rate 0.46 events/hour) and 1/30 quinidine patients (rate 0.05 events/hour). None of the 10 mexiletine patients who had no couplets at baseline had couplets on the final Holter.

A 12-lead electrocardiogram was done at the beginning and end of the study. Mexiletine did not significantly alter mean EKG intervals (PR, QRS, QT_c), regardless of whether patients were concomitantly treated with digitalis, diuretics or beta blockers, with the exception of a statistically significant mean decrease of 0.0091 second (p less than 0.05) in the QT_c in the subgroup of digitalis non-users. Quinidine, however, prolonged the PR interval for the group as a whole (p less than 0.01) and for the subgroups of digitalis and diuretic non-users (p less than 0.01) and beta blocker users (p less than 0.01) and non-users (p less than 0.05). The mean QRS interval was significantly lengthened by quinidine for the group as a whole (p less than 0.05) and for diuretic users (p less than 0.01). Quinidine significantly prolonged the QT_c interval for the group as a whole and for the subgroups of digitalis and diuretic users and beta blocker non-users (p less than 0.01).

Neither mexiletine nor quinidine produced statistically significant changes from baseline in mean pulse rate.

d. Mexiletine vs. Disopyramide

The purpose of this double-blind, parallel-group study was to compare mexiletine and disopyramide in the management of ventricular arrhythmias. In addition, this trial evaluated the effects of the study drugs, alone or with concomitant digitalis or diuretic therapy, on electrocardiogram intervals and assessed changes in left ventricular function, ocular pressure and visual acuity. One hundred and forty-three patients from eleven centers (listed below) were randomly assigned to receive 12 weeks of treatment with mexiletine (74) or disopyramide (69).

<u>Investigator/Address</u>	<u>Number of Patients</u>
Masood Akhtar, M.D. Cardiovascular Disease Section Mount Sinai Medical Center P.O. Box 342 Milwaukee, WI 53201	11
Michael Bilitch, M.D. Parkview Medical Building 1420 San Pablo Street, C-201 Los Angeles, CA 90033	11
Dennis A. Bloomfield, M.D. Director of Medicine St. Vincent's Medical Center of Richmond 355 Bard Avenue Staten Island, NY 10310	10
Michael D. Ezekowitz, M.D., Ph.D. Director, Coronary Care Unit and Heart Station Veterans Administration Hospital (111B2) 921 Northeast 13th Street Oklahoma City, OK 73104	9

<u>Investigator/Address</u>	<u>Number of Patients</u>
Joseph P. Galichia, M.D. Richard A. Steckley, M.D. Wichita Cardiology Associates, P.A. St. Francis Medical Park Building 1035 North Emporia, Suite 1130 Wichita, KS 67201	22
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The cardiovascular diagnoses are presented below (some patients had more than one diagnosis).

<u>Diagnosis</u>	<u>Number of Patients</u>
Atherosclerotic heart disease	79
Idiopathic ventricular arrhythmia	39
Hypertensive heart disease	17
Other	28

The protocol required that patients have an average of at least 30 PVCs per hour, documented by two 24-hour Holter recordings at baseline. Two patients, one in each treatment group, who had baseline PVC rates of 28 and 29 per hour, respectively, were included in the efficacy analysis. The median hourly frequency of PVCs at baseline was 379.4 in the mexiletine group and 347.4 in the disopyramide group.

Patients began treatment with mexiletine 200 mg q8h or disopyramide 100 mg q6h. Because of the different dosing intervals, a third party administered the medications in order to preserve blinding. Although third party blinding of drug administration may not always preserve the blind, the Holters were read by a third party, therefore this defect is not critical. The dose was increased, if necessary, by 100 mg mexiletine q8h (maximum 400 mg q8h) or 50 mg disopyramide q6h (maximum 200 mg q6h) until the PVC rate was reduced by 70% from baseline (determined by 24-hour Holter monitoring as described below). Once 70% suppression was achieved, no further dosage adjustment was made as long as the patient maintained at least 55% suppression on subsequent Holters. The duration of treatment was 12 weeks.

Two consecutive 24-hour Holter recordings were done at baseline. Holter monitoring to assess the therapeutic response was done one week after initiation of treatment and a confirming Holter 48 hours to 8 days later. If titration was necessary, Holter analysis was done at these same intervals after each dosage adjustment. A final 24-hour Holter was done after 12 weeks of treatment.

The original statistical analysis defined treatment success as 70% or greater suppression in PVCs on one Holter and at least 55% suppression maintained on subsequent Holters through the final recording at 12 weeks. The data were reanalyzed, however, with treatment success defined as greater than or equal to 70% suppression in PVCs maintained through the final Holter. The results presented here are based on this efficacy criterion. Patients who did not maintain this degree of suppression were considered efficacy failures. Patients who were dropped because of intolerable side effects were considered side effect failures, regardless of the degree of PVC suppression achieved.

Results

One hundred and forty-three patients were enrolled in this trial (74 mexiletine, 69 disopyramide). Five patients in each treatment group were still in progress at the time the study was analyzed for the NDA and they were excluded from the efficacy analysis. Of the remaining patients (69 mexiletine, 64 disopyramide), all except administrative failures (6 mexiletine and 10 disopyramide patients with protocol violations, missing data or lost to follow-up) were evaluated for treatment success or failure (Table 15). All patients (including administrative failures) who had a Holter evaluation at baseline and during treatment (57 mexiletine, 61 disopyramide) were included in the remaining efficacy analysis, using the last treatment Holter to evaluate reduction of ectopy.

Table 15 presents treatment successes and failures by final dose of each study drug. There was no statistically significant difference between mexiletine and disopyramide in the number of treatment successes (28.6% and 44.4%, respectively). Most of the patients who were controlled on mexiletine were taking 200-300 mg q8h.

TABLE 15

Treatment Successes and Failures by Final Dose
Following Treatment with Mexiletine or Disopyramide

Treatment	Final Dose	Treatment Success*	Treatment Failures	
			Efficacy	Side Effects
Mexiletine (63 patients) ^a	100 mg	1 ^b	0	0
	200 mg	9	5	13
	300 mg	7	5	9
	400 mg	1	9	4
		<u>18</u> (28.6%)**	<u>19</u> (30.2%)	<u>26</u> (41.3%)
Disopyramide (54 patients) ^a	100 mg	8	5	4
	150 mg	7	4	4
	200 mg	9	10	3
		<u>24</u> (44.4%)	<u>19</u> (35.2%)	<u>11</u> (20.4%)

* greater than or equal to 70% reduction from baseline in PVCs

** Difference between treatments not statistically significant ($p = 0.11$)

^a Administrative failures (6 mexiletine, 10 disopyramide) excluded.

^b This patient's dose was reduced from 200 mg because of adverse reactions

Of the treatment failures (Table 15), none of the side effect failures completed the 12 week study. Nine of the 19 efficacy failures in each treatment group failed to complete 12 weeks.

The median percent reductions from baseline PVC rate are presented in three ways in Table 16: for all patients with baseline and treatment Holters; all patients excluding side effect failures; and all patients who completed 12 weeks of treatment. In the mexiletine group, median reductions ranged from 61 to 79% and in the disopyramide group from 73 to 83%. The differences between treatments in median percent reductions were not statistically significant.

TABLE 16

Median Percent Reduction from Baseline in Hourly
PVC Rate on Final Treatment Holter
(Mexiletine vs. Disopyramide)

	<u>Mexiletine (n)</u>	<u>Disopyramide (n)</u>
All patients*	61.0 (57)	72.9 (61)
All patients except side effect failures**	71.9 (39)	76.2 (53)
Patients completing 12 weeks	78.8 (28)	82.5 (34)

* Baseline but no treatment Holter evaluation was available for an additional 12 mexiletine and 3 disopyramide patients

** Baseline but no treatment evaluation was available for 4 additional mexiletine patients

The range of reduction from baseline in PVC rate on the final treatment Holter for all patients with baseline and treatment Holters is shown in Table 16A. Reductions greater than 70% were seen in 49% of mexiletine patients and 52% of disopyramide patients.

TABLE 16A

Range of Reduction from Baseline in Hourly PVC Rate
on Final Treatment Holter for All Patients
(Mexiletine vs. Disopyramide)

% Reduction	Number of Patients	
	Mexiletine (n = 57)	Disopyramide (n = 61)
Increased*	10	5
0 - 25	7	3
26 - 50	6	11
51 - 70	6	10
71 - 80	8	8
81 - 90	6	8
91 - 100	14	16

* A fourfold or greater increase in PVC rate was seen on the final Holter in 3 mexiletine patients (5.3%) and in 2 disopyramide patients (3.3%)

Table 17 presents the median percent reductions from baseline in couplets, VT and R on T for the three patient groups. Median decreases in couplets ranged from 96 to 100% with mexiletine and from 94 to 95% with disopyramide. Median decreases of 100% in VT and R on T were seen with both mexiletine and disopyramide for all patient groups.

TABLE 17

Median Percent Reduction from Baseline in Couplets, VT and R on T (Events/Hour) on Final Treatment Holter for Patients with Complex Forms at Baseline (Mexiletine vs. Disopyramide)

	Couplets		VT		R on T	
	Mex (n)	Diso (n)	Mex (n)	Diso (n)	Mex (n)	Diso (n)
All patients*	96.3 (50)	93.9 (55)	100.0 (36)	100.0 (38)	100.0 (45)	100.0 (38)
All patients except side effect failures**	97.0 (36)	93.9 (48)	100.0 (26)	100.0 (34)	100.0 (31)	100.0 (33)
Patients completing 12 weeks	99.8 (26)	94.7 (32)	100.0 (17)	100.0 (24)	100.0 ^a (24)	100.0 (21)

* Baseline but no treatment Holter evaluation was available for an additional 10 mexiletine and 3 disopyramide patients with baseline couplets; 7 mexiletine and 2 disopyramide patients with baseline VT and R on T data. Four mexiletine and 1 quinidine patient were missing baseline couplet data while 3 mexiletine and 1 quinidine patient were missing baseline VT data.

** Baseline but no treatment evaluation was available for an additional 3 patients with couplets, 1 with VT and 2 with R on T, all in the mexiletine group.

^a Difference between treatments statistically significant, $p = 0.01$. Twenty-one of 24 mexiletine patients had reductions of 100% while 14 of 21 disopyramide patients had reductions of 100%.

The range of reduction from baseline for couplets, VT and R on T on the final treatment Holter for all patients with baseline and treatment Holters is presented in TABLE 17A. The majority of patients in both treatment groups had reductions of greater than 75% in couplets, VT and R on T.

TABLE 17A

Range of Reduction from Baseline in Couplets, VT and R on T
(Events/Hour) on Final Treatment Holter for All
Patients With Complex Forms at Baseline
(Mexiletine vs. Disopyramide)

% Reduction	Couplets		VT		R on T	
	Mex (n=50)	Diso (n=55)	Mex (n=36)	Diso (n=38)	Mex (n=45)	Diso (n=38)
Increased*	9	7	4	1	5	4
0 - 25	1	2	1	1	1	1
26 - 50	3	2	1	2	1	2
51 - 75	4	7	1	4	3	3
76 - 100	33	37	29	30	35	28

- * A tenfold or greater increase from baseline in couplets was seen on the final Holter in 1 patient in each treatment group (2.0 and 1.8% for mexiletine and disopyramide, respectively). A tenfold or greater increase in VT was not observed in either group on the final Holter.

Of those patients who had no evidence of complex arrhythmias at baseline, VT was seen on the final treatment Holter in 1 patient out of 23 in the mexiletine group (rate 0.08 events/hour) and in 4 patients out of 23 in the disopyramide group (maximum rate 0.12 events/hour). None of the 5 patients in each treatment group who had no couplets at baseline had couplets on the final Holter.

A 12-lead electrocardiogram was done at the beginning and end of the study to assess the effects of mexiletine and disopyramide on EKG intervals (PR, QRS, QT_c). There were no statistically significant mean changes from baseline for any interval in the mexiletine treatment group, regardless of whether patients were concomitantly using digitalis or diuretics. In the disopyramide group, the QT_c interval was significantly prolonged as compared to baseline except in those patients concomitantly treated with digitalis and the PR interval was prolonged in patients not using digitalis or diuretics. The difference between treatments was not statistically significant.

Neither mexiletine nor disopyramide produced any significant change from baseline in mean blood pressure or pulse rate.

Mexiletine did not significantly affect visual acuity or intraocular pressure.

The hemodynamic effects of mexiletine and disopyramide were assessed by means of gated radionuclide ventriculogram. There were no significant changes from baseline with either treatment in any of the variables measured (end-systolic and diastolic volumes, stroke volume, cardiac output and ejection fraction).

Summary

The results of the controlled clinical trials conducted in the U.S. demonstrated the efficacy of mexiletine in the treatment of ventricular arrhythmias. Both idiopathic ventricular arrhythmias and ventricular arrhythmias due to underlying cardiovascular illness, such as arteriosclerotic heart disease and hypertensive heart disease, were successfully treated.

In a 4-week, double-blind, crossover study, mexiletine proved to be superior to placebo, with 24/46 patients responding to mexiletine with greater than or equal to 70% suppression of PVCs and only 6/48 patients responding to placebo. The median percent reduction from baseline in PVCs was significantly greater (p less than 0.0001) with mexiletine (70.3%) than with placebo (10.3%). Mexiletine also significantly reduced the median frequency of couplets (p less than 0.0001) and ventricular tachycardia (p less than 0.019) as compared to placebo.

In 12-week, double-blind, parallel group trials comparing mexiletine with the standard antiarrhythmic drugs, mexiletine was superior to procainamide ($p = 0.02$) and comparable to quinidine and disopyramide in the number of patients successfully controlled (greater than or equal to 70% reduction in PVCs). A total of 371 patients were analyzed after treatment with mexiletine. As summarized in the table below, approximately one-third (32%) were treatment successes; most of these patients were taking 200 or 300 mg mexiletine q8h. Slightly more than one-third of patients, however, left the study prematurely because of adverse events with mexiletine, which was more than left the other drug groups.

Table 18

Response to Mexiletine for 371 Patients* in the 12-Week, Double Blind Studies

Mexiletine Dose q&n	Treatment Success**	Treatment Failure		
		Efficacy	Side Effects	Death
100 mg	1	0	1	0
200 mg	39	21	72	3
300 mg	42	22	43	0
400 mg	16	61	30	0
Total (1%)	118 (32%)	104 (28%)	146 (39%)	3

* Administrative failures excluded

** greater than or equal to 70% reduction from baseline in PVCs

The overall response to mexiletine and to the comparison drugs in the 12-week trials is summarized below.

Table 19

Overall Response to Treatment in the 12-Week, Double Blind Studies

Treatment	Total Treated*	Treatment Success**	Treatment Failure		
			Efficacy	Side Effects	Death
Mexiletine	371	118 (32%)	104 (28%)	146 (39%)	3 (1%)
Procainamide	76	15 (20%)	37 (49%)	22 (29%)	2 (3%)
Quinidine	225	73 (32%)	70 (31%)	75 (33%)	7 (3%)
Disopyramide	54	24 (44%)	19 (35%)	11 (20%)	0 (0%)

* Administrative failures excluded

** greater than or equal to 70% reduction from baseline in PVCs

Mexiletine also reduced the frequency of couplets, ventricular tachycardia and R on T, as shown in Table 20. The degree of reduction from baseline exceeded 76% in the majority of patients.

Table 20

Percent Reduction from Baseline in Couplets, Ventricular Tachycardia and R on T after Treatment with Mexiletine in the 12-Week Double-Blind Studies

Percent Reduction from Baseline	Number of Patients		
	Couplets	Ventricular Tachycardia	R on T
Increased	56	34	27
0-25	11	4	6
26-50	14	8	4
51-75	32	10	12
76-100	193	169	153
Total*	311	225	202

* All patients with baseline and treatment Holter and with complex arrhythmia at baseline.

No clinically significant effects on mean blood pressure or pulse rate were noted. Mean EKG intervals showed little or no change after treatment with mexiletine alone or in combination with digitalis, diuretic or beta blocker therapy.

2. Uncontrolled Studies

a. Long Term Follow-Up

Study Design

The purpose of this ongoing open-label trial is to evaluate the efficacy and safety of mexiletine when administered for one year or longer. Participants were chosen from among those patients who had been successfully treated with mexiletine in the previously described placebo, procainamide, quinidine and disopyramide trials and the b.i.d. dosing study. If a patient had achieved adequate suppression of PVCs on mexiletine during the

double-blind, controlled portion of these studies and if, in the opinion of the investigator, he or she would benefit from continued mexiletine therapy, the patient was entered into the long-term study. Patients are seen monthly for recording of vital signs and evaluation of possible adverse reactions. Twenty-four hour Holter recording and 12-lead electrocardiogram are done every three months to assess response to therapy. At the discretion of the investigator, the dose of mexiletine may be adjusted as necessary to maintain suppression of the arrhythmia or to reduce the incidence of side effects. Patients who demonstrate continued suppression at the end of one year of treatment are allowed to remain on mexiletine and are seen for follow-up evaluation every three months.

The following cardiovascular diseases are represented among the patients participating in the long-term program:

<u>Diagnosis</u>	<u>Number of Patients</u>
Atherosclerotic heart disease	112
Idiopathic ventricular arrhythmia	70
Hypertensive heart disease	28
Other	43

Results

This is an ongoing study. The results presented here reflect data received as of 1 September 1983. A total of 197 patients have been treated by 40 investigators and 85 patients continue to receive treatment. Table 2³ presents the status of patients enrolled in the trial.

TABLE 21

Status of Patients Enrolled in
Long-Term Mexiletine Study

<u>Status</u>	<u>Number of Patients</u>
Total treated	197
In progress	85
Completed one year; no further treatment	54
<u>Lost, Dropped, Withdrawn</u>	48
Side effects	19
Lack of efficacy	6
Lost to follow-up	17
Protocol violation	5
Not reported	1
<u>Deaths During Treatment</u>	10
Cardiac	7
Non-cardiac	2
Cause not reported	1

The maximum duration of treatment reported as of 1 September 1983 was 57 months, with most patients (158) on mexiletine for two years or less. One hundred and six patients (including 61 of the 85 in progress) have continued beyond one year of treatment. The total daily dose of mexiletine has generally ranged from 600 to 1200 mg, as summarized below:

<u>Total Daily Dose (mg)</u>	<u>Number of Patients</u>
300	2
300-500	16
600-900	135
1000-1200	41
1500	
Reported	2

Twenty-four hour Holter recordings performed at 3-month intervals were analyzed on 100 patients previously treated in the trials comparing mexiletine with quinidine or disopyramide. Over 1 year of treatment, mexiletine consistently produced a median reduction of 87% or greater in hourly PVC frequency (Table 22).

TABLE 22

Median Hourly PVC Rate and Median Percent Reduction
from Baseline by Month of Treatment

<u>Month</u>	<u>Number of Patients</u>	<u>Median Rate</u>	<u>Median % Reduction</u>
Baseline	108	249.44	
3	106	14.04	-90.80
6	97	29.45	-92.80
9	84	18.50	-92.39
12	72	26.58	-87.25

A median reduction of 99-100% was observed in couplet frequency. Ventricular tachycardia and R on T were consistently reduced by a median of 100% (Table 23).

TABLE 23

Couplets, Ventricular Tachycardia and R on T:
Median Hourly Rate and Median Percent Reduction from
Baseline by Month of Treatment

	<u>Month</u>	<u>Number of Patients*</u>	<u>Median Rate</u>	<u>Median % Reduction</u>
<u>Couplets</u>	Baseline	107	1.37	
	3	104(97)	0.00	-100.00
	6	97(91)	0.04	- 99.43
	9	84(78)	0.00	- 99.97
	12	72(67)	0.04	- 99.40
<u>Ventricular Tachycardia</u>	Baseline	107	0.02	
	3	104(63)	0.00	-100.00
	6	97(58)	0.00	-100.00
	9	84(49)	0.00	-100.00
	12	72(42)	0.00	-100.00
<u>R on T</u>	Baseline	106	0.17	
	3	103(71)	0.00	-100.00
	6	97(67)	0.00	-100.00
	9	84(55)	0.00	-100.00
	12	72(46)	0.00	-100.00

* Numbers in parentheses indicate number of patients used to calculate median % reduction.

The most frequently reported adverse reactions have been upper gastrointestinal distress, lightheadedness and tremor. In 19 of 197 patients (10%), adverse reactions have necessitated discontinuation of treatment.

A variety of concomitant medications have been administered during the long-term follow-up, as listed below

<u>Type of Concomitant Medication</u>	<u>Number of Patients</u>
Antianginals	68
Antiarrhythmics	8
Anticoagulants	10
Antihypertensives	61
Betablockers	13
Cardiotonics	45
Diuretics	70
Potassium supplements	33
Miscellaneous	99

Twelve-lead electrocardiogram analysis has revealed no statistically significant changes from baseline in mean PR interval or QRS duration, regardless of whether patients were receiving mexiletine alone or in combination with other medications.

b. Emergency Mexiletine Program

Study Design

This open-label trial has allowed patients with ventricular arrhythmias to be treated with mexiletine under a compassionate use protocol. Only patients whose arrhythmias, by history, have been said to be refractory to conventional therapy, or who have been unable to tolerate such therapy because of side effects, or in whom such therapy is contraindicated, have been enrolled in the program. As of 1 August 1984, a total of 9353 patients have been treated in the emergency program since its initiation in 1977. The most common cardiovascular diseases among these patients are listed below:

<u>Diagnosis</u>	<u>Number of Patients</u>
Atherosclerotic heart disease	5663
Hypertensive heart disease	1172
Primary myocardial disease	1006
Rheumatic heart disease	307

The following table stratifies patients according to the indication for treatment. The majority (78%) of patients were admitted with refractory ventricular tachycardia or ventricular fibrillation.

<u>Indication</u>	<u>Number of Patients</u>
Ventricular tachycardia	6768
PVCs	1459
Ventricular fibrillation	494
Couplets	176
Other	151
Not reported	305

The protocol requires that patients be seen for follow-up every three months during the first year of treatment and every six months thereafter. Case report forms are submitted to Boehringer Ingelheim Ltd. at these intervals.

Results

Table 24 presents the status of patients treated under the compassionate use protocol as of 1 August 1984.

TABLE 24

Status of Patients Enrolled Since 1977
in Emergency Mexiletine Program

<u>Status</u>	<u>Number of Patients</u>
Total enrolled	9353
In progress	4316 (46%)
<u>Lost, Dropped, Withdrawn</u>	3832 (41%)
Lack of efficacy	1422
Adverse events	1421
Discontinued by patient	147
Need for therapy re-evaluated	127
Switched to another drug (no reason given)	65
Lost to follow-up	115
Discontinued despite good response	12
Other	247
Not reported	276
<u>Death During Treatment</u>	1205 (13%)
Cardiac	853
Non-cardiac	190
Cause not reported	162

Patients have received mexiletine in total daily doses ranging from 50 mg to 3200 mg. The most frequently reported total daily doses have been between 300 and 900 mg, as summarized below:

<u>Total Daily Dose (mg)</u>	<u>Number of Patients</u>
50-250	207
300-550	2186
600-850	4635
900-1100	1378
1200-1600	747
1650-3200	15
Not Reported	185

The maximum duration of treatment has been 78 months, with the majority of patients (8413) on mexiletine therapy for two years or less. Experience with mexiletine under the emergency protocol comprises a total of 6,295 patient-years of treatment. As has been observed in other trials, the most frequently encountered side effects with mexiletine have been upper gastrointestinal distress and central nervous system symptoms of lightheadedness and tremor.

The emergency protocol does not require investigators to submit Holter records to Boehringer Ingelheim Ltd. Instead, investigators are asked to provide on the case report form a global clinical assessment of the patient's response to treatment: improved, no change, worsened. For this reason, it is not possible to evaluate rigorously the degree of arrhythmia control seen overall in the emergency program. However, the results of mexiletine therapy in the Emergency Program have been analyzed further in some centers and these results are presented below.

PES Testing on Mexiletine Therapy

One hundred and forty-eight patients have been evaluated with programmed electrophysiologic stimulation (PES) while on mexiletine therapy by Dr. J. Ruskin and coworkers (mexiletine NDA). Patients had a history of recurrent sustained ventricular tachycardia (56 patients), symptomatic nonsustained VT (21), primary ventricular fibrillation (41) and complex ventricular ectopy (9). Eleven patients had a history of recurrent syncope without documented arrhythmia.

On baseline electrophysiologic testing in the absence of antiarrhythmic therapy, ventricular tachyarrhythmias were inducible in all patients - sustained VT (97 patients), nonsustained VT (43), ventricular fibrillation (8).

i. Acute PES Testing

One hundred and eighteen of the 148 patients underwent PES testing on mexiletine alone (see diagram below); 37 (Group I) of these 118 patients had no further testing, while 81 (Group II) subsequently had serial PES testing with mexiletine combined with another previously ineffective antiarrhythmic agent. The remaining 30 (Group III) patients were tested only on combination therapy. The drugs used in combination with mexiletine and the number of patients receiving each combination are listed below.

<u>Drug</u>	<u>Number of Patients</u>
Quinidine	46
Procainamide	38
Propranolol	5
Disopyramide	4
Amiodarone	4
Metoprolol	2
Nadolol	1
Lorcairide	1
Quinidine + propranolol	5
Procainamide + propranolol	3
Quinidine + metoprolol	1
Procainamide + atenolol	1

During PES testing, fifty-three of the 148 patients (36%) achieved complete suppression of the inducible arrhythmia and 19 (13%) had partial suppression with either mexiletine alone or combined with another drug. On mexiletine alone, 19% achieved complete suppression.

Nineteen of 118 patients (16%) during PES testing on mexiletine alone had exacerbation of arrhythmia, i.e., the arrhythmia was inducible with lesser grades of ventricular stimulation as compared to baseline. The investigators noted that this incidence of facilitation of arrhythmia induction is comparable to that seen with other antiarrhythmic agents they have tested.

Patients whose presenting arrhythmia was sustained VT were generally less responsive to treatment (success rate of 24%) as compared to patients presenting with ventricular fibrillation or nonsustained VT (success rates of 51 & 52%, respectively). This difference was statistically significant, p less than 0.01.

Baseline Electrophysiologic Testing
(no antiarrhythmic therapy)
n = 148

Electrophysiologic Testing Mexiletine alone n=118		Electrophysiologic Testing Mexiletine and 2nd agent n=111		
Group I n=37	Group II n=81	Group II n=81	and	Group III n=30
CS - 22	CS - 1			CS - 31
PS - 3	PS - 15			PS - 16
NC - 9	NC - 47			NC - 43
E - 3	E - 16			E - 21
	NA - 2			

Key: CS-complete suppression of inducible VT, PS-partial suppression, NC-no change, E-exacerbation, NA- not available

ii. Long-Term Follow-Up on Mexiletine Therapy Following PES Evaluation

Eighty-nine patients were discharged on long-term therapy with the treatment regimen that provided optimum arrhythmia control (24 on mexiletine alone, 65 on combination therapy) and followed for a mean of 14 months (maximum 58 months). Eight patients were discontinued and 23 required a reduction in dosage because of side effects. Fifteen patients died: the causes of death were sudden death in 8 patients, refractory heart failure in 5, and myocardial infarction in 2 patients. Three patients had non-fatal recurrence of ventricular tachycardia.

Thus, of the 89 patients who were discharged on mexiletine alone or in combination with another drug, 63 (71%) remained free of recurrence of ventricular arrhythmias.

Ambulatory ECG Monitoring with Exercise Testing on Mexiletine Therapy

Podrid and Lown (1981) evaluated the efficacy of mexiletine after acute administration and after short and long-term maintenance therapy. A total of 108 patients with chronic, symptomatic ventricular arrhythmias were treated. Twenty-five patients had a history of ventricular premature beats (VPBs); 25 had a history of one or more episodes of ventricular fibrillation; 58 patients had a history of spontaneous ventricular tachycardia. Of the 58 patients with spontaneous VT, in 24 VT was sustained, associated with syncope and required cardioversion or lidocaine therapy; among the other 34 patients, VT was associated with dizziness in all and was sustained in 11. Seventy-two patients had been refractory to conventional antiarrhythmic therapy and, in many cases, to investigational agents as well.

During Phase 1 (acute drug testing), suppression was defined as (1) greater than 50% decrease in frequency of VPBs and total elimination of couplets and VT at rest, and (2) greater than 50% decrease in frequency of VPBs and greater than 90% decrease in couplets and VT during exercise testing. The response was considered partial if only one of the above criteria was met or if couplets and VT were reduced by 50-90%, but not totally eliminated.

During Phases 2 (short-term therapy), and 3 (long-term maintenance therapy), a response was considered successful if all of the following criteria were met:

1) 24-hour ambulatory monitoring: greater than or equal to 50% reduction in frequency of VPBs; greater than or equal to 50% reduction in number of hours showing multiform VPBs or greater than 30 VPBs/hour; and elimination of VT and greater than 90% reduction in couplets.

2) Exercise testing: greater than 50% decrease in number of VPBs occurring during exercise and recovery period; greater than 50% decrease in peak rate of VPBs/minute observed throughout exercise and recovery period; total elimination of VT and multiform ectopic beats and greater than 90% reduction in couplets throughout exercise.

The response was considered partial if the criteria were met for only one method of testing.

Phase 1: Eighty-eight patients underwent acute testing with a single 400 mg dose of mexiletine. Suppression of arrhythmia was seen in 57/88 patients (65%) evaluated at rest. Fifty-five of the 88 patients were also evaluated during exercise; arrhythmia was suppressed in 37 (67%) of these 55 patients. In the 55 patients evaluated both at rest and during exercise, suppression was achieved in 32 patients (58%); a partial response was seen in 5 patients (9%).

Phase 2: Seventy-nine patients (59 from Phase 1 plus 20 additional patients) completed a 48 to 72 hour period of multiple dosing with mexiletine (900-1200 mg/day). Patients were evaluated after 24 hours (at which point the dose could be increased if the arrhythmia persisted) and again during the final 24 hours of Phase 2. One patient did not undergo remonitoring because he had ventricular tachycardia with exercise while receiving mexiletine. The other 78 patients had repeat evaluation by 24-hour ambulatory monitoring. Fifty-one of these 78 patients demonstrated a good response to treatment; the hourly frequency of ventricular premature beats (VPBs) was reduced from a control value of 357 ± 58 to 61 ± 18 (p less than 0.001). Sixty-five patients also underwent repeat exercise testing. Forty-three (66%) of these 65 patients had a good response, with a reduction in the hourly frequency of VPBs from a mean of 204 ± 34 to 30 ± 10 (p less than 0.001). Thirty-nine of the 65 patients who underwent both ambulatory monitoring and exercise testing met the criteria for drug efficacy with both methods of evaluation.

Phase 3: Forty-four patients who had responded to mexiletine during Phases 1 and 2 were continued on long-term maintenance therapy. Seven patients were discontinued because of adverse reactions. Six patients who were receiving concomitant antiarrhythmic therapy with quinidine or aprindine were not included in the analysis. Thirty-one patients, therefore, have been maintained on mexiletine as their only antiarrhythmic therapy for 8 to 32 months (mean 17.6 months) and have demonstrated continued suppression on ambulatory monitoring and exercise testing.

Summary

The data available from the long-term follow-up studies and the Emergency Program indicate that mexiletine continues to be effective when administered for periods ranging from several months to several years. In the long-term follow-up studies, mexiletine produced a median suppression of greater than 87% in PVCs over a 12-month period, a median reduction in couplets of 99-100% and a median suppression of 100% in ventricular tachycardia and R on T. The results of electrophysiologic efficacy testing in 148 patients are available from one center in the Emergency Program. Out of 148 patients initially evaluated with electrophysiologic testing, 89 patients were discharged on mexiletine (24 mexiletine alone, 65 combination therapy) and followed for a mean of 14 months. Sixty-three patients were maintained on mexiletine therapy; 8 patients were discontinued because of side effects; 15 patients died; and 3 had non-fatal recurrence of VT. (Ruskin, Mexiletine NDA). In a second center, following efficacy evaluation with 24-hour Holter recording and acute exercise testing, 38 patients were started on maintenance therapy with mexiletine alone and followed for a mean of 17.6 months; 31 patients had continued control of their arrhythmias while 7 patients were discontinued because of side effects (Podrid and Lown, 1981).

C. SAFETY OF MEXILETINE

The clinical safety of mexiletine has been evaluated in a total of 9828 patients treated as of August 1984. Of these, 475 patients were most closely followed, receiving mexiletine in controlled, double-blind trials against placebo, procainamide, quinidine or disopyramide; 197 of these patients continued mexiletine therapy in an open-label extension of the controlled studies (Long-Term Follow-Up Study) and have been followed for periods up to five years. In the emergency mexiletine program, an open-label, compassionate-use cohort survey, 9353 patients have been followed on mexiletine therapy for periods up to six and a half years.

The most common adverse events and effects on laboratory measurements can best be evaluated by data from the controlled trials. Safety data from the emergency use program can aid in predicting rare events, but must be used with the understanding that the severity of patients' underlying disease and frequent use of multiple concurrent medications may confound the contribution of mexiletine to the reported events and that reporting of events, especially non-serious events, is likely to be much less complete than in a controlled trial or formal open study.

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The sponsor has provided data on adverse events, causes of discontinuation of therapy, deaths and laboratory findings in the controlled trials and in their long-term follow-up and in the emergency use program. In addition, the pro-arrhythmic potential of mexiletine, reports of mortality findings in post-infarction secondary trials (not conducted by the sponsor), and abnormal hepatic and hematologic laboratory findings are discussed.

1. Adverse Events in U.S. Controlled Studies

a. Mexiletine vs. Placebo

Mexiletine and placebo were compared in 53 patients in a double-blind, crossover trial with four-week treatment periods. The initial dose of mexiletine was 100 mg q8h, titrated to efficacy or to a maximum of 400 mg q8h. The highest dose level reached was 100 mg in 7 patients, 200 mg in 12 patients, 300 mg in 16 patients and 400 mg in 18 patients. Adverse events, as shown below, were reported by 35/53 patients (66%) while on mexiletine and by 30/49 patients (61%) while on placebo.

Upper GI distress, lightheadedness, tremor and coordination difficulties were observed more frequently during mexiletine therapy than during placebo administration. Changes in sleep habits, which included insomnia and drowsiness, were seen three times more frequently during placebo therapy, suggesting that a relationship to mexiletine is unlikely.

Three patients discontinued mexiletine because of adverse events probably related to the drug: two patients had upper GI distress; the other had a 13-beat run of ventricular tachycardia with dizziness and was hospitalized.

Comparative Incidence (%) of Adverse Events Among Patients
Treated with Mexiletine and Placebo in the
4-Week, Double-Blind, Crossover Trial

	Mexiletine N = 53	Placebo N = 49
<u>Cardiovascular</u>		
Palpitations	7.5	10.2
Chest Pain	7.5	4.1
Increased Ventricular Arrhythmia/PVCs*	1.9	-
<u>Digestive</u>		
Nausea/Vomiting/Heartburn	39.6	6.1
<u>CNS</u>		
Dizziness/Lightheadedness	26.4	14.3
Tremor	13.2	-
Nervousness/Agitation	11.3	6.1
Coordination Difficulties	9.4	-
Changes in Sleep Habits	7.5	16.3
Paresthesias	3.8	2.0
Weakness	1.9	4.1
Fatigue	1.9	2.0
Tinnitus	1.9	4.1
Confusion/Clouded Sensorium	1.9	2.0
<u>Other</u>		
Headache	7.5	6.1
Blurred vision/Visual disturbances	7.5	2.0
Respiratory	5.7	10.2
Rash	3.8	2.0
Non-Specific Edema	3.8	-
Arthralgia	1.9	10.2
Diaphoresis	1.9	2.0
Pharyngitis	1.9	-
Nasal Stuffiness	1.9	-
Shoulder Pain	1.9	-
Chills	1.9	-

* The term "increased ventricular arrhythmias/PVCs" includes any increase in ventricular arrhythmia reported as an adverse event by the investigator. The standard for identifying such events was at the discretion of the investigator.

b. Mexiletine vs. Procainamide, Quinidine and Disopyramide

In three separate trials, mexiletine was compared to procainamide, quinidine and disopyramide in a double-blind, parallel-group design. Four hundred twenty-two patients were treated with mexiletine for a 12-week period. The initial dose of mexiletine was 200 mg t.i.d., titrated to efficacy or to a maximum of 400 mg t.i.d. The highest mexiletine dose level reached was 200 mg in 193 patients, 300 mg in 120 patients, and 400 mg in 109 patients. Adverse events were reported by 287 patients (68%); the type and frequency of events are presented below.

Comparative Incidence (%) of Adverse Events Among Patients Treated
With Mexiletine or Control Drugs in the 12-Week, Double-Blind Trials

	Mexiletine N = 422	Quinidine N = 262	Procainamide N = 78	Disopyramide N = 69
<u>Cardiovascular</u>				
Palpitations	4.3	4.6	1.3	5.8
Chest Pain	2.6	3.4	1.3	2.9
Angina/Angina-like Pain	1.7	1.9	2.6	2.9
Increased Ventricular Arrhythmias/PVCs*	1.0	2.7	2.6	-
<u>Digestive</u>				
Nausea/Vomiting/Heartburn	41.0	21.4	33.3	14.5
Diarrhea	5.0	33.2	2.6	8.7
Constipation	4.3	-	6.4	11.6
Changes in Appetite	2.8	1.9	-	-
Abdominal Pain/Cramps/ Discomfort	1.2	1.5	-	1.4
<u>Central Nervous System</u>				
Dizziness/Lightheadedness	18.5	14.1	14.1	2.9
Tremor	12.6	2.3	3.8	1.4
Coordination Difficulties	10.2	1.1	1.3	-
Changes in Sleep Habits	6.9	2.7	11.5	8.7
Weakness	5.0	5.3	7.7	2.9
Nervousness/Agitation	4.5	1.9	6.4	5.8
Fatigue	3.8	5.7	5.1	1.4
Speech Difficulties	2.6	0.4	-	-
Paresthesias/Numbness	2.4	2.3	2.6	-
Tinnitus	2.4	1.5	-	-
Depression	2.4	1.1	1.3	1.4
Confusion/Clouded Sensorium	1.9	-	3.8	-
<u>Other</u>				
Blurred Vision/Visual Disturbances	5.5	3.1	5.1	7.2
Headache	4.5	6.9	7.7	4.3
Rash	4.2	3.8	10.3	1.4
Respiratory	2.8	3.1	5.1	2.9
Dry Mouth	2.8	1.9	5.1	14.5
Arthralgia	1.7	2.3	5.1	1.4
Fever	1.2	3.1	2.6	-

Less than 1%: Arrhythmia, syncope, edema, hot flashes, hypertension, short-term memory loss, loss of consciousness, other psychological changes, diaphoresis, urinary problems, malaise, impotence/decreased libido, pharyngitis.

* The term "increased ventricular arrhythmias/PVCs" includes any increase in ventricular arrhythmia reported as an adverse event by the investigator. The standard for identifying such events was at the discretion of the investigator.

These three-month double-blind parallel trials confirmed the adverse event pattern seen in the four-week placebo crossover: upper GI distress and central nervous system side effects predominated, and were the major treatment-limiting events. Nausea, vomiting and other forms of upper GI distress caused 20% of patients in the 12-week studies to discontinue mexiletine. Dizziness (6%), lightheadedness (4%) and tremor (2%) were the other events most frequently cited as reason for discontinuation.

Three patients (less than 1%) discontinued mexiletine because of syncope; two withdrew because of chest pain. There was one discontinuation each because of tachycardia and dyspnea. In addition, one patient withdrew when hospitalized for a myocardial infarction two days after study entry.

Additionally, 57 patients (14%) had mexiletine discontinued before completion of 12 weeks of therapy because of inadequate suppression of ventricular arrhythmia (less than 70% reduction in PVCs).

c. Long-term Continuation after Controlled Trials

One-hundred ninety-seven patients who responded to mexiletine in controlled trials continued therapy in the Long-Term Follow-Up Study. Most patients were followed for 2-3 years (range 1 month to 5 years) on total daily doses from less than 300 to 1200 mg of mexiletine. Not surprisingly, since these patients all tolerated mexiletine well enough to complete the 12-week study, they had a lower frequency of adverse effects and were relatively unlikely to leave the study because of an adverse event.

Incidence (%) of Adverse Events Among 197 Patients Treated With
Mexiletine during Long-Term Follow-Up to Controlled Trials

<u>Long-Term Follow-Up</u>	
<u>Cardiovascular</u>	<u>(%)</u>
Chest Pain	3
Angina/angina-like pain	3
Increased Ventricular Arrhythmias/PVCs*	1
Palpitations	1
Syncope	1
CVA	1
 <u>Digestive</u>	
Nausea/Vomiting/Heartburn	29
Changes in Appetite	2
Constipation	2
Diarrhea	2
 <u>Central Nervous System</u>	
Dizziness/Lightheadedness	10
Tremor	5
Changes in Sleep Habits	4
Fatigue	3
Nervousness/Agitation	3
Coordination Difficulties	3
Weakness	3
Tinnitus	3
Depression	2
Speech Difficulties	2
Confusion/Clouded Sensorium	2
Paresthesias/Numbness	2
Short-Term Memory Loss	2
Other Psychological Changes	1
 <u>Other</u>	
Respiratory	4
Headache	3
Impotence/Decreased Libido	2
Arthralgia	2
Dry mouth	2
Blurred Vision/Visual Disturbances	2
Hair Loss	1
Diaphoresis	1
Rash	1

Less than 1%: Congestive heart failure, conjunctivitis.

* The term "increased ventricular arrhythmias/PVCs" includes any increase in ventricular arrhythmia reported as an adverse event by the investigator. The standard for identifying such events was at the discretion of the investigator.

Approximately 10% of the patients withdrew from the follow-up program because of adverse events (some patients had more than one adverse effect at time of discontinuation):

<u>Treatment-limiting Events</u>	<u>No. (%) of Patients</u>	
Nausea/Vomiting/Heartburn	9	(5)
Dizziness/Lightheadedness	3	(2)
Tremor	2	(1)
Fatigue	2	(1)
Coordination Difficulties	2	(1)
Other CNS Effects	2	(1)

Thus, during the follow-up period, the predominance of upper GI and CNS adverse events was similar to experience in the controlled phase of mexiletine studies, but the overall incidence was lower, as expected. The long-term tolerability observed during this period suggests that new adverse events occur less frequently during chronic, stable-dose mexiletine therapy.

2. Adverse Events in the Mexiletine Emergency-Use Program

In addition to the adverse event data for the 475 patients treated in the controlled trials, safety data is available for 9353 patients treated in the emergency-use program. Admission to this program was restricted to patients with clinically significant ventricular arrhythmias who could not be treated with other antiarrhythmic agents because of treatment failure or intolerance. These patients were seriously ill; multiple cardiovascular problems and multiple concurrent medications were common. Treatment was continued for more than one year for over 2000 patients; approximately 900 patients were continued on mexiletine treatment for more than two years and some for over six years.

Although the frequency of adverse events was lower than reported in the controlled trials, the pattern was similar with upper GI and CNS effects most frequently reported. Adverse reactions (also predominantly upper GI distress and CNS effects) led to discontinuation of therapy in 15% of patients (treatment was limited by more than one adverse event in some patients).

<u>Treatment-limiting Events</u>	<u>(%) of 9353 Patients</u>
Nausea/Vomiting/Heartburn	9
Tremor	2
Dizziness/Lightheadedness	2
Coordination Difficulties, Fatigue, Weakness, Confusion, Changes in Appetite	each 1

Incidence (%) of Adverse Events Among 9353 Patients Treated
With Mexiletine in the Emergency Use Program

	<u>Emergency Mexiletine</u> <u>(% of 9353 Patients)</u>
<u>Cardiovascular</u>	
Increased Ventricular Arrhythmias/PVCs*	1
Congestive Heart Failure	1
<u>Digestive</u>	
Nausea/Vomiting/Heartburn	22
Abdominal Pain/Cramps/Discomfort	2
Changes in Appetite	2
Constipation	1
Diarrhea	1
<u>Central Nervous System</u>	
Dizziness/Lightheadedness	8
Tremor	7
Changes in Sleep Habits	2
Fatigue	2
Nervousness/Agitation	1
Coordination Difficulties	2
Weakness	2
Depression	1
Confusion/Clouded Sensorium	2
Paresthesias/Numbness	2
<u>Other</u>	
Rash	2
Blurred Vision/Visual Disturbances	2
Dyspnea	1
Headache	1

Less than 1%:

Cardiovascular: Palpitations, hypotension, chest pain, syncope, bradycardia, angina/angina-like pain, edema, hot flashes, atrioventricular block/conduction disturbances hypertension, atrial arrhythmias.

Central Nervous System Changes: Short-term memory loss, speech difficulties, tinnitus, other psychological changes, mild CNS effects, hallucinations, seizures, psychosis, loss of consciousness.

Gastrointestinal: Abdominal gas/bloating, dysphagia, upper gastrointestinal inflammation, peptic ulcer, upper gastrointestinal bleeding, esophageal ulceration.

Other: Altered taste, arthralgia, diaphoresis, dry mouth, abnormal liver function tests, impotence/decreased libido, malaise, hair loss, urinary hesitancy/retention, respiratory, positive ANA, hematologic (thrombocytopenia, leukopenia/neutropenia, agranulocytosis, anemia), hiccups, dry skin, fever, weight gain, arthritis, nasal stuffiness.

* The term "increased ventricular arrhythmias/PVCs" includes any increase in ventricular arrhythmia reported as an adverse event by the investigator. The standard for identifying such events was at the discretion of the investigator.

3. Laboratory measurements during mexiletine therapy

Laboratory testing to evaluate safety during the U.S. clinical program included complete blood counts (hematocrit, hemoglobin, leukocyte count and differential and platelet count), blood chemistry (SGOT, LDH, alkaline phosphatase, blood urea nitrogen, creatinine, albumin, globulin, sodium, potassium, chloride, calcium, phosphorus, cholesterol, antinuclear antibody and bilirubin) and urinalysis. During the controlled trials, evaluations were done at baseline and at 2-4 week intervals. Baseline testing was repeated at three month intervals during the first year of treatment and every six months thereafter in the long-term follow-up and emergency use programs.

a. Controlled studies (475 patients) and Long-term follow-up (197 patients)

Only one patient was discontinued during a controlled study because of an abnormal laboratory finding (monocytosis). This patient had an elevated baseline value (12%) which rose to 14% during treatment. No patient was discontinued during the follow-up phase because of laboratory abnormality.

Ten patients had SGOT elevations during the controlled trials. These findings are included in the discussion of hepatic function below.

Otherwise, laboratory measurements in the controlled studies and long-term follow-up were unremarkable.

b. Mexiletine Emergency Use Program (9353 Patients)

Evaluation of laboratory results in the mexiletine emergency use program is made difficult by the severely compromised clinical status of many patients, the frequent use of concurrent medications that can cause laboratory changes (e.g., procainamide-associated positive ANA titers, anemia and leukopenia) and the lack of pre-mexiletine baseline values for many patients. Clinically significant laboratory abnormalities during mexiletine therapy are discussed in detail below (see 5c and d).

However, the overall pattern of laboratory abnormalities is consistent with the findings in the controlled studies and long-term follow-up in that an abnormal laboratory measurement was only rarely a factor in the decision to discontinue mexiletine therapy in the emergency use program (33 of 9353 patients; 0.4%):

<u>Treatment-limiting Laboratory Findings</u>	<u>No. (%) of Patients</u>
Abnormal liver function tests	13 (0.14%)
Thrombocytopenia	4 (0.04)
Abnormal BUN, NPN or creatinine	3 (0.03)
Positive ANA	3 (0.03)
Agranulocytosis/neutropenia/leukopenia	3 (0.03)
Anemia	2 (0.02)
Other abnormalities	2 (0.02)
Thrombocytosis	1 (0.01)

Liver function abnormalities are discussed in detail in the section on hepatic function below (5c).

Anemia was associated with GI bleeding in one of the discontinued patients and with concurrent use of sustained release procainamide in the other.

In addition to the three patients who discontinued mexiletine for reductions in white blood cell count, nine other cases of WBC reduction were discovered during emergency-use mexiletine therapy, including two fatal agranulocytoses in patients taking mexiletine concurrently with procainamide. These events are discussed in detail under 5d below.

Thrombocytopenia is discussed in detail in 5d below. One patient, whose platelet count was "high" at baseline, had a platelet count of 628,000/mm³ during treatment.

4. Death During Mexiletine Therapy

a. Deaths in Controlled Trials

No deaths occurred among 53 patients during the placebo-controlled trial.

A total of 831 patients with premature ventricular contractions were entered into four 12-week trials comparing mexiletine (422 patients) to procainamide, quinidine or disopyramide (409 patients overall).

N18-873 3 of 3

At baseline, 307 mexiletine-treated and 293 control patients had a history of cardiac disease, primarily arteriosclerotic heart disease. As shown below, three patients (0.7%) died during mexiletine treatment and nine patients (2.2%) died on the control agents.

Deaths on Mexiletine and Control Drugs In
Twelve-Week Double-Blind Trials

<u>Trial (No. of Patients)</u>	<u>Mexiletine</u>		<u>Control Drug</u>	
	<u>Cause of Death</u>	<u>No. of Patients</u>	<u>Cause of Death</u>	<u>No. of Patients</u>
<u>Mex. vs. procainamide</u> (N=80) (N=78)	Acute MI	1	Acute MI Cardiac Arr.	1 1
<u>Mex. vs. quin.(A)</u> (N=150) (N=148)	Vent.Tach.	1	Vent.Fib. ASHD Sudden Death	1 1 2
<u>Mex. vs. Quin.(B)</u> (N=118) (N=114)	Sudden Death	1	Sudden Death Acute MI	2 1
<u>Mex. vs. disopyramide</u> (N=74) (N=69)	--	<u>0</u>	--	<u>0</u>
Total No. Deaths		3		9
Total No. Patients		422		409
% of Patients Treated		0.7%		2.2%

b. Deaths in the Long-Term Follow-Up Study

Ten of 197 patients (5%) died during treatment with mexiletine in the Long-Term Follow up study. The mean duration of treatment was 12.5 months and the mean daily dose 840 mg. Eight of the ten were receiving concomitant digitalis and/or diuretic therapy.

As would be expected in a patient population with a high incidence of underlying cardiac disease, primarily ASHD, the causes of death were cardiovascular:

<u>Cause</u>	<u>No. of patients</u>
Myocardial infarction	3
Sudden death	2
Vent. tach./fib.	1
Pulmonary Thromboemboli	1
Severe heart failure/coronary artery disease	1
Ruptured basilar artery aneurysm	1
Not obtainable	1

The frequency of possibly arrhythmic deaths (VT/VF, sudden death), 3/197 or about 1.5% of the patients treated for one year or more, does not appear greater than expected for a study group of this type.

c. Deaths in the Mexiletine Emergency Use Program

The emergency-use mexiletine program was restricted to patients in urgent need of antiarrhythmic therapy, in whom other available drugs were ineffective or not tolerated. The most frequent entry arrhythmia (72%: 6780 patients of the 9353 patients treated up to August 1984) was refractory ventricular tachycardia. Approximately 40% of patients had some degree of congestive heart failure at entry; over 60% had ASHD. In 2006 patients (21%), mexiletine treatment was initiated for ventricular arrhythmia in the acute phase of myocardial infarction.

Death occurred during treatment in 1205 patients (13%). As would be expected in this group of patients, cardiac events were the predominant cause of death (70% of patients):

<u>Cause of death</u>	<u>Number of Patients</u>
Sudden death	235
Congestive heart failure	331
Vent. tach./fibrillation	210
Other cardiac	77
Non-cardiac	190
Not obtainable	162

The duration of treatment (based on 1042 deaths where treatment was precisely known) was as follows:

<u>Months of therapy</u>	<u>Proportion of patients</u>
1	23%
1-6	44%
7-12	15%
112	19%

Historical data on syncope, cardiac arrest and arrhythmias prior to initiation of mexiletine therapy were obtained in 952 of the 1205 patients who died. Previous syncope and/or cardiac arrest had occurred in 383 of these patients (40%), while ventricular tachycardia had occurred in 754 (79%) and ventricular fibrillation in 186 patients (20%). The entry history of ventricular tachycardia in the patients who died differs only slightly from the whole emergency use cohort (79% vs. 72%); however, an entry history of ventricular fibrillation is markedly more frequent (20%) in patients who died during treatment than in the overall group (5%).

At the time of death, 905 of the 1205 patients (75%) were taking digitalis or diuretics; congestive heart failure was the stated cause of 28% of the deaths.

The high incidence of previous ventricular fibrillation, congestive heart failure and digitalis/diuretic use illustrates the severity of underlying cardiovascular disease in the patients who died during mexiletine treatment.

5. Special Issues

a. Prophylactic Administration of Mexiletine in Post-Infarction Secondary Prevention Trials

A number of studies of antiarrhythmic agents have investigated the value of prophylactic antiarrhythmic therapy in reducing mortality following myocardial infarction. To date, no trial of any non-beta-blocker antiarrhythmic agent, including mexiletine, has shown a statistically significant difference in mortality between active treatment and placebo. Trends favoring placebo have been observed as well as trends favoring active treatment.

All of these trials, including those employing mexiletine, have substantial design flaws. Most importantly, none of the trials have been large enough to make a valid assessment of mortality as an endpoint. In addition, since the principal entrance criterion in these trials has been acute myocardial infarction, rather than the presence of frequent or serious ventricular arrhythmia, substantial numbers of patients did not have ventricular arrhythmias at baseline. Patients were treated with fixed dosage and administration schedules. The table below compares the mortality experience in mexiletine- and placebo-treated patients in the four post-infarction trials reported to date.

Mortality (Deaths/Total Treated)

<u>Trial</u>	<u>Time Post-MI to Initiation of Therapy</u>	<u>Mexiletine</u>	<u>Placebo</u>
Bell et al	36 hours $\bar{p}$ onset of symptoms	12/103 (12%)	20/113 (18%)
Smyllie et al	12 hours $\bar{p}$ onset of symptoms	25/120 (19%)	32/120 (27%)
Chamberlain et al	6 - 14 days	24/181 (13%)	19/163 (12%)
IMPACT	3 - 25 days	24/317 (8%)	15/313 (5%)

These are total mortality rates, and include death from all causes.

By comparison, in the mexiletine 12-week double-blind trials, all-cause mortality was 0.7% for 422 mexiletine-treated patients (2.2% for control patients). In the emergency use program, all-cause mortality was 12.9%.

The prescribing information indicates that mexiletine should be used only for the treatment of symptomatic, documented ventricular arrhythmias, and that the dose should be carefully titrated to maximize efficacy and tolerance.

b. Arrhythmias

Development or exacerbation of ventricular arrhythmia during mexiletine treatment was reported by the investigator as an adverse event in four of 475 patients (0.8%) treated in the controlled studies, in two of 197 follow-up patients (1.0%) and 102 of 9353 emergency use patients (1.1%). In such cases, it is difficult to distinguish between failure of the drug to produce its intended effect, natural evolution of the arrhythmia or a possible proarrhythmic effect of mexiletine. Ventricular tachycardia was cited as a reason for discontinuation of therapy in two patients (0.4%) in the controlled studies and eight patients (0.08%) in the emergency use program. Six emergency use patients (0.06%) were discontinued for increased PVC's; five (0.05%) stopped mexiletine for unspecified worsened arrhythmias.

Most antiarrhythmic agents have been reported to have proarrhythmic properties (Velebit et al, Cir. 65: 886-894 1982). It is difficult to compare results in various series because definitions vary greatly and the likelihood of worsening undoubtedly depends on the underlying arrhythmias and heart disease. Velebit found that 11 of 144 patients (8%) tested for responsiveness to mexiletine by exercise Holter monitoring or programmed cardiac stimulation and exercise stress testing exhibited an aggravation of arrhythmia. Other agents gave results generally in the same range, but showed somewhat higher rates of worsening. Blood levels were at therapeutic concentrations for all agents tested. In Ruskin's series of patients evaluated with PES, 16% of patients given mexiletine alone had exacerbation of arrhythmia (Schoenfield, MH et al. Am. Heart J. 107(5):1072-1078, 1984).

Mexiletine certainly does not seem more likely than other agents to provoke worsened arrhythmias, but there is no adequate evidence yet that it is better.

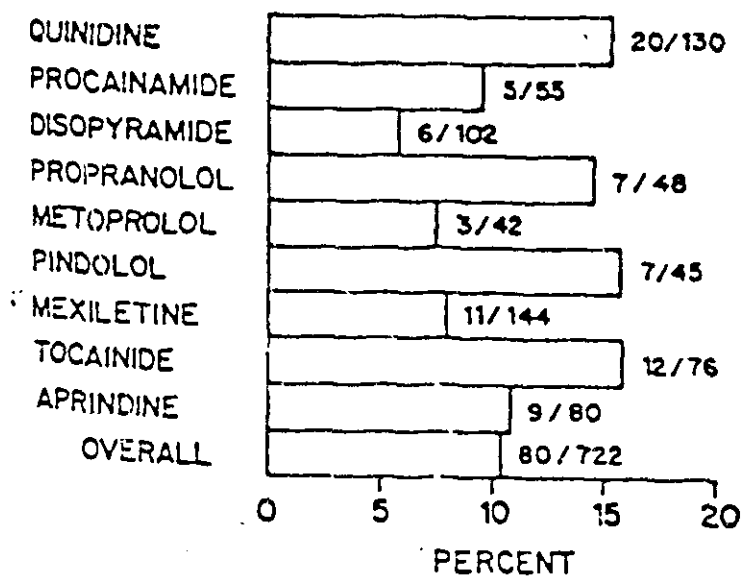
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FREQUENCY OF AGGRAVATION OF VENTRICULAR
ARRHYTHMIAS BY ANTIARRHYTHMIC AGENTS



(From Velebit et al., Circ. 65, No. 5, 1982)

c. Hepatic Function

i. U.S. Controlled Trials

In the placebo-controlled trial and also in the active-controlled trials, liver function observations for both the mexiletine and control groups were unremarkable.

Only one patient in the placebo controlled, crossover trial had an elevated treatment SGOT (64 U/L, upper limit of normal 40 U/L). This SGOT was observed in conjunction with an acute myocardial infarction after two weeks of mexiletine therapy. The highest bilirubin observed during either placebo or mexiletine therapy was 1.2 mg %.

In the active-controlled trials, which were three-month, double-blind, parallel and positively controlled studies, no patients on either mexiletine or control drugs (quinidine, disopyramide, procainamide) had therapy discontinued because of hepatic dysfunction. In these trials, out of a total of 292 patients on mexiletine and 281 on control drug (46 - disopyramide, 67 - procainamide, 158 - quinidine) who had a normal baseline SGOT and at least one treatment SGOT, 12.0% of the patients who received mexiletine and 17.4% of the patients who received control drugs had SGOTs of 48-119 U/L* during treatment.

In 1.0% of the mexiletine group and 1.1% of the control group, treatment SGOTs of 120 U/L or greater were observed. The highest treatment SGOT in the mexiletine group was 190 U/L (control group 293 U/L). Associated clinical events in the three patients on mexiletine with treatment SGOTs greater than 120 U/L were pulmonary embolism (1 patient), acute myocardial infarction (1), and congestive heart failure and a history of heavy alcohol use (1). In the majority of patients with elevated treatment SGOTs, the SGOT values returned to normal on continued therapy with mexiletine. Of the 38 patients on mexiletine and 52 on control drugs with treatment elevations, 57.9% and 59.6%, respectively, had last treatment observations less than 48 U/L.

Baseline SGOTs were elevated in 31 (9.6%) of the 323 patients in the mexiletine group with a baseline and at least one treatment SGOT observation and 19 (6.3%) of the 300 in the control drug group. That is, the mexiletine group had a higher proportion of elevated SGOTs at baseline, before starting mexiletine. The last observed treatment SGOT was less than 48 U/L in 15 (48.4%) of the 31 patients with elevated pretreatment SGOTs who received mexiletine and 12 (63.2%) of the 19 who received control drugs.

* The usual normal range for SGOT is 10-40 U/L. For this analysis, any value of 47 U/L or less was considered normal. Forty-seven U/L was chosen because it is one standard deviation above the upper limit of the normal range (40 U/L), assuming the normal range is plus or minus two standard deviations around the normal mean.

Thus, among patients in the positively controlled trials, the incidence, severity and chronological pattern of hepatic enzyme changes in the mexiletine groups were similar to those in the control drug groups. Hepatic enzyme elevations were transient on treatment in over half the patients in both groups. Bilirubin was only slightly elevated (maximum 1.4 mg %) in two of the patients on mexiletine with hepatic enzyme elevations. As shown by the high frequency of elevated pretreatment SGOTs, a considerable incidence of hepatic enzyme elevation occurs in this population regardless of which antiarrhythmic drug is used. The reduction of raised baseline SGOTs to normal while on mexiletine therapy that occurred in almost half the patients with pretreatment elevations suggests that mexiletine is well tolerated in these patients. Similarly, in three of the four patients with baseline SGOTs greater than 120 U/L, SGOTs were normal at the last treatment observation on mexiletine; and in the fourth, the SGOT was reduced from 172 U/L pretreatment to 144 U/L.

In the long-term follow-up to the controlled trials, out of 197 patients on mexiletine, none had hepatic dysfunction reported as an adverse event and no patients had therapy discontinued because of hepatic abnormalities. In 14 of these 197 patients the first elevation of SGOT on treatment was observed during the long-term follow-up period; in 11 of the 14, the SGOT elevations had declined to less than 48 U/L at the last treatment observation. SGOT elevations were also observed in 19 patients whose initial SGOT elevation occurred during the controlled portion of the trial. In 18 of these 19, SGOT elevations declined to less than 48 U/L at the last treatment observation.

Thus, during the long-term follow-up period, no symptomatic elevations in SGOT were observed. In almost all of the patients (88%) with elevated SGOTs during long-term mexiletine therapy, the elevations were transient.

ii. Emergency-Use Mexiletine Program

The Emergency-Use Mexiletine Program had no control group, so that elucidation of drug effect is confounded by the underlying disease states. In this Program, out of a total of 9353 patients enrolled by August 1984, there were 29 patients (0.3%) in whom elevated hepatic enzymes on treatment were identified by the investigators as a possible drug-related adverse event. Of these 29 patients, therapy was discontinued in 18 (0.2%) because of these hepatic enzyme changes.

Among 2365 patients enrolled in the Emergency Program by September 1983, in whom a normal baseline and at least one treatment SGOT measurement were recorded, there were 284 patients (12.0%) with at least one elevated treatment SGOT. In fifteen of these patients the changes had been identified by the investigators as being a possible drug-related adverse event; the other 269 were identified by the sponsor's screen of laboratory data. Out of these 284 patients, there were 232 (9.8%) with peak treatment elevations of SGOT of 48-119 U/L and 52 (2.2%) with peak treatment elevations of 120 U/L or greater.

Raised treatment SGOTs declined, while on mexiletine therapy, to less than 48 U/L at the last treatment observation in 134 (57.8%) of the 232 patients with peak treatment values of 48-119 U/L, and 21 (40.4%) of the 52 with peak treatment values of 120 U/L or greater. Thus, treatment elevations of SGOT were transient in more than half (54.5%) of the 284 patients.

Baseline SGOTs, before mexiletine therapy, were elevated in 10.2% of the patients with baseline and treatment SGOT measurements enrolled by September 1983. While on mexiletine therapy, SGOT levels declined to normal at the last treatment observation in over half these patients (76.1%). This normalization of previously elevated SGOT values, while on mexiletine therapy, is consistent with the results from the controlled trials. It suggests again that mexiletine is well tolerated in these patients.

Further analysis was done in the group of 298 patients (269 with normal baseline and elevated treatment SGOTs identified by laboratory screen plus the 29 patients with elevated hepatic enzymes on treatment identified by the investigators as a possible drug-related adverse event). Clinical events that can produce hepatic dysfunction, including congestive heart failure, acute myocardial infarction and blood transfusions, were reported in 200 (67.1%) of the 298 patients, and the use of potentially hepatotoxic drugs in 213 (71.5%). A clinical event and/or a drug capable of producing hepatic dysfunction was reported in 270 (90.6%).

Liver biopsy results are available for two patients. The first patient had a baseline SGOT of 28 U/L and a peak of 111 U/L after six days of therapy. No symptomatology was reported. Mexiletine was discontinued and the SGOT had returned to normal six days later. Biopsy done at the time of peak SGOT showed focal parenchymal necrosis, portal inflammation and granulomas and was read as showing granulomatous hepatitis compatible with drug-induced reaction. This picture is also compatible with other causes of granulomatous hepatitis such as fungal infection, tuberculosis, sarcoidosis and various viral and bacterial diseases. It should be noted that granulomatous hepatitis generally takes much longer than six days to develop and may well have been related to previous therapy with procainamide which had produced fever and rash in this patient. The second patient had a peak SGOT of 221 U/L after 148 days of treatment. This was the only value obtained during treatment. The only pretreatment value available, 24 U/L, had been obtained 28 months prior to the initiation of mexiletine. The patient was asymptomatic at the time of the peak SGOT. Mexiletine was discontinued after 152 days of treatment and liver biopsy was done approximately 45 days later. Biopsy showed focal parenchymal necrosis and portal inflammation and was read as being consistent with systemic disease, resolving viral hepatitis or drug-induced hepatic injury. SGOT values had returned to normal 44 days after discontinuation of mexiletine. Rechallenge and subsequent dechallenge were positive, but there was a long latent period of 126 days until the first abnormal SGOT was noted during the second course of treatment.

Hepatic function measurements after mexiletine withdrawal are available for 21 patients. In 11 of these patients the SGOT was less than 48 U/L at the last post-treatment observation; in nine the SGOT was declining at the last post-treatment observation relative to treatment levels and in one, the SGOT (57 U/L) was unchanged. Because of the numerous other clinical events and changes that are involved, it is not possible to regard these observations as supplying clean dechallenge information; rather, these changes illustrate the transience or reversibility of the hepatic effects of the overall set of factors influencing the liver in these patients.

No rigorously performed rechallenge is available. In one case, however, elevated treatment SGOTs were observed during two separate courses of mexiletine therapy. No pretreatment SGOT, and only one SGOT on treatment, are available for the first course of therapy.

During the first course of therapy, the peak SGOT was 221 U/L after 148 days of treatment, and during the second, 183 U/L after 159 days of treatment. Both times mexiletine was discontinued, SGOT levels declined to less than 48 U/L after 40-50 days. Total bilirubin was normal during both courses of therapy.

Hepatic enzyme elevations were generally asymptomatic. However, in eleven of the 29 patients with possible drug related adverse events, all of whom had pretreatment SGOT elevations of 120 U/L or greater and final treatment SGOTs greater than 48 U/L, symptoms that may have been related to hepatic dysfunction were as follows: nausea in six, lethargy in four, anorexia in four, emesis in three, and fever in three. Confusion, icterus, weight loss and right upper quadrant discomfort were each reported once.

Among the 298 patients with normal baseline and elevated treatment SGOTs, abnormal liver function was the sole reason for discontinuation of mexiletine therapy in 12 patients. In another six patients, abnormal liver function was one of several reasons, including nausea, emesis and tremor, for discontinuation of therapy. All of these 18 patients were identified by the investigators as having a possible hepatic, drug-related adverse event. Abnormal liver function was not cited as a reason for discontinuation of mexiletine therapy in any patient in the lab screen group. Of the 18 patients discontinued because of abnormal liver function, 3 died. Death was due to congestive heart failure in 2 patients and metastatic carcinoma in one. One of the three patients had been off mexiletine for 24 days and two for 30 days at the time of death. Liver status at the time of death was not reported in 2 patients and was normal in one.

The sponsor made a special scrutiny of hepatic function in patients who died. Review of the 1387 deaths in the Emergency Program, reported by August 1984, representing 14.8% of the enrollees to that date, identified 65 patients with hepatic dysfunction within 14 days of death by biochemical abnormalities (SGOT greater than 120 U/L, bilirubin greater than 2.5 mg %), clinical findings, and/or autopsy reports. The most common causes of hepatic dysfunction in these patients were progressive congestive heart failure and/or shock, which occurred in 44 patients. In 57 of the 65 patients, hepatic dysfunction was not given as the cause of death or judged likely to have contributed significantly to death. In the remaining eight patients, however, severe hepatic dysfunction was present that may have contributed to death. The clinical profiles for these eight patients are shown in the table below.

Clinical Profile of Patients With Severe Hepatic Dysfunction At the Time of Death

Case No.	Age/ Sex	Mexiletine Daily Dose (mg)	Length of Treatment (Days)	Important Concomitant Illnesses and Treatment	Comment
1 JR	65/M	400	90	Congestive cardiomyop., alc. liver cirrhosis. Rx. quinidine.	Off mex. one year at time of death
2 RM	71/M	900	1530	Alc. liv. cirrhosis, portacaval shunt. RX. propran., chlorthal.	Hepatic encephalopathy after portacaval shunt
3 MS	61/M	400	60	CHF, shock. RX. amiodarone, furosemide, hydralazine, captopril.	Pretreat. CHF. & elev. SGOT. On day of death, white tn shock SGOT 2240 U/L, b111. 9.3 mg%
4 TP	61/M	400	30	Prog. CHF, shock. Rx. dopamine, furosemide.	Pretreat. CHF. Day before death, white tn shock, SGOT 1345 U/L.
5 WD	64/M	600	180	Prog. CHF, shock, pneumonia. Rx. respirator, dopamine, quinidine.	Pretreat. CHF. Day before death SGOT 1042 U/L white tn shock.
6 RB	73/F	400	510	Carcinoma of pancreas diagnosed by ultrasound.	Increasing epigast. pain. B111. rose from 1.0 to 21 mg % over 3 weeks.
7 FG	58/M	600	25	One yr. of prog. wt. loss & increasing liver dysfunction on amiodarone, prior to mex.	Liver function stable during mex. admin over last 25 days of life.
8 DM	62/M	600	10	Shock, hypoxemia, lactic acidosis. Hx of pulm. emboli. Rx. Furosemide, spironolactone, coumadin	SGOT on day of death greater than 10,000 U/L white tn shock

The first two of the eight patients had cirrhosis of the liver at autopsy which was thought, in both cases, to be secondary to alcohol; one of these two patients had been off mexiletine for one year at the time of death and the other died with hepatic encephalopathy after portacaval shunt for ruptured esophageal varices. The next three of the eight patients died with progressive congestive heart failure and cardiogenic shock. Amiodarone was started after mexiletine in the first of these three patients and the second developed pneumonia two weeks before death. In the sixth patient, ultrasound showed a lesion involving the pancreas and a diagnosis of carcinoma of the pancreas was made. The seventh patient developed advanced liver disease during one and a half years of amiodarone therapy. In this patient, mexiletine was administered for the final 25 days of life. The eighth patient, with a radionuclide ejection fraction of 15% just before mexiletine therapy was started and a past history of pulmonary emboli, presented with shock, lactic acidosis and hypoxemia 10 days after institution of mexiletine treatment. On the day of death, when this patient was in shock, the SGOT was greater than 10,000 U/L.

Thus, in all eight patients with severe hepatic dysfunction at the time of death, the liver abnormalities were most likely due to concomitant disease: progressive congestive heart failure and shock in three, alcoholic cirrhosis in two, carcinoma of the pancreas in one, amiodarone liver disease in one, and cardiogenic shock and hypoxemia secondary to cardiopulmonary disease in one.

Increases in hepatic enzymes occur commonly in patients who require ventricular antiarrhythmic therapy, as shown by the 8.0% incidence of elevated SGOTs before mexiletine therapy in the controlled trials and 10.2% in the Emergency Program. Therefore, it is difficult to establish a causal relationship between mexiletine therapy and hepatic dysfunction, or to rule out the possibility that mexiletine therapy may be able to elevate enzymes in an occasional patient.

In summary, in light of the above evidence, the following changes in hepatic function have been observed during mexiletine therapy: 1) hepatic enzyme elevations which often decline to normal during continued therapy and are generally asymptomatic; 2) hepatic enzyme elevations which have been reversible after discontinuation of therapy. These observations occur in patients with a high proportion of elevated hepatic enzymes at baseline, and a causal role of mexiletine cannot be imputed.

In view of these findings, the labelling provides information on the changes in hepatic function that have been observed during mexiletine therapy. It recommends that while no causal relationship to mexiletine therapy has been established, patients with signs or symptoms suggesting liver dysfunction be carefully evaluated.

d. Hematologic function

i. Reductions of White Blood Cell Count

No significant reductions in white blood cell count during mexiletine therapy were seen in the controlled studies (475 patients) or in the 197 patients enrolled in the long-term follow-up program.

In the mexiletine emergency-use program, reduction in white blood cells was reported as an adverse event in 12 of 9353 patients (0.1%):

<u>WBC reduction</u>	<u>No. of patients (%)</u>
Neutropenia (absolute neutrophil count $1500/\text{mm}^3$ and $2000/\text{mm}^3$)	7 (0.07)
Agranulocytosis (absolute neutrophil count $500/\text{mm}^3$)	5 (0.05)
Death due to sepsis-2	
Recovered-3	

Clinical features of these patients are presented in the table below.

WBC COUNTS IN EMERGENCY USE PATIENTS WITH AGRANULOCYTOSIS AND NEUTROPENIA

I. <u>Fatal Agranulocytosis</u>	Age/ Sex	Dur to Nadir	WBC Counts [thous/mm ³] (% Neutrophils)				Concom. Rx.	Rechallenge	Outcome	Comments
			Baseline	Nadir	Final On Rx.	Final Off Rx.				
C.L.	70/M	7 weeks	6.8 (66)	2.1 (5)	2.1 (5)	--	Progestyl Allopurinol	No	Died (sepsis)	Died of septic shock 1 day after diagnosis of agranulocytosis.
T.M.	65/M	5 weeks	8.4 (56)	0.7 (NA)	0.7 (NA)	--	Procan-SR Cimetidine	No	Died (sepsis)	Died of septic shock 1 day after diagnosis of agranulocytosis.

II. Non-Fatal Agranulocytosis

R.A.	54/M	4 days	9.2 (67)	1.8 (2)	1.8 (2)	7.9 (7)	Procan-SR (immediately prior) Furosemide Coumadin Amlodarone Digoxin	Yes (see below)	Discontinued therapy; negative re- challenge.	Asymptomatic decrease WBC after discontinuing Procan-SR and starting mexiletine. Rising uric acid before starting mexiletine suggested pre-existing WBC destruction. WBC increased after discontinuing mexiletine and remained normal with resumption of mexiletine.
<u>Rechallenge</u>										
			7.9 (NA)	7.9 (82)	7.9 (82)	--	Quinidine Digoxin Bumex Synthroid	--		
S.S.	55/M	2 months	10.9 (85)	0.6 (NA)	0.6 (NA)	4.4 (NA)	Procan-SR	Yes (see below)	Discontinued therapy. Negative rechallenge.	Severe pharyngitis with agranulocytosis. WBC increased after discontinuing Procan-SR and mexiletine and remained normal with the resumption of mexiletine.
<u>Rechallenge</u>										
			4.4 (NA)	4.4 (48)	5.2 (48)	--	Insulin Digoxin Nitro-Dur NTG	--		

WBC COUNTS IN EMERGENCY USE PATIENTS WITH AGRANULOCYTOSIS AND NEUTROPENIA

	Age/ Sex	Dur to Nadir	Mex Nadir	WBC Counts [thous/mm ³] (% Neutrophils)			Concom. Rx.	Rechallenge	Outcome	Comments
				Baseline	Final On Rx.	Final Off Rx.				
<u>II. Non-Fatal Agranulocytosis (Cont'd)</u>										
P.D.	45/M	11 days	7.9 (NA)	2.5 (2)	2.5 (2)	13.1 (NA)	Procain-SR (Immediately prior) Captopril Furosemide	No	Discontinued therapy. Recovered	Asymptomatic decrease WBC after discontinuing Procain-SR and start- ing captopril and mexiletine. WBC increased after discontinuing mexiletine, captopril and furosemide.
<u>III. Neutropenia</u>										
R.C.	44/M	17 months	4.7 (44)	3.4 (52)	4.3 (46)	-- --	None	No	Continuing therapy. Improved	Asymptomatic
D.E.	50/F	31 months	3.5 (NA)	2.6 (57)	3.0 (48)	-- --	Unknown	No	Continuing therapy. Stable.	Asymptomatic, chronic low WBC during 4 years therapy.
V.T.	31/F	31 months	6.1 (40)	2.7 (48)	2.7 (48)	3.6 (45)	Amlodarone	No	Discontinued therapy due to neutropenia. Stable.	WBC stable for 1 year on mexiletine and then decreased following addition of amlodarone. WBC remained low off mexiletine and on amlodarone.
H.W.	87/F	2 weeks	6.0 (67)	3.5 (51)	4.8 (56)	4.7 (NA)	Diphenyl- hydantoin (Immediately prior) Furosemide Digoxin Minipress Synthroid	No	Discontinued therapy, un- related to transient neutropenia.	Asymptomatic transient decrease WBC.

WBC COUNTS IN EMERGENCY USE PATIENTS WITH AGRANULOCYTOSIS AND NEUTROPENIA

III. Neutropenia (Cont'd)

Age/ Sex	Dur to Nadir	WBC Counts [thous/mm ³] (% Neutrophils)				Concom. Rx.	Rechallenge	Outcome	Comments
		Baseline	Nadir	Final On Rx.	Final Off Rx.				
J.K.	67/M 1 month	8.4 (72)	3.4 (44)	3.4 (44)	5.4 (45)	Procain-SR (discontinued 6 days prior) Ethacrynic Acid	No	Discontinued therapy due to neutropenia. Improved.	Asymptomatic.
A.B.	67/M 2 months	5.2 (65)	3.7 (NA)	4.1 (63)	--	Captopril quinidine Furosemide	No	Discontinued therapy, un- related to neutropenia.	Asymptomatic transient decrease WBC on mexiletine with mild, persistent decrease WBC and RBC developing after the addition of captopril.
R.P.	67/M 5 months	6.5 (51)	3.6 (NA)	4.8 (60)	--	Hydralazine Furosemide Digoxin Zomax	No	Continued therapy. Stable.	History of metastatic lung cancer. Asymptomatic "neutropenia" with all WBC counts greater than 3500.

Neutropenia

White cell and neutrophil reductions in the seven neutropenia cases were moderate and transient. Four patients discontinued mexiletine; WBC counts were stable in three patients whose therapy was not interrupted.

Only two of these seven patients (RC and DE) were receiving no concomitant therapy. Patient RC had a transient neutropenia (WBC 3400/mm³, 52% neutrophils) after 17 months of therapy that returned to 4300/mm³ after a total of 21 months of therapy. Patient DE had a low WBC count at baseline (3500/mm³) that declined to 2600/mm³ (57% neutrophils) after 31 months of mexiletine therapy, and increased to 3000/mm³ after a total of 44 months of treatment.

Of the remaining five patients with neutropenia, the following associations were observed: leukopenia developing with the addition of amiodarone to mexiletine and persisting on amiodarone after mexiletine was discontinued (VT); concomitant hydralazine (RP) or captopril (AB) therapy; procainamide or phenytoin treatment immediately prior to initiating mexiletine (HW and JK).

Agranulocytosis

The most striking common feature in all five cases of agranulocytosis was the use of procainamide, either immediately prior to mexiletine therapy (in two of the cases who recovered) or concurrently (in one case who recovered and in the two deaths). In four of the five cases, a sustained-release formulation of procainamide was employed.

Non-fatal agranulocytosis: Rechallenge with mexiletine was carried out in two (RA and SS) of the three patients who recovered. Both of these patients were taking multiple concomitant medications.

In the first patient (RA), a white count of 1800 with 2% neutrophils was noted six days after discontinuation of sustained-release procainamide and four days after mexiletine therapy was started. The sustained-release procainamide had been withdrawn for failure to control the patient's ventricular tachycardia. Other medications were furosemide, amiodarone, digoxin, warfarin and nitroglycerin patch. During the first five days of mexiletine therapy, the uric acid level increased from 10.4 mg/ml on day two to 11.9 mg/ml on day five. In the opinion of the investigator, the rise in uric acid, which most likely began before mexiletine was started, indicated white blood cell destruction secondary to procainamide or furosemide. Mexiletine was withheld for one month; bumetanide was substituted for furosemide and warfarin was discontinued. Granulocyte recovery was observed during this time, rising from 19% of 2500 WBC four days after furosemide, mexiletine and warfarin were discontinued to 81% of 8500 WBC on day 25. Mexiletine was restarted; bumetanide, digoxin, quinidine and levothyroxine were administered concurrently. The mexiletine rechallenge was negative; white cell and granulocyte counts remained stable. Six weeks after mexiletine was restarted, WBC was 7900 with 82% neutrophils. The high early uric acid levels and the negative mexiletine rechallenge suggest that mexiletine was not the primary cause of agranulocytosis in this patient.

In the second patient (SS), sustained release procainamide was administered concurrently with mexiletine. At baseline, WBC was 1090/mm³ with 35% neutrophils. The patient presented with severe pharyngitis and a nadir white count of 600/mm³ (differential not available) after two months of concomitant mexiletine/procainamide therapy. Other medications were isosorbide dinitrate, digoxin and Dyazide. Mexiletine and procainamide were discontinued and the white count returned to normal (4400/mm³, differential not available). Mexiletine therapy was resumed fifteen days later and WBC remained within normal limits. At last follow-up, nine months after resumption of mexiletine therapy, WBC was 5200/mm³ with 48% neutrophils. The negative mexiletine rechallenge suggests that mexiletine was not the primary cause of agranulocytosis in this patient.

In the third patient (PD) who recovered, agranulocytosis (WBC $2500/\text{mm}^3$ with 2% neutrophils) was detected 11 days after mexiletine was substituted for sustained-release procainamide. A 1.5 gm procainamide daily dose had produced intolerable diarrhea and toxic procainamide blood levels (12.7 mcg/ml five days before discontinuation; normal range: 4.0-8.0 mcg/ml). Captopril administration (25 mg tid) had been started eight days before mexiletine; other concomitant medications were furosemide, isosorbide and nitroglycerin. Mexiletine, captopril and furosemide were discontinued; 10 days later, the WBC was $11,400/\text{mm}^3$ with 81% neutrophils. The investigator attributed the agranulocytosis to captopril administration; inability to define the onset of the drop in WBC and neutrophil count make it difficult to assess any possible contributory role of the toxic levels of sustained-release procainamide, or of mexiletine administration in the evolution of this case.

Deaths Secondary to Sepsis: The remaining two patients developed agranulocytosis during concurrent use of mexiletine and procainamide, and died as a consequence of sepsis.

One of these patients (TM) had sustained-release procainamide added to his regimen one week after mexiletine therapy was started. Four weeks later, he was admitted to the hospital in septic shock and expired. A WBC (no differential available) after two weeks of combined therapy revealed $6800/\text{mm}^3$; shortly before death, the WBC was $700/\text{mm}^3$ with one granulocyte/ mm^3 . Other concurrent medications were cimetidine, nitroglycerin, chloral hydrate and docusate sodium.

The second death (CL) was caused by pulmonary hemorrhage secondary to pseudomonas infection, seven weeks after mexiletine therapy was started. The patient had temporarily discontinued procainamide (because of rash) when mexiletine was started. However, procainamide was reinstated on the seventh day of mexiletine treatment in an attempt to improve control of the arrhythmia, and was continued until death. Other concurrent medications were allopurinol, prazosin, and potassium iodide. One week after combination therapy was started, the WBC was $7700/\text{mm}^3$ with normal differential. The patient was admitted to the hospital five weeks later with pneumonia and died the following morning. WBC was $2100/\text{mm}^3$ with 5% neutrophils on admission.

Summary

In summary, reductions in white blood cell counts during mexiletine therapy were not observed in 475 patients treated in the controlled studies or in the 197 patient long-term follow-up program. In the emergency use program reductions in white blood cell counts were reported as adverse events in 12 of 9353 patients. Of these 12, seven had asymptomatic neutropenia with nadir white blood cell counts of 2600-3700/mm³. Only two of these seven (RC and DE) did not have possible or probable causes other than mexiletine therapy to account for their neutropenia and one of these (DE) had a white cell count of 3500/mm³ at baseline. Agranulocytosis was reported in the other five of the 12 patients with white cell reductions and could not be attributed to mexiletine alone in any of these five patients. In all five of these patients, procainamide was administered either concurrently (3 cases) or just prior to initiation of mexiletine therapy (2 cases). Four of the five patients received sustained-release procainamide.

Agranulocytosis in association with procainamide therapy was first reported in 1951. It was initially considered to be rare; 17 cases were reported prior to 1980 [Ellrodt et al, Ann Int Med 1984, 100:197-201]. In a cohort drawn from the medical records of the Group Health Cooperative of Puget Sound, Danielson et al identified one granulocytopenia (less than 5000 WBC and less than 1000 neutrophils/mm³) among 422 patients (0.2%) treated with procainamide HCl from 1976 to 1981 [JAMA 1984 252:3257-3260].

Sustained-release procainamide became available in 1980. Between 1980 and 1982, Ellrodt and his colleagues discovered eight cases of severe neutropenia-agranulocytosis (less than 100 neutrophils/mm³) in patients taking sustained-release procainamide at their center. Five cases occurred among 114 patients discharged on sustained-release procainamide after open-heart surgery (4.4%). The authors suggest that the sustained-release formulation may have contributed to the high frequency of severe neutropenia.

All five agranulocytoses observed during mexiletine therapy were associated with procainamide use. Four of these five received sustained-release procainamide. Overall, three of the 582 patients (0.5%) known to have received concurrent procainamide therapy in the mexiletine emergency use program had agranulocytosis. Two patients had agranulocytosis diagnosed shortly after procainamide discontinuation. The incidence is consistent with the incidence of severe neutropenia-agranulocytosis (less than 100 neutrophils/mm³) during procainamide therapy (0.2-4.4%) reported by Danielson and by Ellrodt, and may be somewhat overstated because of under-reporting of concomitant medications in patients who had no adverse experience.

Furthermore, there were two instances of negative rechallenge with mexiletine. Thus, the likelihood of a causal relationship between mexiletine therapy and reduced white blood cell counts is remote.

The sponsors' proposed labeling describes the association of procainamide use with the cases of agranulocytosis observed in the mexiletine emergency use program and advises that caution be used when mexiletine/procainamide concurrent therapy is considered.

Reduction in Platelet Count

Reduced platelet count was reported as an adverse event in 10 of 9353 (0.1%) patients enrolled in the mexiletine emergency-use program:

<u>Nadir of platelet count (per mm³)</u>	<u>Number of Patients</u>	<u>Baseline value Normal/Not done</u>
100,000 - 150,000	4	3 / 1
50,000 - 99,999	2	2 / 0
50,000	4	2 / 2

None of the patients had clinical evidence of bleeding related to platelet count reduction. All received at least one (most had several) concurrent medications, several of which (phenytoin, furosemide, haloperidol, procainamide, captopril and metolazone) have been reported to produce thrombocytopenia.

Six of the ten patients had mexiletine discontinued when thrombocytopenia was diagnosed; one discontinued for unrelated reasons; three continued therapy with normal to slightly depressed platelet counts on follow-up.

Two patients in whom mexiletine was discontinued for thrombocytopenia had mexiletine therapy reinstated; rechallenge was negative in both cases.

The four cases with platelet determinations under 50,000 are discussed in detail below.

Platelet Count 50,000 During Mexiletine Therapy:

One patient with congestive heart failure and severe vascular insufficiency had normal platelet values before mexiletine therapy was instituted. Two months after starting mexiletine, progression of the underlying vascular insufficiency necessitated bilateral leg amputation; platelet count on admission for surgery was described as "low". Mexiletine was discontinued shortly after surgery; the lowest platelet count ($39,000/\text{mm}^3$) was recorded two days after discontinuation. Concurrent medications included furosemide, digoxin, haloperidol, nitroglycerin ointment and cefazolin. The patient's platelet count rose after transfusion and was normal three weeks after the surgery.

In a second patient no baseline value was available, but four days after mexiletine therapy was started, platelet count was reported as "decreased". Concurrent medications were phenytoin, metolazone, dobutamine, captopril, furosemide and procainamide. Platelet count decreased to $19,000/\text{mm}^3$ on the 13th day of mexiletine therapy. Phenytoin was discontinued on the 10th day and mexiletine and metolazone administration stopped on day 13. The investigator reported that the platelet count subsequently improved.

In the third patient, no baseline was available, but the platelet count was normal after nine months of therapy with mexiletine, digoxin, furosemide, nitroglycerin patch, probenecid/colchicine, hydralazine and potassium chloride. Phenytoin was added to the regimen during the 21st month of therapy; approximately two weeks later, the platelet count was less than $10,000/\text{mm}^3$. Both phenytoin and mexiletine were discontinued and three days later,

the platelet count was 179,000/mm³. Phenobarbital was substituted for phenytoin and mexiletine restarted. The patient's platelet count remained normal during continued mexiletine treatment. The negative mexiletine challenge and the time course of the thrombocytopenia strongly implicate phenytoin as the causative agent.

In the fourth case, platelets were normal at baseline and at three determinations during the next 23 months. Besides mexiletine, propranolol and isosorbide were administered. At 24 months the platelet count fell to 19,000/mm³. The thrombocytopenia resolved during therapy with 80 mg of prednisone 80 mg/day, but recurred when the dose of prednisone was reduced to 40-60 mg/day. Discontinuation of mexiletine did not improve the platelet count. The problem was diagnosed as idiopathic thrombocytopenia and a splenectomy was performed. Mexiletine therapy was restarted and the rechallenge was negative. Normal platelet values were seen over the next 30 months of treatment.

Conclusions

In summary, the association of the thrombocytopenias observed in the mexiletine emergency use program with underlying disease states and multiple concomitant medications indicates that a causal role of mexiletine therapy is unlikely. This conclusion draws strong support from the two cases where mexiletine rechallenge was negative. In the two cases with concurrent phenytoin therapy, mexiletine rechallenge was negative in one case.

VI. Approved Package Insert:

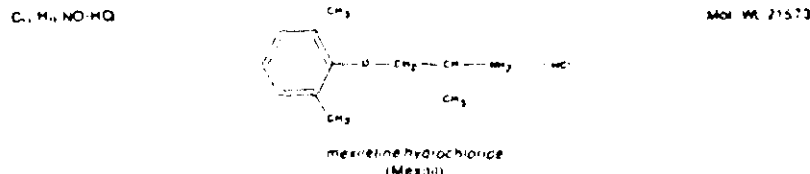
A copy of the package insert is attached.

Mexitil® (mexiletine hydrochloride)

Capsules of 150 mg, 200 mg and 250 mg
Oral Antiarrhythmic

Prescribing Information

DESCRIPTION: Mexitil® (mexiletine hydrochloride) is an orally active antiarrhythmic agent available as 150 mg, 200 mg and 250 mg capsules. 100 mg of mexiletine hydrochloride is equivalent to 83.31 mg of mexiletine base. It is a white to off-white crystalline powder with slightly bitter taste, freely soluble in water and in alcohol. Mexitil has a pKa of 8.4. Chemically, Mexitil is 1-methyl-2-(2,6-dimethyl-4-piperonyl)ethylamine hydrochloride and has the following structural formula:



Mexitil Capsules contain the following inactive ingredients: colloidal silicon dioxide, corn starch, magnesium stearate.

CLINICAL PHARMACOLOGY: Mechanism of Action: Mexitil® (mexiletine hydrochloride) is a local anesthetic, antiarrhythmic agent, structurally similar to lidocaine but orally active. In animal studies, Mexitil has been shown to be effective in the suppression of induced ventricular arrhythmias, including those induced by procaine toxicity and coronary artery ligation. Mexitil, like lidocaine, inhibits the inward sodium current, thus reducing the rate of rise of the action potential. Phase 0 Mexitil decreased the effective refractory period (ERP) in Purkinje fibers. The decrease in ERP was of lesser magnitude than the decrease in action potential duration (APD), with a resulting increase in the ERP/APD ratio.

Electrophysiology in Man: Mexiletine is a Class 1B antiarrhythmic compound with electrophysiologic properties in man similar to those of lidocaine, but dissimilar from quinidine, procainamide, and disopyramide.

In patients with normal conduction systems, Mexitil has a minimal effect on cardiac impulse generation and propagation. In clinical trials, no development of second degree or third degree AV block was observed. Mexitil did not prolong ventricular depolarization (QRS duration) or repolarization (QT intervals) as measured by electrocardiography. Theoretically, therefore, Mexitil may be useful in the treatment of ventricular arrhythmias associated with a prolonged QT interval.

In patients with pre-existing conduction defects, depression of the sinus rate, prolongation of sinus node recovery time, decreased conduction velocity and increased effective refractory period of the intraventricular conduction system have occasionally been observed.

The antiarrhythmic effect of Mexitil has been established in controlled comparative trials against placebo, quinidine, procainamide and disopyramide. Mexitil at doses of 200-400 mg q8h produced a significant reduction of ventricular premature beats, paired beats, and episodes of non-sustained ventricular tachycardia compared to placebo and was similar in effectiveness to the active agents. Among all patients entered into the studies, about 30% in each treatment group had a 70% or greater reduction in PVC count and about 40% failed to complete the 3 month studies because of adverse effects. Follow-up of patients from the controlled trials has demonstrated continued effectiveness of Mexitil in long term use.

Hemodynamics: Hemodynamic studies in a limited number of patients with normal or abnormal myocardial function, following oral administration of Mexitil, have shown small, usually not statistically significant, decreases in cardiac output and increase in systemic vascular resistance, but no significant negative inotropic effect. Blood pressure and pulse rate remain essentially unchanged. Mild depression of myocardial function, similar to that produced by lidocaine, has occasionally been observed following intravenous Mexitil therapy in patients with cardiac disease.

Pharmacokinetics: Mexitil is well absorbed: 90% from the gastrointestinal tract. Unlike lidocaine, its first pass metabolism is low. Peak blood levels are reached in two to three hours. In normal subjects, the plasma elimination half-life of Mexitil is approximately 10-12 hours. It is 50-60% bound to plasma protein, with a volume of distribution of 5.7 liters/kg. Mexitil is metabolized in the liver. Approximately 10% is excreted unchanged by the kidney. While urinary pH does not normally have much influence on elimination, marked changes in urinary pH influence the rate of excretion: acidification accelerates excretion, while alkalinization retards it.

Several metabolites of mexiletine have shown minimal antiarrhythmic activity in animal models. The most active is the minor metabolite N-methylmexiletine, which is less than 20% as potent as mexiletine. The urinary excretion of N-methylmexiletine in man is less than 0.5%. Thus the therapeutic activity of Mexitil is due to the parent compound.

hepatic impairment prolongs the elimination half-life of Mexitil: in eight patients with moderate to severe liver disease, the mean half-life was approximately 25 hours.

Consistent with the limited renal elimination of Mexitil, little change in the half-life has been detected in patients with reduced renal function. In eight patients with creatinine clearance less than 10 ml/min, the mean plasma elimination half-life was 15.7 hours; in seven patients with creatinine clearance between 11-40 ml/min, the mean half-life was 13.4 hours.

The absorption rate of Mexitil is reduced in clinical situations such as acute myocardial infarction in which gastric emptying time is increased. Narcotics, atropine and magnesium aluminum hydroxide have also been reported to slow the absorption of Mexitil. Metoclopramide has been reported to accelerate absorption.

Mexiletine plasma levels of at least 0.5 mcg/ml are generally required for therapeutic response. An increase in the frequency of central nervous system adverse effects has been observed when plasma levels exceed 2.0 mcg/ml. Thus the therapeutic range is approximately 0.5 to 2.0 mcg/ml. Plasma levels within the therapeutic range can be attained with either three times daily or twice daily dosing but peak to trough differences are greater with the latter regimen, creating the possibility of adverse effects at peak and arrhythmic escape at trough. Nevertheless, some patients may be transferred successfully to the twice daily regimen. (See Dosage and Administration.)

INDICATIONS: Mexitil® (mexiletine hydrochloride) is indicated for the suppression of symptomatic ventricular arrhythmias, including frequent premature ventricular contractions, unifocal or multifocal couplets and ventricular tachycardia.

Like other antiarrhythmics, mexiletine has not been shown to prevent sudden death in patients with serious ventricular ectopic activity and also, like other antiarrhythmics, it has potentially serious adverse effects, including the ability to worsen arrhythmias. It is therefore essential that each patient given mexiletine be evaluated electrocardiographically and clinically prior to and during mexiletine therapy to determine whether the response to mexiletine supports continued treatment.

CONTRAINDICATIONS: Mexitil® (mexiletine hydrochloride) is contraindicated in the presence of cardiogenic shock or pre-existing second or third degree AV block (if no pacemaker is present).

PRECAUTIONS: General: If a ventricular pacemaker is operative, patients with second or third degree heart block may be treated with Mexitil® (mexiletine hydrochloride) if continuously monitored. A limited number of patients (45 of 475 in controlled clinical trials) with pre-existing first degree AV block were treated with Mexitil; none of these patients developed second or third degree AV block. Caution should be exercised when it is used in such patients or in patients with pre-existing sinus node dysfunction or intraventricular conduction abnormalities.

Like other antiarrhythmics, Mexitil® (mexiletine hydrochloride) can cause worsening of arrhythmias. This has been uncommon in patients with less serious arrhythmias (frequent premature beats or non-sustained ventricular tachycardia; see Adverse Reactions); but is of greater concern in patients with life-threatening arrhythmias such as sustained ventricular tachycardia. In patients with such arrhythmias subjected to programmed electrical stimulation or in exercise provocation, 10-15% of patients had exacerbation of the arrhythmia, a rate not greater than that of other agents.

Mexitil should be used with caution in patients with hypotension and severe congestive heart failure.

Since Mexitil is metabolized in the liver and hepatic impairment has been reported to prolong the elimination half-life of Mexitil, patients with liver disease should be followed carefully while receiving Mexitil. The same caution should be observed in patients with hepatic dysfunction secondary to congestive heart failure.

Concurrent drug therapy or dietary regimens which may markedly alter urinary pH should be avoided during Mexitil therapy. The minor fluctuations in urinary pH associated with normal diet do not affect the excretion of Mexitil.

SGOT Elevation and Liver Injury: In three month controlled trials, elevations of SGOT greater than three times the upper limit of normal occurred in about 14% of both mexiletine treated and control patients. Subsequently, 2% of patients in the mexiletine compassionate use program had elevations of SGOT greater than or equal to three times the upper limit of normal. These elevations frequently occurred in association with identifiable clinical events and therapeutic measures such as congestive heart failure, acute myocardial infarction, blood transfusions and other medications. These elevations were often asymptomatic and transient, usually not associated with elevated bilirubin levels and usually did not require discontinuation of therapy. Marked elevations of SGOT (>1000 U/L) were seen before death in four patients with end stage cardiac disease (severe congestive heart failure, cardiogenic shock).

In foreign marketing experience rare instances of severe liver injury, including hepatic necrosis, have been reported in association with Mexitil treatment. It is recommended that patients in whom an abnormal liver test has occurred or who have signs or symptoms suggesting liver dysfunction be carefully evaluated. If persistent or worsening elevation of hepatic enzymes is detected, consideration should be given to discontinuing therapy.

Blood Dyscrasias: Blood dyscrasias were not seen in the controlled trials. Among 10,867 patients treated with mexiletine in the compassionate use program, marked leukopenia (neutrophils less than 1000/mm³) or agranulocytosis were seen in 0.06% and milder depressions of leukocytes were seen in 0.08% and thrombocytopenia was observed in 0.16%. Many of these patients were seriously ill and receiving concomitant medications with known hematologic adverse effects. Rechallenge with mexiletine in several cases was negative. Marked leukopenia or agranulocytosis did not occur in any patient receiving Mexitil alone. Five of the six cases of agranulocytosis were associated with procainamide (sustained release preparations in four) and one with vinorelbine. If significant hematologic changes are observed the patient should be carefully evaluated and if warranted, Mexitil should be discontinued. Blood counts usually return to normal within one month of discontinuation. (See Adverse Reactions.)

Convulsions (seizures) did not occur in Mexitil controlled clinical trials. In the compassionate use program, convulsions were reported in about 2 of 1000 patients. Twenty-eight percent of these patients discontinued therapy. Convulsions were reported in patients with and without a prior history of seizures. Mexiletine should be used with caution in patients with known seizure disorder.

Drug Interactions: In a large compassionate use program, Mexitil has been used concurrently with commonly employed antianginal, antihypertensive and anticoagulant drugs without observed interactions. A variety of antiarrhythmics such as quinidine or procainamide were also added, sometimes with improved control of ventricular ectopy. When phenytoin or other hepatic enzyme inducers such as rifampin and phenobarbital have been taken concurrently with Mexitil, lowered Mexitil plasma levels have been reported. Monitoring of Mexitil plasma levels is recommended during such concurrent use to avoid ineffective therapy.

In a formal study benzodiazepines were shown not to affect Mexitil plasma concentrations. ECG intervals (PR, QRS and QT) were not affected by concurrent Mexitil and digoxin, diuretics or propranolol.

Emetidine has been shown to raise Mexitil plasma levels. During concurrent therapy, the patient should be monitored carefully for adverse effects.

Mexitil does not alter serum digoxin levels but magnesium aluminum hydroxide, when used to treat gastrointestinal symptoms due to Mexitil, has been reported to lower serum digoxin levels.

Carcinomas, Neoplasms and Treatment of Fertility: Studies of carcinogenesis in rats (24 months) and mice (18 months) did not demonstrate any tumorigenic potential. Mexitil was found to be non-mutagenic in the Ames test. Mexitil did not impair fertility in the rat.

Pregnancy Teratogenic Effects: PREGNANCY CATEGORY C. Reproduction studies performed with Mexitil® in rats, mice and rabbits at doses up to four times the maximum human oral dose (20 mg/kg in a 50 kg patient), revealed no evidence of teratogenicity or impaired fertility but did show an increase in fetal resorption. There are no adequate and well-controlled studies in pregnant women; this drug should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Mexitil appears in human milk in concentrations similar to those observed in plasma. Therefore, if the Mexitil is deemed essential, an alternative method of infant feeding should be considered.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Mexitil® (mexiletine hydrochloride) commonly produces reversible gastrointestinal and nervous system adverse reactions but is otherwise well tolerated. Mexitil has been evaluated in 483 patients in one month and three month controlled studies and in over 10,000 patients in a large compassionate use program. Dosages in the controlled studies ranged from 600-1200 mg/day; some patients (8%) in the compassionate use program were treated with higher daily doses (1800-3200 mg/day). In the three month controlled trials comparing Mexitil to quinidine, procainamide and disopyramide, the most frequent adverse reactions were upper gastrointestinal distress (41%), light-headedness (10.5%), tremor (12.6%), and coordination difficulties (10.2%). Similar frequency and incidence were observed in the one month placebo-controlled trial. Although these reactions were generally not serious and were dose-related and reversible with a reduction in dosage by taking the drug with food or antacid or by therapy discontinuation, they led to therapy discontinuation in 40% of patients in the controlled trials. A tabulation of the adverse events reported in the one month placebo-controlled trial follows.

COMPARATIVE INCIDENCE (%) OF ADVERSE EVENTS AMONG PATIENTS TREATED WITH MEXILETINE AND PLACEBO IN THE 4 WEEK, DOUBLE-BLIND CROSSOVER TRIAL.

	Mexiletine N = 53	Placebo N = 49
Cardiovascular		
Palpitations	7.5	10.2
Chest Pain	7.5	4.1
Increased Ventricular Arrhythmias (PVCs)	1.9	—
Digestive		
Nausea/Vomiting/Heartburn	39.6	6.1
Central Nervous System		
Dizziness	26.4	14.3
Light-headedness	13.2	—
Tremor	13.2	—
Nervousness	13.2	6.1
Coordination Difficulties	9.4	—

	Mexiletine N = 53	Placebo N = 49
Changes in Sleep Habits	7.5	16.3
Paresthesias/Numbness	3.8	2.0
Weakness	1.9	4.1
Fatigue	1.9	2.0
Tinnitus	1.9	4.1
Confusion/Clouded Sensorium	1.9	2.0
Other		
Headache	7.5	6.1
Blurred Vision/Visual Disturbances	7.5	2.0
Dyspnea/Respiratory	5.7	10.2
Rash	1.9	2.0
Non-specific Edema	3.8	—

A tabulation of adverse reactions occurring in one percent or more of patients in the three-month controlled studies follows. **COMPARATIVE INCIDENCE (%) OF ADVERSE EVENTS AMONG PATIENTS TREATED WITH MEXILETINE OR CONTROL DRUGS IN THE 12-WEEK DOUBLE-BLIND TRIALS**

	Mexiletine N = 430	Quinidine N = 262	Procainamide N = 78	Disopyramide N = 69
Cardiovascular				
Palpitations	4.3	4.6	1.3	5.8
Chest Pain	2.6	3.4	1.3	2.9
Anginal/Angina-like Pain	1.7	1.9	2.6	2.9
Increased Ventricular Arrhythmias/PVC's	1.0	2.7	2.6	—
Digestive				
Nausea/Vomiting/Heartburn	39.3	21.4	33.3	14.5
Diarrhea	5.2	33.2	2.6	8.7
Constipation	4.0	—	6.4	11.6
Changes in Appetite	2.6	1.9	—	—
Abdominal Pain/Cramps/Discomfort	1.2	1.5	—	1.4
Central Nervous System				
Dizziness/Light-headedness	18.9	14.1	14.1	2.9
Tremor	13.2	2.3	3.8	1.4
Coordination Difficulties	9.7	1.1	1.3	—
Changes in Sleep Habits	7.1	2.7	11.5	8.7
Weakness	5.0	5.3	7.7	2.9
Nervousness	5.0	1.9	6.4	5.8
Fatigue	3.8	5.7	5.1	1.4
Speech Difficulties	2.6	0.4	—	—
Confusion/Clouded Sensorium	2.6	—	3.8	—
Paresthesias/ Numbness	2.4	2.3	2.6	—
Tinnitus	2.4	1.5	—	—
Depression	2.4	1.1	1.3	1.4
Other				
Blurred Vision/Visual Disturbances	5.7	3.1	5.1	7.2
Headache	5.7	6.9	7.7	4.3
Rash	4.2	3.8	10.3	1.4
Dyspnea/Respiratory	3.3	3.1	5.1	2.9
Dry Mouth	2.8	1.9	5.1	14.5
Arrhythmia	1.7	2.3	5.1	1.4
Fever	1.2	3.1	2.6	—

Less than 1%: Syncope/edema/hot flashes/hypertension/short-term memory loss/loss of consciousness/other psychological changes/diaphoresis/urinary hesitancy/retention/maaise/impotence/decreased libido/pharyngitis

An additional group of over 10,000 patients has been treated in a program allowing administration of Mexilit® (mexiletine hydrochloride) under compassionate use circumstances. These patients were seriously ill with the large majority on multiple drug therapy. Twenty-four percent of the patients continued in the program for one year or longer. Adverse reactions leading to therapy discontinuation occurred in 15 percent of patients (usually upper gastrointestinal system or nervous system effects). In general, the more common adverse reactions were similar to those in the controlled trials. Less common adverse events possibly related to Mexilit use include:

Cardiovascular System: Syncope and hypotension, each about 6 in 1000; bradycardia, about 1 in 1000; anginal/angina like pain, about 3 in 1000; edema, atrioventricular block/conduction disturbances and hot rashes, each about 2 in 1000; atrial arrhythmias, hypertension and cardiogenic shock, each about 1 in 1000.

Central Nervous System: Short-term memory loss, about 9 in 1000 patients; hallucinations and other psychological changes, each about 3 in 1000; psychosis and convulsions/seizures, each about 2 in 1000; loss of consciousness, about 6 in 10,000.

Digestive: Dysphagia, about 2 in 1000; peptic ulcer, about 8 in 10,000; upper gastrointestinal bleeding, about 7 in 10,000; esophageal ulceration, about 1 in 10,000.

Laboratory: Abnormal liver function tests, about 5 in 1000 patients; positive ANA and thrombocytopenia, each about 2 in 1000; leukopenia (including neutropenia and agranulocytosis), about 1 in 1000; myelofibrosis, about 2 in 10,000 patients.

Other: Diaphoresis, about 6 in 1000; altered taste, about 5 in 1000; urinary changes, hair loss and impotence/decreased libido, each about 4 in 1000; malaise, about 3 in 1000; urinary hesitancy/retention, each about 2 in 1000; hiccups, dry skin, laryngeal and pharyngeal changes and changes in oral mucous membranes, each about 1 in 1000; SLE syndrome, about 4 in 10,000.

Hematology: Blood dyscrasias were not seen in the controlled trials but did occur among 10,867 patients treated with mexiletine in the compassionate use program (see Precautions).

Myelofibrosis was reported in two patients in the compassionate use program; one was receiving long-term therapy and the other had pretreatment myeloid abnormalities.

OVERDOSAGE: Marked overdosage in humans has not been reported. On the basis of acute toxicity studies in animals, the most toxic would be expected to be related to the central nervous system, including ataxia and convulsions.

There is no specific antidote for Mexilit® (mexiletine hydrochloride). Acidification of the urine, which will accelerate excretion of mexiletine, may be useful. Treatment of overdosage should be supportive, and may include the administration of atropine if hypotension or bradycardia occurs.

DOSEAGE AND ADMINISTRATION: The dosage of Mexilit® (mexiletine hydrochloride) must be individualized on the basis of response and tolerance, both of which are dose-related. Administration with food or antacid is recommended. Initiate Mexilit therapy with 200 mg every eight hours when rapid control of arrhythmia is not essential. A minimum of two to three days before dose adjustments is recommended. Dose may be adjusted in 50 or 100 mg increments up or down.

As with any antiarrhythmic drug, clinical and electrocardiographic evaluation (including Holter monitoring if necessary) are needed to determine whether the desired antiarrhythmic effect has been obtained and to guide titration and dose adjustment.

Satisfactory control can be achieved in most patients by 200 to 300 mg given every eight hours with food or antacid. Satisfactory response has not been achieved at 300 mg q8h and the patient tolerates Mexilit well, a dose of 400 mg q8h may be tried. As the severity of CNS side effects increases with total daily dose, the dose should not exceed 1200 mg/day. In general, patients with renal failure will require the usual doses of Mexilit. Patients with severe liver disease, however, require lower doses and must be monitored closely. Similarly, marked right-sided congestive heart failure can reduce hepatic metabolism and reduce the needed dose. Plasma level may also be affected by certain concomitant drugs (see Precautions: Drug Interactions).

Loading Dose: When rapid control of ventricular arrhythmia is essential, an initial loading dose of 400 mg of Mexilit may be administered, followed by a 200 mg dose in eight hours. Onset of therapeutic effect is usually observed within 30 minutes to two hours.

12-Hour Dosage Schedule: Some patients responding to Mexilit may be transferred to a 12-hour dosage schedule to improve convenience and compliance. If adequate suppression is achieved on a Mexilit dose of 300 mg or less every eight hours, same total daily dose may be given in divided doses every 12 hours while carefully monitoring the degree of suppression of ventricular ectopy. This dose may be adjusted up to a maximum of 450 mg every 12 hours to achieve the desired response.

Transferring to Mexilit: The following dosage schedule, based on theoretical considerations rather than experimental data, suggested for transferring patients from other Class I oral antiarrhythmic agents to Mexilit. Mexilit treatment may be initiated with a 200 mg dose and titrated to response as described above. 6-12 hours after the last dose of quinidine sulfate, 3-6 hours after the last dose of procainamide, 6-12 hours after the last dose of disopyramide or 8-12 hours after the last dose of tocainide.

In patients in whom withdrawal of the previous antiarrhythmic agent is likely to produce life-threatening arrhythmia, hospitalization of the patient is recommended.

When transferring from lidocaine to Mexilit, the lidocaine infusion should be stopped when the first oral dose of Mexilit is administered. The infusion line should be left open until suppression of the arrhythmia appears to be satisfactorily maintained. Consideration should be given to the similarity of the adverse effects of lidocaine and Mexilit, and the possibility that they may be additive.

NEW SUPPLIES: Mexilit® (mexiletine hydrochloride) is supplied in hard gelatin capsules containing 150 mg, 200 mg or 250 mg of mexiletine hydrochloride.

Mexilit® 150 mg capsules are red and caramel with the marking BI 66. Available in bottles of 100 (NDC 0597-0066-01), individually blister sealed unit-dose cartons of 100 (NDC 0597-0066-61).

Mexilit® 200 mg capsules are red with the marking BI 67. Available in bottles of 100 (NDC 0597-0067-01) and individually blister sealed unit-dose cartons of 100 (NDC 0597-0067-61).

Mexilit® 250 mg capsules are red and aqua green with the marking BI 68. Available in bottles of 100 (NDC 0597-0068-01) and individually blister sealed unit-dose cartons of 100 (NDC 0597-0068-61).

Store below 86°F (30°C).

Caution: Federal law prohibits dispensing without prescription.



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Pharmaceuticals, Inc.
a subsidiary of
Boehringer Ingelheim Corporation
90 East Ridge
P.O. Box 368
Ridgefield, Connecticut 06877

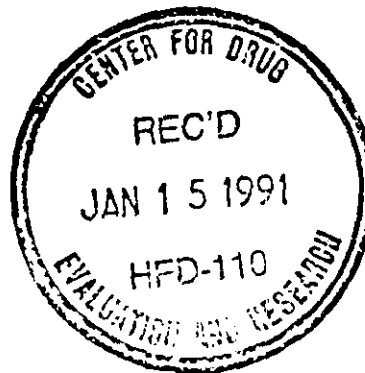
FOOD AND DRUG ADMINISTRATION
CENTRAL DOCUMENT ROOM
PARK BUILDING, ROOM 214
12420 PARKLAWN DRIVE
ROCKVILLE, MD 20857

DEAR SIR/MADAM:

WE ARE SUBMITTING FOLLOW-UP REPORT(S) ON FORM FDA-1639 FOR THE FOLLOWING ADVERSE EVENT(S):

DRUG	NDA/IND	MFR. CONTROL NO.	ADVERSE EVC. T
MEXITIL CAPSULES	NDA# 18-873	MMEX 06/28/90	CONGESTIVE HEART FAILURE LIVER FUNCTION TESTS ABNORMAL NCS

ORIGINAL



91 JAN -7 AM 11:37

Division of Drug Research
FDA, Silver Spring, MD

IF ANY ADDITIONAL INFORMATION BECOMES AVAILABLE, WE WILL FORWARD IT PROMPTLY.

SINCERELY,

SALLY BROWN, Ph.D.
MANAGER
DRUG REGULATORY AFFAIRS

CC: DR. TAYLOR (BIGmbH)
CLINICAL DRUG SAFETY

NAT
Ch 1/15/91

Telephone: (203) 798-9988
Telex: 179153 Answer back: BIC UT



Boehringer Ingelheim

February 11, 1991

Boehringer Ingelheim
Pharmaceuticals, Inc.
a subsidiary of
Boehringer Ingelheim Corporation
30 East Ridge
P.O. Box 368
Ridgefield, Connecticut 06877

FOOD AND DRUG ADMINISTRATION
CENTRAL DOCUMENT ROOM
PARK BUILDING, ROOM 214
12420 PARKLAWN DRIVE
ROCKVILLE, MD 20857

DEAR SIR/MADAM:

WE ARE SUBMITTING INITIAL REPORT(S) ON FORM FDA-1639 FOR THE FOLLOWING ADVERSE EVENT(S):

DRUG	NDA/IND	MFR. CONTROL NO.	ADVERSE EVENT
MEXITIL CAPSULES	NDA# 18-873	MME: 01/23/91	LIVER FUNCTION TESTS ABNORMAL NOS PANCREATITIS



01/19/91

IF ANY ADDITIONAL INFORMATION BECOMES AVAILABLE, WE WILL FORWARD IT PROMPTLY.

SINCERELY,

SALLY BROWN, PH.D
MANAGER
DRUG REGULATORY AFFAIRS

CC: DR. TAYLOR (BIGmbH)
CLINICAL DRUG SAFETY

NAT
2/19/91

ORIGINAL



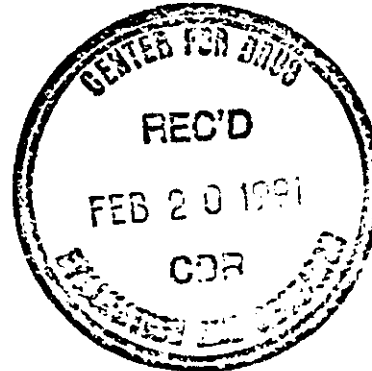
Boehringer Ingelheim

February 14, 1991

Boehringer Ingelheim
Pharmaceuticals, Inc.
a subsidiary of
Boehringer Ingelheim Corporation
90 East Ridge
P.O. Box 368
Ridgefield, Connecticut 06877

Food and Drug Administration
Central Document Room
Park Building, Room 214
12320 Parklawn Drive
Rockville, MD 20857

Re: MEXITIL® Capsules
(mexiletine hydrochloride)
NDA 18-873



Dear Madam or Sir:

Pursuant to 21 CFR 314.80, enclosed is the Periodic ADR Report for the above-referenced product.

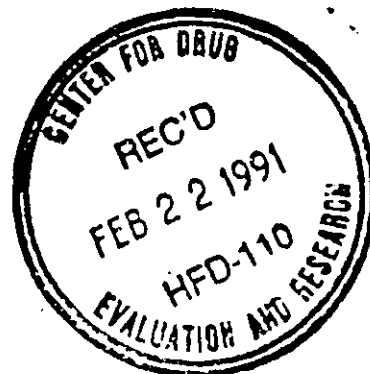
Following this letter is a Table of Contents for this report. Included in this submission are 45 Initial Reports and one (1) follow-up report on Forms FDA 1639. This report covers the reporting period of December 31, 1989 to December 30, 1990.

Sincerely,

Sally Brown, Ph.D.
Manager
Drug Regulatory Affairs

SB:tkb

Enclosure



NAF 2/25/91
P014
Div 110
ORIGINAL



Boehringer Ingelheim

REPORTS

March 5, 1991

Boehringer Ingelheim
Pharmaceuticals, Inc.
a subsidiary of
Boehringer Ingelheim Corporation
30 East Ridge
P.O. Box 368
Ridgefield Connecticut 06877

FOOD AND DRUG ADMINISTRATION
CENTRAL DOCUMENT ROOM
PARK BUILDING, ROOM 214
12420 PARKLAWN DRIVE
ROCKVILLE, MD 20857

DEAR SIR/MADAM:

WE ARE SUBMITTING FOLLOW-UP REPORT(S) ON FORM FDA-1639 FOR THE FOLLOWING ADVERSE EVENT(S):

DRUG	NDA/IND	MFR. CONTROL NO.	ADVERSE EVENT
MEXITIL CAPSULES	NDA# 18-873	MMEX 06/28/90	CONGESTIVE HEART FAILURE LIVER FUNCTION TESTS ABNORMAL NOS



91158-6 11:7:00

IF ANY ADDITIONAL INFORMATION BECOMES AVAILABLE, WE WILL FORWARD IT PROMPTLY.

SINCERELY,

DAVID BRILL, Ph.D.
ASSOCIATE DIRECTOR
DRUG REGULATORY AFFAIRS

CC: DR. TAYLOR (BIGmbH)
CLINICAL DRUG SAFETY

ORIGINAL

*NAI
Chen 3/11/91*

Telephone: (203) 798-9983
Telex: 179153 Answer back. BIC UT



Boehringer Ingelheim

REPORTS

March 14, 1991

**Boehringer Ingelheim
Pharmaceuticals, Inc.**
A subsidiary of
Boehringer Ingelheim Corporation
90 East Ridge
P.O. Box 368
Ridgefield, Connecticut 06877

FOOD AND DRUG ADMINISTRATION
CENTRAL DOCUMENT ROOM
PARK BUILDING, ROOM 214
12420 PARKLAWN DRIVE
ROCKVILLE, MD 20857

DEAR SIR/MADAM:

WE ARE SUBMITTING INITIAL REPORT(S) ON FORM FDA-1639 FOR THE FOLLOWING ADVERSE EVENT(S):

DRUG	NDA/IND	MFR. CONTROL NO.	ADVERSE EVENT
MEXITIL CAPSULES	NDA# 18-873	FD E91-0091	EOSINOPHILIA PNEUMONIA



011110101010

IF ANY ADDITIONAL INFORMATION BECOMES AVAILABLE, WE WILL FORWARD IT PROMPTLY.

SINCERELY,

ORIGINAL

Handwritten signature and date: 3/21/91



Boehringer
Ingelheim

March 20, 1991

Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room 16B-30, HFD-110
5600 Fishers Lane
Rockville, Maryland 20857

Boehringer Ingelheim
Pharmaceuticals, Inc.
a subsidiary of
Boehringer Ingelheim Corporation
90 East Ridge
P.O. Box 368
Ridgely, Connecticut 06877

Attention: Raymond J. Lipicky, M.D., Director
Division of Cardio-Renal Drug Products

SUPPL NEW CORRES

Subject: MEXITIL (mexiletine) Capsules
NDA 18-873

Dear Dr. Lipicky:

Reference is made to a telephone conversation between myself and Mr. Tom Conrad on March 18, 1991. The subject of the discussion centered upon the inclusion of "congestive heart failure" into the package insert of MEXITIL. Mr. Conrad has had discussions with Dr. S. Chun and she has formally requested that a summary document be sent to her which describes all spontaneous adverse events reported as congestive heart failure.

Please find attached the tabular summary of spontaneous adverse events as described above.

Please call me at the number listed below if any additional information and/or clarification is required.

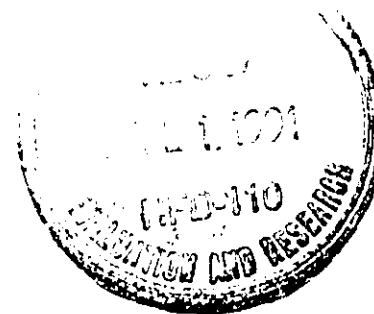
Sincerely,

David R. Brill

David R. Brill, Ph.D.
Associate Director
Drug Regulatory Affairs
(203) 798-4340

Desk Copy: Mr. Tom Conrad
HFD - 111

DRB:akt
k.35



ORIGINAL



SUPPL NEW CORRES

Boehringer
Ingelheim

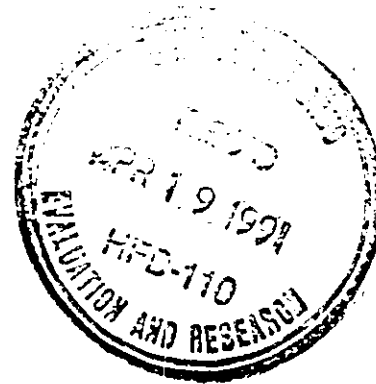
April 18, 1991

Boehringer Ingelheim
Pharmaceuticals, Inc.
a subsidiary of
Boehringer Ingelheim Corporation
90 East Ridge
P.O. Box 368
Ridgefield, Connecticut 06877

Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room 16B-30, HFD-110
5600 Fishers Lane
Rockville, Maryland 20857

Attention: Raymond J. Lipicky, M.D., Director
Division of Cardio-Renal Drug Products

Subject: MEXITIL Capsules (mexiletine HCl)
NDA 18-873



Dear Dr. Lipicky:

(cont'd)

ORIGINAL

Telephone: (203) 798-9988
100155 Tenney Park Blvd

Page 2

April 18, 1991

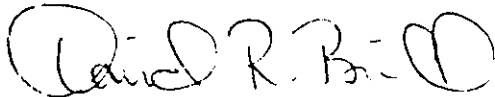
R. J. Lipicky, M.D.

Mexitil - NDA 18-873

Page 3
April 13, 1991
To R. J. Lipicky, M.D.
Mexitil - NDA 18-873

Please feel free to call me if you require any further information and/or clarification.

Sincerely,

A handwritten signature in cursive script that reads "David R. Brill". The signature is enclosed in a hand-drawn oval.

David R. Brill, Ph.D.
Associate Director
Drug Regulatory Affairs
(203) 798-4340

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NOV 10 1988

NDA 18-873

Drug Generic Name:
Mexiletine Hydrochloride

Applicant:
Boehringer Ingelheim Ltd.
90 East Ridge Road
P.O. Box 368
Ridgefield, Ct 06877

Drug Trade Name:
Mexitil

I. Indications for Use:

Mexitil is indicated for the suppression of symptomatic ventricular arrhythmias, including frequent premature ventricular contractions, unifocal or multifocal, couplets and ventricular tachycardia. Like other antiarrhythmics, mexiletine has not been shown to prevent sudden death in patients with serious ventricular ectopic activity, and also, like other antiarrhythmics, it has potentially serious adverse effects, including the ability to worsen arrhythmias. It is therefore essential that each patient given mexiletine be evaluated electrocardiographically and clinically prior to and during mexiletine therapy to determine whether the response to mexiletine supports continued treatment.

II. Dosage form, route of administration and recommended dosage:

A. Dosage Form:

Mexitil is available as hard gelatin capsules containing 150 mg, 200 mg and 250 mg of mexiletine hydrochloride.

B. Dosage and Administration:

The dosage of Mexitil must be individualized on the basis of response and tolerance. Administration with food is strongly recommended. Initiate Mexitil therapy with 200 mg every eight hours when rapid control of arrhythmia is not essential. A minimum of two-three days between dose adjustments is recommended. Dose may be adjusted up or down by 50 or 100 mg. Satisfactory control can be achieved in most patients by 200 to 300 mg given every eight hours with food. If satisfactory response has not been achieved at 300 mg q8h, and the patient tolerates Mexitil well, a dose of 400 mg q8h may be tried. The dose should not exceed 1200 mg/day as the severity of CNS side effects increases with the total daily dose.

Loading Dose: When rapid control of ventricular arrhythmias is essential, an initial loading dose of 400 mg of Mexitil may be administered, followed by a 200 mg dose in eight hours. Onset of therapeutic effect is usually observed within 30 minutes to two hours.

Q12H Dosage Schedule: If adequate suppression is achieved on a Mexitil dose of 300 mg or less every eight hours, a 12-hour schedule may be employed to improve patient compliance or convenience.

This may be started by giving the q8h dose every 12 hours while carefully monitoring the degree of suppression of ventricular ectopy and then, if necessary, the dose may be adjusted to maintain the desired response.

Transferring to Mexitil: The following dosage schedule, based on theoretical considerations rather than experimental data, is suggested for transferring patients from other Class I oral antiarrhythmic agents to Mexitil. Mexitil treatment may be initiated with a 200 mg dose, and titrated to response as described above, 6-12 hours after the last dose of quinidine sulfate, 3-6 hours after the last dose of procainamide, or 6-12 hours after the last dose of disopyramide.

In patients for whom withdrawal of the previous antiarrhythmic agent is likely to produce life-threatening arrhythmias, hospitalization of the patient is recommended.

When transferring from lidocaine to Mexitil, the lidocaine infusion should be stopped when the first oral dose of Mexitil is administered, but the infusion line should be left open until suppression of the arrhythmia appears to be satisfactorily maintained. Consideration should be given to the similarity of the adverse effects of lidocaine and Mexitil and the possibility that they may be additive.

III. Manufacturing and Controls:

A. Manufacturing and Controls

Mexiletine hydrochloride is prepared by a synthetic process that has been described in sufficient detail to permit a determination of the validity of the assigned chemical structure and the suitability of the specifications and test methods for the bulk new drug substance. The compound is a racemic mixture. Raw materials and intermediates are satisfactorily characterized, and sufficient attention is given to isolation and purification of the new drug substance.

The controls over the manufacturing procedures which include specifications and test methods for the new drug substance, the inactive ingredients, and the finished dosage form give sufficient assurance of the identity, strength, quality and purity of the drug.

B. Stability

Stability studies have been conducted on the new drug substance, the dosage forms in the proposed market container (opaque HDPE bottles and blister packages). The data submitted adequately support the 36 month expiration date for the drug product.

The applicant has made the commitment to place initial production lots on stability study when they become available.

C. Methods Validation

The analytical methods for control of the new drug substance and drug product are being validated by FDA Laboratories. The methods are considered suitable for control and regulatory purposes after incorporation of minor changes.

D. Labeling

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

Insofar as could be determined from a thorough search of available references, the trade name Mexitil is not in conflict with the name of any other drug.

E. Establishment Inspection

Inspection of Boehringer Ingelheim KG, Boehringer Ingelheim Ltd., and other facilities that do the contract packing of the drug product has been performed to determine their compliance with "Current Good Manufacturing Practice Regulations." A satisfactory report was received from the Office of Compliance which states there is no reason to withhold approval of the NDA.

F. Environmental Impact Analysis Report

The Environmental Impact Analysis Report states that the manufacture of Mexitil is expected to have little or no impact on the environment.

IV. Pharmacology:

A. Pharmacodynamics

Mexiletine hydrochloride is a new Class IB antiarrhythmic agent whose chemical structure and electrophysiological properties resemble those of lidocaine, although its anticonvulsant and pharmacokinetic properties differ from that drug. Unlike lidocaine, it is effective following oral administration and possesses a long plasma half-life.

The efficacy of mexiletine hydrochloride was determined in various animal screening models and was compared with that of other known antiarrhythmic agents. In isolated guinea pig and rabbit atrial tissues, therapeutically relevant concentrations of mexiletine hydrochloride (1-5 ug/ml) reduced the maximal rate of depolarization of the action potential so that the conduction velocity was slowed, the excitability threshold was increased and the effective refractory period was lengthened without a significant change in the resting membrane potential or the spontaneous frequency of the sinoatrial node. In the isolated canine Purkinje fiber system the effective refractory period was shortened but not as much as the action potential duration, so that the ratio of the effective period to the action potential duration was increased by mexiletine.

In intact animals mexiletine hydrochloride increased the fibrillation threshold of the ischemic myocardium and reversed ventricular tachyarrhythmias resulting from ouabain intoxication or coronary ligation.

Generally, in terms of dose (mg/kg), the activity of mexiletine hydrochloride was found to be superior to quinidine, lidocaine, phenytoin and procainamide in the various antiarrhythmic and antifibrillatory screening studies conducted.

The secondary pharmacological effects of mexiletine hydrochloride include local anesthetic and anticonvulsive activity. The anticonvulsive activity was demonstrated in a number of animal models and may be due to its inhibitory effect on the uptake and release of gamma aminobutyric acid. The compound has no effect on the autonomic nervous system and does not interfere with the function of biogenic amines. It has neither antihistaminic activity nor alpha- or beta-adrenergic blocking properties.

B. Pharmacokinetics

The pharmacokinetic profile of mexiletine hydrochloride is characterized by high systemic availability (88%) following oral administration, with peak levels attained in 1-1.5 hours; plasma half-lives in rats and dogs ranged from 8 to 23 hours.

Following both oral and intravenous administration, renal excretion of metabolites and parent drug accounted for 80-90% of the administered substance regardless of the species studied; fecal excretion was always less than 10%. Renal clearance of the compound was increased by urinary acidosis. The excretion pattern in rats, dogs and monkeys was not altered by chronic dosing.

Tissue distribution studies conducted in rats and rabbits after oral and intravenous dosing, showed the highest concentrations of the radio-labeled substance within 30 minutes of administration. Radioactivity decreased rapidly, and by 6 hours significant levels could only be found in gastrointestinal tract tissue; by 24 hours, only minimal residual levels were seen. The drug was found to penetrate the blood/brain barrier and placental barrier in trace amounts.

Mexiletine hydrochloride was extensively metabolized in all species studied. In rats, 90% of the radioactivity in urine was due to polar nonextractable conjugates of the hydroxy-metabolites, predominantly glucuronides. The two major metabolites in human urine were a parahydroxy-derivative, which was present as a glucuronide, and a hydroxymethyl derivative which was present in both free and conjugate forms. Multiple dosing studies in rats, dogs and monkeys indicated that accumulation of the compound did not occur.

C. Toxicology

The toxicity of mexiletine hydrochloride was evaluated in a variety of animal species, both rodent and non-rodent, following acute, subchronic and chronic administration. Carcinogenicity, reproduction and mutagenicity studies were also performed. Acute oral and intravenous administration studies in mice, rats, rabbits (p.o. only) and dogs, revealed LD₅₀'s ranging from 112 (dog) to 630 (rat) mg/kg p.o. (which is approximately 5 to 26 times the maximum [24 mg/kg] recommended daily dose in a 50kg human) and 19 to 60 mg/kg i.v. The major signs and symptoms of toxicity were related to the effect of the drug on the central nervous system.

Subchronic oral toxicity studies included the following: mouse, 4 weeks at doses of 40, 80 and 160 mg/kg; rat, 4 weeks at doses of 40, 100 and 250 mg/kg; rat, 13 weeks at doses of 15, 30, 60 and 150-200 mg/kg; and dog, 13 weeks at doses of 3, 9 and 15-30 mg/kg. In the 4-week mouse and rat studies, doses of 80 and 100 mg/kg, respectively, produced slight transient ataxia, whereas the higher doses caused ataxia and convulsions. In male mice, myocardial necrosis (3/25) and deaths (4/25) were recorded at the highest dose level. In rats, a reversible decrease in total protein, increase in cholesterol and a slight increase in liver weights (females only) were noted in the high-dose group; however, no significant pathological findings were observed. In the 13-week rat study, no clinical signs of intolerance other than a slight reduction in mean food consumption in the high-dose males were observed. Histopathological examination revealed fatty changes in the livers of animals in the two highest dosage groups, which appeared to be largely reversible in recovery animals. In the 13-week dog study, diarrhea and emesis were the only symptoms noted. Histopathological examination showed a fatty degeneration of myocardial fibers in 2/6 middle-dose and 4/6 high-dose animals, and peripheral fatty degeneration of the liver in 1/6 high-dose animals.

Subchronic intravenous studies of 4 weeks duration were also conducted in dogs (at doses of 1.5, 3.0 and 13.5 mg/kg), monkeys (at doses of 1.5, 4.5 and 12.0 mg/kg) and rats (at doses of 5, 10 and 20 mg/kg). In the dog and monkey, doses of 12.0 and 13.5 mg/kg produced muscular incoordination, ataxia and convulsions. A transient increase in heart rate was also noted in dogs. In rats, dosages of 10 and 20 mg/kg caused ataxia, tonic spasms, hyperventilation and mortalities (two deaths occurred at 10 mg/kg and 17 [57%] at 20 mg/kg). However, in all three species histopathological examination failed to indicate any treatment-related findings.

Chronic oral toxicity studies were conducted in rats and dogs. Three studies were performed in rats: two of 26-weeks duration at doses of 20, 40, 80 and 120 mg/kg (gavage) and 40, 90 and 200 mg/kg (diet), respectively; and one of 78-weeks duration at doses of 20, 40 and 240 mg/kg (diet). Following oral administration to rats at doses of 80 mg/kg and higher, effects on the central nervous system were observed which included ataxia and convulsions. Other effects included decreased food consumption, weight loss, fatty livers and mortalities. Reversible increases in organ weights (*i.e.*, adrenals, males; ovaries and thyroids, females) were also noted. In the 78-week study, elevations in SGPT and serum alkaline phosphatase values were observed in the high-dose group, but were not associated with any histopathological findings.

In the dog, oral studies of 27 and 52 weeks duration were conducted at dose levels of 5, 10, 20 and 40 mg/kg. Except for an increased incidence of emesis, the 20 mg/kg dose level was well tolerated in both the 27 and 52 week studies. At the high-dose (40 mg/kg), ataxia, tremors, salivation and tonic-clonic convulsions were observed. In the 52-week study, a transient increase in heart rate was also noted and three of the six high-dose animals died (after 36 weeks). Histopathological examination of animals in the 27-week study revealed fatty changes in the heart in the two low-dose groups (2/6 animals at 5 mg/kg, 1/6 at 10 mg/kg) and in the liver in the two high-dose groups (1/6 animals at 20 mg/kg and in 4/6 at 40 mg/kg). In the 52-week study, fatty changes were observed in the livers of 1/6 controls, 2/6 low and 2/6 mid-dose dogs. These changes were not observed in the high-dose group.

In summary, in the subchronic and chronic studies in mice, rats and dogs, some fatty changes have been seen microscopically in the liver but specific liver enzyme levels were unimpressive. Alkaline phosphatase (AP) and SGPT levels were raised in moderate degree and apparently treatment-related only in high-dose animals in the 78-week rat study and were not associated with significant morphologic changes in the liver. Although this compound may be capable of producing minor changes in liver fat content at high doses in rats and dogs, these changes appear to be of little clinical significance.

An 18-month oral carcinogenicity study in mice and a two-year study in rats did not establish a carcinogenic potential for mexiletine hydrochloride at doses up to 160 and 240 mg/kg, respectively, (via dietary admixture) which is 7 to 10 times the maximum recommended human daily dose. Anemias and abnormally low WBC levels were seen sporadically in treated rats. High dose male rats exhibited fatty liver changes at twice the rate of controls.

All three segments of the reproduction studies were performed. Effects of mexiletine on fertility and general reproductive performance were determined in rats; teratogenic potential was evaluated in mice, rats and rabbits; and peri/postnatal effects were studied in rats. Following oral administration of up to 200 mg/kg (approximately 8 times the maximum recommended human daily dose), no effect on fertility was noted; however, drug-treated animals exhibited slight ataxic movements, tremors and weakness immediately post-dosing. Although high dose levels produced side effects in dams, there were no effects on litter parameters or on the

development, behavior, function or reproductive capability of F_{1a}, fetuses of a second litter (F_{1b}) or second generation (F₂). Similarly, oral doses of up to 60 mg/kg administered during gestation and throughout lactation were without effect on litter parameters or progeny. Although segment II studies via the oral route of administration in 3 species failed to reveal a teratogenic potential at doses of up to 80 mg/kg/day, these studies suggested an increased sensitivity to the convulsant action of mexiletine with pregnancy. Rat and rabbit intravenous administration studies at doses up to 10 mg/kg also did not result in any teratogenic effects, although the increased numbers of dead implants observed only in rabbits in the middle dose group (7 dead implants among 14 pregnant animals in the control group, 8/13 at 2.5 mg/kg, 15/15 at 5 mg/kg, 4/15 at 10 mg/kg) suggested a reduced viability at these levels.

Mexiletine hydrochloride did not induce any mutagenic effects in the Ames test, with or without microsomal enzyme activation, at concentrations of 3.2 - 3000 mcg/plate.

V. Medical:

A. Clinical Pharmacology

Eleven phase I and II studies (See Table I) have defined the bioavailability and pharmacokinetics of mexiletine, provided evidence of effectiveness in two dosage regimens and explored drug-drug and drug-disease interactions. In addition, a substantial body of published literature is available reflecting experience with mexiletine in the United Kingdom and Europe. (Mexiletine was marketed in the U.K. in 1975 and subsequently in 31 other countries).

Table 1: Clinical Pharmacology of Mexiletine

Type of Study	Investigator	Enrolled/ Analyzed	Patient Characteristics	Dose of mexiletine	Duration of Treatment	Summary
Bioavailability (open label)	Zinney, M.	4/4	Healthy males 18-50 yrs.	200 mg solution 100 mg capsules 200 mg capsules 400 mg capsules	single dose single dose single dose single dose	Bioavailability of capsule approximately 80% of oral solution
Bioavailability (open label)	Zinney, M.	26/24	Healthy males 18-50 yrs	200 mg solution 200 mg capsules with food 200 mg capsules without food	single dose single dose single dose	No significant difference among treatments.
Pharmacokinetics/ Pharmacodynamics (open label)	Yozeh, S. Follath, F.	58/58	Ventricular ar- rhythmias; CHF(27) 5M/8F	200-250 mg q8h 400-600 mg loading dose	variable single dose	Dose-plasma level relationship found to be linear. Loading dose suppressed ectopy. Therapeutic plasma levels sustained six hours post dose.
Pharmacokinetics/ Pharmacodynamics (open label)	Podrid P. Lown, B.	137/122	Symptomatic VE resistant to conventional drug therapy.	400 mg (loading)	Assessment of single dose	The 400 mg loading dose produced plasma levels within the therapeutic range, and suppressed ventricular ectopy.
Single-blind multiple rising dose response and tolerance also dose-related	Ruskin, J. Steen, S. Thompson, M.	50/35	Inpatients with 130 PVC/hr; 29M/21F	placebo q8h 200 mg q8h 300 mg q8h 400 mg q8h Placebo q8h	Day 1 Days 2-4 Days 5-7 Days 8-10 Days 11-12	Reduction in PVC's was dose-related: 64% at 200 mg, 89% at 300 mg and 90% at 400 mg. Frequency of adverse events was also dose-related.
Multiple rising dose-response and tolerance.(open label)	Podrid, P. Lown, P.	15/15	130 PVC/hr at rest or 12 PVC/ minute during exercise testing	200-400 mg q8h	4-7 days	Mexiletine significantly reduced PVC, couplet and VT frequency at rest and during exercise. Tolerance was dose- related.
Comparison of Dosage Intervals (open label)	Ruskin, J. Steen, S.	31/28	19M/12F patients with chronic VE. Median PVC/hr:199.	100-400 mg q8h 200-450 mg q12h	1-7 days 4-60 days	19 of 28 patients were controlled on q8h dosing. 17 of 19 patients were also controlled on q12h dosing

Table 1: Clinical Pharmacology of Mexiletine
(Continued)

Type of Study	Investigator	Enrolled/ Analyzed	Patient Characteristics	Dose of mexiletine	Duration of Treatment	Summary
Non-invasive hemodynamic assessment (open label)	Podrid, P. Lown, B.	16/14	IM:6/F MI:7; VT:6; CHF:6;Cardiomy- opathy:4	400 mg loading dose 300-400 mg q8h	single dose 3-5 days	Mexiletine did not impair right or left ventricular ejection fractions, and significantly reduced PVC's, couplets and VT.
Non-invasive hemodynamic	Sami, M.	20/18	CHF + ventricular ectopy	400 mg loading dose 300 mg q8h	single dose 7-10 days	Mexiletine did not significantly change stroke volume, end diastolic volume, ejection fraction/rate or cardiac output, and significantly reduced ventricular ectopy.
Pharmacokinetics and Safety in Renal Failure (open label)	Woosley, R.	16/16	Creatinine clearance: 0-10: 6 11-40: 6 41-70: 4	200 mg	1-2 single doses	There were no significant differences across the creatinine clearance groups in AUC, peak plasma concentrations or time-to-peak.
Digitalis-inter-action (open label)	Lowenthal, D.	10/9	Healthy males	Digoxin 0.5mg/day mexiletine 200mg q8h	Days 1-14 Days 8-14	Mexiletine did not alter serum digoxin levels.

1. Bioavailability and Pharmacokinetics

a. Bioavailability and Absorption:

Unlike lidocaine, mexiletine is well-absorbed from the gastrointestinal tract. Plasma mexiletine levels can be reliably quantitated using a gas-liquid chromatographic method. Plasma concentrations after intravenous (100 mg over four minutes) and oral (3mg/kg in solution) administration of mexiletine were obtained in four healthy volunteers (See Figure 1). The area under the mean curve was 2.05 mcg.hr/ml following intravenous administration and 1.81 mcg.hr/ml with oral solution (88% systemic availability). [Prescott, et al: Postgrad Med J 53 (Suppl 1):50-55, 1977]

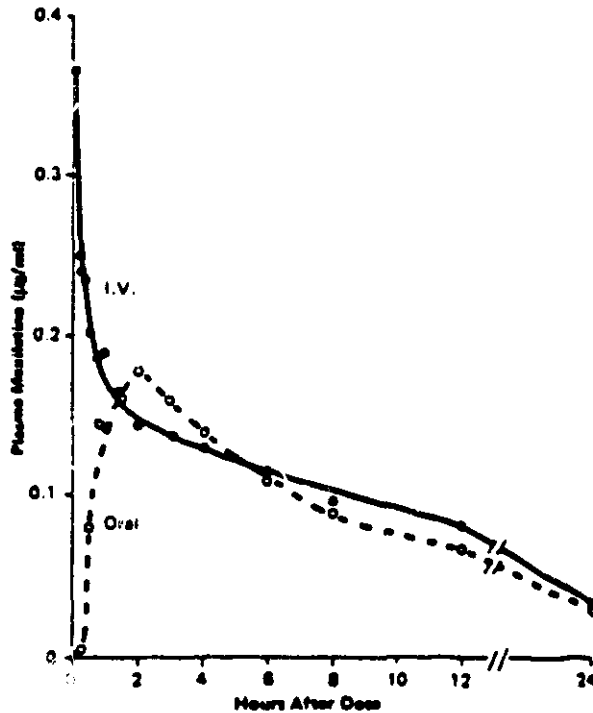


FIGURE 1

Mean plasma mexiletine concentrations in four healthy volunteers given 100 mg intravenously (●—●) and the concentrations corresponding to an equivalent oral dose (○—○). See text.

Two studies (Zinney) compared the bioavailability of mexiletine capsules to oral solution in healthy male volunteers. In the first, a pilot study involving four healthy subjects, plasma concentrations and urinary excretion of mexiletine were evaluated after administration of single oral doses of 200 mg in solution and 100, 200 and 400 mg as capsules. Each volunteer received all four doses; a washout period of seven days separated each dose. The bioavailability of the capsule was approximately 80% of oral solution; for four subjects, this did not differ significantly from 100%. Plasma levels were proportional to dose. Urinary excretion of unchanged mexiletine was low (2-10%) and variable.

The second study by Zinney compared the oral absorption of two 200 mg mexiletine capsules administered with or without food to 400 mg of oral solution in 24 healthy male patients. Treatments were separated by a five-day washout period. As shown in Table 2, areas under the curve for mexiletine taken with or without food did not differ significantly from one another or from the AUC of solution. There was a slight (0.1 hr) but significant increase in the time to peak when mexiletine was given with food.

Table 2

<u>Mexiletine 400 mg</u>	<u>AUC(48 hrs, mcg. hrs/ml)</u>	<u>Peak concen- tration(mcg/ml)</u>	<u>Time-to-peak (hours)</u>
reference solution	12.8 ± 0.70	0.82 ± 0.02	2.8 ± 0.2
capsules without food (% solution)	11.4 ± 0.5 (89.1)	0.72 ± 0.02 (87.8)	2.8 ± 0.2 (100.0)
capsules with food (% solution)	12.2 ± 0.7 (95.3)	0.77 (93.9)	2.9 ± 0.2 (103.6)

b. Dose linearity

Plasma concentrations were proportional to dose in the four-subject bioavailability study, but the number of subjects is too small for the study to serve as primary evidence of dose proportionality. Plasma concentrations were also available on the third day of each dose for twenty patients in the single-blind, multiple rising dose response and tolerance study. An analysis of the mean plasma levels of mexiletine after 200, 300 and 400 mg qd showed the concentrations to be proportional to dose and linear. However, interpatient variation was too great to permit this analysis alone to be accepted as definitive proof of dose proportionality.

Dr. S. Vozech et al included an assessment of dose linearity in their analysis of pharmacokinetic parameters of mexiletine in 58 patients with ventricular arrhythmias [Eur. J. Clin. Pharmacol. 23, 445-451, 1982]. The analysis was based on 452 plasma mexiletine determinations. Individual results as well as group averages were available. Approximately 80% of the individual plasma mexiletine concentrations were between 0.5 and 2.0 mcg/ml, consistent with concentrations commonly reported during chronic therapy.

Vozech and his colleagues used NONMEM, a data analysis approach developed and tested by Sheiner and Beal [Beal S, Sheiner LB(1979) NONMEM Users Guide] to develop population pharmacokinetic parameters for mexiletine. NONMEM has previously been shown to be capable of detecting the difference between linear and non-linear kinetics (as in case of phenytoin). As shown in Table 3, Vozech's estimates of mexiletine pharmacokinetics are similar to results obtained at other centers in both patients and normals, and by both oral and intravenous routes of administration.

Table 3

Pharmacokinetic Parameters of Mexiletine

Population	N	Treatment	k_a (hr ⁻¹)	$t_{1/2}$ (hr)	Vd (l/kg)	K_{el} (l/hr/kg)	t_{lag} (hr)	
Patients [Vozech et al 1982]	58	p.o.	3.1 ± 0.5	0.072	9.7	5.3 ± 0.2	0.38	0.3
Patients [Campbell et al 1978]	10	i.v.	-	0.060	11.6*	6.6 ± 0.9	0.39	-
Normals [Zinney]	24	p.o.	0.9 ± 0.3	0.067	10.3	6.8 ± 1.6	0.45	0.1

* Harmonic mean calculation from Campbell [Br. J. Clin. Pharmacol 6: 103-108]

NONMEM analysis demonstrated that the data fit a one-compartment linear pharmacokinetic model. The assumption of linearity was rigorously tested with respect to time dependence, which was possible because data points were well distributed among a loading dose phase, a nonsteady-state maintenance dose, and a steady-state phase. The data were consistent with linear pharmacokinetics for mexiletine in the recommended dose range. Furthermore, in this representative, stable, patient population, there was no indication of changing pharmacokinetic parameters over the course of treatment with a fixed maintenance dose of mexiletine.

Vozech et al also verified the reliability of the mexiletine analysis by comparing the NONMEM parameter estimates with results reported by others, evaluating the goodness of fit and predicting the serum concentrations of patients not included in the analysis. As shown above, the NONMEM results are consistent with findings in normals and intravenously dosed patients.

Goodness of fit was indicated by the small standard errors of parameter estimates and good agreement between measured data and predicted values and their respective standard deviations. Moreover, estimates of values for mexiletine patients not included in the analysis corresponded closely to those predicted by NONMEM.

Among the patients studied by Vozech et al, there were 27 with congestive heart failure and 8 with abnormal liver function. In this study, the pharmacokinetic parameters of mexiletine were not affected by congestive heart failure or liver disease. According to the authors, the lack of effect of liver disease was probably due to the small number of patients with severe hepatic impairment and the large interpatient variability of mexiletine clearance.

A relevant study by Prescott et al determined the average oral clearance of mexiletine in 101 patients on chronic therapy to be 0.34 l/h/kg, which agrees closely with the Vozech estimate of 0.38 l/h/kg.

Additional evidence of dose linearity was provided by Pottage et al, who reported a significant linear relationship between mean steady-state plasma mexiletine concentration and daily dose in 101 patients on chronic oral therapy [Postgrad Med J 53 (Suppl 1): 155-157, 1977]. Average mexiletine concentration was approximately 2.0 mcg/ml for patients dosed with 1200 mg/day and approximately 1.0 mcg/ml for patients receiving 600 mg/day.

Thus, the available data, most of it obtained from patients in typical therapeutic settings, shows that mexiletine possesses linear pharmacokinetic characteristics in the recommended dose range (up to 1200 mg/day).

c. Metabolism

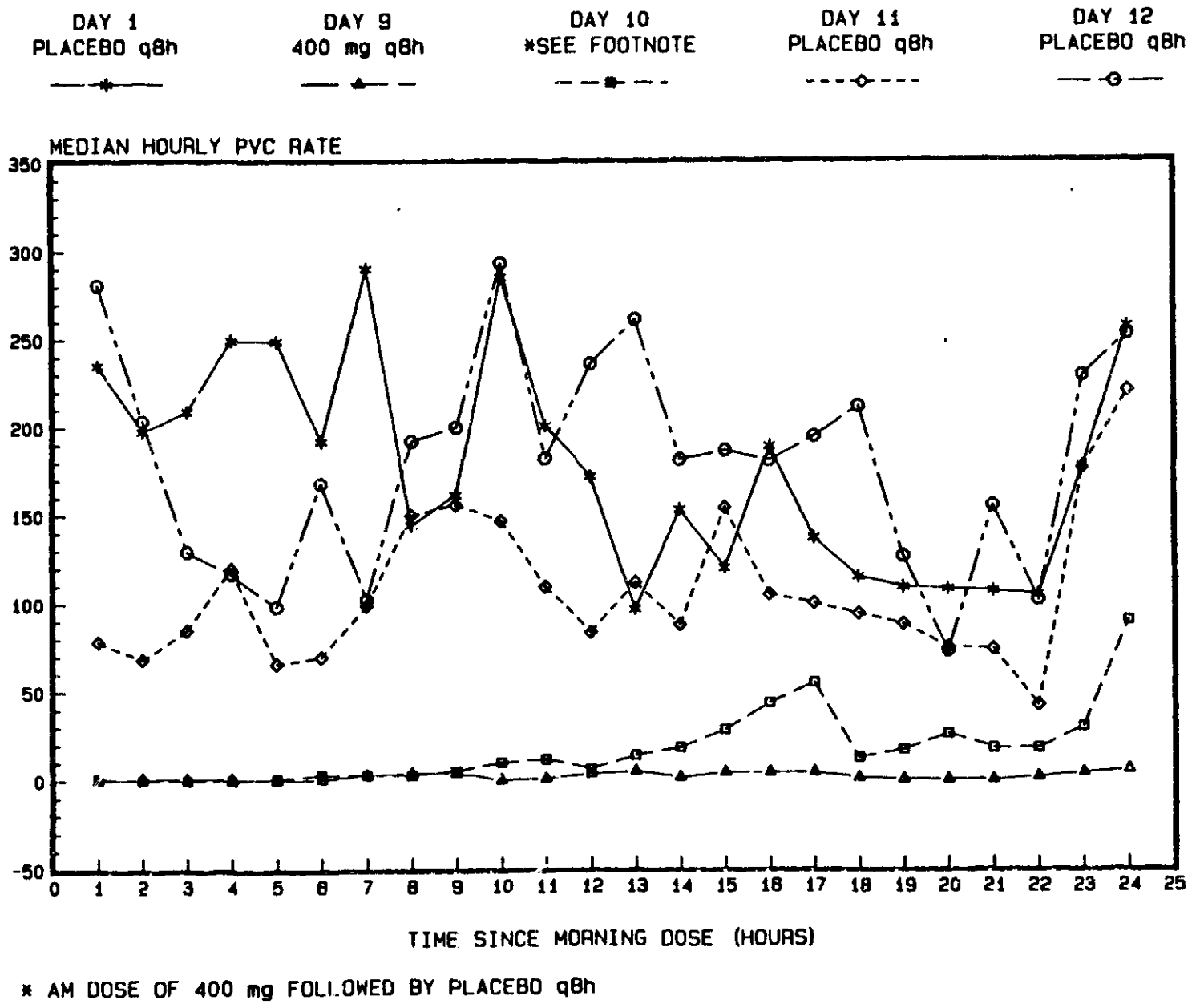
Mexiletine is extensively metabolized in the liver. Further information on metabolism is given in Section 4 (Drug-Disease and Drug-Drug Interaction.)

Several metabolites of mexiletine have shown minimal antiarrhythmic activity in animal models. The most active is the minor metabolite N-methylmexiletine, which is less than 20% as potent as mexiletine. The urinary excretion of N-methylmexiletine in man is less than 0.5%. Thus, the therapeutic activity of MEXITIL is due to the parent compound.

Figure 2 present. the median hourly PVC rates for 15 patients who received the full ten days of prescribed therapy in the dose-ranging study and achieved at least a 70% reduction in PVCs from baseline. Patients received their last full dose of mexiletine therapy on Day 9 and on Day 10 received a single morning dose of 400 mg mexiletine. They then entered the placebo washout phase. The median PVC rates began to increase slightly within 12 hours after the last mexiletine dose. By Day 11, the median frequency was approaching baseline levels and by Day 12 it had essentially returned to baseline. This time course for the return of ectopy is consistent with the plasma half-life of mexiletine (10-12 hours) observed in patients and shows there is no clinically significant plasma level of an active metabolite present whose half-life is longer than that of mexiletine.

FIGURE 2

RETURN OF ECTOPY AFTER DISCONTINUATION OF MEXILETINE THERAPY IN 15 PATIENTS WHO RESPONDED (70% REDUCTION) IN THE DOSE RANGING STUDIES



d. Excretion

Less than 10% is excreted unchanged by the kidney. While urinary pH does not normally have much influence on elimination, marked changes in urinary pH influence the rate of excretion: acidification accelerates excretion while alkalinization retards it. Further information is given in section 4. There is a single report [Lewis, Postgrad. Med J. 57 (671):546-7, Sept. 1981] indicating that mexiletine appears in breast milk in concentrations similar to those in plasma.

2. Pharmacodynamics of Loading and Maintenance Doses of Mexiletine

The recommended dosage of mexiletine, 200 to 400 mg every eight hours, initiated with a 400 mg loading dose where rapid control of arrhythmia is desired, was based on early experience with mexiletine in the United Kingdom and further assessed in the sponsor's program of U.S. studies.

The loading dose is intended to more rapidly yield the therapeutic plasma concentrations of 0.50-2.0 mcg/ml. This range is based on some early British studies and on more recent dose-response information (see section b below).

N.P.S. Campbell et al [(Postgrad Med J 53 (Suppl 1): 114-117, 1977] studied both intravenous and oral administration of mexiletine in 156 patients, most of whom had recent myocardial infarction. Treatment was prophylactic in 33 patients with persistent ST depression, but 123 patients had ventricular ectopy so that effectiveness could be evaluated. At plasma concentrations of 0.5-0.74 mcg/ml, 51% of observations were associated with satisfactory suppression of ventricular ectopy; when plasma levels were between 0.75-2.0 mcg/ml, 79% of observations denoted efficacy and 5.5% were associated with adverse effects. Above 2.0 mcg/ml, there was no increase in effectiveness, while the frequency of adverse effects rose to 30%; the incidence of severe adverse effects (e.g. bradycardia, hypotension) was 19%.

a. Loading Dose

Pettage (1977) and Campbell et al [Br. J. Clin Pharmacol 6:103-108, 1978] both observed that if no loading dose of mexiletine is given and the drug is administered every eight hours, it requires 40 - 50 hours (consistent with the 12 hour half-life of the drug) for steady-state plasma concentrations to be reached. This interval may be shortened by use of a 400 mg loading dose. The sponsor has presented data from two studies which assessed the efficacy of the loading dose.

Podrid and Lown studied 137 patients by continuous electrocardiographic recording for 30 minutes prior to oral administration of 400 mg of mexiletine and for three hours thereafter. One hundred patients had at least 15 PVC's in 30 minutes at rest before administration (median: 225 PVC's/30 minutes). As shown in Figure 3, a median reduction in PVC's of 55.1% was observed 120 minutes after the loading dose, with a maximum reduction of 73% observed at 150 minutes. A 70% or greater reduction in PVC's at rest was observed in 63 of the 100 patients.

Patients were also assessed during exercise 30 minutes before the loading dose was administered and hourly for the next three hours; 122 of the 137 patients had at least two PVC's/three minutes during the five minutes of exercise and 5 minutes of recovery. As shown in Table 4, the 400 mg loading dose of mexiletine reduced PVC's during exercise with the maximum reduction occurring at the last observation.

Table 4

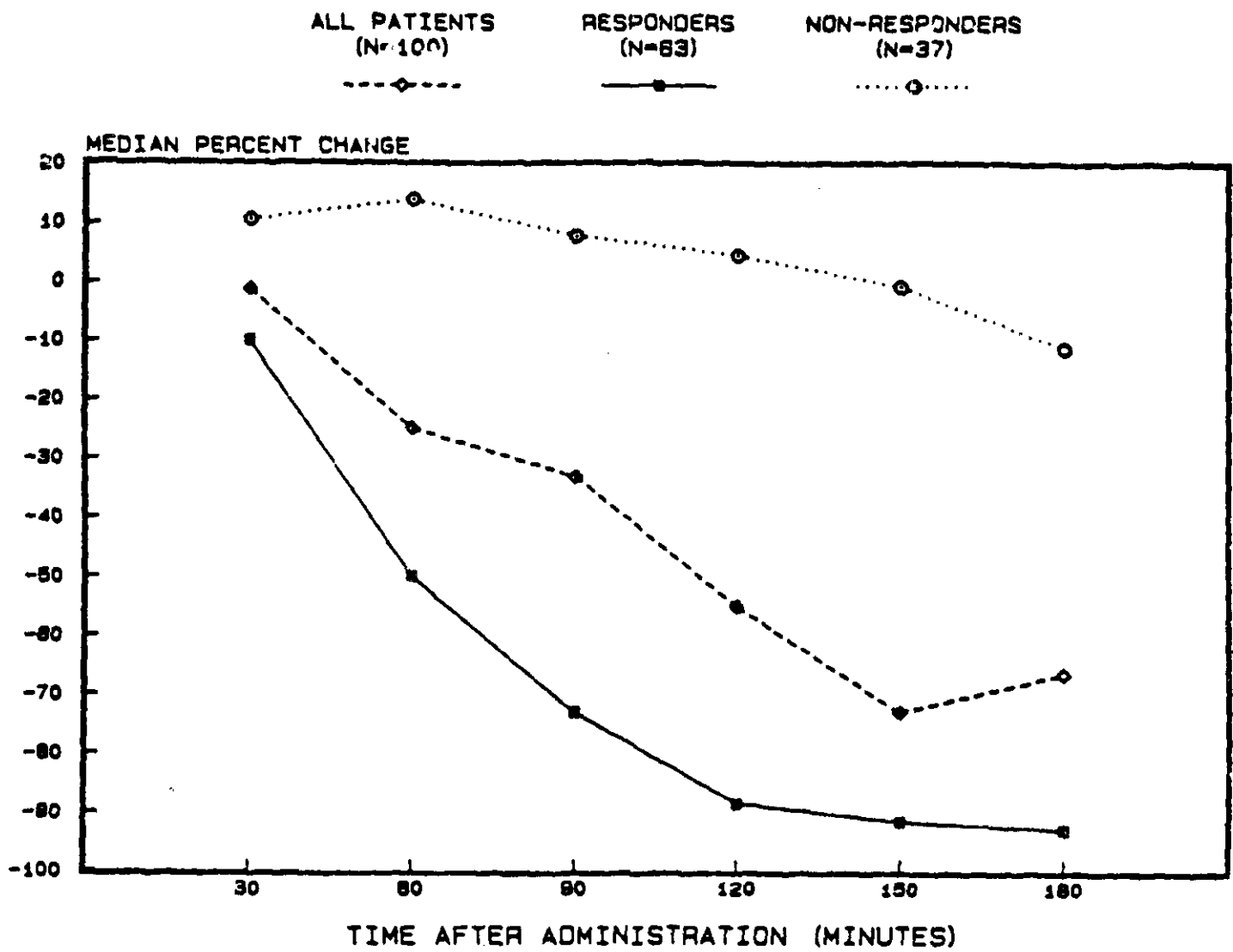
Median % Change
in PVC's During Exercise

<u>Time after 400 mg Dose</u>	<u>All patients (N=122)</u>		<u>Responders* (N=69)</u>		<u>Non-responders (N=53)</u>	
	<u>Median</u>	<u>%Change</u>	<u>Median</u>	<u>%Change</u>	<u>Median</u>	<u>%Change</u>
Control(-30min)	101.0	-	111.0		90	
1 hour	74.0	-36.5	33.0	-61.5	86.0	-12.7
2 hours	38.0	-56.3	11.5	-88.5	82.0	-14.8
3 hours	24.0	-68.5	6.5	-88.5	82.0	-19.6

*At least 70% reduction in PVC's during exercise

FIGURE 3

PERCENT CHANGE IN PVCs/30 MINUTES IN 100 PATIENTS
FOLLOWING A 400 MG LOADING DOSE OF MEXITIL

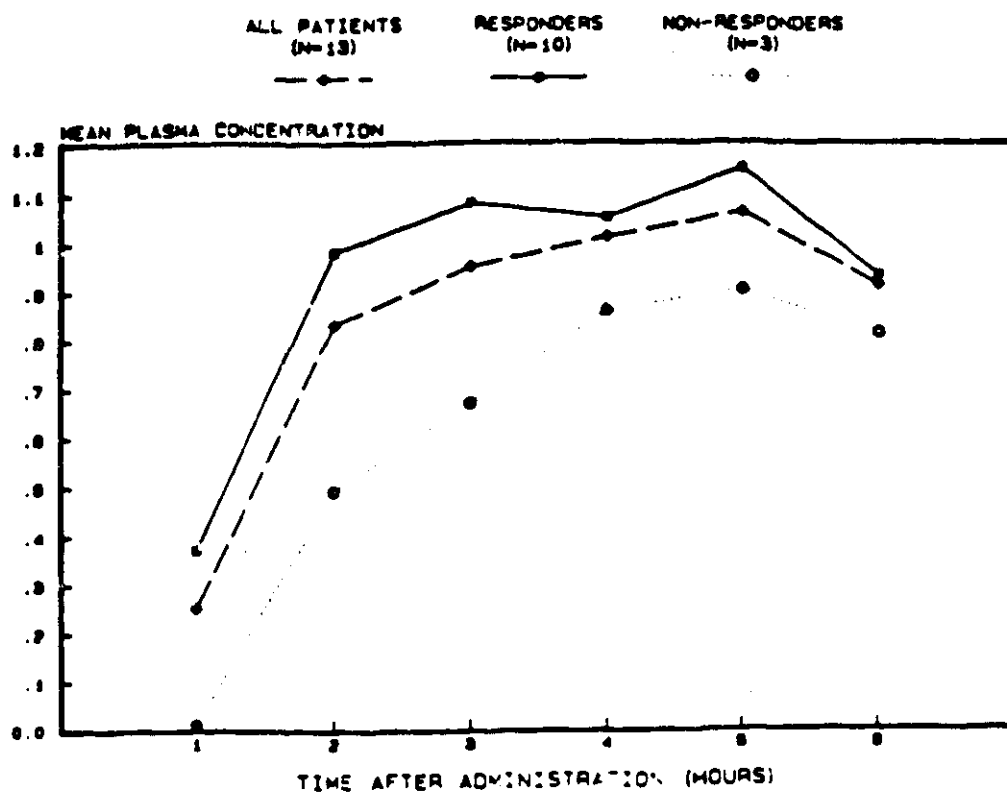


Plasma concentrations were obtained for 57 of the patients in this study, and were similar in responders and non-responders. Mean plasma levels were within the therapeutic range (0.5-2.0 mcg/ml) one hour after dosing and continued to rise at the second and third hour, consistent with the improved response seen by Campbell as plasma concentrations above 0.75 mcg/ml are reached.

<u>Time after Dose</u>	<u>Mean mexiletine plasma level (mcg/ml) (n=57)</u>
1 hr	0.74±0.11
2 hr	0.96±0.10
3 hr.	1.15±0.10

Vozech and Follath (1982) assessed the 400 mg mexiletine loading dose in 13 patients with chronic ventricular ectopy. As shown in Figure 4, the 400 mg dose suppressed ventricular ectopy and maintained therapeutic plasma concentrations throughout the six hour observation period.

MEXITIL PLASMA LEVELS OVER SIX HOURS IN 13 PATIENTS FOLLOWING A 400 MG LOADING DOSE



HOURLY PERCENT CHANGE IN PVC RATE IN 13 PATIENTS
FOR SIX HOURS FOLLOWING A 400 MG LOADING DOSE OF MEXITIL

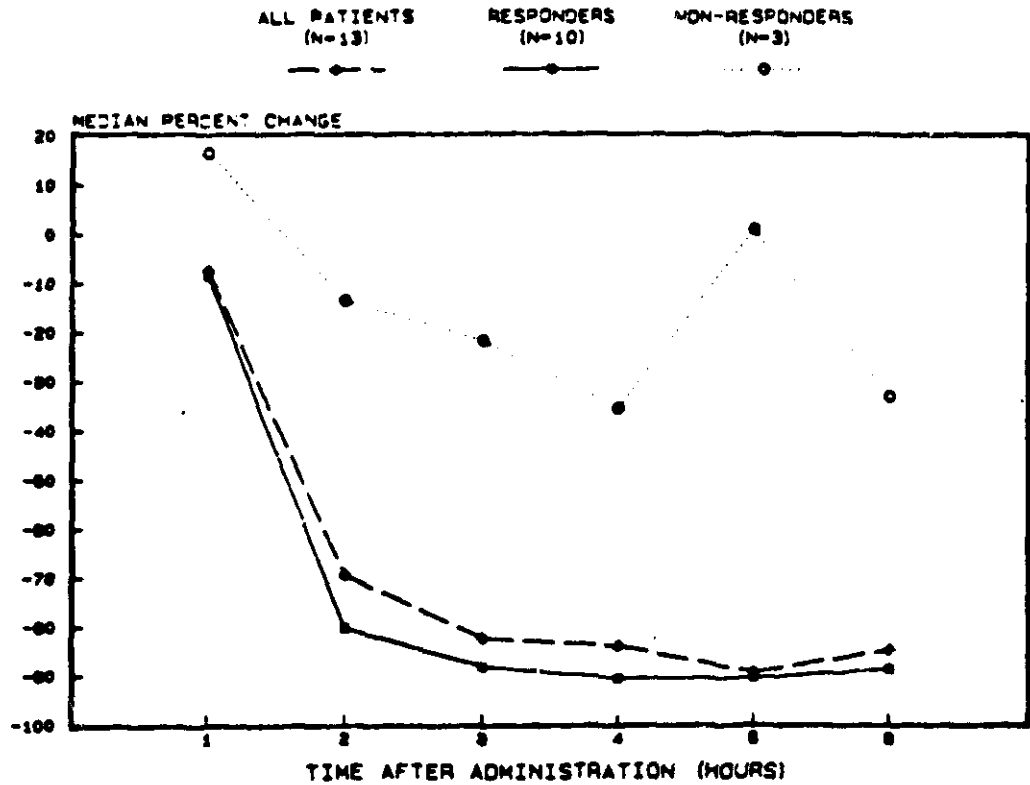


FIGURE 4

b. Dose Response

Dose response to mexiletine was investigated in a multi-center single-blind dose-ranging study. This study was designed to assess the efficacy and tolerability of mexiletine in patients with chronic ventricular ectopy (at least 30 PVC's/hour) by comparing three dose levels to placebo lead-in and run-out periods. The schedule of treatments was:

Day 1	Placebo
Days 2-4	200 mg q8h
Days 5-6	300 mg q8h
Days 7-9	400 mg q8h
Days 10-12	Placebo

Twenty-four hour Holter ECG monitoring was performed on each day of the study; efficacy at each dose was assessed by comparing PVC frequencies on the last day of each dose regimen (when steady state should have been reached) to baseline. When a patient had adverse effects at the 300 mg or 400 mg dose level, the dose was reduced to the previous level.

Fifty patients entered the study at three centers, but 15 could not be analyzed for efficacy because of: medication errors (5); failure to obtain a placebo Holter recording (5); insufficient PVC rate at entry (2); intercurrent non-cardiac illness (2); or concurrent administration of lidocaine (1).

As shown in Table 5, all 35 analyzable patients completed 200 mg q8h; 20 completed all three dose levels.

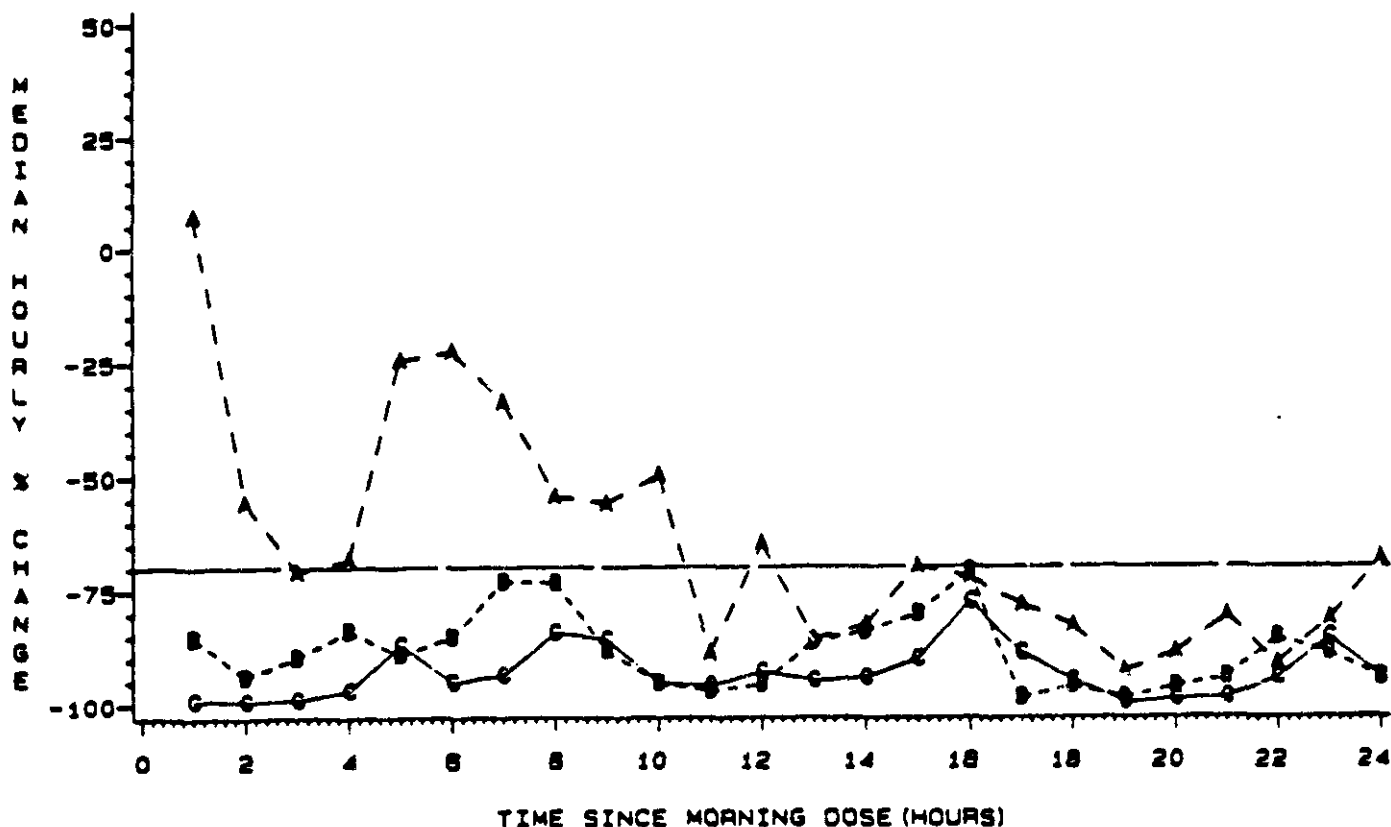
Table 5

PVC Reduction in Mexiletine Dose-Ranging Trial

	200 mg q8h	300 mg q8h	400 mg q8h
Number of Pts. completing dose level	35	31	20
No. of Pts. with ≥70% PVC reduction (% of Pts.)	14 (40%)	20 (65%)	15 (75%)
Median % reduction PVC's all pts.	64%	89%	95%

In this study, which did not include a loading dose, there was a marked drop ($\pm 55\%$) in PVC rate in patients who responded to mexiletine within two hours after the first 200 mg dose. During the first day, PVC's increased somewhat near the end of the eight hour dose interval. By the second day of active therapy, the PVC rate was reduced by at least 70% from the baseline obtained during placebo therapy throughout the dose interval. See Figure 5. Presumably, peak concentrations on day 1 entered the therapeutic range but trough values did not stay in that range. With accumulation on days 3 and 4, the therapeutic range was maintained throughout the day.

MEDIAN PERCENT CHANGE FROM BASELINE IN PVC'S/HOUR
FOR 14 PATIENTS WHO RESPONDED (70% REDUCTION)
TO 200MG MEXITIL IN THE DOSE RANGING STUDIES



LEGEND:
A=DAY 2
B=DAY 3
C=DAY 4

FIGURE 5

In the twenty patients who completed all three dose levels, the reduction in PVC's, proportion of responders and plasma levels of mexiletine were clearly dose related, at least up to 300 mg. (See Figures 6 and 7). The increase from 300 to 400 mg, with a resulting increase of plasma concentrations from peaks of 2.2 to 2.8 and troughs of 1.0 to 1.3, did not have much effect.

Lown and Podrid evaluated 15 patients for response to mexiletine by means of 24-hour Holter monitoring and treadmill exercise testing before and on the last day of mexiletine therapy. Patients were treated for up to seven days. On Day 1, they received a 400 mg loading dose of mexiletine followed by 200 mg at eight hour intervals. On days 2, 3 and 4, the dose was increased daily by 100 mg increments up to a maximum of 400 mg q8h. Treatment at the lower dose was resumed if side effects occurred when the dose was increased.

Holter findings revealed a statistically significant reduction in the median PVC rate from a baseline of 166/hour to 29/hour at the end of treatment ($p = 0.0008$). The median percentage of hours in which couplets or ventricular tachycardia occurred dropped from 39% to 6% for couplets ($p = 0.0008$) and from 5% to 0% for VT ($p = 0.04$).

On exercise testing at the end of treatment, median PVCs/minute were significantly reduced as compared to baseline from 5.0 to 0 during the pre-exercise period ($p = 0.0118$), from 5.4 to 0.2 during exercise ($p = 0.002$) and from 10.0 to 0.5 ($p = 0.008$) during the post-exercise period.

MEDIAN % REDUCTION

NUMBER OF RESPONDERS

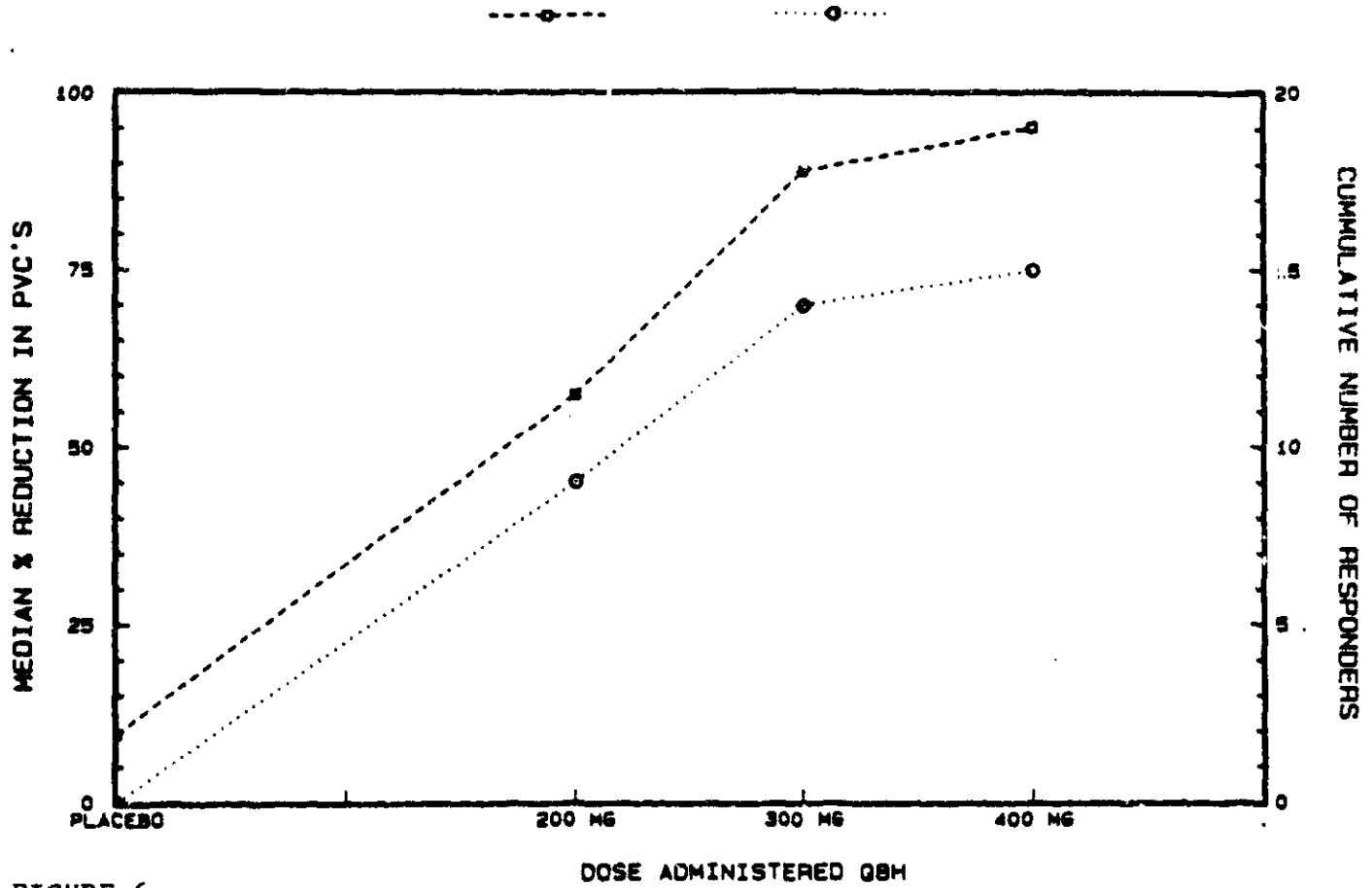


FIGURE 6

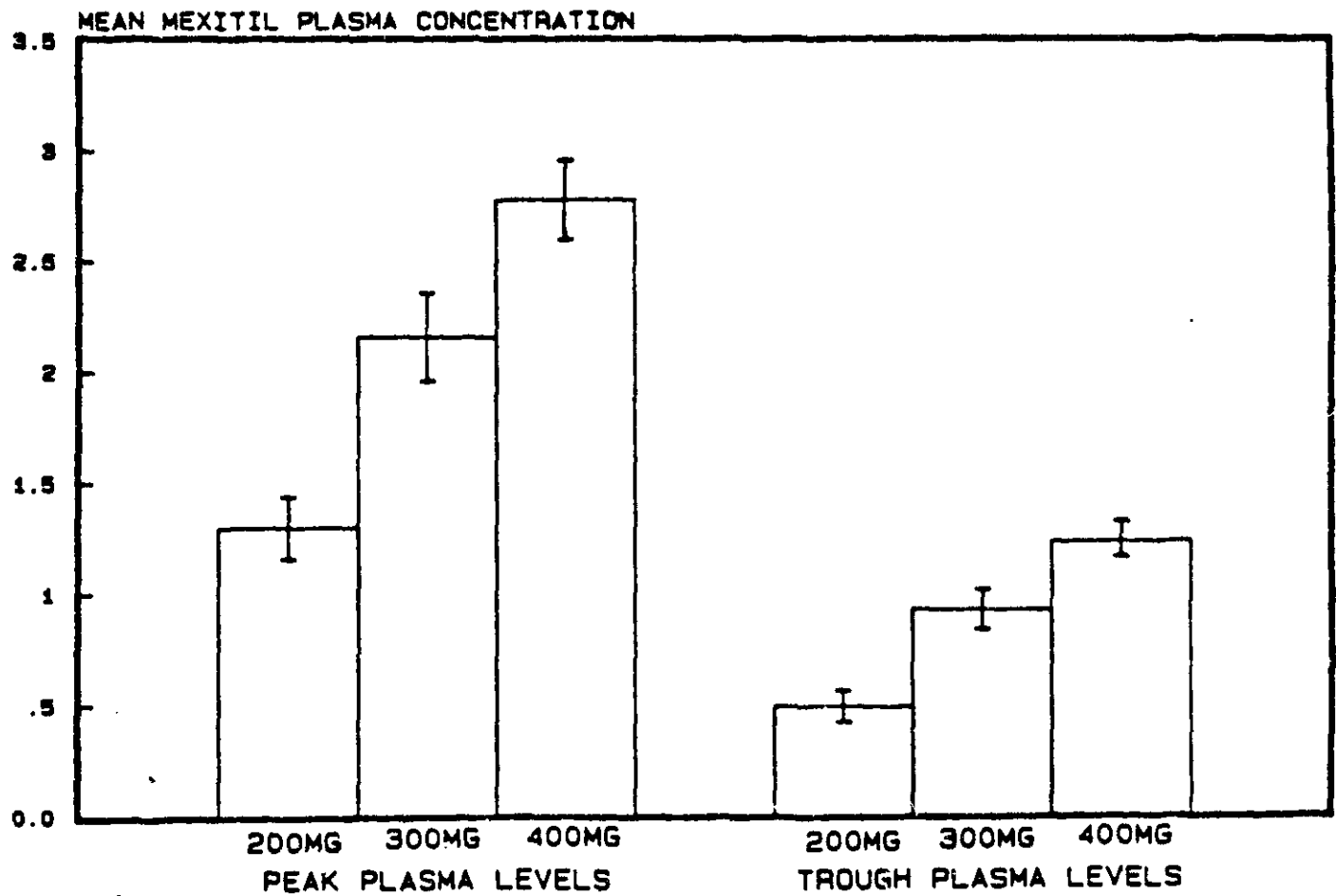


FIGURE 7
±STANDARD ERROR

c. Q12H Dose Regimen

Mexiletine's half-life of 10-12 hours suggests that twice daily administration may be effective, at least in some patients. A single-blind study compared the q8h and q12h regimens in 31 patients at two centers. Patients with chronic ventricular ectopy (at least 30 PVC's/hr) were evaluated by 24-hour Holter recordings on both dosage regimens. After two 24-hour baseline Holter recordings, patients were given a 400 mg loading dose of mexiletine, followed by 200 mg q8h. The dose was increased by 100 mg q8h to a maximum of 400 mg if subsequent Holter recordings did not show total suppression of ventricular tachycardia and at least 50% reduction in PVC rate. A confirming Holter recording was obtained one week later.

If satisfactory control was observed and confirmed during q8h dosing, the patient was switched to the q12h regimen. Dosage was again titrated until a 24-hour Holter ECG showed total suppression of VT and greater than 50% reduction in PVC's.

Three patients could not be evaluated; two had insufficient PVC's at study entry (less than 30/hr) and one was given disopyramide and mexiletine during the baseline evaluations.

Nineteen of the 28 analyzable patients (68%) were controlled on the q8h dose regimen; 17 of these 19 patients (89%) were successfully controlled on q12h dosing as well.

As shown in Figure 8, PVC suppression was consistent throughout the dose interval for both 8 and 12 hour dosing schedules. The mean daily dose of mexiletine was 600 mg when given q8h and 655 mg q12h.

Mexiletine plasma levels were available at the end of the dose interval and two hours post dose for seven patients:

Mean Mexiletine Plasma Levels (N=7 pts.)

	<u>end of dose interval</u>	<u>2 hours post-dose</u>
q8h	1.00 mcg/ml	1.29 mcg/ml
q12h	0.93 mcg/ml	1.79 mcg/ml

The trough levels were comparable on both regimens; the higher two-hour value for the q12h schedule can be attributed to the higher individual dose (mean 327 mg q12h vs 200 mg q8h). However, on each dose regimen, both peak and trough plasma levels were well within the target range of 0.5 to 2.0 mcg/ml. The data suggest that it will be possible to maintain some patients on a q12hr schedule, but that other patients more sensitive to the side effects of mexiletine or resistant to its effectiveness will do better with the smaller peak-trough differences attainable with q8hr dosing.

MEDIAN NUMBER OF PVC'S/HOUR
FOR 19 ANALYZED PATIENTS

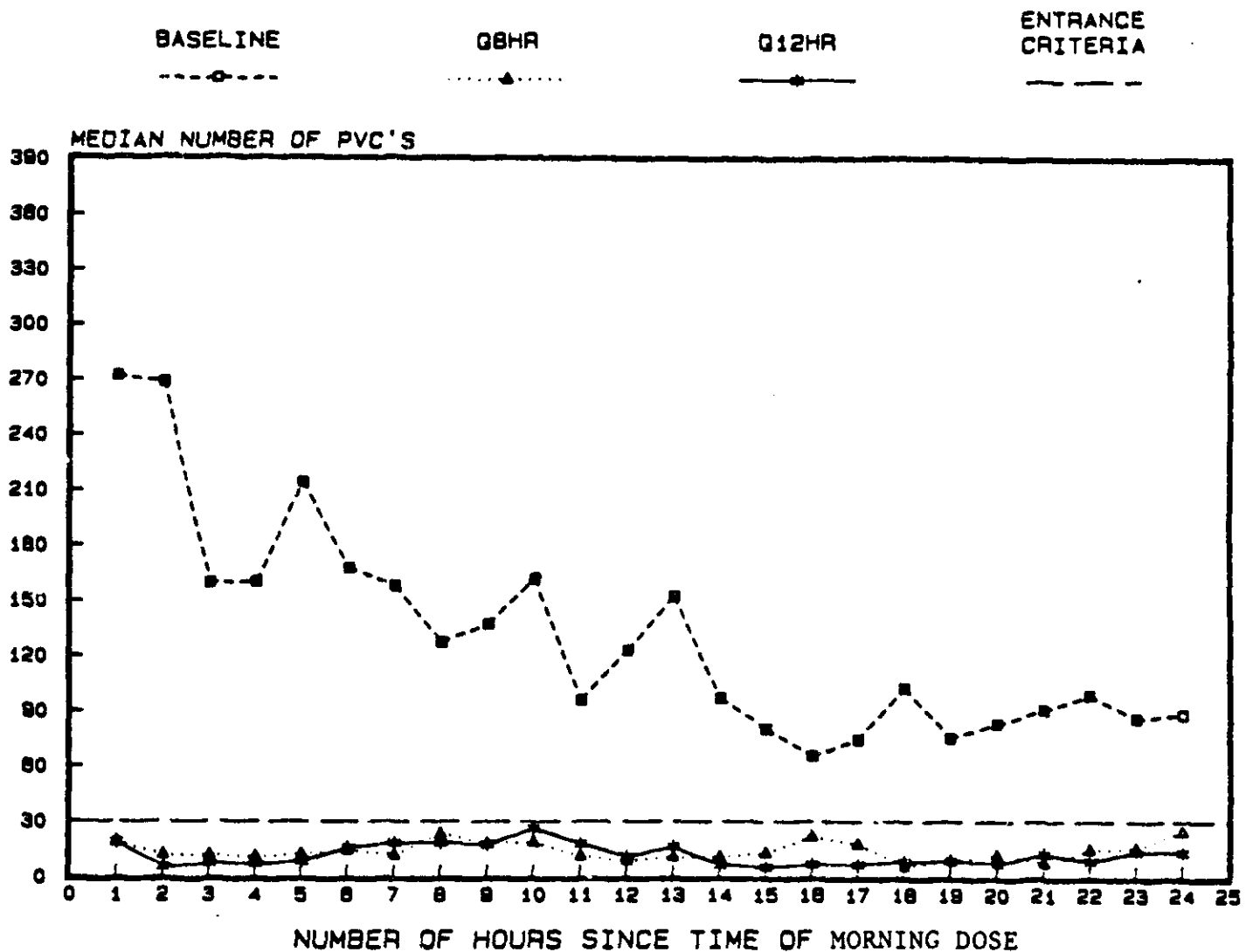


FIGURE 8

3. Hemodynamic effects of Mexiletine

Non-Invasive

Chronic oral mexiletine therapy had no effect on radionuclide ejection fractions in 35 patients with moderate to severe left ventricular ejection fractions in the studies conducted by Podrid and Sami (see Table 1).

Invasive studies

There have been eight reports of invasive measurement of hemodynamic parameters during mexiletine (see following reference list). The 123 patients studied had a variety of cardiac problems:

<u>Cardiac Status</u>	<u>No. of Patients</u>
Acute MI	52
Old MI	31
Valvular HD	16
ASHD	13
Digitalis Recipients	6
Myocarditis	2
Other	3
	<u>123</u>

Mexiletine was administered orally in two studies and intravenously in six.

Kuhn et al studied the effects of a single oral dose of 600 mg of mexiletine in 13 patients with chronic ventricular ectopy. Hemodynamic data were obtained for at least 30 minutes prior to drug administration and for six hours thereafter. Three hours after dosing the mean pulmonary artery diastolic pressure (PADP) increased from 12.1 ± 3.2 to 13.8 ± 3.5 mmHg and the mean cardiac output decreased from 7.4 ± 0.93 to 6.44 ± 0.79 l/min (see Figure 9). These changes were not statistically significant.

Merx et al studied 57 patients on the first and second days of acute myocardial infarction; 29 were randomized to mexiletine treatment and 28 to a nontreatment control group. Mexiletine was given as an intravenous loading dose of 2mg/kg body weight. This was followed two hours later and then every six hours by 200 mg orally for a total of 48 hours. Hemodynamic monitoring was performed in 22 patients in the mexiletine group and 21 patients in the control group. Pulmonary artery end diastolic pressure, cardiac index, systemic blood pressure and

heart rate were measured before mexiletine therapy and 3 to 6 times per 24 hours according to the clinical situation during mexiletine administration. Although differences were not statistically significant, PADP decreased less in the mexiletine group (6% day 1 and 2% increase day 2) than the control group (14% day 1 and 24% day 2). Over the same observation period, cardiac index decreased more in the mexiletine group (10% day 1 and 6% day 2) than the control group (3% day 1 and 6% day 2). See Figure 9.

KUHN, 1977 (single 600 mg dose)				
	<u>Mean PADP*</u>		<u>Mean Cardiac Output</u>	
Baseline	12.1 ± 3.2 mm Hg		7.4 ± 0.9 l/min	
3 hours post dose	13.8 ± 3.5 mm Hg		6.4 ± 0.8 l/min	

MERX, 1978 ^a (200 mg q6h)				
	<u>Mean PAEDP**</u>		<u>Mean Cardiac Index</u>	
	<u>Mexiletine</u>	<u>Control^b</u>	<u>Mexiletine</u>	<u>Control^b</u>
Baseline	12.8 (n=21)	14.4 (n=16)	3.1 (n=21)	3.2 (n=16)
Day 1	12.0 (n=22)	12.4 (n=16)	2.8 (n=22)	3.1 (n=16)
Day 2	13.0 (n=17)	11.0 (n=15)	2.9 (n=17)	3.0 (n=15)

*PADP - pulmonary artery diastolic pressure
 **PAEDP - pulmonary artery end-diastolic pressure
^aValues are approximated from graphs
^bControl group received no treatment

FIGURE 9: Mean Values for Hemodynamic Parameters Following Oral Administration of Mexiletine

The differences between the groups were not statistically significant. The findings of Kuhn and Merx suggest oral mexiletine may have a mild myocardial depressant effect.

Intravenous doses ranging from 1.0-3.6 mg/kg were administered at the other six centers. Pulmonary artery pressure appeared to rise with increased dosing while cardiac output was reduced slightly or not at all. No consistent change was seen in arterial pressure.

At the highest doses used (3.6mg/kg), two patients treated by Bernard et al in the acute stage of myocardial infarction developed an adverse cardiovascular reaction of hypotension and bradycardia after rapid intravenous infusion. This responded to treatment with i.v. atropine. Otherwise no symptomatic, clinically evident deterioration was seen in any of the patients.

The invasive hemodynamic studies suggest that mexiletine has a mild myocardial depressant effect and a mild vasoconstrictive effect. With oral mexiletine therapy, only mild, statistically insignificant, increases in pulmonary artery pressures occurred. Table 6 presents the mexiletine infusion rates, peak plasma levels, and both significant and insignificant changes in hemodynamic parameters observed in these studies.

TABLE 6

Author/ Number of Patients	NEXITIL®: IV Dose and Rate	Peak Plasma Level	Mean Baseline, Peak & Time of Peak PAP	Hemodynamic Parameters	
				Change Statistically Significant	Change Not Statistically Significant
Baniw/10	1.5mg/kg over 30 sec.	NR	NR	At Rest: ↑ HR, ↑ PASP, ↑ LVEDP During 2nd minute of atrial pacing at 100 bpm: None	At Rest: ↑ CO, ↓ SV, ↑ MPAP, and ↑ LVdp/dt During 2nd minute of atrial pacing at 100 bpm: CO, SV and MPAP unchanged, ↑ PASP & LVEDP, ↓ PLVdp/dt
Bernard/10	25 mg/min	NR	11.9 mm Hg at baseline, 15.5 mm Hg at 60 min (p < 0.01)	During 2nd minute of handclap exercise: ↓ CO, ↓ PLVdp/dt	During 2nd minute of handclap exercise: ↓ HR, ↓ SV, ↓ PASP, ↓ MPAP, ↑ LVEDP, ↓ LVSP
				At 10 + 20 min post dose (mean of two observations): ↑ HR, ↓ CO, ↓ SV, ↑ MBP & DBP, ↑ PASP, ↑ MPAP, ↑ PCWP	At 10 + 20 min post dose (mean of two observations): ↑ SBP, ↑ SR
				At 60 min post dose: ↑ MBP & ↑ DBP, ↑ SR, ↑ PASP, ↑ MPAP, ↑ PCWP	At 60 min post dose: ↓ HR, CO no change, ↓ SV, ↑ SBP
Campbell/16	6/16: 150 mg bolus	NR	13 mm Hg at baseline, 15 mm Hg at 5 min (p < 0.02)	At 5 min post injection: ↑ MPAP	At 5 min post injection: ↑ HR, ↑ MPAP, ↑ LVEDP, CI no change, ↓ SWI, ↑ PVR, ↑ SVR
				At 10 + 20 min post injection: None	At 10 + 20 min post injection: At 20 mins no change in HR, MPAP, LVEDP and CI, ↑ MPAP, ↑ SWI, ↑ PVR & ↑ SVR

TABLE 6
(Continued)

Author/ Number of Patients	HEXITIL®: IV Dose and Rate	Peak Plasma Level	Mean Baseline, Peak & Time of Peak PAP	Hemodynamic Parameters	
				Change Statistically Significant	Change Not Statistically Significant
Campbell cont'd	5/16: 2.7 mg/kg over 2-5 min	NR	16 mm Hg at baseline, 19 mm Hg at 2 min (p < 0.05)	At 2 min post injection: ↑ MPAP	At 2 min post injection: All factors (except mean PAP) at 2, 5 and 10 mins post injection. At 10 mins: ↑ HR, MFAP no change, ↓ LVFSP, ↓ LVEDP, ↑ CI, ↑ SWI, ↓ PVR & ↓ SVR
Henrard/15	1.5 mg/kg at 25 mg/min	NR	23.0 at baseline, 23.7 at 15 min (n.s.)	5 mins post injection: ↑ HAPS, ↑ HAPM & ↑ SVR 15 mins post injection: ↑ SVR	5 mins post injection: ↑ HAPD, ↓ HR, ↓ CI, ↓ SV, ↑ RAP, ↑ PAP, ↑ PCWP & ↑ PVR 15 mins post injection: ↑ HAPS, ↑ HAPD, ↑ HR, ↓ CI, ↓ SV, ↓ RAP, ↑ PAP, ↑ PCP, ↑ SVR & ↑ PVR
Pozenel/24	1-2 mg/kg bolus then 350-500 mg over 20-50 min	NR	16.1 mm Hg at baseline, 15.9 mm Hg post infusion (n.s.)	30 mins post injection: ↓ SV & ↑ SVR Post-infusion None	30 mins post injection: ↑ HR, ↓ CI, ↓ SV, ↑ MAP, ↑ RAP, ↑ PAP, ↑ PCP, ↑ SVR & ↑ PVR Post-infusion ↓ SBP, ↓ DBP, ↓ MBP, ↓ HR, ↓ CI, ↑ SVI, ↓ LVSW, ↓ TPR ↓ PIHR/100, ↓ TTI, ↓ MPAP & ↓ EDPAP

TABLE 6
(Continued)

Author/ Number of Patients	HEXITIL®: IV Dose and Rate	Peak Plasma Level	Hemodynamic Parameters		
			Mean Baseline, Peak & Time of Peak PAP	Change Statistically Significant	Change Not Statistically Significant
Saunamaki/6	10 mg/min for 10 mins.	2.70 ug/ml ± 0.68 at	31.7 at baseline	13-22 min after initiation of infusion Statistical significance for mean values not given ↑ HR, CO, PASP, PADD, mPAP, PCWP ↓ SV, BASP, BADD, BAMP, LVSW, PVR, PEVR	
	↓ 6.5 mg/min during testing	10 min after initiation of infusion, 1.68 ± 0.73 at 15 min.	37.2 post infusion		

Abbreviations

- CO Cardiac Output
- SV Stroke Volume
- HR Heart Rate
- PASP Pulmonary Artery Systolic Pressure
- PADD Pulmonary Artery Diastolic Pressure
- mPAP Mean Pulmonary Artery Pressure
- LVEDP Left Ventricular End-Diastolic Pressure
- LVSP Left Ventricular Systolic Pressure
- PLV dp/dt Peak Left Ventricular dp/dt
- MBP Mean Blood Pressure
- DBP Diastolic Blood Pressure
- PCWP Pulmonary Capillary Wedge Pressure
- SR Systemic Resistance
- mFAP Mean Femoral Artery Pressure
- SWI Stroke Work Index
- PVR Pulmonary Vascular Resistance
- PEVR Peripheral Vascular Resistance
- HAP Humeral Artery Pressure (S-Systolic, D-Diastolic, M-Mean)
- RAP Right Arterial Pressure
- LVSW Left Ventricular Stroke Work
- TPR Total Peripheral Resistance
- TTI Tension Time Index
- EDPAP End Diastolic Pulmonary Artery Pressure
- PMHR/100 Pressure Heart Rate Product Divided by 100
- BAP Brachial Artery Pressure (S-Systolic, D-Diastolic, M-Mean)

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4. Drug-Disease and Drug-Drug Interactions of Clinical Significance

Information on a number of drug-disease and drug-drug interactions involving mexiletine has appeared in the medical literature. Two studies (see Table 1) were conducted by the sponsor: one investigated mexiletine pharmacokinetics and safety in 16 patients with varying degrees of renal failure; the other assessed the effect of concurrent mexiletine administration on serum digoxin levels in healthy volunteers.

a. Drug-Disease Interactions

Hepatic Disease

The plasma elimination half-life of mexiletine was significantly increased to 25.3 ± 6.4 hours in eight cirrhotic patients compared to 17.4 ± 1.8 in seven healthy subjects [El Allaf et al (1982a)]. Similar results were described by Nitsch et al (1982) who found an elevated mean peak plasma concentration of 2.21 ± 0.94 mcg/ml in nine patients with severe hepatic disease compared with 0.63 ± 0.22 mcg/ml in 24 control patients with cardiac disease. In contrast Vozen et al (1982) found no change in mexiletine kinetics in eight patients with abnormal liver function. Transaminases were elevated in all 8 of these patients and in 4 of the 8, serum bilirubin was greater than 1.3 mg% and the prothrombin time was less than 60% of normal. The authors attributed the lack of change to the small number of patients with severe hepatic impairment and the large interpatient variability of mexiletine clearance.

Thus, smaller doses of mexiletine may be required to maintain therapeutic plasma levels in patients with moderate to severe hepatic disease. These patients should be monitored carefully, particularly during dose adjustments.

Congestive Heart Failure

Leahey (1980b) found a mexiletine mean elimination half-life of 15.4 ± 5.8 hours in 14 patients with left ventricular failure compared to 8.1 ± 1.8 hours in normal volunteers. However, Campbell et al (1978) found no significant prolongation of elimination half-life in six patients with clinical evidence of congestive heart failure. Similarly, in patients with cardiac insufficiency, Pottage et al (1978; 13 patients) and Nitsch et al (1982a; eight patients) found no change in mexiletine plasma levels. El Allaf et al (1982a) investigated the kinetics of mexiletine in nine patients with clinical and hemodynamic manifestations of advanced right-sided heart failure. The mean plasma half-life in these patients was increased to 23.2 ± 11.2 hours compared to 11.4 ± 1.8 hours in seven normal subjects.

Therefore, smaller doses of mexiletine may be required to maintain therapeutic plasma concentrations in patients with severe congestive heart failure and secondary hepatic dysfunction. These patients should be monitored carefully during therapy.

Renal Disease

Renal excretion accounts for only a small portion of mexiletine elimination (about 10% is excreted unchanged in the urine). Consistent with this, studies in patients with renal impairment have shown little or no change in the pharmacokinetics of mexiletine. In a study conducted by Woosley, 16 patients with creatine clearances of 5-55 ml/min received single doses of 200 mg of mexiletine. Areas under the curve were similar for patients with creatinine clearances of less than 10, 10-30 and 30-70 ml/min. In six patients a second dose of 200 mg was given during hemodialysis. Mean mexiletine plasma concentrations during dialysis were very close to those obtained on a non-dialysis day. El Allaf et al (1982b) found no significant change in the elimination half-life of mexiletine after chronic oral administration of 50 mg t.i.d. in patients with renal impairment and creatinine clearances of 10-30 ml/min. Patients with creatinine clearances less than 10 ml/min, however, showed an increase from 10.4 hr in normals to 15.7 hr. Nitsch et al (1982a) found no increase in peak and trough blood levels in 14 patients with serum creatinines of 1.8 to 6.3 mg%.

Thus, patients with severe renal impairment, i.e., with creatinine clearances less than 10 ml/min, may require slightly lower doses of mexiletine to maintain therapeutic concentrations. These patients should be carefully monitored during therapy.

Acute Myocardial Infarction

Delayed and possibly incomplete absorption of mexiletine has been described in patients with acute myocardial infarction [Prescott et al, (1977); Pottage, et al (1978)]. Administration of narcotics further delayed absorption, prolonging the time from initial dosing to peak concentration from approximately 2-3 hours to 6 hours. The delay in absorption associated with acute myocardial infarction may be related to an increase in gastric emptying time; narcotics exacerbate this process.

Pentikainen et al (1983) likewise found delayed absorption of mexiletine in 7 patients with acute myocardial infarction, 6 of whom had received oxycodone. The patients were studied first within 24 hours after the onset of symptoms of acute myocardial infarction and then re-studied 7-14 days later. A single dose of 400 mg of mexiletine was administered orally. Samples of venous blood were collected at specified intervals through 48 hours after dosing and all urine was collected through 72 hours after dosing. During the acute phase of myocardial infarction the mean time from dose administration to peak concentration was 4.68 ± 2.04 hours and during the chronic phase, 1.45 ± 0.17 hours (N.S.). Areas under the plasma concentration-time curves and plasma protein binding of mexiletine were similar during the acute and chronic phases of myocardial infarction. The elimination half-life, however, was 15.03 ± 0.61 hours during the acute phase and 11.75 ± 0.80 hours (p less than 0.01) in the chronic phase.

Pentikainen et al (1984) also studied the kinetics of intravenous mexiletine during acute myocardial infarction in 11 patients using a study design similar to that described above for oral mexiletine. Patients were studied within 24 hours of the onset of myocardial infarction and again 7 - 14 days later. An intravenous dose of 200 mg mexiletine was infused over a 30 minute period. Samples of venous blood were drawn at intervals through 48 hours after dosing and all urine was collected through 72 hours after dosing. During the acute phase of myocardial infarction the mean plasma terminal half-life was 14.7 ± 3.4 hours and 11.3 ± 0.4 hours (p less than 0.05) during the chronic phase. The mean steady-state volume of distribution was 578 ± 97 liters during the acute phase and 405 ± 33 liters during the chronic phase (p less than 0.05). Plasma protein binding was similar for the acute and chronic phase as was total plasma clearance.

Thus, during the first 12-24 hours of acute myocardial infarction the absorption of mexiletine may be delayed and incomplete. Administration of narcotics during this time exacerbates the absorption delay. Plasma elimination half-life is mildly prolonged to approximately 15 hours during the first 12-24 hours of acute myocardial infarction.

b. Drug-Drug Interactions

Absorption

Several pharmacokinetic drug interactions have been described that affect the absorption of mexiletine. Mexiletine, a weak base (pK_a 8.4), is poorly absorbed in the stomach. Therefore, drugs that affect gastric emptying time alter the absorption kinetics of mexiletine without altering the extent of bioavailability.

Narcotics such as morphine and diamorphine have been found to prolong the absorption half-life of mexiletine; myocardial infarction itself may produce this effect [Pottage et al (1978)]. Gelusil [$Al(OH)_3 + Mg(OH)_2$] [Herzog et al (1982)] and atropine [Wing et al (1980)] have also been shown to prolong the time-to-peak of mexiletine. Conversely, metoclopramide accelerates gastric emptying and decreases the time-to-peak [Wing et al (1980)].

Since narcotics, antacids, and myocardial infarction prolong absorption, the onset of mexiletine's therapeutic action may be somewhat delayed.

Metabolism

Drugs that affect the hepatic mixed function oxidase system can influence the metabolism of mexiletine. Co-administration of liver enzyme inducers such as phenytoin [Begg et al (1982)] and rifampin [Pentikainen et al (1982)] cause a decrease in mexiletine elimination half-life and plasma concentrations. Conversely, concomitant administration of cimetidine increases mexiletine plasma levels [Nitsch and Luderitz (1982)].

Thus, when liver enzyme inducers are administered concurrently with mexiletine, the dosage of mexiletine may have to be increased to maintain therapeutic blood levels. When an inhibitor of hepatic enzymes is co-administered, dose reduction may be necessary. In either case, careful monitoring of efficacy and tolerance should guide dose adjustment.

Concurrent Drug Administration

Mexiletine has been administered concomitantly with warfarin without evidence of interaction [Esser and Kikis (1978), Esser (unpublished report, Appendix E), Pottage et al (1978)].

Digoxin blood levels were unchanged by concomitant mexiletine therapy [Leahey and Reiffel (1980)] or slightly but not significantly lowered [Saris, Lowenthal et al (1983); Day and Hunt (1983)]. In the latter studies, magnesium-aluminum hydroxide, which was administered concurrently to alleviate gastrointestinal upset, accounts for the reduction in digoxin blood levels.

Concurrent administration of mexiletine and amiodarone has generally been well tolerated [Waleffe et al (1980); Koonlawee et al (1983); Heger et al (1983); Hoffman et al (1983)]. There is one report of atypical ventricular tachyarrhythmia with this combination [Tartini et al (1982)]. In some patients combination therapy may have increased efficacy [Waleffe et al (1980)].

Duff and coworkers (1983) have described a beneficial pharmacodynamic interaction between mexiletine and quinidine. In this patient group, combination therapy increased efficacy over either drug alone. Greater efficacy was achieved even though lower doses of both drugs were used. Toxicity with the combination was less than with single therapy. Similarly, a beneficial effect on efficacy has been seen with the combination of mexiletine and propranolol [Leahey (1980)].

No interaction was found between mexiletine and diazepam or nitrazepam [Pottage et al (1978)].

In general, both response and tolerance should be carefully monitored during concurrent administration of mexiletine and other drugs.

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*Published report of study conducted by D. Lowenthal.

B. Efficacy in Clinical Trials

1. Controlled Trials

The antiarrhythmic efficacy of mexiletine was compared to that of placebo and the conventional oral antiarrhythmic agents, procainamide, quinidine and disopyramide, in five multicenter, double-blind trials. A total of 884 patients, males and females ranging in age from 18 to 77 years, with baseline PVC rates exceeding 30 per hour, participated in these trials. Additionally, many patients had complex arrhythmia forms - couplets, ventricular tachycardia and R on T. Both idiopathic ventricular arrhythmias and ventricular arrhythmias secondary to underlying cardiovascular disease were represented. The design and results of these trials are summarized in Table 1 and a more detailed discussion of each multicenter trial follows.

TABLE 1
U.S. Controlled Clinical Trials with Mexiletine

Trial	Trial Design	Dose and Duration	Number of Patients Entered	Number of Patients Analyzed	Lack of Efficacy	Treatment Failures Adverse Event	Death	Total	Dropouts (other than treatment failures)	Results
Multicenter Placebo Trial (4 centers)	Double-blind, randomized, crossover study evaluating antiarrhythmic efficacy & safety of mexiletine as compared to placebo in patients with ≥ 30 PVCs/hour.	Single loading dose: 400 mg q8h or placebo 4 capsules. Mexiletine 100-400 mg q8h; placebo 1-4 capsules q8h. Dose titrated to efficacy or maximum tolerated dose. Duration: 4 weeks/treatment.	53	Mexiletine 46 Placebo 48	See Results				5	$\geq 70\%$ reduction in PVCs in 24 patients on mexiletine. 6 patients on placebo. Median reduction in PVCs 70% in mexiletine group, 10% in placebo group (significantly different, $p < 0.0001$). Mexiletine significantly better than placebo in reducing maximum frequency of couplets ($p < 0.001$) and VT ($p = 0.019$).
Multicenter Procaïnamide Trial (5 centers)	Double-blind, randomized, parallel-group study comparing efficacy & safety of mexiletine vs. procaïnamide in controlling ventricular arrhythmias in patients with ≥ 20 PVCs/hr.	Single loading dose: mexiletine 400 mg or procaïnamide 1000 mg. Mexiletine 200-400 mg q8h or procaïnamide 500-1000 mg q6h. Dose titrated to efficacy or maximum tolerated dose. Duration: 12 weeks.	Mexiletine 80 Procaïnamide 78	Mexiletine 76 Procaïnamide 76	19 (25%) 37 (49%)	27 (36%) 22 (29%)	1 (1%) 2 (3%)	47 (62%) 61 (80%)	4 (5%) 2 (3%)	Significantly more ($p=0.02$) treatment successes* with mexiletine (38%) than with procaïnamide (20%). Frequency of couplets and VT reduced by both drugs in majority of patients with these forms at baseline.

TABLE 1 (Cont'd)

U.S. Controlled Clinical Trials with Mexiletine											
Trial	Trial Design	Dose and Duration	Number of Patients Entered	Number of Patients Analyzed	Treatment Failures			Total	Dropouts (other than treatment failures)	Results	
					Lack of Efficacy	Adverse Event	Death				
Multicenter Quinidine Trials Study A (15 centers)	Double-blind, randomized, crossover study comparing efficacy & safety of mexiletine vs. quinidine in the management of ventricular arrhythmias in patients with >30 PVCs/hour.	Mexiletine 100-400 mg q8h or quinidine 200-400 mg q6h. Dose titrated to efficacy or maximum tolerated dose. Duration: 12 weeks.	Mexiletine	150	127	38 (30%)	49 (39%)	1 (1%)	88 (69%)	8 (6%)	Treatment success* achieved in 31% on mexiletine, 38% on quinidine (not significantly different). Frequency of couplets and VT reduced by both drugs in majority of patients with these forms at baseline.
			Quinidine	148	128	37 (29%)	39 (30%)	4 (3%)	80 (63%)	12 (9%)	
Study B (14 centers)	Same as Study A	Same as Study A	Mexiletine	118	105	28 (27%)	44 (42%)	1 (1%)	73 (70%)	6 (6%)	Treatment success* achieved in 30% on mexiletine, 26% on quinidine (not significantly different). Couplets and VT reduced by both drugs in majority of patients with these forms at baseline.
			Quinidine	114	97	34 (35%)	35 (36%)	3 (3%)	72 (74%)	9 (9%)	

TABLE 1 (Cont'd)
U.S. Controlled Clinical Trials with Mexiletine

Trial	Trial Design	Dose and Duration	Treatment Failures					Dropouts (other than treatment failures)	Results	
			Number of Patients Entered	Number of Patients Analyzed	Lack of Efficacy	Adverse Event	Death			Total
Multicenter Disopyramide Trial (11 centers)	Double-blind, randomized, parallel-group study com- paring efficacy & safety of mexiletine vs. disopyr- amide in the management of ventricular arrhyth- mias in patients with <u>230</u> PVCs/hour.	Mexiletine 200-400 mg q8h or disopyramide 100-200 mg q6h. Dose titrated to efficacy or maximum tolerated dose. Duration: 12 weeks.	Mexiletine	Disopyramide						
			74	63	19 (30%)	26 (41%)	0 (0%)	45 (71%)	6 (10%)	Treatment success* achieved in 29% on mexiletine, 44% on diso- pyramide (not signif- icantly different). Couplets and VT reduced by both drugs in major- ity of patients with these forms at baseline.
			59	54	19 (35%)	11 (20%)	0 (0%)	30 (56%)	10 (19%)	

* Treatment success was defined as ≥70% reduction from baseline in PVCs.

a. Mexiletine vs. Placebo

Study Design

The purpose of this double-blind, crossover study was to compare the antiarrhythmic efficacy and safety of mexiletine and placebo. The effects of concomitant digitalis administration on response to treatment were also evaluated. Fifty-three patients from four centers participated in this study. The investigators and the number of patients enrolled at each center are listed below.

<u>Investigator/Address</u>	<u>Number of Patients</u>
C. Richard Conti, M.D. University of Florida JHM Health Center, Box J-277 Gainesville, FL 32610	12
Rolf Gunnar, M.D. Loyola University Stritch School of Medicine 2160 South First Avenue Maywood, IL 60153	17
G. Douglas Moir, M.D. 210 South Juniper Street Escondido, CA 92025	12
Joel Morganroth, M.D. Lankenau Hospital City Line & Lancaster Avenues Philadelphia, PA 19151	12

Mexiletine and placebo were each administered for 4 weeks in randomly assigned sequence. Patients had the following cardiovascular diseases.

<u>Diagnosis</u>	<u>Number of Patients</u>
Atherosclerotic heart disease	26
Idiopathic ventricular arrhythmia	11
Hypertensive heart disease	3
Other	13

In order to enter the study, patients had to have an average PVC rate greater than 30 per hour, documented by two 24-hour Holter recordings. The median frequency of PVCs at baseline was 289/hour.

Following a loading dose of 400 mg mexiletine or 4 placebo capsules, patients took 100 mg mexiletine or 1 placebo capsule q8h. The dose was titrated, if necessary, at weekly intervals in increments of 100 mg mexiletine q8h (maximum 400 mg q8h) or 1 placebo capsule q8h (maximum 4 capsules q8h) until greater than 50% suppression of PVCs was achieved or the maximum dose was reached. Reduction of dosage was permitted if intolerable side effects occurred. After four weeks on one treatment, patients immediately crossed over to the other treatment.

Two 24-hour Holter recordings were done at baseline. Holter monitoring was done weekly throughout the study to assess the response to treatment.

The protocol and original statistical analysis defined a treatment response as greater than or equal to 50% reduction from baseline in PVCs on the Holter evaluation obtained at the completion of 4 weeks of treatment. The data were reanalyzed using 70% suppression of PVCs as the criterion for response. The results presented here reflect the revised analysis.

Results

Of the 53 patients enrolled in the study, 48 completed four weeks on mexiletine and 49 completed four weeks on placebo. Five patients were dropped during the study: two because of adverse reactions to mexiletine (both gastrointestinal distress), one because of a myocardial infarction (not related to the study drug), and one because the Holter tape was unreadable. Each of these four patients was excluded from both the mexiletine and placebo analyses. In the fifth patient (who completed the placebo treatment period), the Holter recording after the second week of mexiletine therapy showed one 13-beat run of ventricular tachycardia associated with dizziness. The patient was admitted to the hospital and mexiletine was discontinued. This patient was included only in the placebo efficacy analysis. In addition, two patients were excluded from the mexiletine efficacy analysis and one from the placebo analysis because their Holter recordings could not be interpreted. Thus, 46 patients were analyzed after mexiletine and 48 after placebo. A 70% or greater reduction from baseline in PVCs was achieved by 24 patients on mexiletine and 6 patients on placebo (Table 2). The majority of mexiletine responders were taking 200 to 400 mg q8h. The response to mexiletine 100 mg q8h was indistinguishable from the response to placebo.

TABLE 2

Response to 4 Weeks of Treatment
(Mexiletine vs. Placebo)

Treatment	Final Dose (q8h)	Number of Patients	
		Responders ($\geq$ 70% reduction)	Non-responders
Mexiletine (n=46)	100 mg	2	2
	200 mg	6	1
	300 mg	9	8
	400 mg	<u>7</u>	<u>11</u>
	Total	24	22
Placebo (n=48)	1 cap	1	2
	2 caps	2	3
	3 caps	1	9
	4 caps	<u>2</u>	<u>28</u>
	Total	6	42

The degree of reduction from baseline for all patients completing 4 weeks of treatment (Table 3) was greater with mexiletine (70.3%) than with placebo (10.3%). This difference was statistically significant (p less than 0.0001). The study design, which called for maintaining any dose that yielded at least a 50% reduction in PVCs may have led to underestimating the maximum effect of mexiletine as only 18 patients reached the 400 mg dose; larger doses might have given a larger than 50% response.

TABLE 3

Percent Reduction from Baseline in PVCs/Hour
After Four Weeks of Treatment
(Mexiletine vs. Placebo)

	Number of Patients	
	<u>Mexiletine</u>	<u>Placebo</u>
Total analyzed	46	48
<u>Percent Reduction from Baseline</u>		
Increased	10	21
0 - 25	1	9
26 - 50	5	7
51 - 70	6	5
71 - 80	7	4
81 - 90	9	1
91 - 100	8	1

Mean Reduction:	44.8%	11.6% increase
Median Reduction:	70.3%*	10.3%

* Difference between treatments statistically significant, p less than 0.0001

Among all patients who received treatment with mexiletine (53) or placebo (49), one patient in each treatment group had a fourfold or greater increase from baseline in PVC rate on the final treatment Holter.

The reduction in PVCs was further evaluated to determine whether concomitant administration of digitalis altered the response to treatment. There was no appreciable difference in response between digitalis users and non-users. The median percent reduction in PVCs was 66.2% in 13 patients using digitalis and 75.2% in 33 patients not using digitalis.

Forty-one patients had couplets at baseline. Couplet frequency was reduced in 36/41 patients (88%) after mexiletine and 20/41 (49%) after placebo. Mexiletine produced a median decrease from baseline of 94.9%, while a median increase of 17.7% was seen with placebo.

TABLE 4

Percent Reduction from Baseline in Couplets/Hour
(Mexiletine vs. Placebo)

	Number of Patients	
	<u>Mexiletine</u>	<u>Placebo</u>
Patients with couplets at baseline	41	41
<u>% Percent Reduction from Baseline</u>		
Increased	5	21
0 - 25	0	2
26 - 50	3	3
51 - 75	3	4
76 -100	30	11

Mean change
from baseline: 45.2% increase 160.3% increase

Median change
from baseline: 94.9% decrease 17.7% increase

Median couplet frequency at baseline was 21.8/day. This decreased to 1.4/day following mexiletine treatment and was essentially unchanged following placebo (22.1). The difference between treatments was statistically significant, p less than 0.0001.

Among all patients (including those excluded from the efficacy analysis) who had couplets at baseline (48 patients treated with mexiletine, 44 with placebo), a tenfold or greater increase from baseline in couplets on the final treatment Holter was seen in 1 patient on mexiletine and in 2 on placebo.

Four patients had no couplets at baseline. Couplets were seen on the final treatment Holter in one of these patients during mexiletine treatment (rate 0.04/hour) and in two patients during placebo (rates 0.04 and 0.09/hour).

The rate of ventricular tachycardia (beats/hour) was reduced from baseline in 25/26 patients (96%) on mexiletine and 18/27 patients (67%) on placebo. The median percent reduction from baseline in the mexiletine group was 100%.

TABLE 5

Percent Reduction in VT (Beats/Hour)
(Mexiletine vs. Placebo)

	Number of Patients	
	<u>Mexiletine</u>	<u>Placebo</u>
Number of patients with VT at baseline	26	27
<u>Percent Reduction</u>		
Increased	1	9
0 - 25	2	0
26 - 50	3	3
51 - 75	3	2
76 - 100	17	13

Mean % reduction	5.2%*	146.7% (increase)
Median % reduction	100.0%	60.0%

* This mean is due to an outlier who had an increase in VT from a baseline of 0.12 beats per hour to 2.36 beats per hour at 4 weeks, an increase of 1889%.

The median rate of ventricular tachycardia at baseline was 5.4 beats/day. This decreased to 0 after mexiletine treatment and to 3.1 beats/day after placebo. The difference between treatments was statistically significant, $p = 0.019$.

Among all patients (including those excluded from the efficacy analysis) who had ventricular tachycardia at baseline (33 patients treated with mexiletine, 29 with placebo), a tenfold or greater increase from baseline in VT on the final treatment Holter was seen in 2 patients on mexiletine and in 3 on placebo.

Twenty patients had no evidence of ventricular tachycardia at baseline. None of these patients had VT on the final mexiletine treatment Holter, while 3 had VT (maximum rate 0.51 beats/hour) on the final placebo Holter.

There were no clinically significant changes in mean blood pressure or pulse rate after treatment with either mexiletine or placebo.

All patients had a 12-lead electrocardiogram at baseline and at the end of the 8-week study (or at the time of discontinuation from the study). Mexiletine did not produce any significant changes from baseline in the mean PR, QRS or QT intervals, regardless of whether patients were receiving concomitant digitalis therapy.

b. Mexiletine vs. Procainamide

Study Design

This double-blind, parallel-group study compared mexiletine and procainamide in the treatment of ventricular arrhythmias. This study also evaluated the effects of the study drugs, alone or with concomitant digitalis, diuretic or beta blocker therapy, on electrocardiogram intervals. One hundred and fifty-eight patients from the five centers listed were randomly assigned to 12 weeks of treatment with either mexiletine (80) or procainamide (78).

<u>Investigator/Address</u>	<u>Number of Patients</u>
Michael Bilitch M.D. Parkview Medical Building 1429 San Pablo Street, C-201 Los Angeles, CA 90033	33
Patrick C., Breaux, M.D. Cardiology Department East New Orleans Medical Center 5640 Read Boulevard New Orleans, LA 70127	34
Robert H. Eich, M.D. Professor of Medicine Chief, Cardiology Section State University of New York Upstate Medical Center 750 East Adams Street Syracuse, NY 13210	28
Sidney Goldstein, M.D. Henry Ford Hospital 2799 West Grand Boulevard Detroit, MI 48202	32
Bramah N. Singh, M.D., Ph.D. Department of Cardiology Wadsworth VA Hospital Wilshire and Sawtelle Boulevards Los Angeles, CA 90073	31

Patients had one or more of the following cardiovascular diagnoses:

<u>Diagnosis</u>	<u>Number of Patients</u>
Atherosclerotic heart disease	91
Idiopathic ventricular arrhythmia	48
Hypertensive heart disease	32
Other	33

To qualify for entry into the study, patients were required to have a baseline PVC rate greater than or equal to 20 per hour (average of two 24-hour Holter recordings).* The median hourly frequency of PVCs at baseline was 242.4 in the mexiletine group and 208.1 in the procainamide group.

Following a loading dose of 400 mg mexiletine or 1000 mg procainamide, patients received mexiletine 200 mg q8h or procainamide 500 mg q6h**. Because of the different dosing schedules, the medications were dispensed by a third party in order to preserve blinding, but in fact the whole procedure casts doubt upon the blinding as casual contacts among patients or discussions with physicians could reveal the differences in therapy. As the Holters were read by third parties, this defect in blinding is not critical.

The dose was titrated, if necessary, at biweekly intervals in increments of 100 mg mexiletine (maximum 400 mg q8h) or 250 mg procainamide (maximum 1000 mg q6h), until greater than or equal to 50% suppression of PVCs was achieved (assessed by 24-hour Holter monitoring as described below) or intolerable side effects occurred. If 50% reduction in PVCs was achieved at any dose level (as confirmed by Holter done two weeks after initial dose and 48 hours to 8 days after each dosage adjustment) and at least 40% suppression was maintained on subsequent Holters, no further dosage adjustment was made. However, if this degree of PVC suppression was attained and the patient was not yet at the maximum dose, titration could be continued if one or more of the following were present: R on T phenomenon; persistence or appearance of significant numbers of multiform PVCs, couplets, or ventricular tachycardia. Patients were treated for a total of 12 weeks. As noted for the placebo study, this design could lead to an underestimate of the effect of mexiletine; patients achieving a modest response (50% reduction) would not be given larger doses in most cases.

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- * Although the criterion for entry was a baseline PVC rate greater than or equal to 20 per hour, all but two patients had baseline PVC rates exceeding 30 per hour.
- ** The recommended dosing schedule for procainamide is 250 - 500 mg q3h. The 500 - 1000 mg q6h dose selected for the protocol corresponds to the investigators' usual clinical practice and was chosen to improve patient compliance.

Response to treatment was evaluated by means of 24-hour Holter monitoring. Two consecutive 24-hour Holters were done at baseline and at the end of 12 weeks of treatment. Holter monitoring was routinely done during the study at weeks 2, 4 and 8, and more frequently if dose titration was necessary.

In the original statistical analysis, treatment success was defined as greater than or equal to 50% reduction in PVCs on one Holter, with continued suppression of at least 40% through the final Holter at 12 weeks. The data were reanalyzed, however, using 70% suppression of PVCs through the final Holter as the criterion for success. The findings presented here reflect the revised analysis. Patients who did not achieve and maintain this level of suppression were considered efficacy failures. Patients who were discontinued because of intolerable side effects were considered side effect failures, regardless of the degree of PVC suppression achieved.

Results

One hundred and fifty-eight patients (80 mexiletine, 78 procainamide) were enrolled in the trial. All patients except those dropped for administrative reasons (4 mexiletine and 2 procainamide patients who had protocol violations or were lost to follow-up) were included in the analysis of treatment success or failure (Table 6). All patients (including administrative failures) who had a baseline and a treatment Holter (69 mexiletine, 72 procainamide) were included in the remaining efficacy analysis, using their last treatment Holter to evaluate suppression of ectopy.

Table 6 presents the treatment successes and failures in each treatment group. More patients were controlled with mexiletine (38.2%) than with procainamide (19.7%); this difference was statistically significant ($p = 0.02$). The majority of mexiletine responders (greater than or equal to 70% suppression of PVCs) were controlled at the 200 and 300 mg q3h dose levels.

TABLE 6

Treatment Successes and Failures by Final Dose
Following Treatment with Mexiletine or Procainamide

Treatment	Final Dose	Treatment Success*	Treatment Failures		
			Efficacy	Side Effects	Deaths
Mexiletine (76 patients) ^a	200 mg	12	3	13	1
	300 mg	13	1	8	0
	400 mg	4	15	6	0
		<u>29 (38.2%)**</u>	<u>19 (25.0%)</u>	<u>27 (35.5%)</u>	<u>1 (1.3%)</u>
Procainamide (76 patients) ^a	500 mg	6	2	12	1
	750 mg	5	5	4	1
	1000 mg	4	30	6	0
		<u>15 (19.7%)</u>	<u>37 (48.7%)</u>	<u>22 (28.9%)</u>	<u>2 (2.5%)</u>

^a Excluding administrative failures (4 mexiletine, 2 procainamide)

* greater than or equal to 70% reduction from baseline in PVCs

** Difference between treatments statistically significant (p = 0.02)

Of the treatment failures (Table 6), all those with side effects or death (except for 1 side effect failure in the procainamide group) failed to complete the 12 weeks of study while 10 of the 19 mexiletine and 26 of the 37 procainamide efficacy failures failed to complete the 12 weeks.

Gastrointestinal and central nervous system side effects were the most common with both mexiletine and procainamide. The percentage of treatment failures due to side effects was similar in both groups. Death was due to myocardial infarction in one patient in each treatment group and to cardiac arrest in one patient in the procainamide group. None of the deaths were believed to be related to the study medications. A detailed discussion of adverse experiences and deaths will be found in Section C, Safety.

N18873 - 2

There are many possible measures of the reduction from baseline in PVC rates, depending on the patient population. An "all patient" analysis involves the least patient selection but could be biased against a drug with more drop-outs due to side effects, as the optimally effective dose might not be reached. An analysis of all patients except those dropped for side effects would overcome that problem. An analysis of 12 week completers would tend, in this case, to favor procainamide as many of the procainamide non-responders were not allowed to complete the 12 weeks. Table 7 shows all three of these analyses.

TABLE 7

Median Percent Reduction from Baseline in Hourly PVC Rate on Final Treatment Holter (Mexiletine vs. Procainamide)

	<u>Mexiletine (n)</u>	<u>Procainamide (n)</u>
All patients*	69.9 ^a (69)	34.4 (72)
All patients except side effect failures	77.8 ^b (53)	34.1 (56)
Patients completing 12 weeks	85.4 (38)	75.4 (27)

-
- ^a Difference between treatments statistically significant, P = 0.006.
^b Difference between treatments statistically significant, P = 0.002.
* Baseline but no treatment Holter evaluation was available for an additional 11 mexiletine and 6 procainamide patients.

The range of reduction from baseline in PVCs for all patients with baseline and treatment Holters is presented in Table 7A. Thirty-four patients (49%) in the mexiletine group and 23 (32%) in the procainamide group had reductions greater than 70% on their final treatment Holter.

TABLE 7A

Range of Reduction from Baseline in Hourly PVC Rate
on Final Treatment Holter for All Patients
with Baseline and Treatment Holters
(Mexiletine vs. Procainamide)

<u>Percent Reduction</u>	<u>Number of Patients</u>	
	<u>Mexiletine (n = 69)</u>	<u>Procainamide (n = 72)</u>
Increased*	15	30
0 - 25	3	4
26 - 50	6	10
51 - 70	11	5
71 - 80	8	8
81 - 90	10	4
91 - 100	16	11

* Three (4.3%) patients in the mexiletine group and 1 (1.4%) in the procainamide group had a fourfold or greater increase in PVCs on the final treatment Holter.

Table 8 presents the median percent reduction from baseline in couplets and ventricular tachycardia on the final treatment Holter for the three patient groups (all patients with baseline and treatment Holters; all patients except side effect failures; and 12-week completers) for those patients who had couplets or VT at baseline. Mexiletine produced median decreases ranging from 83 to 96% in couplets and 97 to 100% in VT. Procainamide produced median decreases of 40 to 77% in couplets and 88 to 93% in VT.

TABLE 8

Median Percent Reduction from Baseline in Couplets (Events/Hour)
and VT (Beats/Hour) on Final Treatment Holter for
Patients with Couplets or VT at Baseline
(Mexiletine vs. Procainamide)

	Couplets		VT	
	Mex (n)	Proc (n)	Mex (n)	Proc (n)
All patients*	83.0 ^a (62)	44.9 (64)	96.5 (47)	93.1 (45)
All patients except side effect failures	86.8 ^b (46)	40.0 (49)	100.0 (36)	37.9 (35)
Patients completing 12 weeks	96.4 (33)	77.0 (25)	100.0 (23)	90.5 (16)

* Ten additional mexiletine patients and 5 additional procainamide patients had couplets at baseline but were missing treatment couplet evaluation, while an additional 7 mexiletine and 3 procainamide patients who had VT at baseline were missing treatment VT evaluation. One patient in the mexiletine group had no baseline couplet or VT data.

a Difference between treatments statistically significant, $P = 0.03$.

b Difference between treatments statistically significant, $p = 0.05$.

Table 8A presents the range of reduction from baseline in couplets and VT on the final treatment Holter for all patients. Reductions in couplets of 76% or greater were seen in 61% of the mexiletine patients and 41% of the procainamide patients. For VT, 72 and 62% of mexiletine and procainamide treated patients, respectively, had reductions greater than or equal to 76%.

TABLE 8A

Range of Reduction from Baseline in Couplets (Events/Hour)
and VT (Beats/Hour) on Final Treatment Holter for All
Patients with Couplets or VT at Baseline*
(Mexiletine vs. Procainamide)

% Reduction	Couplets		VT	
	Mex (n=62)	Proc (n=64)	Mex (n=47)	Proc (n=45)
Increased*	13	25	10	15
0-25	3	4	0	0
26-50	4	4	1	1
51-75	4	5	2	1
76-100	38	26	34	28

- * A tenfold or greater increase in couplet rate on the final treatment Holter was seen in 3 mexiletine patients (4.8%) and 1 procainamide patient (1.6%). For VT, 1 mexiletine patient (2.1%) and 2 procainamide patients (4.4%) had a tenfold or greater increase.

A small number of patients who had no evidence of complex forms at baseline had couplets or ventricular tachycardia on the final treatment Holter. In the mexiletine group, 2/7 patients had couplets (0.04, 0.21 events/hour) and 2/25 had VT (0.06, 0.85 beats/hour). In the procainamide group, 1/9 patients had couplets (2.58 events/hour) and 2/30 had VT (0.25 and 0.13 beats/hour) on the final Holter.

Mexiletine did not significantly alter mean EKG intervals (PR, QRS, QT_C) as compared to baseline, regardless of whether patients were concomitantly taking digitalis and/or diuretics. Procainamide significantly increased all three intervals for the group as a whole and for the subgroup of patients not using digitalis. Procainamide also significantly increased the PR and QT_C intervals for diuretic users and the QRS and QT_C intervals for diuretic non-users.

Mean systolic and diastolic blood pressure showed an increase of 4.5 mm Hg after mexiletine, a statistically significant difference. Mexiletine had no significant effect on mean pulse rate.

c. Mexiletine vs. Quinidine

Study Design

Two multicentered, double-blind, parallel group trials - Study A and Study B - compared mexiletine and quinidine in the management of ventricular arrhythmias. The trials also assessed whether adverse effects on EKG intervals occurred with the study drugs alone or in combination with digitalis, diuretic or beta blocker therapy.

Two hundred and ninety-eight patients from fifteen centers participated in Study A and were randomly assigned to 12 weeks of treatment with mexiletine (150) or quinidine (148). Two hundred and thirty-two patients from fourteen centers were enrolled in Study B (118 mexiletine, 114 quinidine). The investigators and the number of patients enrolled at each center are listed below.

<u>Mexitil vs. Quinidine - Study A</u>	<u>Number of Patients</u>
Reuben Berman, M.D. Marvin Segal, M.D. Mount Sinai Hospital 2215 Park Avenue Minneapolis, MN 55404	22
Patrick C. Breaux, M.D. Cardiology Department East New Orleans Medical Center 5640 Read Boulevard New Orleans, LA 70127	29
Paul E. Fenster, M.D. Assistant Professor Cardiology Section Arizona Health Sciences Center Tucson, AZ 85724	27

<u>Mexitil vs. Quinidine - Study A</u>	<u>Number of Patients</u>
Thomas Glatter, M.D. Robert Conn, M.D. Thomas Terry, M.D. Charles Ray Webb, M.D. University of Missouri Kansas City School of Medicine 2411 Holmes Street Kansas City, MO 64108	10
Morrison Hodges, M.D. Director, Cardiology Section Hennepin County Medical Center 701 Park Avenue Minneapolis, MN 55415	20
Richard C. Klein, M.D. Veterans Administration Medical Center 2100 Ridgecrest Drive, S.E. Albuquerque, NM 87108	27
Norman Krasnow, M.D. Chief of Cardiology State University of New York Downstate Medical Center 450 Clarkson Avenue Brooklyn, NY 11203	18
Syed Mohiuddin, M.D. St. Joseph's Hospital Cardiac Center 601 North 30th Street Omaha, NE 68131	16
E. Alan Paulk, M.D. 4553 North Shallowford Road Suite 90C Atlanta, GA 30338	27
William A. Pitt, M.D. Associate Director Cardiopulmonary Department Mercy Hospital and Medical Center 4077 Fifth Avenue San Diego, CA 92103	20

<u>Mexitil vs. Quinidine - Study A</u>	<u>Number of Patients</u>
Philip R. Reid, M.D. Assistant Professor of Medicine Division of Cardiology & Clinical Pharmacology The John Hopkins Hospital 600 North Wolfe Street Baltimore, MD 21205	15
Rodolphe Ruffy, M.D. Cardiology Division The Jewish Hospital of St. Louis 216 South Kingshighway P.O. Box 14109 St. Louis, MO 63178	19
Jang B. Singh, M.D. Director Cardiac Catheterization Laboratory St. Vincent Hospital 25 Winthrop Street Worcester, MA 01604	23
Douglas K. Stewart, M.D. Director, Cardiac Catheterization Laboratory University of Washington Division of Cardiology, RG-20 Cardiovascular Research & Training Center Seattle, WA 98195	20
Albert L. Waldo, M.D. University of Alabama Medical Center University Station Birmingham, AL 35294	5

<u>Mexitil vs. Quinidine - Study B</u>	<u>Number of Patients</u>
Michael E. Assey, M.D. Assistant Professor of Medicine Division of Cardiology 816 C Clinical Science Building Medical University of South Carolina 171 Ashley Avenue Charleston, SC 29403	22
Kul Deep Chadda, M.D. Long Island Jewish Hospital Hillside Medical Center, Room 2135 New Hyde Park, NY 11040	10
R. Charles Curry Jr., M.D. 2400 Bedford Road Orlando, FL 32803	22
Henry DeMots, M.D. Chief, Cardiology Veterans Administration Medical Center 3710 Southwest U.S. Veterans Hospital Road Portland, OR 97201	21
Joel Kupersmith, M.D. Mount Sinai Medical Center One Gustave L. Levy Place New York, NY 10029	30
Anthony M. Marlon, M.D. Southwest Heart Associates 2040 W. Charleston Boulevard Suite 400 Las Vegas, NV 89102	23
David McCall, M.D. Director, Adult Cardiology University of Nebraska Medical Center 42nd and Dewey Avenue Omaha, NE 68105	4
Joel Morganroth, M.D. Chief, Cardiac Research & Education Cardiovascular Division The Lankenau Hospital Lancaster Avenue West of City Line Philadelphia, PA 19151	20

<u>Mexitil vs. Quinidine - Study B</u>	<u>Number of Patients</u>
Ravindra Prabhu, M.D. Director, Heart Station Cardiovascular Institute Department of Medicine Michael Rees Hospital & Medical Center 29th Street & Ellis Avenue Chicago, IL 60616	10
Robert C. Schlant, M.D. Professor of Medicine/Cardiology Director, Division of Cardiology Emory University School of Medicine 69 Butler Street, S.E. Atlanta, GA 30303	12
Peter Schulman, M.D. James A. Haley Veterans Hospital (111A) 13000 North 30th Street Tampa, FL 33612	6
Arvindkumar R. Shah, M.D. Director, Noninvasive Laboratory Veterans Administration Hospital 10701 East Boulevard Cleveland, OH 44106	28
Barry D. Silverman, M.D. Northside Hospital 1000 Jackson Ferry Road, N.E. Atlanta, GA 30342	14
Pitambar Somani, M.D., Ph.D. Peter N. Temesy-Armos, M.D. Medical College of Ohio C.S. #10008 Toledo, OH 43699	10

Patients had been diagnosed as having one or more of the following cardiovascular diseases:

Diagnosis	Number of Patients	
	Study A	Study B
Atherosclerotic heart disease	128	110
Idiopathic ventricular arrhythmia	76	68
Hypertensive heart disease	72	58
Other	75	73
Not reported	2	0

To qualify for entry into the study, patients were required to have a minimum of 30 PVCs per hour (average of two 24-hour Holter recordings). In Study A, the median hourly frequency of PVCs at baseline was 196 in the mexiletine group and 271 in the quinidine group. In Study B, it was 349 and 341 in the mexiletine and quinidine groups, respectively. The difference between treatment groups was not statistically significant in either study.

Patients began treatment with mexiletine 200 mg q8h or quinidine 200 mg q6h. Because of the different dosing intervals, the medications were administered by a third party in order to preserve blinding. As noted above, third party blinding may not always preserve the blind, but that is not critical here, as the Holters were read by a third party. The dose was titrated, if necessary, in 100 mg increments (to a maximum of 400 mg mexiletine q8h or 400 mg quinidine q6h) until 70% suppression of PVCs was achieved or intolerable side effects occurred. Once a patient achieved 70% reduction from baseline, no further dosage adjustment was made so long as the patient maintained at least 55% suppression on subsequent Holters. Patients were treated for a total of 12 weeks.

Two consecutive 24-hour Holter recordings were done at baseline. Holter monitoring to evaluate the therapeutic response was done one week after initiation of treatment and a confirming Holter 48 hours to 8 days later. If titration was necessary, Holter analysis was done at these same intervals after each dosage adjustment. A final Holter evaluation was done at 12 weeks.

The protocol and original statistical analysis defined treatment successes as patients who achieved 70% suppression of PVCs on one Holter and subsequently maintained at least 55% suppression through the final Holter at 12 weeks. The data were reanalyzed, however, using a more stringent standard that defined treatment successes as those patients who, after reaching 70% reduction in PVCs, maintained that degree of suppression through the final Holter. Patients who did not maintain 70% suppression were considered efficacy failures. Patients who were dropped because of intolerable side effects were considered side effect failures, regardless of the degree of PVC control they achieved.

Results - Study A

Two hundred and ninety-eight patients were enrolled in this trial (150 mexiletine, 148 quinidine). Fifteen mexiletine and eight quinidine patients who were still in progress at the time the study was analyzed for the NDA were excluded from the efficacy analysis. Of the remaining patients (135 mexiletine, 140 quinidine), all except administrative failures (8 mexiletine and 12 quinidine patients with protocol violations, missing data or lost to follow-up) were included in the analysis of treatment success or failure (Table 9). All patients (including administrative failures) who had a baseline and a treatment Holter (117 mexiletine, 122 quinidine) were included in the remaining efficacy analysis, using the last treatment Holter to evaluate arrhythmia suppression.

Table 9 presents the treatment successes and failures in both treatment groups. Treatment success (greater than or equal to 70% reduction in PVCs) was achieved in 39 patients (30.7%) on mexiletine and 48 patients (37.5%) on quinidine; this difference was not statistically significant. The majority of mexiletine treatment successes (33/39) occurred at the 200 and 300 mg q8h dose levels. The percentages of efficacy and side effect failures were similar for both treatment groups.

TABLE 9

Treatment Successes and Failures by Final Dose
(Mexiletine vs. Quinidine Study A)

Treatment	Final Dose	Treatment Success*	Treatment Failure		
			Lack of Efficacy	Side Effects	Deaths
Mexiletine (127 patients) ^a	100 mg ^b	0	0	1	0
	200 mg	22	6	26	1
	300 mg	11	9	13	0
	400 mg	6	23	9	0
	<u>Total</u>	<u>39 (30.7%)**</u>	<u>38 (29.9%)</u>	<u>49 (38.6%)</u>	<u>1 (0.8%)</u>
Quinidine (128 patients) ^a	200 mg	25	14	29	2
	300 mg	14	6	6	1
	400 mg	9	16	5	1
	<u>Total</u>	<u>48 (37.5%)</u>	<u>36 (28.1%)</u>	<u>40 (31.3%)</u>	<u>4 (3.1%)</u>

^a Administrative failures (8 mexiletine, 12 quinidine) excluded.

^b One patient had his dose reduced to 100 mg because of an adverse event and was subsequently discontinued as a side effect failure

* greater than or equal to 70% reduction from baseline in PVCs

** Not significantly different from quinidine (p = 0.27)

Of the treatment failures (Table 9), all of the side effect failures and deaths failed to complete the 12 weeks of the study, while 23 of the 38 mexiletine and 19 of the 36 quinidine efficacy failures failed to complete 12 weeks.

The most common side effects were gastrointestinal or central nervous system in nature. One patient in the mexiletine group died of ventricular tachycardia. In the quinidine group, the causes of death were ventricular fibrillation (1 patient), arteriosclerotic heart disease (1 patient) and sudden death (2 patients). In no case was death attributed to the study medication. Side effects and deaths are discussed in detail in Section C, Safety.

As in the previous study, the median percent reductions from baseline PVC rate on the final treatment Holter were examined in three ways: for all patients who had a baseline and treatment Holter; for all patients except side effect failures; and for those patients who completed the 12-week study (Table 10). Median reductions ranged from 60 to 92% for mexiletine and 81 to 92% for quinidine.

TABLE 10

Median Percent Reduction from Baseline in Hourly PVC Rate on Final Treatment Holter (Mexiletine vs. Quinidine Study A)

	<u>Mexiletine (n)</u>	<u>Quinidine (n)</u>
All patients*	59.6 ^a (117)	81.0 (122)
All patients except side effect failures**	69.5 (83)	86.4 (94)
Patients completing 12 weeks	92.3 (54)	91.8 (65)

-
- * An additional 18 patients in each treatment group were missing treatment Holter evaluation
 - ** Treatment Holter evaluation was not available for 2 additional mexiletine and 6 quinidine patients. One mexiletine patient had no Holter data.
 - ^a Difference between treatments marginally statistically significant, $p = 0.06$.

The range of reduction from baseline in PVCs for all patients with baseline and treatment Holters is presented below (Table 10A). Forty-four percent of the mexiletine patients and 57% of the quinidine patients had reductions greater than 70%.

TABLE 10A

Range of Reduction from Baseline in Hourly PVC Rate
on Final Treatment Holter for All Patients
(Mexiletine vs. Quinidine Study A)

% Reduction	Number of Patients	
	Mexiletine (n = 117)	Quinidine (n = 122)
Increased*	24	20
0 - 25	9	6
26 - 50	19	10
51 - 70	13	17
71 - 80	5	8
81 - 90	12	14
91 - 100	35	47

* A fourfold or greater increase in PVCs on the final treatment Holter was seen in 1 mexiletine patient, (0.9%) and 5 quinidine patients, (4.1%).

For the three patient groups, median reductions from baseline in couplets ranged from 93 - 99% with mexiletine and 98 - 100% with quinidine, while median reductions of 100% in ventricular tachycardia and R on T were seen with both treatments, as shown in Table 11.

TABLE 11

Median Percent Reduction from Baseline in Couplets, VT and R on T (Events/Hour) on Final Treatment Holter for Patients with Complex Forms at Baseline (Mexiletine vs. Quinidine Study A)

	Couplets		VT		R on T	
	Mex (n)	Quin (n)	Mex (n)	Quin (n)	Mex (n)	Quin (n)
All patients*	92.5 (107)	98.3 (102)	100.0 (73)	100.0 (64)	100.0 (78)	100.0 (81)
All patients except side effect failures**	93.4 ^a (76)	99.3 (78)	100.0 (50)	100.0 (48)	100.0 (52)	100.0 (64)
Patients completing 12 weeks	99.1 (51)	100.0 (56)	100.0 (33)	100.0 (34)	100.0 (36)	100.0 (44)

* In addition, baseline but no treatment evaluation was available for couplets in 14 mexiletine and 15 quinidine patients; for VT in 9 mexiletine and 14 quinidine patients; and for R on T in 12 mexiletine and 14 quinidine patients. Four mexiletine patients and 1 quinidine patient were missing baseline couplet and VT data.

** In addition, baseline but no treatment evaluation was available for 1 mexiletine and 3 quinidine patients with baseline couplets, 1 mexiletine and 4 quinidine patients with baseline VT and 6 quinidine patients with baseline R on T.

^a Difference between treatments statistically significant, $p = 0.05$

Table 11A presents the range of reduction from baseline in couplets, ventricular tachycardia and R on T on the final treatment Holter for all patients who had these forms at baseline. Reductions greater than 75% were seen in the majority of patients in both treatment groups.

TABLE 11A

Range of Reduction from Baseline in Couplets, VT and R on T (Events/Hour) on Final Treatment Holter for All Patients with Complex Forms at Baseline (Mexiletine vs. Quinidine Study A)

% Reduction	Couplets		VT		R on T	
	Mex (n=107)	Quin (n=102)	Mex (n=73)	Quin (n=64)	Mex (n=78)	Quin (n=81)
Increased*	16	14	8	11	9	14
0 - 25	3	2	2	2	1	2
26 - 50	4	4	2	0	0	1
51 - 75	14	7	1	3	5	2
76 - 100	70	75	60	48	63	62

- * A tenfold or greater increase from baseline in couplet rate on the final Holter was seen in 1 mexiletine patient (0.9%) and 3 quinidine patients (2.9%). For VT, 1 mexiletine patient (1.4%) and 6 quinidine patients (9.4%) had a tenfold or greater increase.

Of those patients who had no evidence of complex arrhythmias at baseline, 5 patients out of 22 in the quinidine group had couplets (maximum rate, 17.21 events/hour); 3 patients out of 49 in the mexiletine group and 6 out of 61 in the quinidine group had ventricular tachycardia on the final Holter (maximum rate 0.06 events/hour with mexiletine, 0.88 with quinidine). None of the 10 patients in the mexiletine group who had no couplets at baseline had couplets on the final Holter.

Mexiletine did not significantly affect mean EKG intervals (PR, QRS, QT_c), regardless of whether patients were receiving concomitant treatment with digitalis, diuretics or beta blockers, with the exception of a statistically significant (p less than 0.05) prolongation of the PR interval by 0.0058 second in patients not using beta blockers. Quinidine statistically significantly prolonged the QT_c interval for the group as a whole (p less than 0.01) and for patients who were not concomitantly using digitalis (p less than 0.01), beta blockers (p less than 0.01), or diuretics (p less than 0.05).

Neither treatment produced any significant change from baseline in mean pulse rate.

Results - Study B

Of the 232 patients enrolled in this trial (118 mexiletine, 114 quinidine), fifteen (7 mexiletine, 8 quinidine) were still in progress when the study was analyzed for the NDA and were excluded from the efficacy analysis. Of the remaining patients (111 mexiletine, 106 quinidine), all except administrative failures (6 mexiletine and 9 quinidine patients with protocol violations, missing data or lost to follow-up) were evaluated for treatment success or failure (Table 12). All patients (including administrative failures) who had a baseline and a treatment Holter (100 mexiletine, 89 quinidine) were included in the remaining efficacy analysis, using the last treatment Holter to assess suppression of ectopy.

Treatment successes and failures are tabulated below. Treatment success (greater than or equal to 70% reduction in PVCs) was achieved in 32 patients (30.5%) on mexiletine and 25 patients (25.8%) on quinidine; this difference was not statistically significant. Most of the mexiletine treatment successes (27/32) reached control at the 200 and 300 mg q8h dose levels. The frequency of efficacy and side effect failures was similar for both drugs.

TABLE 12

Treatment Successes and Failures by Final Dose
(Mexiletine vs. Quinidine Study B)

Treatment	Final Dose	Treatment Success*	Treatment Failure		
			Lack of Efficacy	Side Effects	Deaths
Mexiletine (105 patients) ^a	200 mg	16	7	19	1
	300 mg	11	7	13	0
	400 mg	5	14	12	0
	Total	32 (30.5%)**	28 (26.7%)	44 (41.9%)	1 (1.0%)
Quinidine (97 patients) ^a	200 mg	15	12	29	1
	300 mg	7	6	3	2
	400 mg	3	16	3	0
	Total	25 (25.8%)	34 (35.1%)	35 (36.1%)	3 (3.1%)

- ^a Administrative failures (6 mexiletine, 9 quinidine) excluded
* greater than or equal to 70% reduction from baseline in PVCs
** Not significantly different from quinidine (p = 0.48)

Of the treatment failures (Table 12), all of the side effect failures and deaths failed to complete the 12 week study, while 16 of the 28 mexiletine and 16 of the 34 quinidine efficacy failures failed to complete 12 weeks.

Gastrointestinal and central nervous system side effects were the most frequently reported. The causes of death for the four patients who died during the study were sudden death (1 mexiletine, 2 quinidine) and myocardial infarction (1 quinidine). A fifth patient died in ventricular fibrillation four days after being discontinued from the study as a mexiletine efficacy failure. None of these deaths were believed to be related to the study medications. Side effects and deaths are discussed in greater detail in Section C, Safety.

Table 13 presents the median reductions from baseline PVC rate on the final treatment Holter for three patient groups: all patients with a baseline and treatment Holter, all patients excluding side effect failures; and patients who completed the 12 week study. The median reductions ranged from 63 to 87% in the mexiletine treatment group and from 60 to 77% in the quinidine group. The differences between treatments in median percent reductions were not statistically significant.

TABLE 13

Median Percent Reduction from Baseline in Hourly
PVC Rate on Final Treatment Holter
(Mexiletine vs. Quinidine Study B)

	<u>Mexiletine (n)</u>	<u>Quinidine (n)</u>
All patients*	63.4 (100)	60.4 (89)
All patients except side effect failures**	75.3 (65)	64.5 (69)
Patients completing 12 weeks.	37.2 (44)	77.4 (43)

-
- * Baseline but no treatment Holter evaluation was available for an additional 11 mexiletine and 17 quinidine patients.
 - ** Baseline but no treatment Holter evaluation was available for an additional 2 mexiletine and 2 quinidine patients.

The range of reduction from baseline in PVC rate on the final treatment Holter for all patients with baseline and treatment Holters is presented in Table 13A. Forty percent of patients in the mexiletine group and 42% in the quinidine group had reductions greater than 70%.

TABLE 13A

Range of Reduction from Baseline in Hourly PVC Rate on
Final Treatment Holter for All Patients
(Mexiletine vs. Quinidine Study B)

% Reduction	Number of Patients	
	Mexiletine (n = 100)	Quinidine (n = 89)
Increased*	17	18
0 - 25	11	4
26 - 50	11	13
51 - 70	17	17
71 - 80	5	6
81 - 90	8	12
91 - 100	27	19

* A fourfold or greater increase from baseline in PVC rate was seen on the final Holter in 1 mexiletine patient (1.0%) and 3 quinidine patients (3.4%).

For couplets, VT and R on T, the median percent reductions from baseline for the three patient groups are shown in Table 14. The median reductions in couplets ranged from 94 to 100% with mexiletine and 93 to 99% with quinidine. For VT and R on T median reductions of 99 - 100% were seen in all patient groups with both study drugs. The differences between treatments in median percent reductions were not statistically significant.

TABLE 14

Median Percent Reduction from Baseline in Couplets, VT and R on T
(Events/Hour) on Final Treatment Holter for Patients
with Complex Forms at Baseline
(Mexiletine vs. Quinidine Study B)

	Couplets		VT		R on T	
	Mex (n)	Quin (n)	Mex (n)	Quin (n)	Mex (n)	Quin (n)
All patients*	93.7 (92)	92.7 (80)	100.0 (69)	99.6 (63)	100.0 (79)	100.0 (74)
All patients except side effect failures**	96.2 (61)	95.0 (61)	100.0 (45)	99.8 (48)	100.0 (51)	100.0 (58)
Patients completing 12 weeks	99.4 (41)	98.7 (37)	100.0 (29)	100.0 (25)	100.0 (32)	100.0 (35)

* In addition, baseline but no treatment evaluation was available for 9 mexiletine and 17 quinidine patients with baseline couplets; 6 mexiletine and 13 quinidine patients with baseline VT; and 8 mexiletine and 8 quinidine patients with baseline R on T. One quinidine patient was missing baseline couplet data.

** Baseline but no treatment evaluation was available for 1 mexiletine and 2 quinidine patients with couplets, 1 mexiletine and 1 quinidine patient with VT and 1 quinidine patient with R on T.

As shown in Table 14A, the majority of patients in both treatment groups had reductions of more than 75% from baseline in couplets, VT and R on T.

TABLE 14A

Range of Reduction from Baseline in Couplets, VT and R on T (Events/Hour) on Final Treatment Holter for All Patients with Complex Forms at Baseline (Mexiletine vs. Quinidine Study B)

% Reduction	Couplets		VT		R on T	
	Mex (n=92)	Quin (n=80)	Mex (n=69)	Quin (n=63)	Mex (n=79)	Quin (n=74)
Increased*	18	15	12	15	13	11
0 - 25	4	2	1	1	4	2
26 - 50	3	6	4	1	3	3
51 - 75	10	7	6	4	4	4
76 - 100	57	50	46	42	55	54

- * A tenfold or greater increase from baseline on the final Holter was observed in couplets in 3 mexiletine (3.3%) and 2 quinidine patients (2.5%) and in VT in 3 mexiletine (4.3%) and 1 quinidine patient (1.6%).

Of those patients who had no evidence of complex arrhythmia forms at baseline, couplets were seen on the final Holter in 1/8 quinidine patients (rate 0.04) and VT was seen in 1/36 mexiletine (rate 0.46 events/hour) and 1/30 quinidine patients (rate 0.05 events/hour). None of the 10 mexiletine patients who had no couplets at baseline had couplets on the final Holter.

A 12-lead electrocardiogram was done at the beginning and end of the study. Mexiletine did not significantly alter mean EKG intervals (PR, QRS, QT_c), regardless of whether patients were concomitantly treated with digitalis, diuretics or beta blockers, with the exception of a statistically significant mean decrease of 0.0091 second (p less than 0.05) in the QT_c in the subgroup of digitalis non-users. Quinidine, however, prolonged the PR interval for the group as a whole (p less than 0.01) and for the subgroups of digitalis and diuretic non-users (p less than 0.01) and beta blocker users (p less than 0.01) and non-users (p less than 0.05). The mean QRS interval was significantly lengthened by quinidine for the group as a whole (p less than 0.05) and for diuretic users (p less than 0.01). Quinidine significantly prolonged the QT_c interval for the group as a whole and for the subgroups of digitalis and diuretic users and beta blocker non-users (p less than 0.01).

Neither mexiletine nor quinidine produced statistically significant changes from baseline in mean pulse rate.

d. Mexiletine vs. Disopyramide

The purpose of this double-blind, parallel-group study was to compare mexiletine and disopyramide in the management of ventricular arrhythmias. In addition, this trial evaluated the effects of the study drugs, alone or with concomitant digitalis or diuretic therapy, on electrocardiogram intervals and assessed changes in left ventricular function, ocular pressure and visual acuity. One hundred and forty-three patients from eleven centers (listed below) were randomly assigned to receive 12 weeks of treatment with mexiletine (74) or disopyramide (69).

<u>Investigator/Address</u>	<u>Number of Patients</u>
Masood Akhtar, M.D. Cardiovascular Disease Section Mount Sinai Medical Center P.O. Box 342 Milwaukee, WI 53201	11
Michael Bilitch, M.D. Parkview Medical Building 1420 San Pablo Street, C-201 Los Angeles, CA 90033	11
Dennis A. Bloomfield, M.D. Director of Medicine St. Vincent's Medical Center of Richmond 355 Bard Avenue Staten Island, NY 10310	10
Michael D. Ezekowitz, M.D., Ph.D. Director, Coronary Care Unit and Heart Station Veterans Administration Hospital (111B2) 921 Northeast 13th Street Oklahoma City, OK 73104	9

<u>Investigator/Address</u>	<u>Number of Patients</u>
Joseph P. Galichia, M.D. Richard A. Steckley, M.D. Wichita Cardiology Associates, P.A. St. Francis Medical Park Building 1035 North Emporia, Suite 1130 Wichita, KS 67201	22
Fred J. Harris, M.D. Assistant Professor of Medicine University of California, Davis UCD Professional Building, Room 202 4301 X Street Sacramento, CA 95817	21
Larry K. Jackson, M.D. Albert A. Del Negro, M.D. Georgetown University Hospital 3800 Reservoir Road, N.W. Washington, DC 20007	4
Nicholas Z. Kerin, M.D. Director, Noninvasive Laboratory Section of Cardiovascular Diseases Sinai Hospital of Detroit 6767 West Outer Drive Detroit, MI 48235	20
Niall P. Madigan, M.D. Director, Cardiovascular Laboratory University of Missouri Columbia School of Medicine Columbia, MI 65212	10
William Mandel, M.D. Department of Cardiology Cedars-Sinai Medical Center 8700 Beverly Boulevard Los Angeles, CA 90048	3
Peter Steele, M.D. Chief of Cardiology Veterans Administration Medical Center 1055 Clermont Street Denver, CO 80220	22

The cardiovascular diagnoses are presented below (some patients had more than one diagnosis).

<u>Diagnosis</u>	<u>Number of Patients</u>
Atherosclerotic heart disease	79
Idiopathic ventricular arrhythmia	39
Hypertensive heart disease	17
Other	28

The protocol required that patients have an average of at least 30 PVCs per hour, documented by two 24-hour Holter recordings at baseline. Two patients, one in each treatment group, who had baseline PVC rates of 28 and 29 per hour, respectively, were included in the efficacy analysis. The median hourly frequency of PVCs at baseline was 379.4 in the mexiletine group and 347.4 in the disopyramide group.

Patients began treatment with mexiletine 200 mg q8h or disopyramide 100 mg q6h. Because of the different dosing intervals, a third party administered the medications in order to preserve blinding. Although third party blinding of drug administration may not always preserve the blind, the Holters were read by a third party, therefore this defect is not critical. The dose was increased, if necessary, by 100 mg mexiletine q8h (maximum 400 mg q8h) or 50 mg disopyramide q6h (maximum 200 mg q6h) until the PVC rate was reduced by 70% from baseline (determined by 24-hour Holter monitoring as described below). Once 70% suppression was achieved, no further dosage adjustment was made as long as the patient maintained at least 55% suppression on subsequent Holters. The duration of treatment was 12 weeks.

Two consecutive 24-hour Holter recordings were done at baseline. Holter monitoring to assess the therapeutic response was done one week after initiation of treatment and a confirming Holter 48 hours to 8 days later. If titration was necessary, Holter analysis was done at these same intervals after each dosage adjustment. A final 24-hour Holter was done after 12 weeks of treatment.

The original statistical analysis defined treatment success as 70% or greater suppression in PVCs on one Holter and at least 55% suppression maintained on subsequent Holters through the final recording at 12 weeks. The data were reanalyzed, however, with treatment success defined as greater than or equal to 70% suppression in PVCs maintained through the final Holter. The results presented here are based on this efficacy criterion. Patients who did not maintain this degree of suppression were considered efficacy failures. Patients who were dropped because of intolerable side effects were considered side effect failures, regardless of the degree of PVC suppression achieved.

Results

One hundred and forty-three patients were enrolled in this trial (74 mexiletine, 69 disopyramide). Five patients in each treatment group were still in progress at the time the study was analyzed for the NDA and they were excluded from the efficacy analysis. Of the remaining patients (69 mexiletine, 64 disopyramide), all except administrative failures (6 mexiletine and 10 disopyramide patients with protocol violations, missing data or lost to follow-up) were evaluated for treatment success or failure (Table 15). All patients (including administrative failures) who had a Holter evaluation at baseline and during treatment (57 mexiletine, 61 disopyramide) were included in the remaining efficacy analysis, using the last treatment Holter to evaluate reduction of ectopy.

Table 15 presents treatment successes and failures by final dose of each study drug. There was no statistically significant difference between mexiletine and disopyramide in the number of treatment successes (28.6% and 44.4%, respectively). Most of the patients who were controlled on mexiletine were taking 200-300 mg q8h.

TABLE 15

Treatment Successes and Failures by Final Dose
Following Treatment with Mexiletine or Disopyramide

Treatment	Final Dose	Treatment Success*	Treatment Failures	
			Efficacy	Side Effects
Mexiletine (63 patients) ^a	100 mg	1 ^b	0	0
	200 mg	9	5	13
	300 mg	7	5	9
	400 mg	1	9	4
		<u>18</u> (28.6%)**	<u>19</u> (30.2%)	<u>26</u> (41.3%)
Disopyramide (54 patients) ^a	100 mg	8	5	4
	150 mg	7	4	4
	200 mg	9	10	3
		<u>24</u> (44.4%)	<u>19</u> (35.2%)	<u>11</u> (20.4%)

* greater than or equal to 70% reduction from baseline in PVCs

** Difference between treatments not statistically significant (p = 0.11)

^a Administrative failures (6 mexiletine, 10 disopyramide) excluded.

^b This patient's dose was reduced from 200 mg because of adverse reactions

Of the treatment failures (Table 15), none of the side effect failures completed the 12 week study. Nine of the 19 efficacy failures in each treatment group failed to complete 12 weeks.

The median percent reductions from baseline PVC rate are presented in three ways in Table 16: for all patients with baseline and treatment Holters; all patients excluding side effect failures; and all patients who completed 12 weeks of treatment. In the mexiletine group, median reductions ranged from 61 to 79% and in the disopyramide group from 73 to 83%. The differences between treatments in median percent reductions were not statistically significant.

TABLE 16

Median Percent Reduction from Baseline in Hourly
PVC Rate on Final Treatment Holter
(Mexiletine vs. Disopyramide)

	<u>Mexiletine (n)</u>	<u>Disopyramide (n)</u>
All patients*	61.0 (57)	72.9 (61)
All patients except side effect failures**	71.9 (39)	76.2 (53)
Patients completing 12 weeks	78.8 (28)	82.5 (34)

* Baseline but no treatment Holter evaluation was available for an additional 12 mexiletine and 3 disopyramide patients

** Baseline but no treatment evaluation was available for 4 additional mexiletine patients

The range of reduction from baseline in PVC rate on the final treatment Holter for all patients with baseline and treatment Holters is shown in Table 16A. Reductions greater than 70% were seen in 49% of mexiletine patients and 52% of disopyramide patients.

TABLE 16A

Range of Reduction from Baseline in Hourly PVC Rate
on Final Treatment Holter for All Patients
(Mexiletine vs. Disopyramide)

<u>% Reduction</u>	<u>Number of Patients</u>	
	<u>Mexiletine</u> <u>(n = 57)</u>	<u>Disopyramide</u> <u>(n = 61)</u>
Increased*	10	5
0 - 25	7	3
26 - 50	6	11
51 - 70	6	10
71 - 80	8	8
81 - 90	6	8
91 - 100	14	16

* A fourfold or greater increase in PVC rate was seen on the final Holter in 3 mexiletine patients (5.3%) and in 2 disopyramide patients (3.3%)

Table 17 presents the median percent reductions from baseline in couplets, VT and R on T for the three patient groups. Median decreases in couplets ranged from 96 to 100% with mexiletine and from 94 to 95% with disopyramide. Median decreases of 100% in VT and R on T were seen with both mexiletine and disopyramide for all patient groups.

TABLE 17

Median Percent Reduction from Baseline in Couplets, VT and R on T (Events/Hour) on Final Treatment Holter for Patients with Complex Forms at Baseline (Mexiletine vs. Disopyramide)

	Couplets		VT		R on T	
	Mex (n)	Diso (n)	Mex (n)	Diso (n)	Mex (n)	Diso (n)
All patients*	96.3 (50)	93.9 (55)	100.0 (36)	100.0 (38)	100.0 (45)	100.0 (38)
All patients except side effect failures**	97.0 (36)	93.9 (48)	100.0 (26)	100.0 (34)	100.0 (31)	100.0 (33)
Patients completing 12 weeks	99.8 (26)	94.7 (32)	100.0 (17)	100.0 (24)	100.0 ^a (24)	100.0 (21)

* Baseline but no treatment Holter evaluation was available for an additional 10 mexiletine and 3 disopyramide patients with baseline couplets; 7 mexiletine and 2 disopyramide patients with baseline VT and R on T data. Four mexiletine and 1 quinidine patient were missing baseline couplet data while 3 mexiletine and 1 quinidine patient were missing baseline VT data.

** Baseline but no treatment evaluation was available for an additional 3 patients with couplets, 1 with VT and 2 with R on T, all in the mexiletine group.

^a Difference between treatments statistically significant, $p = 0.01$. Twenty-one of 24 mexiletine patients had reductions of 100% while 14 of 21 disopyramide patients had reductions of 100%.

The range of reduction from baseline for couplets, VT and R on T on the final treatment Holter for all patients with baseline and treatment Holters is presented in TABLE 17A. The majority of patients in both treatment groups had reductions of greater than 75% in couplets, VT and R on T.

TABLE 17A

Range of Reduction from Baseline in Couplets, VT and R on T
(Events/Hour) on Final Treatment Holter for All
Patients With Complex Forms at Baseline
(Mexiletine vs. Disopyramide)

% Reduction	Couplets		VT		R on T	
	Mex (n=50)	Diso (n=55)	Mex (n=35)	Diso (n=33)	Mex (n=45)	Diso (n=38)
Increased*	9	7	4	1	5	4
0 - 25	1	2	1	1	1	1
26 - 50	3	2	1	2	1	2
51 - 75	4	7	1	4	3	3
76 - 100	33	37	29	30	35	28

- * A tenfold or greater increase from baseline in couplets was seen on the final Holter in 1 patient in each treatment group (2.0 and 1.8% for mexiletine and disopyramide, respectively). A tenfold or greater increase in VT was not observed in either group on the final Holter.

Of those patients who had no evidence of complex arrhythmias at baseline, VT was seen on the final treatment Holter in 1 patient out of 23 in the mexiletine group (rate 0.08 events/hour) and in 4 patients out of 23 in the disopyramide group (maximum rate 0.12 events/hour). None of the 5 patients in each treatment group who had no couplets at baseline had couplets on the final Holter.

A 12-lead electrocardiogram was done at the beginning and end of the study to assess the effects of mexiletine and disopyramide on EKG intervals (PR, QRS, QT_c). There were no statistically significant mean changes from baseline for any interval in the mexiletine treatment group, regardless of whether patients were concomitantly using digitalis or diuretics. In the disopyramide group, the QT_c interval was significantly prolonged as compared to baseline except in those patients concomitantly treated with digitalis and the PR interval was prolonged in patients not using digitalis or diuretics. The difference between treatments was not statistically significant.

Neither mexiletine nor disopyramide produced any significant change from baseline in mean blood pressure or pulse rate.

Mexiletine did not significantly affect visual acuity or intraocular pressure.

The hemodynamic effects of mexiletine and disopyramide were assessed by means of gated radionuclide ventriculogram. There were no significant changes from baseline with either treatment in any of the variables measured (end-systolic and diastolic volumes, stroke volume, cardiac output and ejection fraction).

Summary

The results of the controlled clinical trials conducted in the U.S. demonstrated the efficacy of mexiletine in the treatment of ventricular arrhythmias. Both idiopathic ventricular arrhythmias and ventricular arrhythmias due to underlying cardiovascular illness, such as arteriosclerotic heart disease and hypertensive heart disease, were successfully treated.

In a 4-week, double-blind, crossover study, mexiletine proved to be superior to placebo, with 24/46 patients responding to mexiletine with greater than or equal to 70% suppression of PVCs and only 6/48 patients responding to placebo. The median percent reduction from baseline in PVCs was significantly greater (p less than 0.0001) with mexiletine (70.3%) than with placebo (10.3%). Mexiletine also significantly reduced the median frequency of couplets (p less than 0.0001) and ventricular tachycardia (p less than 0.019) as compared to placebo.

In 12-week, double-blind, parallel group trials comparing mexiletine with the standard antiarrhythmic drugs, mexiletine was superior to procainamide ($p = 0.02$) and comparable to quinidine and disopyramide in the number of patients successfully controlled (greater than or equal to 70% reduction in PVCs). A total of 371 patients were analyzed after treatment with mexiletine. As summarized in the table below, approximately one-third (32%) were treatment successes; most of these patients were taking 200 or 300 mg mexiletine q8h. Slightly more than one-third of patients, however, left the study prematurely because of adverse events with mexiletine, which was more than left the other drug groups.

Table 18

Response to Mexiletine for 371 Patients* in the
12-Week, Double Blind Studies

Mexiletine Dose qd ⁿ	Treatment Success**	Treatment Failure		
		Efficacy	Side Effects	Death
100 mg	1	0	1	0
200 mg	59	21	72	3
300 mg	42	22	43	0
400 mg	<u>16</u>	<u>61</u>	<u>30</u>	<u>0</u>
Total (1%)	118 (32%)	104 (28%)	146 (39%)	3

* Administrative failures excluded

** greater than or equal to 70% reduction from baseline in PVCs

The overall response to mexiletine and to the
comparison drugs in the 12-week trials is summarized
below.

Table 19

Overall Response to Treatment in the
12-Week, Double Blind Studies

Treatment	Total Treated*	Treatment Success**	Treatment Failure		
			Efficacy	Side Effects	Death
Mexiletine	371	118 (32%)	104 (28%)	146 (39%)	3 (1%)
Procainamide	76	15 (20%)	37 (49%)	22 (29%)	2 (3%)
Quinidine	225	73 (32%)	70 (31%)	75 (33%)	7 (3%)
Disopyramide	54	24 (44%)	19 (35%)	11 (20%)	0 (0%)

* Administrative failures excluded

** greater than or equal to 70% reduction from baseline in PVCs

Mexiletine also reduced the frequency of couplets, ventricular tachycardia and R on T, as shown in Table 20. The degree of reduction from baseline exceeded 76% in the majority of patients.

Table 20

Percent Reduction from Baseline in Couplets, Ventricular Tachycardia and R on T after Treatment with Mexiletine in the 12-Week Double-Blind Studies

Percent Reduction from Baseline	Number of Patients		
	Couplets	Ventricular Tachycardia	R on T
Increased	56	34	27
0-25	11	4	6
26-50	14	8	4
51-75	32	10	12
76-100	198	169	153
Total*	311	225	202

* All patients with baseline and treatment Holter and with complex arrhythmia at baseline.

No clinically significant effects on mean blood pressure or pulse rate were noted. Mean EKG intervals showed little or no change after treatment with mexiletine alone or in combination with digitalis, diuretic or beta blocker therapy.

2. Uncontrolled Studies

a. Long Term Follow-Up

Study Design

The purpose of this ongoing open-label trial is to evaluate the efficacy and safety of mexiletine when administered for one year or longer. Participants were chosen from among those patients who had been successfully treated with mexiletine in the previously described placebo, procainamide, quinidine and disopyramide trials and the b.i.d. dosing study. If a patient had achieved adequate suppression of PVCs on mexiletine during the

double-blind, controlled portion of these studies and if, in the opinion of the investigator, he or she would benefit from continued mexiletine therapy, the patient was entered into the long-term study. Patients are seen monthly for recording of vital signs and evaluation of possible adverse reactions. Twenty-four hour Holter recording and 12-lead electrocardiogram are done every three months to assess response to therapy. At the discretion of the investigator, the dose of mexiletine may be adjusted as necessary to maintain suppression of the arrhythmia or to reduce the incidence of side effects. Patients who demonstrate continued suppression at the end of one year of treatment are allowed to remain on mexiletine and are seen for follow-up evaluation every three months.

The following cardiovascular diseases are represented among the patients participating in the long-term program:

<u>Diagnosis</u>	<u>Number of Patients</u>
Atherosclerotic heart disease	112
Idiopathic ventricular arrhythmia	70
Hypertensive heart disease	28
Other	43

Results

This is an ongoing study. The results presented here reflect data received as of 1 September 1983. A total of 197 patients have been treated by 40 investigators and 85 patients continue to receive treatment. Table 21 presents the status of patients enrolled in the trial.

TABLE 21

Status of Patients Enrolled in
Long-Term Mexiletine Study

<u>Status</u>	<u>Number of Patients</u>
Total treated	197
In progress	85
Completed one year; no further treatment	54
<u>Lost, Dropped, Withdrawn</u>	48
Side effects	19
Lack of efficacy	6
Lost to follow-up	17
Protocol violation	5
Not reported	1
<u>Deaths During Treatment</u>	10
Cardiac	7
Non-cardiac	2
Cause not reported	1

The maximum duration of treatment reported as of 1 September 1983 was 57 months, with most patients (158) on mexiletine for two years or less. One hundred and six patients (including 61 of the 85 in progress) have continued beyond one year of treatment. The total daily dose of mexiletine has generally ranged from 600 to 1200 mg, as summarized below:

<u>Total Daily Dose (mg)</u>	<u>Number of Patients</u>
300	2
300-500	16
600-900	135
1000-1200	41
1500	
Reported	2

Twenty-four hour Holter recordings performed at 3-month intervals were analyzed on 100 patients previously treated in the trials comparing mexiletine with quinidine or disopyramide. Over 1 year of treatment, mexiletine consistently produced a median reduction of 87% or greater in hourly PVC frequency (Table 22).

TABLE 22

Median Hourly PVC Rate and Median Percent Reduction
from Baseline by Month of Treatment

<u>Month</u>	<u>Number of Patients</u>	<u>Median Rate</u>	<u>Median % Reduction</u>
Baseline	108	249.44	
3	106	14.04	-90.80
6	97	29.45	-92.80
9	84	18.50	-92.39
12	72	26.58	-87.25

A median reduction of 99-100% was observed in couplet frequency. Ventricular tachycardia and R on T were consistently reduced by a median of 100% (Table 23).

TABLE 23

Couplets, Ventricular Tachycardia and R on T:
Median Hourly Rate and Median Percent Reduction from
Baseline by Month of Treatment

	<u>Month</u>	<u>Number of Patients*</u>	<u>Median Rate</u>	<u>Median % Reduction</u>
<u>Couplets</u>	Baseline	107	1.37	
	3	104(97)	0.00	-100.00
	6	97(91)	0.04	- 99.43
	9	84(78)	0.00	- 99.97
	12	72(67)	0.04	- 99.40

<u>Ventricular Tachycardia</u>	Baseline	107	0.02	
	3	104(63)	0.00	-100.00
	6	97(58)	0.00	-100.00
	9	84(49)	0.00	-100.00
	12	72(42)	0.00	-100.00

<u>R on T</u>	Baseline	106	0.17	
	3	103(71)	0.00	-100.00
	6	97(67)	0.00	-100.00
	9	84(55)	0.00	-100.00
	12	72(46)	0.00	-100.00

* Numbers in parentheses indicate number of patients used to calculate median % reduction.

The most frequently reported adverse reactions have been upper gastrointestinal distress, lightheadedness and tremor. In 19 of 197 patients (10%), adverse reactions have necessitated discontinuation of treatment.

A variety of concomitant medications have been administered during the long-term follow-up, as listed below

<u>Type of Concomitant Medication</u>	<u>Number of Patients</u>
Antianginals	68
Antiarrhythmics	8
Anticoagulants	10
Antihypertensives	61
Betablockers	13
Cardiotonics	45
Diuretics	70
Potassium supplements	33
Miscellaneous	99

Twelve-lead electrocardiogram analysis has revealed no statistically significant changes from baseline in mean PR interval or QRS duration, regardless of whether patients were receiving mexiletine alone or in combination with other medications.

b. Emergency Mexiletine Program

Study Design

This open-label trial has allowed patients with ventricular arrhythmias to be treated with mexiletine under a compassionate use protocol. Only patients whose arrhythmias, by history, have been said to be refractory to conventional therapy, or who have been unable to tolerate such therapy because of side effects, or in whom such therapy is contraindicated, have been enrolled in the program. As of 1 August 1984, a total of 9353 patients have been treated in the emergency program since its initiation in 1977. The most common cardiovascular diseases among these patients are listed below:

<u>Diagnosis</u>	<u>Number of Patients</u>
Atherosclerotic heart disease	5663
Hypertensive heart disease	1172
Primary myocardial disease	1006
Rheumatic heart disease	307

The following table stratifies patients according to the indication for treatment. The majority (78%) of patients were admitted with refractory ventricular tachycardia or ventricular fibrillation.

<u>Indication</u>	<u>Number of Patients</u>
Ventricular tachycardia	6768
PVCs	1459
Ventricular fibrillation	494
Couplets	176
Other	151
Not reported	305

The protocol requires that patients be seen for follow-up every three months during the first year of treatment and every six months thereafter. Case report forms are submitted to Boehringer Ingelheim Ltd. at these intervals.

Results

Table 24 presents the status of patients treated under the compassionate use protocol as of 1 August 1984.

TABLE 24

Status of Patients Enrolled Since 1977
in Emergency Mexiletine Program

<u>Status</u>	<u>Number of Patients</u>
Total enrolled	9353
In progress	4316 (46%)
<u>Lost, Dropped, Withdrawn</u>	3832 (41%)
Lack of efficacy	1422
Adverse events	1421
Discontinued by patient	147
Need for therapy re-evaluated	127
Switched to another drug (no reason given)	65
Lost to follow-up	115
Discontinued despite good response	12
Other	247
Not reported	276
<u>Death During Treatment</u>	1205 (13%)
Cardiac	853
Non-cardiac	190
Cause not reported	162

Patients have received mexiletine in total daily doses ranging from 50 mg to 3200 mg. The most frequently reported total daily doses have been between 300 and 900 mg, as summarized below:

<u>Total Daily Dose (mg)</u>	<u>Number of Patients</u>
50-250	207
300-550	2186
600-850	4635
900-1100	1378
1200-1600	747
1650-3200	15
Not Reported	185

The maximum duration of treatment has been 78 months, with the majority of patients (8413) on mexiletine therapy for two years or less.

Experience with mexiletine under the emergency protocol comprises a total of 6,295 patient-years of treatment. As has been observed in other trials, the most frequently encountered side effects with mexiletine have been upper gastrointestinal distress and central nervous system symptoms of lightheadedness and tremor.

The emergency protocol does not require investigators to submit Holter records to Boehringer Ingelheim Ltd. Instead, investigators are asked to provide on the case report form a global clinical assessment of the patient's response to treatment: improved, no change, worsened. For this reason, it is not possible to evaluate rigorously the degree of arrhythmia control seen overall in the emergency program. However, the results of mexiletine therapy in the Emergency Program have been analyzed further in some centers and these results are presented below.

PES Testing on Mexiletine Therapy

One hundred and forty-eight patients have been evaluated with programmed electrophysiologic stimulation (PES) while on mexiletine therapy by Dr. J. Ruskin and coworkers (mexiletine NDA). Patients had a history of recurrent sustained ventricular tachycardia (56 patients), symptomatic nonsustained VT (21), primary ventricular fibrillation (41) and complex ventricular ectopy (9). Eleven patients had a history of recurrent syncope without documented arrhythmia.

On baseline electrophysiologic testing in the absence of antiarrhythmic therapy, ventricular tachyarrhythmias were inducible in all patients - sustained VT (97 patients), nonsustained VT (43), ventricular fibrillation (8).

i. Acute PES Testing

One hundred and eighteen of the 148 patients underwent PES testing on mexiletine alone (see diagram below); 37 (Group I) of these 118 patients had no further testing, while 81 (Group II) subsequently had serial PES testing with mexiletine combined with another previously ineffective antiarrhythmic agent. The remaining 30 (Group III) patients were tested only on combination therapy. The drugs used in combination with mexiletine and the number of patients receiving each combination are listed below.

<u>Drug</u>	<u>Number of Patients</u>
Quinidine	46
Procainamide	38
Propranolol	5
Disopyramide	4
Amiodarone	4
Metoprolol	2
Nadolol	1
Lorcainide	1
Quinidine + propranolol	5
Procainamide + propranolol	3
Quinidine + metoprolol	1
Procainamide + atenolol	1

During PES testing, fifty-three of the 148 patients (36%) achieved complete suppression of the inducible arrhythmia and 19 (13%) had partial suppression with either mexiletine alone or combined with another drug. On mexiletine alone, 19% achieved complete suppression.

Nineteen out of 118 patients (16%) during PES testing on mexiletine alone had exacerbation of arrhythmia, i.e., the arrhythmia was inducible with lesser grades of ventricular stimulation as compared to baseline. The investigators noted that this incidence of facilitation of arrhythmia induction is comparable to that seen with other antiarrhythmic agents they have tested.

Patients whose presenting arrhythmia was sustained VT were generally less responsive to treatment (success rate of 24%) as compared to patients presenting with ventricular fibrillation or nonsustained VT (success rates of 51 & 52%, respectively). This difference was statistically significant, p less than 0.01.

Baseline Electrophysiologic Testing
(no antiarrhythmic therapy)
n = 148

Electrophysiologic Testing Mexiletine alone n=118		Electrophysiologic Testing Mexiletine and 2nd agent n=111		
Group I n=37	Group II n=81	Group II n=81	and	Group III n=30
CS - 22	CS - 1			CS - 31
PS - 3	PS - 15			PS - 16
NC - 9	NC - 47			NC - 43
E - 3	E - 16			E - 21
	NA - 2			

Key: CS-complete suppression of inducible VT, PS-partial suppression, NC-no change, E-exacerbation, NA- not available

ii. Long-Term Follow-Up on Mexiletine Therapy Following PES Evaluation

Eighty-nine patients were discharged on long-term therapy with the treatment regimen that provided optimum arrhythmia control (24 on mexiletine alone, 65 on combination therapy) and followed for a mean of 14 months (maximum 58 months). Eight patients were discontinued and 23 required a reduction in dosage because of side effects. Fifteen patients died: the causes of death were sudden death in 8 patients, refractory heart failure in 5, and myocardial infarction in 2 patients. Three patients had non-fatal recurrence of ventricular tachycardia.

Thus, of the 89 patients who were discharged on mexiletine alone or in combination with another drug, 63 (71%) remained free of recurrence of ventricular arrhythmias.

Ambulatory ECG Monitoring with Exercise Testing on Mexiletine Therapy

Podrid and Lown (1981) evaluated the efficacy of mexiletine after acute administration and after short and long-term maintenance therapy. A total of 108 patients with chronic, symptomatic ventricular arrhythmias were treated. Twenty-five patients had a history of ventricular premature beats (VPBs); 25 had a history of one or more episodes of ventricular fibrillation; 58 patients had a history of spontaneous ventricular tachycardia. Of the 58 patients with spontaneous VT, in 24 VT was sustained, associated with syncope and required cardioversion or lidocaine therapy; among the other 34 patients, VT was associated with dizziness in all and was sustained in 11. Seventy-two patients had been refractory to conventional antiarrhythmic therapy and, in many cases, to investigational agents as well.

During Phase 1 (acute drug testing), suppression was defined as (1) greater than 50% decrease in frequency of VPBs and total elimination of couplets and VT at rest, and (2) greater than 50% decrease in frequency of VPBs and greater than 90% decrease in couplets and VT during exercise testing. The response was considered partial if only one of the above criteria was met or if couplets and VT were reduced by 50-90%, but not totally eliminated.

During Phases 2 (short-term therapy), and 3 (long-term maintenance therapy), a response was considered successful if all of the following criteria were met:

- 1) 24-hour ambulatory monitoring: greater than or equal to 50% reduction in frequency of VPBs; greater than or equal to 50% reduction in number of hours showing multiform VPBs or greater than 30 VPBs/hour; and elimination of VT and greater than 90% reduction in couplets.
- 2) Exercise testing: greater than 50% decrease in number of VPBs occurring during exercise and recovery period; greater than 50% decrease in peak rate of VPBs/minute observed throughout exercise and recovery period; total elimination of VT and multiform ectopic beats and greater than 90% reduction in couplets throughout exercise.

The response was considered partial if the criteria were met for only one method of testing.

Phase 1: Eighty-eight patients underwent acute testing with a single 400 mg dose of mexiletine. Suppression of arrhythmia was seen in 57/88 patients (65%) evaluated at rest. Fifty-five of the 88 patients were also evaluated during exercise; arrhythmia was suppressed in 37 (67%) of these 55 patients. In the 55 patients evaluated both at rest and during exercise, suppression was achieved in 32 patients (58%); a partial response was seen in 5 patients (9%).

Phase 2: Seventy-nine patients (59 from Phase 1 plus 20 additional patients) completed a 48 to 72 hour period of multiple dosing with mexiletine (900-1200 mg/day). Patients were evaluated after 24 hours (at which point the dose could be increased if the arrhythmia persisted) and again during the final 24 hours of Phase 2. One patient did not undergo remonitoring because he had ventricular tachycardia with exercise while receiving mexiletine. The other 78 patients had repeat evaluation by 24-hour ambulatory monitoring. Fifty-one of these 78 patients demonstrated a good response to treatment; the hourly frequency of ventricular premature beats (VPBs) was reduced from a control value of 357 ± 58 to 61 ± 18 (p less than 0.001). Sixty-five patients also underwent repeat exercise testing. Forty-three (66%) of these 65 patients had a good response, with a reduction in the hourly frequency of VPBs from a mean of 204 ± 34 to 30 ± 10 (p less than 0.001). Thirty-nine of the 65 patients who underwent both ambulatory monitoring and exercise testing met the criteria for drug efficacy with both methods of evaluation.

Phase 3: Forty-four patients who had responded to mexiletine during Phases 1 and 2 were continued on long-term maintenance therapy. Seven patients were discontinued because of adverse reactions. Six patients who were receiving concomitant antiarrhythmic therapy with quinidine or aprindine were not included in the analysis. Thirty-one patients, therefore, have been maintained on mexiletine as their only antiarrhythmic therapy for 8 to 32 months (mean 17.6 months) and have demonstrated continued suppression on ambulatory monitoring and exercise testing.

Summary

The data available from the long-term follow-up studies and the Emergency Program indicate that mexiletine continues to be effective when administered for periods ranging from several months to several years. In the long-term follow-up studies, mexiletine produced a median suppression of greater than 87% in PVCs over a 12-month period, a median reduction in couplets of 99-100% and a median suppression of 100% in ventricular tachycardia and R on T. The results of electrophysiologic efficacy testing in 148 patients are available from one center in the Emergency Program. Out of 148 patients initially evaluated with electrophysiologic testing, 89 patients were discharged on mexiletine (24 mexiletine alone, 65 combination therapy) and followed for a mean of 14 months. Sixty-three patients were maintained on mexiletine therapy; 8 patients were discontinued because of side effects; 15 patients died; and 3 had non-fatal recurrence of VT. (Ruskin, Mexiletine NDA). In a second center, following efficacy evaluation with 24-hour Holter recording and acute exercise testing, 38 patients were started on maintenance therapy with mexiletine alone and followed for a mean of 17.6 months; 31 patients had continued control of their arrhythmias while 7 patients were discontinued because of side effects (Podrid and Lown, 1981).

C. SAFETY OF MEXILETINE

The clinical safety of mexiletine has been evaluated in a total of 9828 patients treated as of August 1984. Of these, 475 patients were most closely followed, receiving mexiletine in controlled, double-blind trials against placebo, procainamide, quinidine or disopyramide; 197 of these patients continued mexiletine therapy in an open-label extension of the controlled studies (Long-Term Follow-Up Study) and have been followed for periods up to five years. In the emergency mexiletine program, an open-label, compassionate-use cohort survey, 9353 patients have been followed on mexiletine therapy for periods up to six and a half years.

The most common adverse events and effects on laboratory measurements can best be evaluated by data from the controlled trials. Safety data from the emergency use program can aid in predicting rare events, but must be used with the understanding that the severity of patients' underlying disease and frequent use of multiple concurrent medications may confound the contribution of mexiletine to the reported events and that reporting of events, especially non-serious events, is likely to be much less complete than in a controlled trial or formal open study.

The sponsor has provided data on adverse events, causes of discontinuation of therapy, deaths and laboratory findings in the controlled trials and in their long-term follow-up and in the emergency use program. In addition, the pro-arrhythmic potential of mexiletine, reports of mortality findings in post-infarction secondary trials (not conducted by the sponsor), and abnormal hepatic and hematologic laboratory findings are discussed.

1. Adverse Events in U.S. Controlled Studies

a. Mexiletine vs. Placebo

Mexiletine and placebo were compared in 53 patients in a double-blind, crossover trial with four-week treatment periods. The initial dose of mexiletine was 100 mg q8h, titrated to efficacy or to a maximum of 400 mg q8h. The highest dose level reached was 100 mg in 7 patients, 200 mg in 12 patients, 300 mg in 16 patients and 400 mg in 18 patients. Adverse events, as shown below, were reported by 35/53 patients (66%) while on mexiletine and by 30/49 patients (61%) while on placebo.

Upper GI distress, lightheadedness, tremor and coordination difficulties were observed more frequently during mexiletine therapy than during placebo administration. Changes in sleep habits, which included insomnia and drowsiness, were seen three times more frequently during placebo therapy, suggesting that a relationship to mexiletine is unlikely.

Three patients discontinued mexiletine because of adverse events probably related to the drug: two patients had upper GI distress; the other had a 13-beat run of ventricular tachycardia with dizziness and was hospitalized.

Comparative Incidence (%) of Adverse Events Among Patients
Treated with Mexiletine and Placebo in the
4-Week, Double-Blind, Crossover Trial

	<u>Mexiletine</u> N = 53	<u>Placebo</u> N = 49
<u>Cardiovascular</u>		
Palpitations	7.5	10.2
Chest Pain	7.5	4.1
Increased Ventricular Arrhythmia/PVCs*	1.9	-
<u>Digestive</u>		
nausea/Vomiting/Heartburn	39.6	6.1
<u>CNS</u>		
Dizziness/Lightheadedness	26.4	14.3
Tremor	13.2	-
Nervousness/Agitation	11.3	6.1
Coordination Difficulties	9.4	-
Changes in Sleep Habits	7.5	16.3
Paresthesias	3.3	2.0
Weakness	1.9	4.1
Fatigue	1.9	2.0
Tinnitus	1.9	4.1
Confusion/Clouded Sensorium	1.9	2.0
<u>Other</u>		
Headache	7.5	6.1
Blurred vision/Visual disturbances	7.5	2.0
Respiratory	5.7	10.2
Rash	3.8	2.0
Non-Specific Edema	3.8	-
Arthralgia	1.9	10.2
Diaphoresis	1.9	2.0
Pharyngitis	1.9	-
Nasal Stuffiness	1.9	-
Shoulder Pain	1.9	-
Chills	1.9	-

* The term "increased ventricular arrhythmias/PVCs" includes any increase in ventricular arrhythmia reported as an adverse event by the investigator. The standard for identifying such events was at the discretion of the investigator.

b. Mexiletine vs. Procainamide, Quinidine and Disopyramide

In three separate trials, mexiletine was compared to procainamide, quinidine and disopyramide in a double-blind, parallel-group design. Four hundred twenty-two patients were treated with mexiletine for a 12-week period. The initial dose of mexiletine was 200 mg t.i.d., titrated to efficacy or to a maximum of 400 mg t.i.d. The highest mexiletine dose level reached was 200 mg in 193 patients, 300 mg in 120 patients, and 400 mg in 109 patients. Adverse events were reported by 287 patients (68%); the type and frequency of events are presented below.

Comparative Incidence (%) of Adverse Events Among Patients Treated
With Mexiletine or Control Drugs in the 12-Week, Double-Blind Trials

	Mexiletine N = 422	Quinidine N = 262	Procainamide N = 78	Disopyramide N = 69
<u>Cardiovascular</u>				
Palpitations	4.3	4.6	1.3	5.8
Chest Pain	2.6	3.4	1.3	2.9
Angina/Angina-like Pain	1.7	1.9	2.6	2.9
Increased Ventricular Arrhythmias/PVCs*	1.0	2.7	2.6	-
<u>Digestive</u>				
Nausea/Vomiting/Heartburn	41.0	21.4	33.3	14.5
Diarrhea	5.0	33.2	2.6	8.7
Constipation	4.3	-	6.4	11.6
Changes in Appetite	2.8	1.9	-	-
Abdominal Pain/Cramps/ Discomfort	1.2	1.5	-	1.4
<u>Central Nervous System</u>				
Dizziness/Lightheadedness	18.5	14.1	14.1	2.9
Tremor	12.6	2.3	3.8	1.4
Coordination Difficulties	10.2	1.1	1.3	-
Changes in Sleep Habits	6.9	2.7	11.5	8.7
Weakness	5.0	5.3	7.7	2.9
Nervousness/Agitation	4.5	1.9	6.4	5.8
Fatigue	3.8	5.7	5.1	1.4
Speech Difficulties	2.6	0.4	-	-
Paresthesias/Numbness	2.4	2.3	2.6	-
Tinnitus	2.4	1.5	-	-
Depression	2.4	1.1	1.3	1.4
Confusion/Clouded Sensorium	1.9	-	3.8	-
<u>Other</u>				
Blurred Vision/Visual Disturbances	5.5	3.1	5.1	7.2
Headache	4.5	6.9	7.7	4.3
Rash	4.2	3.8	10.3	1.4
Respiratory	2.8	3.1	5.1	2.9
Dry Mouth	2.8	1.9	5.1	14.5
Arthralgia	1.7	2.3	5.1	1.4
Fever	1.2	3.1	2.6	-

Less than 1%: Arrhythmia, syncope, edema, hot flashes, hypertension, short-term memory loss, loss of consciousness, other psychological changes, diaphoresis, urinary problems, malaise, impotence/decreased libido, pharyngitis.

* The term "increased ventricular arrhythmias/PVCs" includes any increase in ventricular arrhythmia reported as an adverse event by the investigator. The standard for identifying such events was at the discretion of the investigator.

These three-month double-blind parallel trials confirmed the adverse event pattern seen in the four-week placebo crossover: upper GI distress and central nervous system side effects predominated, and were the major treatment-limiting events. Nausea, vomiting and other forms of upper GI distress caused 20% of patients in the 12-week studies to discontinue mexiletine. Dizziness (6%), lightheadedness (4%) and tremor (2%) were the other events most frequently cited as reason for discontinuation.

Three patients (less than 1%) discontinued mexiletine because of syncope; two withdrew because of chest pain. There was one discontinuation each because of tachycardia and dyspnea. In addition, one patient withdrew when hospitalized for a myocardial infarction two days after study entry.

Additionally, 57 patients (14%) had mexiletine discontinued before completion of 12 weeks of therapy because of inadequate suppression of ventricular arrhythmia (less than 70% reduction in PVCs).

c. Long-term Continuation after Controlled Trials

One-hundred ninety-seven patients who responded to mexiletine in controlled trials continued therapy in the Long-Term Follow-Up Study. Most patients were followed for 2-3 years (range 1 month to 5 years) on total daily doses from less than 300 to 1200 mg of mexiletine. Not surprisingly, since these patients all tolerated mexiletine well enough to complete the 12-week study, they had a lower frequency of adverse effects and were relatively unlikely to leave the study because of an adverse event.

Incidence (%) of Adverse Events Among 197 Patients Treated With
Mexiletine during Long-Term Follow-Up to Controlled Trials

<u>Long-Term Follow-Up</u>	
<u>Cardiovascular</u>	(%)
Chest Pain	3
Angina/angina-like pain	3
Increased Ventricular Arrhythmias/PVCs*	1
Palpitations	1
Syncope	1
CVA	1
<u>Digestive</u>	
Nausea/Vomiting/Heartburn	29
Changes in Appetite	2
Constipation	2
Diarrhea	2
<u>Central Nervous System</u>	
Dizziness/Lightheadedness	10
Tremor	5
Changes in Sleep Habits	4
Fatigue	3
Nervousness/Agitation	3
Coordination Difficulties	3
Weakness	3
Tinnitus	3
Depression	2
Speech Difficulties	2
Confusion/Clouded Sensorium	2
Paresthesias/Numbness	2
Short-Term Memory Loss	2
Other Psychological Changes	1
<u>Other</u>	
Respiratory	4
Headache	3
Impotence/Decreased Libido	2
Arthralgia	2
Dry mouth	2
Blurred Vision/Visual Disturbances	2
Hair Loss	1
Diaphoresis	1
Rash	1

Less than 1%: Congestive heart failure, conjunctivitis.

* The term "increased ventricular arrhythmias/PVCs" includes any increase in ventricular arrhythmia reported as an adverse event by the investigator. The standard for identifying such events was at the discretion of the investigator.

Approximately 10% of the patients withdrew from the follow-up program because of adverse events (some patients had more than one adverse effect at time of discontinuation):

<u>Treatment-limiting Events</u>	<u>No. (%) of Patients</u>	
Nausea/Vomiting/Heartburn	9	(5)
Dizziness/Lightheadedness	3	(2)
Tremor	2	(1)
Fatigue	2	(1)
Coordination Difficulties	2	(1)
Other CNS Effects	2	(1)

Thus, during the follow-up period, the predominance of upper GI and CNS adverse events was similar to experience in the controlled phase of mexiletine studies, but the overall incidence was lower, as expected. The long-term tolerability observed during this period suggests that new adverse events occur less frequently during chronic, stable-dose mexiletine therapy.

2. Adverse Events in the Mexiletine Emergency-Use Program

In addition to the adverse event data for the 475 patients treated in the controlled trials, safety data is available for 9353 patients treated in the emergency-use program. Admission to this program was restricted to patients with clinically significant ventricular arrhythmias who could not be treated with other antiarrhythmic agents because of treatment failure or intolerance. These patients were seriously ill; multiple cardiovascular problems and multiple concurrent medications were common. Treatment was continued for more than one year for over 2000 patients; approximately 900 patients were continued on mexiletine treatment for more than two years and some for over six years.

Although the frequency of adverse events was lower than reported in the controlled trials, the pattern was similar with upper GI and CNS effects most frequently reported. Adverse reactions (also predominantly upper GI distress and CNS effects) led to discontinuation of therapy in 15% of patients (treatment was limited by more than one adverse event in some patients).

<u>Treatment-limiting Events</u>	<u>(%) of 9353 Patients</u>
Nausea/Vomiting/Heartburn	9
Tremor	2
Dizziness/Lightheadedness	2
Coordination Difficulties, Fatigue, Weakness, Confusion, Changes in Appetite	each 1

Incidence (%) of Adverse Events Among 9353 Patients Treated
With Mexiletine in the Emergency Use Program

	<u>Emergency Mexiletine</u> <u>(% of 9353 Patients)</u>
<u>Cardiovascular</u>	
Increased Ventricular Arrhythmias/PVCs*	1
Congestive Heart Failure	1
<u>Digestive</u>	
Nausea/Vomiting/Heartburn	22
Abdominal Pain/Cramps/Discomfort	2
Changes in Appetite	2
Constipation	1
Diarrhea	1
<u>Central Nervous System</u>	
Dizziness/Lightheadedness	8
Tremor	7
Changes in Sleep Habits	2
Fatigue	2
Nervousness/Agitation	1
Coordination Difficulties	2
Weakness	2
Depression	1
Confusion/Clouded Sensorium	2
Paresthesias/Numbness	2
<u>Other</u>	
Rash	2
Blurred Vision/Visual Disturbances	2
Dyspnea	1
Headache	1

Less than 1%:

Cardiovascular: Palpitations, hypotension, chest pain, syncope, bradycardia, angina/angina-like pain, edema, hot flashes, atrioventricular block/conduction disturbances hypertension, atrial arrhythmias.

Central Nervous System Changes: Short-term memory loss, speech difficulties, tinnitus, other psychological changes, mild CNS effects, hallucinations, seizures, psychosis, loss of consciousness.

Gastrointestinal: Abdominal gas/bloating, dysphagia, upper gastrointestinal inflammation, peptic ulcer, upper gastrointestinal bleeding, esophageal ulceration.

Other: Altered taste, arthralgia, diaphoresis, dry mouth, abnormal liver function tests, impotence/decreased libido, malaise, hair loss, urinary hesitancy/retention, respiratory, positive ANA, hematologic (thrombocytopenia, leukopenia/neutropenia, agranulocytosis, anemia), hiccups, dry skin, fever, weight gain, arthritis, nasal stuffiness.

* The term "increased ventricular arrhythmias/PVCs" includes any increase in ventricular arrhythmia reported as an adverse event by the investigator. The standard for identifying such events was at the discretion of the investigator.

3. Laboratory measurements during mexiletine therapy

Laboratory testing to evaluate safety during the U.S. clinical program included complete blood counts (hematocrit, hemoglobin, leukocyte count and differential and platelet count), blood chemistry (SGOT, LDH, alkaline phosphatase, blood urea nitrogen, creatinine, albumin, globulin, sodium, potassium, chloride, calcium, phosphorus, cholesterol, antinuclear antibody and bilirubin) and urinalysis. During the controlled trials, evaluations were done at baseline and at 2-4 week intervals. Baseline testing was repeated at three month intervals during the first year of treatment and every six months thereafter in the long-term follow-up and emergency use programs.

a. Controlled studies (475 patients) and Long-term follow-up (197 patients)

Only one patient was discontinued during a controlled study because of an abnormal laboratory finding (monocytosis). This patient had an elevated baseline value (12%) which rose to 14% during treatment. No patient was discontinued during the follow-up phase because of laboratory abnormality.

Ten patients had SGOT elevations during the controlled trials. These findings are included in the discussion of hepatic function below.

Otherwise, laboratory measurements in the controlled studies and long-term follow-up were unremarkable.

b. Mexiletine Emergency Use Program (9353 Patients)

Evaluation of laboratory results in the mexiletine emergency use program is made difficult by the severely compromised clinical status of many patients, the frequent use of concurrent medications that can cause laboratory changes (e.g., procainamide-associated positive ANA titers, anemia and leukopenia) and the lack of pre-mexiletine baseline values for many patients. Clinically significant laboratory abnormalities during mexiletine therapy are discussed in detail below (see 5c and d).

However, the overall pattern of laboratory abnormalities is consistent with the findings in the controlled studies and long-term follow-up in that an abnormal laboratory measurement was only rarely a factor in the decision to discontinue mexiletine therapy in the emergency use program (33 of 9353 patients; 0.4%):

<u>Treatment-limiting Laboratory Findings</u>	<u>No. (%) of Patients</u>
Abnormal liver function tests	13 (0.14%)
Thrombocytopenia	4 (0.04)
Abnormal BUN, NPN or creatinine	3 (0.03)
Positive ANA	3 (0.03)
Agranulocytosis/neutropenia/leukopenia	3 (0.03)
Anemia	2 (0.02)
Other abnormalities	2 (0.02)
Thrombocytosis	1 (0.01)

Liver function abnormalities are discussed in detail in the section on hepatic function below (5c).

Anemia was associated with GI bleeding in one of the discontinued patients and with concurrent use of sustained release procainamide in the other.

In addition to the three patients who discontinued mexiletine for reductions in white blood cell count, nine other cases of WBC reduction were discovered during emergency-use mexiletine therapy, including two fatal agranulocytoses in patients taking mexiletine concurrently with procainamide. These events are discussed in detail under 5d below.

Thrombocytopenia is discussed in detail in 5d below. One patient, whose platelet count was "high" at baseline, had a platelet count of 628,000/mm³ during treatment.

4. Death During Mexiletine Therapy

a. Deaths in Controlled Trials

No deaths occurred among 53 patients during the placebo-controlled trial.

A total of 831 patients with premature ventricular contractions were entered into four 12-week trials comparing mexiletine (422 patients) to procainamide, quinidine or disopyramide (409 patients overall).

At baseline, 307 mexiletine-treated and 293 control patients had a history of cardiac disease, primarily arteriosclerotic heart disease. As shown below, three patients (0.7%) died during mexiletine treatment and nine patients (2.2%) died on the control agents.

Deaths on Mexiletine and Control Drugs In
Twelve-Week Double-Blind Trials

Trial (No. of Patients)	Mexiletine		Control Drug	
	Cause of Death	No. of Patients	Cause of Death	No. of Patients
<u>Mex. vs. procainamide</u> (N=80) (N=78)	Acute MI	1	Acute MI Cardiac Arr.	1 1
<u>Mex. vs. quin.(A)</u> (N=150) (N=148)	Vent.Tach.	1	Vent.Fib. ASHD Sudden Death	1 1 2
<u>Mex. vs. Quin.(B)</u> (N=118) (N=114)	Sudden Death	1	Sudden Death Acute MI	2 1
<u>Mex. vs. disopyramide</u> (N=74) (N=69)	--	<u>0</u>	--	<u>0</u>
Total No. Deaths		3		9
Total No. Patients		422		409
% of Patients Treated		0.7%		2.2%

b. Deaths in the Long-Term Follow-Up Study

Ten of 197 patients (5%) died during treatment with mexiletine in the Long-Term Follow up study. The mean duration of treatment was 12.5 months and the mean daily dose 840 mg. Eight of the ten were receiving concomitant digitalis and/or diuretic therapy.

As would be expected in a patient population with a high incidence of underlying cardiac disease, primarily ASHD, the causes of death were cardiovascular:

<u>Cause</u>	<u>No. of patients</u>
Myocardial infarction	3
Sudden death	2
Vent. tach./fib.	1
Pulmonary Thromboemboli	1
Severe heart failure/coronary artery disease	1
Ruptured basilar artery aneurysm	1
Not obtainable	1

The frequency of possibly arrhythmic deaths (VT/VF, sudden death), 3/197 or about 1.5% of the patients treated for one year or more, does not appear greater than expected for a study group of this type.

c. Deaths in the Mexiletine Emergency Use Program

The emergency-use mexiletine program was restricted to patients in urgent need of antiarrhythmic therapy, in whom other available drugs were ineffective or not tolerated. The most frequent entry arrhythmia (72%: 6780 patients of the 9353 patients treated up to August 1984) was refractory ventricular tachycardia. Approximately 40% of patients had some degree of congestive heart failure at entry; over 60% had ASHD. In 2006 patients (21%), mexiletine treatment was initiated for ventricular arrhythmia in the acute phase of myocardial infarction.

Death occurred during treatment in 1205 patients (13%). As would be expected in this group of patients, cardiac events were the predominant cause of death (70% of patients):

<u>Cause of death</u>	<u>Number of Patients</u>
Sudden death	235
Congestive heart failure	331
Vent. tach./fibrillation	210
Other cardiac	77
Non-cardiac	190
Not obtainable	162

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The duration of treatment (based on 1042 deaths where treatment was precisely known) was as follows:

<u>Months of therapy</u>	<u>Proportion of patients</u>
1	23%
1-6	44%
7-12	15%
12	19%

Historical data on syncope, cardiac arrest and arrhythmias prior to initiation of mexiletine therapy were obtained in 952 of the 1205 patients who died. Previous syncope and/or cardiac arrest had occurred in 383 of these patients (40%), while ventricular tachycardia had occurred in 754 (79%) and ventricular fibrillation in 185 patients (20%). The entry history of ventricular tachycardia in the patients who died differs only slightly from the whole emergency use cohort (79% vs. 72%); however, an entry history of ventricular fibrillation is markedly more frequent (20%) in patients who died during treatment than in the overall group (5%).

At the time of death, 905 of the 1205 patients (75%) were taking digitalis or diuretics; congestive heart failure was the stated cause of 28% of the deaths.

The high incidence of previous ventricular fibrillation, congestive heart failure and digitalis/diuretic use illustrates the severity of underlying cardiovascular disease in the patients who died during mexiletine treatment.

5. Special Issues

a. Prophylactic Administration of Mexiletine in Post-Infarction Secondary Prevention Trials

A number of studies of antiarrhythmic agents have investigated the value of prophylactic antiarrhythmic therapy in reducing mortality following myocardial infarction. To date, no trial of any non-beta-blocker antiarrhythmic agent, including mexiletine, has shown a statistically significant difference in mortality between active treatment and placebo. Trends favoring placebo have been observed as well as trends favoring active treatment.

All of these trials, including those employing mexiletine, have substantial design flaws. Most importantly, none of the trials have been large enough to make a valid assessment of mortality as an endpoint. In addition, since the principal entrance criterion in these trials has been acute myocardial infarction, rather than the presence of frequent or serious ventricular arrhythmia, substantial numbers of patients did not have ventricular arrhythmias at baseline. Patients were treated with fixed dosage and administration schedules. The table below compares the mortality experience in mexiletine- and placebo-treated patients in the four post-infarction trials reported to date.

Mortality (Deaths/Total Treated)

<u>Trial</u>	<u>Time Post-MI to Initiation of Therapy</u>	<u>Mexiletine</u>	<u>Placebo</u>
Bell et al	36 hours $\bar{p}$ onset of symptoms	12/103 (12%)	20/113 (18%)
Smyllie et al	12 hours $\bar{p}$ onset of symptoms	23/120 (19%)	32/120 (27%)
Chamberlain et al	6 - 14 days	24/181 (13%)	19/163 (12%)
IMPACT	3 - 25 days	24/317 (8%)	15/313 (5%)

These are total mortality rates, and include death from all causes.

By comparison, in the mexiletine 12-week double-blind trials, all-cause mortality was 0.7% for 422 mexiletine-treated patients (2.2% for control patients). In the emergency use program, all-cause mortality was 12.9%.

The prescribing information indicates that mexiletine should be used only for the treatment of symptomatic, documented ventricular arrhythmias, and that the dose should be carefully titrated to maximize efficacy and tolerance.

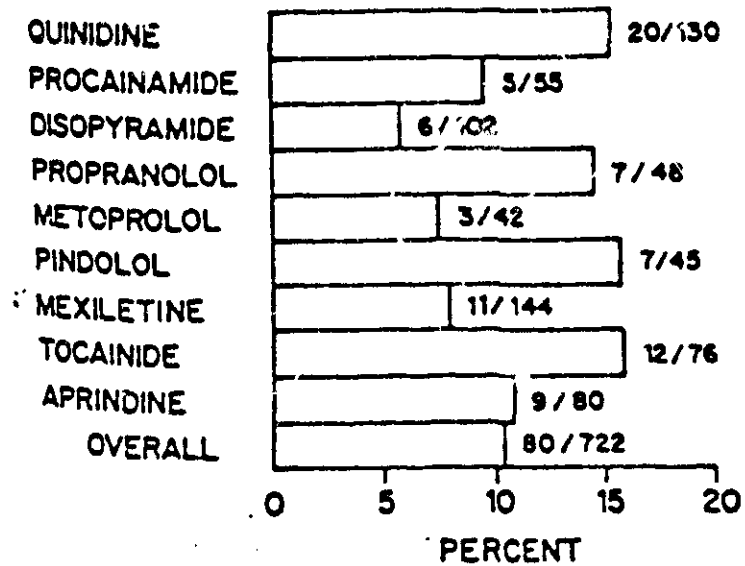
b. Arrhythmias

Development or exacerbation of ventricular arrhythmia during mexiletine treatment was reported by the investigator as an adverse event in four of 475 patients (0.8%) treated in the controlled studies, in two of 197 follow-up patients (1.0%) and 102 of 9353 emergency use patients (1.1%). In such cases, it is difficult to distinguish between failure of the drug to produce its intended effect, natural evolution of the arrhythmia or a possible proarrhythmic effect of mexiletine. Ventricular tachycardia was cited as a reason for discontinuation of therapy in two patients (0.4%) in the controlled studies and eight patients (0.08%) in the emergency use program. Six emergency use patients (0.06%) were discontinued for increased PVC's; five (0.05%) stopped mexiletine for unspecified worsened arrhythmias.

Most antiarrhythmic agents have been reported to have proarrhythmic properties (Velebit et al, Cir. 65: 886-894 1982). It is difficult to compare results in various series because definitions vary greatly and the likelihood of worsening undoubtedly depends on the underlying arrhythmias and heart disease. Velebit found that 11 of 144 patients (8%) tested for responsiveness to mexiletine by exercise Holter monitoring or programmed cardiac stimulation and exercise stress testing exhibited an aggravation of arrhythmia. Other agents gave results generally in the same range, but showed somewhat higher rates of worsening. Blood levels were at therapeutic concentrations for all agents tested. In Ruskin's series of patients evaluated with PES, 16% of patients given mexiletine alone had exacerbation of arrhythmia (Schoenfield, MH et al. Am. Heart J. 107(5):1072-1078, 1984).

Mexiletine certainly does not seem more likely than other agents to provoke worsened arrhythmias, but there is no adequate evidence yet that it is better.

FREQUENCY OF AGGRAVATION OF VENTRICULAR
ARRHYTHMIAS BY ANTIARRHYTHMIC AGENTS



(From Velebit et al., Circ. 65, No. 5, 1982)

c. Hepatic Function

i. U.S. Controlled Trials

In the placebo-controlled trial and also in the active-controlled trials, liver function observations for both the mexiletine and control groups were unremarkable.

Only one patient in the placebo controlled, crossover trial had an elevated treatment SGOT (64 U/L, upper limit of normal 40 U/L). This SGOT was observed in conjunction with an acute myocardial infarction after two weeks of mexiletine therapy. The highest bilirubin observed during either placebo or mexiletine therapy was 1.2 mg %.

In the active-controlled trials, which were three-month, double-blind, parallel and positively controlled studies, no patients on either mexiletine or control drugs (quinidine, disopyramide, procainamide) had therapy discontinued because of hepatic dysfunction. In these trials, out of a total of 292 patients on mexiletine and 281 on control drug (46 - disopyramide, 67 - procainamide, 168 - quinidine) who had a normal baseline SGOT and at least one treatment SGOT, 12.0% of the patients who received mexiletine and 17.4% of the patients who received control drugs had SGOTs of 48-119 U/L* during treatment.

In 1.0% of the mexiletine group and 1.1% of the control group, treatment SGOTs of 120 U/L or greater were observed. The highest treatment SGOT in the mexiletine group was 190 U/L (control group 293 U/L). Associated clinical events in the three patients on mexiletine with treatment SGOTs greater than 120 U/L were pulmonary embolism (1 patient), acute myocardial infarction (1), and congestive heart failure and a history of heavy alcohol use (1). In the majority of patients with elevated treatment SGOTs, the SGOT values returned to normal on continued therapy with mexiletine. Of the 38 patients on mexiletine and 52 on control drugs with treatment elevations, 57.9% and 59.6%, respectively, had last treatment observations less than 48 U/L.

Baseline SGOTs were elevated in 31 (9.6%) of the 323 patients in the mexiletine group with a baseline and at least one treatment SGOT observation and 19 (6.3%) of the 300 in the control drug group. That is, the mexiletine group had a higher proportion of elevated SGOTs at baseline, before starting mexiletine. The last observed treatment SGOT was less than 48 U/L in 15 (48.4%) of the 31 patients with elevated pretreatment SGOTs who received mexiletine and 12 (63.2%) of the 19 who received control drugs.

* The usual normal range for SGOT is 10-40 U/L. For this analysis, any value of 47 U/L or less was considered normal. Forty-seven U/L was chosen because it is one standard deviation above the upper limit of the normal range (40 U/L), assuming the normal range is plus or minus two standard deviations around the normal mean.

Thus, among patients in the positively controlled trials, the incidence, severity and chronological pattern of hepatic enzyme changes in the mexiletine groups were similar to those in the control drug groups. Hepatic enzyme elevations were transient on treatment in over half the patients in both groups. Bilirubin was only slightly elevated (maximum 1.4 mg %) in two of the patients on mexiletine with hepatic enzyme elevations. As shown by the high frequency of elevated pretreatment SGOTs, a considerable incidence of hepatic enzyme elevation occurs in this population regardless of which antiarrhythmic drug is used. The reduction of raised baseline SGOTs to normal while on mexiletine therapy that occurred in almost half the patients with pretreatment elevations suggests that mexiletine is well tolerated in these patients. Similarly, in three of the four patients with baseline SGOTs greater than 120 U/L, SGOTs were normal at the last treatment observation on mexiletine; and in the fourth, the SGOT was reduced from 172 U/L pretreatment to 144 U/L.

In the long-term follow-up to the controlled trials, out of 197 patients on mexiletine, none had hepatic dysfunction reported as an adverse event and no patients had therapy discontinued because of hepatic abnormalities. In 14 of these 197 patients the first elevation of SGOT on treatment was observed during the long-term follow-up period; in 11 of the 14, the SGOT elevations had declined to less than 48 U/L at the last treatment observation. SGOT elevations were also observed in 19 patients whose initial SGOT elevation occurred during the controlled portion of the trial. In 18 of these 19, SGOT elevations declined to less than 48 U/L at the last treatment observation.

Thus, during the long-term follow-up period, no symptomatic elevations in SGOT were observed. In almost all of the patients (88%) with elevated SGOTs during long-term mexiletine therapy, the elevations were transient.

ii. Emergency-Use Mexiletine Program

The Emergency-Use Mexiletine Program had no control group, so that elucidation of drug effect is confounded by the underlying disease states. In this Program, out of a total of 9353 patients enrolled by August 1984, there were 29 patients (0.3%) in whom elevated hepatic enzymes on treatment were identified by the investigators as a possible drug-related adverse event. Of these 29 patients, therapy was discontinued in 18 (0.2%) because of these hepatic enzyme changes.

Among 2365 patients enrolled in the Emergency Program by September 1983, in whom a normal baseline and at least one treatment SGOT measurement were recorded, there were 284 patients (12.0%) with at least one elevated treatment SGOT. In fifteen of these patients the changes had been identified by the investigators as being a possible drug-related adverse event; the other 269 were identified by the sponsor's screen of laboratory data. Out of these 284 patients, there were 232 (9.8%) with peak treatment elevations of SGOT of 48-119 U/L and 52 (2.2%) with peak treatment elevations of 120 U/L or greater.

Raised treatment SGOTs declined, while on mexiletine therapy, to less than 48 U/L at the last treatment observation in 134 (57.8%) of the 232 patients with peak treatment values of 48-119 U/L, and 21 (40.4%) of the 52 with peak treatment values of 120 U/L or greater. Thus, treatment elevations of SGOT were transient in more than half (54.5%) of the 284 patients.

Baseline SGOTs, before mexiletine therapy, were elevated in 10.2% of the patients with baseline and treatment SGOT measurements enrolled by September 1983. While on mexiletine therapy, SGOT levels declined to normal at the last treatment observation in over half these patients (76.1%). This normalization of previously elevated SGOT values, while on mexiletine therapy, is consistent with the results from the controlled trials. It suggests again that mexiletine is well tolerated in these patients.

Further analysis was done in the group of 298 patients (269 with normal baseline and elevated treatment SGOTs identified by laboratory screen plus the 29 patients with elevated hepatic enzymes on treatment identified by the investigators as a possible drug-related adverse event). Clinical events that can produce hepatic dysfunction, including congestive heart failure, acute myocardial infarction and blood transfusions, were reported in 200 (67.1%) of the 298 patients, and the use of potentially hepatotoxic drugs in 213 (71.5%). A clinical event and/or a drug capable of producing hepatic dysfunction was reported in 270 (90.6%).

Liver biopsy results are available for two patients. The first patient had a baseline SGOT of 28 U/L and a peak of 111 U/L after six days of therapy. No symptomatology was reported. Mexiletine was discontinued and the SGOT had returned to normal six days later. Biopsy done at the time of peak SGOT showed focal parenchymal necrosis, portal inflammation and granulomas and was read as showing granulomatous hepatitis compatible with drug-induced reaction. This picture is also compatible with other causes of granulomatous hepatitis such as fungal infection, tuberculosis, sarcoidosis and various viral and bacterial diseases. It should be noted that granulomatous hepatitis generally takes much longer than six days to develop and may well have been related to previous therapy with procainamide which had produced fever and rash in this patient. The second patient had a peak SGOT of 221 U/L after 148 days of treatment. This was the only value obtained during treatment. The only pretreatment value available, 24 U/L, had been obtained 28 months prior to the initiation of mexiletine. The patient was asymptomatic at the time of the peak SGOT. Mexiletine was discontinued after 152 days of treatment and liver biopsy was done approximately 45 days later: Biopsy showed focal parenchymal necrosis and portal inflammation and was read as being consistent with systemic disease, resolving viral hepatitis or drug-induced hepatic injury. SGOT values had returned to normal 44 days after discontinuation of mexiletine. Rechallenge and subsequent dechallenge were positive, but there was a long latent period of 126 days until the first abnormal SGOT was noted during the second course of treatment.

Hepatic function measurements after mexiletine withdrawal are available for 21 patients. In 11 of these patients the SGOT was less than 48 U/L at the last post-treatment observation; in nine the SGOT was declining at the last post-treatment observation relative to treatment levels and in one, the SGOT (57 U/L) was unchanged. Because of the numerous other clinical events and changes that are involved, it is not possible to regard these observations as supplying clean dechallenge information; rather, these changes illustrate the transience or reversibility of the hepatic effects of the overall set of factors influencing the liver in these patients.

No rigorously performed rechallenge is available. In one case, however, elevated treatment SGOTs were observed during two separate courses of mexiletine therapy. No pretreatment SGOT, and only one SGOT on treatment, are available for the first course of therapy.

During the first course of therapy, the peak SGOT was 221 U/L after 148 days of treatment, and during the second, 183 U/L after 159 days of treatment. Both times mexiletine was discontinued, SGOT levels declined to less than 48 U/L after 40-50 days. Total bilirubin was normal during both courses of therapy.

Hepatic enzyme elevations were generally asymptomatic. However, in eleven of the 29 patients with possible drug related adverse events, all of whom had treatment SGOT elevations of 120 U/L or greater and final treatment SGOTs greater than 48 U/L, symptoms that may have been related to hepatic dysfunction were as follows: nausea in six, lethargy in four, anorexia in four, emesis in three, and fever in three. Confusion, icterus, weight loss and right upper quadrant discomfort were each reported once.

Among the 298 patients with normal baseline and elevated treatment SGOTs, abnormal liver function was the sole reason for discontinuation of mexiletine therapy in 12 patients. In another six patients, abnormal liver function was one of several reasons, including nausea, emesis and tremor, for discontinuation of therapy. All of these 18 patients were identified by the investigators as having a possible hepatic, drug-related adverse event. Abnormal liver function was not cited as a reason for discontinuation of mexiletine therapy in any patient in the lab screen group. Of the 18 patients discontinued because of abnormal liver function, 3 died. Death was due to congestive heart failure in 2 patients and metastatic carcinoma in one. One of the three patients had been off mexiletine for 24 days and two for 30 days at the time of death. Liver status at the time of death was not reported in 2 patients and was normal in one.

The sponsor made a special scrutiny of hepatic function in patients who died. Review of the 1387 deaths in the Emergency Program, reported by August 1984, representing 14.8% of the enrollees to that date, identified 65 patients with hepatic dysfunction within 14 days of death by biochemical abnormalities (SGOT greater than 120 U/L, bilirubin greater than 2.5 mg %), clinical findings, and/or autopsy reports. The most common causes of hepatic dysfunction in these patients were progressive congestive heart failure and/or shock, which occurred in 44 patients. In 57 of the 65 patients, hepatic dysfunction was not given as the cause of death or judged likely to have contributed significantly to death. In the remaining eight patients, however, severe hepatic dysfunction was present that may have contributed to death. The clinical profiles for these eight patients are shown in the table below.

**Clinical Profile of Patients With Severe Hepatic
Dysfunction At the Time of Death**

<u>Case No.</u>	<u>Age/ Sex</u>	<u>Mexiletine Daily Dose (mg)</u>	<u>Length of Treatment (Days)</u>	<u>Important Concomitant Illnesses and Treatment</u>	<u>Comment</u>
1 JR	65/M	400	90	Congestive cardiomyop., alc. liver cirrhosis. Rx. quinidine.	Off mex. one year at time of death
2 RM	71/M	900	1530	Alc. liv. cirrhosis, portacaval shunt. Rx. propran., chlorthal.	Hepatic encephalopathy after portacaval shunt
3 MS	61/M	400	60	CHF, shock. Rx. amiodarone, furosemide, hydralazine, captopril.	Pretreat. CHF. & elev. SGOT. On day of death, white in shock SGOT 2240 U/L, b11t. 9.3 mg%
4 TP	61/M	400	30	prog. CHF, shock. Rx. dopamine, furosemide.	Pretreat. CHF. Day before death, white in shock, SGOT 1345 U/L.
5 WD	64/M	600	180	prog. CHF, shock, pneumonia. Rx. respirator, dopamine, quinidine.	Pretreat. CHF. Day before death SGOT 1042 U/L white in shock.
6 RB	73/F	400	510	Carcinoma of pancreas diagnosed by ultrasound.	Increasing epigast. pain. B11t. rose from 1.0 to 21 mg % over 3 weeks.
7 FG	58/M	600	25	One yr. of prog. wt. loss & increasing liver dysfunction on amiodarone, prior to mex.	Liver function stable during mex. admin over last 25 days of life.
8 DM	62/M	600	10	Shock, hypoxemia, lactic acidosis. Hx of pulm. emboli. Rx. Furosemide, spironolactone, coumadin	SGOT on day of death greater than 10,000 U/L white in shock

The first two of the eight patients had cirrhosis of the liver at autopsy which was thought, in both cases, to be secondary to alcohol; one of these two patients had been off mexiletine for one year at the time of death and the other died with hepatic encephalopathy after portacaval shunt for ruptured esophageal varices. The next three of the eight patients died with progressive congestive heart failure and cardiogenic shock. Amiodarone was started after mexiletine in the first of these three patients and the second developed pneumonia two weeks before death. In the sixth patient, ultrasound showed a lesion involving the pancreas and a diagnosis of carcinoma of the pancreas was made. The seventh patient developed advanced liver disease during one and a half years of amiodarone therapy. In this patient, mexiletine was administered for the final 25 days of life. The eighth patient, with a radionuclide ejection fraction of 15% just before mexiletine therapy was started and a past history of pulmonary emboli, presented with shock, lactic acidosis and hypoxemia 10 days after institution of mexiletine treatment. On the day of death, when this patient was in shock, the SGOT was greater than 10,000 U/L.

Thus, in all eight patients with severe hepatic dysfunction at the time of death, the liver abnormalities were most likely due to concomitant disease: progressive congestive heart failure and shock in three, alcoholic cirrhosis in two, carcinoma of the pancreas in one, amiodarone liver disease in one, and cardiogenic shock and hypoxemia secondary to cardiopulmonary disease in one.

Increases in hepatic enzymes occur commonly in patients who require ventricular antiarrhythmic therapy, as shown by the 8.0% incidence of elevated SGOTs before mexiletine therapy in the controlled trials and 10.2% in the Emergency Program. Therefore, it is difficult to establish a causal relationship between mexiletine therapy and hepatic dysfunction, or to rule out the possibility that mexiletine therapy may be able to elevate enzymes in an occasional patient.

In summary, in light of the above evidence, the following changes in hepatic function have been observed during mexiletine therapy: 1) hepatic enzyme elevations which often decline to normal during continued therapy and are generally asymptomatic; 2) hepatic enzyme elevations which have been reversible after discontinuation of therapy. These observations occur in patients with a high proportion of elevated hepatic enzymes at baseline, and a causal role of mexiletine cannot be imputed.

In view of these findings, the labelling provides information on the changes in hepatic function that have been observed during mexiletine therapy. It recommends that while no causal relationship to mexiletine therapy has been established, patients with signs or symptoms suggesting liver dysfunction be carefully evaluated.

d. Hematologic function

i. Reductions of White Blood Cell Count

No significant reductions in white blood cell count during mexiletine therapy were seen in the controlled studies (475 patients) or in the 197 patients enrolled in the long-term follow-up program.

In the mexiletine emergency-use program, reduction in white blood cells was reported as an adverse event in 12 of 9353 patients (0.1%):

<u>WBC reduction</u>	<u>No. of patients (%)</u>	
Neutropenia (absolute neutrophil count $1500/\text{mm}^3$ and $2000/\text{mm}^3$)	7	(0.07)
Agranulocytosis (absolute neutrophil count $500/\text{mm}^3$)	5	(0.05)
Death due to sepsis-2		
Recovered-3		

Clinical features of these patients are presented in the table below.

WBC COUNTS IN EMERGENCY USE PATIENTS WITH AGRANULOCYTOSIS AND NEUTROPENIA

	Age/ Sex	Dur Mex to Nadir	WBC Counts [thous/mm ³] (% Neu)			Concom. Rx.	Rechallenge	Outcome	Comments	
			Baseline	Nadir	Final On Rx.					Final Off Rx.
I. Fatal Agranulocytosis										
C.L.	70/M	7 weeks	6.8 (66)	2.1 (5)	2.1 (5)	---	---	Pronestyl Allopurinol	No	Died (sepsis) Died of septic shock 1 day after diagnosis of agranulocytosis.
T.M.	65/M	5 weeks	8.4 (56)	0.7 (NA)	0.7 (NA)	---	---	Procan-SR Cimetidine	No	Died (sepsis) Died of septic shock 1 day after diagnosis of agranulocytosis.
II. Non-Fatal Agranulocytosis										
R.A.	54/M	4 days	9.2 (67)	1.8 (2)	1.8 (2)	7.9 (7)	---	Procan-SR (immediately prior) Furosemide Coumadin Amiodarone Digoxin	Yes (see below)	Discontinued therapy: negative re- challenge. Asymptomatic decrease WBC after discontinuing Procan-SR and start- ing mexiletine. Rising uric acid before starting mexiletine sugges- ted pre-existing WBC destruction. WBC increased after discontinuing mexiletine and remained normal with resumption of mexiletine.
<u>Rechallenge</u>										
			7.9 (NA)	7.9 (82)	7.9 (82)	---	---	Quintidine Digoxin Bumex Synthroid		
S.S.	55/M	2 months	10.9 (85)	0.6 (NA)	0.6 (NA)	4.4 (NA)	---	Procan-SR	Yes (see below)	Discontinued therapy. Negative rechallenge. Severe pharyngitis with agranulocy- tosis. WBC increased after dis- continuing Procan-SR and mexiletine and remained normal with the resumption of mexiletine.
<u>Rechallenge</u>										
			4.4 (NA)	4.4 (48)	5.2 (48)	---	---	Insulin Digoxin Nitro-Dur NTG		

MBC COUNTS IN EMERGENCY USE PATIENTS WITH AGRANULOCYTOSIS AND NEUTROPENIA

II. <u>Non-Fatal</u> Agranulocytosis (Cont'd)	Age/ Sex	Dur Mex to Nadir	MBC Counts [thous/mm ³] (% Neutrophils)				Concom. Rx.	Rechallenge	Outcome	Comments
			Baseline	Nadir	Final On Rx.	Final Off Rx.				
P.D.	45/M	11 days	7.9 (NA)	2.5 (2)	2.5 (2)	13.1 (NA)	Procain-SR (immediately prior) Captopril Furosemide	No	Discontinued therapy. Recovered	Asymptomatic decrease WBC after discontinuing Procain-SR and start- ing captopril and mexiletine. WBC increased after discontinuing mexiletine, captopril and furosemide.

III. Neutropenia

R.C.	44/M	17 months	4.7 (44)	3.4 (52)	4.3 (46)	---	None	No	Continuing therapy. Improved	Asymptomatic
D.E.	50/F	31 months	3.5 (NA)	2.6 (57)	3.0 (48)	---	Unknown	No	Continuing therapy. Stable.	Asymptomatic, chronic low WBC during 4 years therapy.
V.T.	31/F	31 months	6.1 (40)	2.7 (48)	2.7 (48)	3.6 (45)	Amiodarone	No	Discontinued therapy due to neutropenia. Stable.	WBC stable for 1 year on mexiletine and then decreased following addition of amiodarone. WBC remained low off mexiletine and on amiodarone.
H.M.	87/F	2 weeks	6.0 (67)	3.5 (51)	4.8 (56)	4.7 (NA)	Dihydrate- hydnantoin (immediately prior) Furosemide Digoxin Minipress Synthroid	No	Discontinued therapy, un- related to transient neutropenia.	Asymptomatic transient decrease WBC.

MBC COUNTS IN EMERGENCY USE PATIENTS WITH AGRANULOCYTOSIS AND NEUTROPENIA

III. <u>Neutropenia (Cont'd)</u>	<u>Age/ Sex</u>	<u>Dur Mex to Nadir</u>	<u>MBC Counts [thous/mm³] (% Neutrophils)</u>				<u>Concom. Rx.</u>	<u>Rechallenge</u>	<u>Outcome</u>	<u>Comments</u>
			<u>Baseline</u>	<u>Nadir</u>	<u>On Rx.</u> Final	<u>Off Rx.</u> Final				
J.K.	67/M	1 month	8.4 (72)	3.4 (44)	3.4 (44)	5.4 (45)	Procar-SR (discontinued 6 days prior) Ethacrynic Acid	No	Discontinued therapy due to neutropenia. Improved.	Asymptomatic.
A.B.	67/M	2 months	5.2 (65)	3.7 (NA)	4.1 (63)	--	Captopril Quintidine Furosemide	No	Discontinued therapy, un- related to neutropenia.	Asymptomatic transient decrease WBC on mexiletine with mild, persistent decrease WBC and RBC developing after the addition of captopril.
R.P.	67/M	5 months	6.5 (51)	3.6 (NA)	4.8 (60)	--	Hydralazine Furosemide Digoxin Zomax	No	Continued therapy. Stable.	History of metastatic lung cancer. Asymptomatic "neutropenia" with all WBC counts greater than 3500.

Neutropenia

White cell and neutrophil reductions in the seven neutropenia cases were moderate and transient. Four patients discontinued mexiletine; WBC counts were stable in three patients whose therapy was not interrupted.

Only two of these seven patients (RC and DE) were receiving no concomitant therapy. Patient RC had a transient neutropenia (WBC 3400/mm³, 52% neutrophils) after 17 months of therapy that returned to 4300/mm³ after a total of 21 months of therapy. Patient DE had a low WBC count at baseline (3500/mm³) that declined to 2600/mm³ (57% neutrophils) after 31 months of mexiletine therapy and increased to 3000/mm³ after a total of 44 months of treatment.

Of the remaining five patients with neutropenia, the following associations were observed: leukopenia developing with the addition of amiodarone to mexiletine and persisting on amiodarone after mexiletine was discontinued (VT); concomitant hydralazine (RP) or captopril (AB) therapy; procainamide or phenytoin treatment immediately prior to initiating mexiletine (HW and JK).

Agranulocytosis

The most striking common feature in all five cases of agranulocytosis was the use of procainamide, either immediately prior to mexiletine therapy (in two of the cases who recovered) or concurrently (in one case who recovered and in the two deaths). In four of the five cases, a sustained-release formulation of procainamide was employed.

Non-fatal agranulocytosis: Rechallenge with mexiletine was carried out in two (RA and SS) of the three patients who recovered. Both of these patients were taking multiple concomitant medications.

In the first patient (RA), a white count of 1800 with 2% neutrophils was noted six days after discontinuation of sustained-release procainamide and four days after mexiletine therapy was started. The sustained-release procainamide had been withdrawn for failure to control the patient's ventricular tachycardia. Other medications were furosemide, amiodarone, digoxin, warfarin and nitroglycerin patch. During the first five days of mexiletine therapy, the uric acid level increased from 10.4 mg/ml on day two to 11.9 mg/ml on day five. In the opinion of the investigator, the rise in uric acid, which most likely began before mexiletine was started, indicated white blood cell destruction secondary to procainamide or furosemide. Mexiletine was withheld for one month; bumetanide was substituted for furosemide and warfarin was discontinued. Granulocyte recovery was observed during this time, rising from 19% of 2500 WBC four days after furosemide, mexiletine and warfarin were discontinued to 81% of 8500 WBC on day 25. Mexiletine was restarted; bumetanide, digoxin, quinidine and levothyroxine were administered concurrently. The mexiletine rechallenge was negative; white cell and granulocyte counts remained stable. Six weeks after mexiletine was restarted, WBC was 7900 with 82% neutrophils. The high early uric acid levels and the negative mexiletine rechallenge suggest that mexiletine was not the primary cause of agranulocytosis in this patient.

In the second patient (SS), sustained release procainamide was administered concurrently with mexiletine. At baseline, WBC was 1090/mm³ with 35% neutrophils. The patient presented with severe pharyngitis and a nadir white count of 600/mm³ (differential not available) after two months of concomitant mexiletine/procainamide therapy. Other medications were isosorbide dinitrate, digoxin and Dyazide. Mexiletine and procainamide were discontinued and the white count returned to normal (4400/mm³, differential not available). Mexiletine therapy was resumed fifteen days later and WBC remained within normal limits. At last follow-up, nine months after resumption of mexiletine therapy, WBC was 5200/mm³ with 48% neutrophils. The negative mexiletine rechallenge suggests that mexiletine was not the primary cause of agranulocytosis in this patient.

In the third patient (PD) who recovered, agranulocytosis (WBC 2500/mm³ with 2% neutrophils) was detected 11 days after mexiletine was substituted for sustained-release procainamide. A 1.5 gm procainamide daily dose had produced intolerable diarrhea and toxic procainamide blood levels (12.7 mcg/ml five days before discontinuation; normal range: 4.0-8.0 mcg/ml). Captopril administration (25 mg tid) had been started eight days before mexiletine; other concomitant medications were furosemide, isosorbide and nitroglycerin. Mexiletine, captopril and furosemide were discontinued; 10 days later, the WBC was 11,400/mm³ with 81% neutrophils. The investigator attributed the agranulocytosis to captopril administration; inability to define the onset of the drop in WBC and neutrophil count make it difficult to assess any possible contributory role of the toxic levels of sustained-release procainamide, or of mexiletine administration in the evolution of this case.

Deaths Secondary to Sepsis: The remaining two patients developed agranulocytosis during concurrent use of mexiletine and procainamide, and died as a consequence of sepsis.

One of these patients (TM) had sustained-release procainamide added to his regimen one week after mexiletine therapy was started. Four weeks later, he was admitted to the hospital in septic shock and expired. A WBC (no differential available) after two weeks of combined therapy revealed 6800 WBC/mm³; shortly before death, the WBC was 700 with one granulocyte/mm³. Other concurrent medications were cimetidine, nitroglycerin, chloral hydrate and docusate sodium.

The second death (CL) was caused by pulmonary hemorrhage secondary to pseudomonas infection, seven weeks after mexiletine therapy was started. The patient had temporarily discontinued procainamide (because of rash) when mexiletine was started. However, procainamide was reinstated on the seventh day of mexiletine treatment in an attempt to improve control of the arrhythmia, and was continued until death. Other concurrent medications were allopurinol, prazosin, and potassium iodide. One week after combination therapy was started, the WBC was 7700/mm³ with normal differential. The patient was admitted to the hospital five weeks later with pneumonia and died the following morning. WBC was 2100/mm³ with 5% neutrophils on admission.

Summary

In summary, reductions in white blood cell counts during mexiletine therapy were not observed in 475 patients treated in the controlled studies or in the 197 patient long-term follow-up program. In the emergency use program reductions in white blood cell counts were reported as adverse events in 12 of 9353 patients. Of these 12, seven had asymptomatic neutropenia with nadir white blood cell counts of 2600-3700/mm³. Only two of these seven (RC and DE) did not have possible or probable causes other than mexiletine therapy to account for their neutropenia and one of these (DE) had a white cell count of 3500/mm³ at baseline. Agranulocytosis was reported in the other five of the 12 patients with white cell reductions and could not be attributed to mexiletine alone in any of these five patients. In all five of these patients, procainamide was administered either concurrently (3 cases) or just prior to initiation of mexiletine therapy (2 cases). Four of the five patients received sustained-release procainamide.

Agranulocytosis in association with procainamide therapy was first reported in 1951. It was initially considered to be rare; 17 cases were reported prior to 1980 [Ellrodt et al, Ann Int Med 1984, 100:197-201]. In a cohort drawn from the medical records of the Group Health Cooperative of Puget Sound, Danielson et al identified one granulocytopenia (less than 5000 WBC and less than 1000 neutrophils/mm³) among 422 patients (0.2%) treated with procainamide HCl from 1976 to 1981 [JAMA 1984 252:3257-3260].

Sustained-release procainamide became available in 1980. Between 1980 and 1982, Ellrodt and his colleagues discovered eight cases of severe neutropenia-agranulocytosis (less than 100 neutrophils/mm³) in patients taking sustained-release procainamide at their center. Five cases occurred among 114 patients discharged on sustained-release procainamide after open-heart surgery (4.4%). The authors suggest that the sustained-release formulation may have contributed to the high frequency of severe neutropenia.

All five agranulocytoses observed during mexiletine therapy were associated with procainamide use. Four of these five received sustained-release procainamide. Overall, three of the 582 patients (0.5%) known to have received concurrent procainamide therapy in the mexiletine emergency use program had agranulocytosis. Two patients had agranulocytosis diagnosed shortly after procainamide discontinuation. The incidence is consistent with the incidence of severe neutropenia-agranulocytosis (less than 100 neutrophils/mm³) during procainamide therapy (0.2-4.4%) reported by Danielson and by Ellrodt, and may be somewhat overstated because of under-reporting of concomitant medications in patients who had no adverse experience.

Furthermore, there were two instances of negative rechallenge with mexiletine. Thus, the likelihood of a causal relationship between mexiletine therapy and reduced white blood cell counts is remote.

The sponsors' proposed labeling describes the association of procainamide use with the cases of agranulocytosis observed in the mexiletine emergency use program and advises that caution be used when mexiletine/procainamide concurrent therapy is considered.

Reduction in Platelet Count

Reduced platelet count was reported as an adverse event in 10 of 9353 (0.1%) patients enrolled in the mexiletine emergency-use program:

<u>Nadir of platelet count (per mm³)</u>	<u>Number of Patients</u>	<u>Baseline value Normal/Not done</u>
100,000 - 150,000	4	3 / 1
50,000 - 99,999	2	2 / 0
50,000	4	2 / 2

None of the patients had clinical evidence of bleeding related to platelet count reduction. All received at least one (most had several) concurrent medications, several of which (phenytoin, furosemide, haloperidol, procainamide, captopril and metolazone) have been reported to produce thrombocytopenia.

Six of the ten patients had mexiletine discontinued when thrombocytopenia was diagnosed; one discontinued for unrelated reasons; three continued therapy with normal to slightly depressed platelet counts on follow-up.

Two patients in whom mexiletine was discontinued for thrombocytopenia had mexiletine therapy reinstated; rechallenge was negative in both cases.

The four cases with platelet determinations under 50,000 are discussed in detail below.

Platelet Count 50,000 During Mexiletine Therapy:

One patient with congestive heart failure and severe vascular insufficiency had normal platelet values before mexiletine therapy was instituted. Two months after starting mexiletine, progression of the underlying vascular insufficiency necessitated bilateral leg amputation; platelet count on admission for surgery was described as "low". Mexiletine was discontinued shortly after surgery; the lowest platelet count ($39,000/\text{mm}^3$) was recorded two days after discontinuation. Concurrent medications included furosemide, digoxin, haloperidol, nitroglycerin ointment and cefazolin. The patient's platelet count rose after transfusion and was normal three weeks after the surgery.

In a second patient no baseline value was available, but four days after mexiletine therapy was started, platelet count was reported as "decreased". Concurrent medications were phenytoin, metolazone, dobutamine, captopril, furosemide and procainamide. Platelet count decreased to $19,000/\text{mm}^3$ on the 13th day of mexiletine therapy. Phenytoin was discontinued on the 10th day and mexiletine and metolazone administration stopped on day 13. The investigator reported that the platelet count subsequently improved.

In the third patient, no baseline was available, but the platelet count was normal after nine months of therapy with mexiletine, digoxin, furosemide, nitroglycerin patch, probenecid/colchicine, hydralazine and potassium chloride. Phenytoin was added to the regimen during the 21st month of therapy; approximately two weeks later, the platelet count was less than $10,000/\text{mm}^3$. Both phenytoin and mexiletine were discontinued and three days later,

the platelet count was 179,000/mm³. Phenobarbital was substituted for phenytoin and mexiletine restarted. The patient's platelet count remained normal during continued mexiletine treatment. The negative mexiletine challenge and the time course of the thrombocytopenia strongly implicate phenytoin as the causative agent.

In the fourth case, platelets were normal at baseline and at three determinations during the next 23 months. Besides mexiletine, propranolol and isosorbide were administered. At 24 months the platelet count fell to 19,000/mm³. The thrombocytopenia resolved during therapy with 80 mg of prednisone 80 mg/day, but recurred when the dose of prednisone was reduced to 40-60 mg/day. Discontinuation of mexiletine did not improve the platelet count. The problem was diagnosed as idiopathic thrombocytopenia and a splenectomy was performed. Mexiletine therapy was restarted and the rechallenge was negative. Normal platelet values were seen over the next 30 months of treatment.

Conclusions

In summary, the association of the thrombocytopenias observed in the mexiletine emergency use program with underlying disease states and multiple concomitant medications indicates that a causal role of mexiletine therapy is unlikely. This conclusion draws strong support from the two cases where mexiletine rechallenge was negative. In the two cases with concurrent phenytoin therapy, mexiletine rechallenge was negative in one case.

VI. Approved Package Insert:

A copy of the package insert is attached.

Mexitil® (mexiletine hydrochloride)

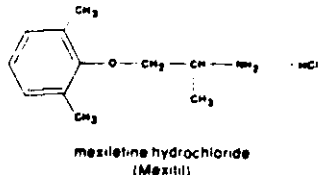
Capsules of 150 mg, 200 mg and 250 mg
Oral Antiarrhythmic

Prescribing Information

DESCRIPTION Mexitil® (mexiletine hydrochloride) is an orally active antiarrhythmic agent available as 150 mg, 200 mg and 250 mg capsules. 100 mg of mexiletine hydrochloride is equivalent to 83.31 mg of mexiletine base. It is a white to off-white crystalline powder with slightly bitter taste, freely soluble in water and in alcohol. Mexitil has a pKa of 8.4.

Chemically, Mexitil is 1-methyl-2-(2,6-dimethyl-ethylamino)ethylamine hydrochloride and has the following structural formula:

C. H., NO-HCl



Mol. Wt. 215.73

Mexitil Capsules contain the following inactive ingredients: colloidal silicon dioxide, corn starch, magnesium stearate.

CLINICAL PHARMACOLOGY Mechanism of Action: Mexitil® (mexiletine hydrochloride) is a local anesthetic, antiarrhythmic agent, structurally similar to lidocaine, but orally active. In animal studies, Mexitil has been shown to be effective in the suppression of induced ventricular arrhythmias, including those induced by glycoside toxicity and coronary artery ligation. Mexitil, like lidocaine, inhibits the inward sodium current, thus reducing the rate of rise of the action potential. Phase 0 Mexitil decreased the effective refractory period (ERP) in Purkinje fibers. The decrease in ERP was of lesser magnitude than the decrease in action potential duration (APD), with a resulting increase in the ERP/APD ratio.

Electrophysiology in Man: Mexitil is a Class 1B antiarrhythmic compound with electrophysiologic properties in man similar to those of lidocaine, but dissimilar from quinidine, procainamide, and disopyramide.

In patients with normal conduction systems, Mexitil has a minimal effect on cardiac impulse generation and propagation. In clinical trials, no development of second-degree or third-degree AV block was observed. Mexitil did not prolong ventricular depolarization (QRS duration) or repolarization (QT intervals) as measured by electrocardiography. Theoretically, therefore, Mexitil may be useful in the treatment of ventricular arrhythmias associated with a prolonged QT interval.

In patients with pre-existing conduction defects, depression of the sinus rate, prolongation of sinus node recovery time, decreased conduction velocity and increased effective refractory period of the intraventricular conduction system have occasionally been observed.

The antiarrhythmic effect of Mexitil has been established in controlled comparative trials against placebo, quinidine, procainamide and disopyramide. Mexitil, at doses of 200-400 mg q8h produced a significant reduction of ventricular premature beats, paired beats, and episodes of non-sustained ventricular tachycardia compared to placebo and was similar in effectiveness to the active agents. Among all patients entered into the studies, about 30% in each treatment group had a 70% or greater reduction in PVC count and about 40% failed to complete the 3 month studies because of adverse effects. Follow-up of patients from the controlled trials has demonstrated continued effectiveness of Mexitil in long-term use.

Hemodynamics: Hemodynamic studies in a limited number of patients, with normal or abnormal myocardial function, following oral administration of Mexitil, have shown small, usually not statistically significant, decreases in cardiac output and increases in systemic vascular resistance, but no significant negative inotropic effect. Blood pressure and pulse rate remain essentially unchanged. Mild depression of myocardial function, similar to that produced by lidocaine, has occasionally been observed following intravenous Mexitil therapy in patients with cardiac disease.

Pharmacokinetics: Mexitil is well absorbed (~90%) from the gastrointestinal tract. Unlike lidocaine, its first-pass metabolism is low. Peak blood levels are reached in two to three hours. In normal subjects, the plasma elimination half-life of Mexitil is approximately 10-12 hours. It is 50-60% bound to plasma protein, with a volume of distribution of 5-7 liters/kg. Mexitil is metabolized in the liver. Approximately 10% is excreted unchanged by the kidney. While urinary pH does not normally have much influence on elimination, marked changes in urinary pH influence the rate of excretion; acidification accelerates excretion, while alkalinization retards it.

Several metabolites of mexiletine have shown minimal antiarrhythmic activity in animal models. The most active is the minor metabolite N-methylmexiletine, which is less than 20% as potent as mexiletine. The urinary excretion of N-methylmexiletine in man is less than 0.5%. Thus the therapeutic activity of Mexitil is due to the parent compound.

Hepatic impairment prolongs the elimination half-life of Mexitil. In eight patients with moderate to severe liver disease, the mean half-life was approximately 25 hours.

Consistent with the limited renal elimination of Mexitil, little change in the half-life has been detected in patients with reduced renal function. In eight patients with creatinine clearance less than 10 ml/min, the mean plasma elimination half-life was 15.7 hours, in seven patients with creatinine clearance between 11-40 ml/min, the mean half-life was 13.4 hours.

The absorption rate of Mexitil is reduced in clinical situations such as acute myocardial infarction in which gastric emptying time is increased. Narcotics, atropine and magnesium-aluminum hydroxide have also been reported to slow the absorption of Mexitil. Metoclopramide has been reported to accelerate absorption.

Mexiletine plasma levels of at least 0.5 mcg/ml are generally required for therapeutic response. An increase in the frequency of central nervous system adverse effects has been observed when plasma levels exceed 2.0 mcg/ml. Thus the therapeutic range is approximately 0.5 to 2.0 mcg/ml. Plasma levels within the therapeutic range can be attained with either three times daily or twice daily dosing but peak to trough differences are greater with the latter regimen, creating the possibility of adverse effects at peak and arrhythmic escape at trough. Nevertheless, some patients may be transferred successfully to the twice daily regimen (See Dosage and Administration).

INDICATIONS Mexitil® (mexiletine hydrochloride) is indicated for the suppression of symptomatic ventricular arrhythmias, including frequent premature ventricular contractions, unifocal or multifocal couplets and ventricular tachycardia.

Like other antiarrhythmics, mexiletine has not been shown to prevent sudden death in patients with serious ventricular ectopic activity and also, like other antiarrhythmics, it has potentially serious adverse effects, including the ability to worsen arrhythmias. It is therefore essential that each patient given mexiletine be evaluated electrocardiographically and clinically prior to and during mexiletine therapy to determine whether the response to mexiletine supports continued treatment.

CONTRAINDICATIONS Mexitil® (mexiletine hydrochloride) is contraindicated in the presence of cardiogenic shock or pre-existing second or third degree AV block (if no pacemaker is present).

PRECAUTIONS General: If a ventricular pacemaker is operative, patients with second or third degree heart block may be treated with Mexitil® (mexiletine hydrochloride) if continuously monitored. A limited number of patients (45 of 475 in controlled clinical trials) with pre-existing first degree AV block were treated with Mexitil, none of these patients developed second or third degree AV block. Caution should be exercised when it is used in such patients or in patients with pre-existing sinus node dysfunction or intraventricular conduction abnormalities.

Like other antiarrhythmics, Mexitil® (mexiletine hydrochloride) can cause worsening of arrhythmias. This has been uncommon in patients with less serious arrhythmias (frequent premature beats or non-sustained ventricular tachycardia; see Adverse Reactions) but is of greater concern in patients with life-threatening arrhythmias such as sustained ventricular tachycardia. In patients with such arrhythmias subjected to programmed electrical stimulation or to exercise provocation, 10-15% of patients had exacerbation of the arrhythmia, a rate not greater than that of other agents.

Mexitil should be used with caution in patients with hypotension and severe congestive heart failure.

Since Mexitil is metabolized in the liver, and hepatic impairment has been reported to prolong the elimination half-life of Mexitil, patients with liver disease should be followed carefully while receiving Mexitil. The same caution should be observed in patients with hepatic dysfunction secondary to congestive heart failure.

Concurrent drug therapy or dietary regimens which may markedly alter urinary pH should be avoided during Mexitil therapy. The minor fluctuations in urinary pH associated with normal diet do not affect the excretion of Mexitil.

SGOT Elevation and Liver Injury: In three month controlled trials, elevations of SGOT greater than three times the upper limit of normal occurred in about 1% of both mexiletine treated and control patients. Approximately 2% of patients in the mexiletine compassionate use program had elevations of SGOT greater than or equal to three times the upper limit of normal. These elevations frequently occurred in association with identifiable clinical events and therapeutic measures such as congestive heart failure, acute myocardial infarction, blood transfusions and other medications. These elevations were often asymptomatic and transient, usually not associated with elevated bilirubin levels and usually did not require discontinuation of therapy. Marked elevations of SGOT (>1000 U/L) were seen before death in four patients with end-stage cardiac disease (severe congestive heart failure, cardiogenic shock).

In foreign marketing experience rare instances of severe liver injury, including hepatic necrosis, have been reported in association with Mexitil treatment. It is recommended that patients in whom an abnormal liver test has occurred or who have signs or symptoms suggesting liver dysfunction, be carefully evaluated. If persistent or worsening elevation of hepatic enzymes is detected, consideration should be given to discontinuing therapy.

Blood Dyscrasias: Blood dyscrasias were not seen in the controlled trials. Among 10,867 patients treated with mexiletine in the compassionate use program, marked leukopenia (neutrophils less than 1000/mm³) or agranulocytosis were seen in 0.06%, and milder depressions of leukocytes were seen in 0.08%, and thrombocytopenia was observed in 0.16%. Many of these patients were seriously ill and receiving concomitant medications with known hematologic adverse effects. Rechallenge with mexiletine in several cases was negative. Marked leukopenia or agranulocytosis did not occur in any patient receiving Mexitil alone. Five of the six cases of agranulocytosis were associated with procainamide (sustained release preparations in four) and one with vinblastine. If significant hematologic changes are observed, the patient should be carefully evaluated, and, if warranted, Mexitil should be discontinued. Blood counts usually return to normal within one month of discontinuation. (See Adverse Reactions).

Convulsions (seizures) did not occur in Mexitil controlled clinical trials. In the compassionate use program, convulsions were reported in about 2 of 1000 patients. Twenty-eight percent of these patients discontinued therapy. Convulsions were reported in patients with and without a prior history of seizures. Mexiletine should be used with caution in patients with known seizure disorder.

Drug Interactions: In a large compassionate use program Mexitil has been used concurrently with commonly employed antianginal, antihypertensive, and anticoagulant drugs without observed interactions. A variety of antiarrhythmics such as quinidine or propranolol were also added, sometimes with improved control of ventricular ectopy. When phenytoin or other hepatic enzyme inducers such as rifampin and phenobarbital have been taken concurrently with Mexitil, lowered Mexitil plasma levels have been reported. Monitoring of Mexitil plasma levels is recommended during such concurrent use to avoid ineffective therapy.

In a formal study, benzodiazepines were shown not to affect Mexitil plasma concentrations. ECG intervals (PR, QRS and QT) were not affected by concurrent Mexitil and digoxin, diuretics, or propranolol.

Clonidine has been shown to raise Mexitil plasma levels. During concurrent therapy, the patient should be monitored carefully for adverse effects.

Mexitil does not alter serum digoxin levels but magnesium-aluminum hydroxide, when used to treat gastrointestinal symptoms due to Mexitil, has been reported to lower serum digoxin levels.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Studies of carcinogenesis in rats (24 months) and mice (18 months) did not demonstrate any tumorigenic potential. Mexitil was found to be non-mutagenic in the Ames test. Mexitil did not impair fertility in the rat.

Pregnancy Teratogenic Effects: PREGNANCY CATEGORY C. Reproduction studies performed with Mexitil® in rats, mice and rabbits at doses up to four times the maximum human oral dose (20 mg/kg in a 50 kg patient) revealed no evidence of teratogenicity or impaired fertility but did show an increase in fetal resorption. There are no adequate and well-controlled studies in pregnant women, this drug should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Mexitil appears in human milk in concentrations similar to those observed in plasma. Therefore, if the use of Mexitil is deemed essential, an alternative method of infant feeding should be considered.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS Mexitil® (mexiletine hydrochloride) commonly produces reversible gastrointestinal and nervous system adverse reactions but is otherwise well tolerated. Mexitil has been evaluated in 483 patients in one-month and three-month controlled studies and in over 10,000 patients in a large compassionate use program. Dosages in the controlled studies ranged from 600-1200 mg/day, some patients (8%) in the compassionate use program were treated with higher daily doses (1600-3200 mg/day). In the three month controlled trials comparing Mexitil to quinidine, procainamide and disopyramide the most frequent adverse reactions were upper gastrointestinal distress (41%), lightheadedness (10.5%), tremor (12.6%) and coordination difficulties (10.2%). Similar frequency and incidence were observed in the one-month placebo-controlled trial. Although these reactions were generally not serious, and were dose-related and reversible with a reduction in dosage, by taking the drug with food or antacid or by therapy discontinuation, they led to therapy discontinuation in 40% of patients in the controlled trials. A tabulation of the adverse events reported in the one-month placebo-controlled trial follows:

COMPARATIVE INCIDENCE (%) OF ADVERSE EVENTS AMONG PATIENTS TREATED WITH MEXILETINE AND PLACEBO IN THE 4-WEEK, DOUBLE-BLIND CROSSOVER TRIAL

	Mexiletine N = 53	Placebo N = 49
Cardiovascular		
Palpitations	7.5	10.2
Chest Pain	7.5	4.1
Increased Ventricular Arrhythmia/PVC's	1.9	—
Digestive		
Nausea/Vomiting/Heartburn	39.6	6.1
Central Nervous System		
Dizziness/Lightheadedness	26.4	14.3
Tremor	13.2	—
Nervousness	11.3	6.1
Coordination Difficulties	9.4	—

	Mexiletine N = 53	Placebo N = 49
Changes in Sleep Habits	7.5	16.3
Paresthesias/Numbness	3.8	2.0
Weakness	1.9	4.1
Fatigue	1.9	2.0
Tinnitus	1.9	4.1
Confusion/Clouded Sensorium	1.9	2.0
Other		
Headache	7.5	6.1
Blurred Vision/Visual Disturbances	7.5	2.0
Dyspnea/Respiratory	5.7	10.2
Rash	3.8	2.0
Non-specific Edema	3.8	--

A tabulation of adverse reactions occurring in one percent or more of patients in the 12-month controlled studies follows. **COMPARATIVE INCIDENCE (%) OF ADVERSE EVENTS AMONG PATIENTS TREATED WITH MEXILETINE OR CONTROL DRUGS IN THE 12-WEEK DOUBLE-BLIND TRIALS**

	Mexiletine N = 430	Quinidine N = 262	Procainamide N = 78	Disopyramide N = 60
Cardiovascular				
Palpitations	4.3	4.6	1.3	5.8
Chest Pain	2.6	3.4	1.3	2.9
Angina/Angina-like Pain	1.7	1.9	2.6	2.9
Increased Ventricular Arrhythmias/PVC's	1.0	2.7	2.6	--
Digestive				
Nausea/Vomiting/Heartburn	39.3	21.4	33.3	14.5
Diarrhea	5.2	33.2	2.6	8.7
Constipation	4.0	--	6.4	11.6
Changes in Appetite	2.6	1.9	--	--
Abdominal Pain/ Cramps/Discomfort	1.2	1.5	--	1.4
Central Nervous System				
Dizziness/Lightheadedness	18.9	14.1	14.1	2.9
Tremor	13.2	2.3	3.8	1.4
Coordination Difficulties	9.7	1.1	1.3	--
Changes in Sleep Habits	7.1	2.7	11.5	8.7
Weakness	5.0	5.3	7.7	2.9
Nervousness	5.0	1.9	6.4	5.8
Fatigue	3.8	5.7	5.1	1.4
Speech Difficulties	2.6	0.4	--	--
Confusion/Clouded Sensorium	2.6	--	3.8	--
Paresthesias/ Numbness	2.4	2.3	2.6	--
Tinnitus	2.4	1.5	--	--
Depression	2.4	1.1	1.3	1.4
Other				
Blurred Vision/Visual Disturbances	5.7	3.1	5.1	7.2
Headache	5.7	6.9	7.7	4.3
Rash	4.2	3.8	10.3	1.4
Dyspnea/Respiratory	3.3	3.1	5.1	2.9
Dry Mouth	2.8	1.9	5.1	14.5
Arthralgia	1.7	2.3	5.1	1.4
Fever	1.2	3.1	2.6	--

Less than 1%: Syncope, edema, hot flashes, hypertension, short-term memory loss, loss of consciousness, other psychological changes, diaphoresis, urinary hesitancy/retention, malaise, impotence/decreased libido, pharyngitis.

An additional group of over 10,000 patients has been treated in a program allowing administration of Mexilit® (mexiletine hydrochloride) under compassionate use circumstances. These patients were seriously ill with the large majority on multiple drug therapy. Twenty-four percent of the patients continued in the program for one year or longer. Adverse reactions leading to therapy discontinuation occurred in 15 percent of patients (usually upper gastrointestinal system or nervous system effects). In general, the more common adverse reactions were similar to those in the controlled trials. Less common adverse events possibly related to Mexilit use include:

Cardiovascular System: Syncope and hypertension, each about 6 in 1000; bradycardia, about 4 in 1000; angina/angina-like pain, about 3 in 1000; edema, atrioventricular block/conduction disturbances and hot flashes, each about 2 in 1000; atrial arrhythmias, hypertension and cardiogenic shock, each about 1 in 1000.

Central Nervous System: Short-term memory loss, about 9 in 1000 patients; hallucinations and other psychological changes, each about 3 in 1000; psychosis and convulsions/seizures, each about 2 in 1000; loss of consciousness, about 6 in 10,000.

Digestive: Dysphagia, about 2 in 1000; peptic ulcer, about 8 in 10,000; upper gastrointestinal bleeding, about 7 in 10,000; esophageal ulceration, about 1 in 10,000.

Laboratory: Abnormal liver function tests, about 5 in 1000 patients; positive ANA and thrombocytopenia, each about 2 in 1000; leukopenia (including neutropenia and agranulocytosis), about 1 in 1000; myelofibrosis, about 2 in 10,000 patients.

Other: Diaphoresis, about 6 in 1000; altered taste, about 5 in 1000; salivary changes, hair loss and impotence/decreased libido, each about 4 in 1000; malaise, about 3 in 1000; urinary hesitancy/retention, each about 2 in 1000; hiccups, dry skin, laryngeal and pharyngeal changes and changes in oral mucous membranes, each about 1 in 1000; SLE syndrome, about 4 in 10,000.

Warnings: Blood dyscrasias were not seen in the controlled trials but did occur among 10,867 patients treated with mexiletine in the compassionate use program (see Precautions).

Myelofibrosis was reported in two patients in the compassionate use program; one was receiving long-term thiolepa therapy and the other had pretreatment myeloid abnormalities.

OVERDOSEAGE: Marked overdosage in humans has not been reported. On the basis of acute toxicity studies in animals, the major toxicity would be expected to be related to the central nervous system, including ataxia and convulsions.

There is no specific antidote for Mexilit® (mexiletine hydrochloride). Acidification of the urine, which will accelerate the excretion of mexiletine, may be useful. Treatment of overdosage should be supportive, and may include the administration of atropine if hypotension or bradycardia occurs.

DOSEAGE AND ADMINISTRATION: The dosage of Mexilit® (mexiletine hydrochloride) must be individualized on the basis of response and tolerance, both of which are dose-related. Administration with food or antacid is recommended. Initiate Mexilit® therapy with 200 mg every eight hours when rapid control of arrhythmia is not essential. A minimum of two to three days between dose adjustments is recommended. Dose may be adjusted in 50 or 100 mg increments up or down.

As with any antiarrhythmic drug, clinical and electrocardiographic evaluation (including Holter monitoring if necessary for evaluation) are needed to determine whether the desired antiarrhythmic effect has been obtained and to guide titration and dose adjustment.

Satisfactory control can be achieved in most patients by 200 to 300 mg given every eight hours with food or antacid. If satisfactory response has not been achieved at 300 mg q8h and the patient tolerates Mexilit well, a dose of 400 mg q8h may be tried. As the severity of CNS side effects increases with total daily dose, the dose should not exceed 1200 mg/day.

In general, patients with renal failure will require the usual doses of Mexilit. Patients with severe liver disease, however, may require lower doses and must be monitored closely. Similarly, marked right-sided congestive heart failure can reduce hepatic metabolism and reduce the needed dose. Plasma level may also be affected by certain concomitant drugs (see Precautions Drug Interactions).

Loading Dose: When rapid control of ventricular arrhythmia is essential, an initial loading dose of 400 mg of Mexilit may be administered, followed by a 200 mg dose in eight hours. Onset of therapeutic effect is usually observed within 30 minutes to two hours.

(12H) Dosage Schedule: Some patients responding to Mexilit may be transferred to a 12-hour dosage schedule to improve convenience and compliance. If adequate suppression is achieved on a Mexilit dose of 300 mg or less every eight hours, the same total daily dose may be given in divided doses every 12 hours while carefully monitoring the degree of suppression of ventricular ectopy. This dose may be adjusted up to a maximum of 450 mg every 12 hours to achieve the desired response.

Transferring to Mexilit: The following dosage schedule, based on theoretical considerations rather than experimental data, is suggested for transferring patients from other Class I oral antiarrhythmic agents to Mexilit. Mexilit treatment may be initiated with a 200 mg dose and titrated to response as described above. 6-12 hours after the last dose of quinidine sulfate, 3-6 hours after the last dose of procainamide, 6-12 hours after the last dose of disopyramide or 8-12 hours after the last dose of lidocaine.

In patients in whom withdrawal of the previous antiarrhythmic agent is likely to produce life-threatening arrhythmias, hospitalization of the patient is recommended.

When transferring from lidocaine to Mexilit, the lidocaine infusion should be stopped when the first oral dose of Mexilit is administered. The infusion line should be left open until suppression of the arrhythmia appears to be satisfactorily maintained. Consideration should be given to the similarity of the adverse effects of lidocaine and Mexilit and the possibility that they may be additive.

HOW SUPPLIED: Mexilit® (mexiletine hydrochloride) is supplied in hard gelatin capsules containing 150 mg, 200 mg or 250 mg of mexiletine hydrochloride.

Mexilit® 150 mg capsules are red and caramel with the marking BI 66. Available in bottles of 100 (NDC 0597-0066-01) and individually blister-sealed unit-dose cartons of 100 (NDC 0597-0066-61).

Mexilit® 200 mg capsules are red with the marking BI 67. Available in bottles of 100 (NDC 0597-0067-01) and individually blister-sealed unit-dose cartons of 100 (NDC 0597-0067-61).

Mexilit® 250 mg capsules are red and arsa green with the marking BI 68. Available in bottles of 100 (NDC 0597-0068-01) and individually blister-sealed unit-dose cartons of 100 (NDC 0597-0068-61).

Store below 86°F (30°C).

Caution: Federal law prohibits dispensing without prescription.



**Boehringer
Ingelheim**

Boehringer Ingelheim
Pharmaceuticals, Inc.
Ridgefield, Connecticut 06877

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Mexiletine HCl
(MEXITIL)
100, 150, 200, 250 mg Capsules
NDA 18-873
Reviewer: M.Y. Huang, Ph.D.
Wang [REDACTED]

Boehringer Ingelheim Ltd.
Ridgefield, Connecticut 06877
Submission Date:
September 30, 1982

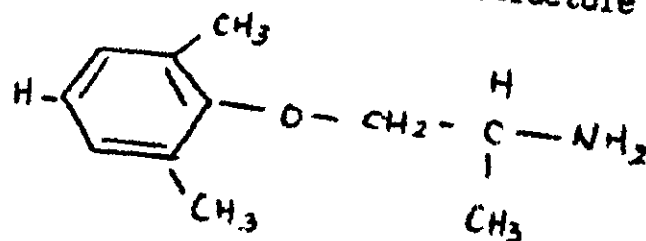
REVIEW OF BIOAVAILABILITY AND PHARMACOKINETIC STUDIES (6 studies)

BACKGROUND

Mexiletine (Mexitil) is a new drug used in ventricular arrhythmias. The Division of Biopharmaceutics has not documented any submissions of Mexiletine till this submission. The current submission contains the following studies:

1. Absolute bioavailability study (Literature)
2. Pilot methodology study (E 82-1677)
3. Bioavailability study (E 82-94)
4. Dose proportionality study (E-78-419, E-78-415, E-78-417)
5. Dissolution study

Mexiletine HCl has a pKa of 8.4 and the structure is shown below:



STUDIES

I Absolute Bioavailability Study
(clin. Pharmacol. Ther. June 1981 p. 729)

1. Single-dose kinetics of mexiletine was studied in six healthy subjects after three different formulations. The respective doses were 200 mg (intravenous infusion), 400 mg (two conventional capsules), and 432 mg (sustained-release dosage forms). By a three-compartment open model with lag time the kinetic parameters of the drug were calculated from the experimental plasma level data. The pharmacokinetic parameters can be described as follows:

- a. $t_{1/2} (\text{gamma}) = 6.34 \pm 1.5 \text{ h}$
- b. $V_{d\text{tot}} = 5.5 \text{ L/kg}$
- c. $CL_{\text{tot}} = 10.3 \text{ ml/min/kg}$
- d. $C_{\text{max}} (\text{cap}) = 0.77 \text{ ug/ml}$
- e. $T_{\text{max}} (\text{cap}) = 2.2 \text{ hrs}$
- f. $C_{\text{max}} (\text{sustained release}) = 0.34 \text{ ug/ml}$
- g. $T_{\text{max}} (\text{sustained release}) = 9.2 \text{ hrs.}$
- h. $F (\text{cap}) = 87.3\%$
- i. $F (\text{sustained release}) = 78.7\%$
- j. $\% \text{ Dose excreted unchanged (cap)} = 7.5\%$
- k. $\% \text{ Dose excreted unchanged (sustained release)} = 9.2\%$

2. Table 1.1 lists all the kinetic parameters after intravenous infusion.
3. Fig. 1.1 and 1.2 show the plasma profiles and cumulative renal excretions for 6 subjects respectively.

Comments for the Absolute Bioavailability Study

1. The absolute bioavailability was 87.3%, thus there was negligible first pass effect.
2. The 7.5% of dose excreted as unchanged drug in the treatment of 2x200 mg capsules indicated that there was extensive metabolism. The negligible first pass, and high volume of distribution indicated high tissue distribution.
3. In a telephone conversation, the firm's representative, Mrs. Marilyn Roger verified that the final marketed formulation is the same as the capsule formulation in this study.
4. The half-life described in this study (6.34 ± 1.5 hours) is shorter than those in other studies. (e.g. $10.4 \pm 2.8 \text{ hr}$ or $11.8 \pm 1.5 \text{ hr}$).

II Pilot Methodology Study (E 82-1677)

Objective

To obtain data for planning the 24-subject bioavailability study. Particular concerns were reliability of determination of mexiletine in plasma and urine and dose proportionality.

Subjects

All four male subjects completed the study and were used in the analysis. Age: 26-43 years
Height: 69 to 72 inches
Weight: 142 to 186 pounds
Clinical chemistry and hematology : normal

Clinical Laboratory and Investigator

Miguel A. Zinny, M.D.
Medical & Technical Research Associates, Inc.
32 Kearney Road
Neadham, MA 65205

Assay Laboratory

Treatments

200 mg Mexiletine Soln. (#90828)
2 x 50 mg Capsules (#PD-0247)
4 x 50 mg Capsules (#PD-0247)
8 x 50 mg Capsules (#PD-0247)

The subjects fasted 10 hours pre-dose and till 4.5 hours post-dose.

Design

4 way crossover
1 week washout
Subjects fasted 10 hour prior to dose and 4.5 hours post dosing.

Analytical Method

GC Method

RESULTS

Methodology

1. Sensitivity - [redacted] ng/ml
2. Linearity - the assay was linear over the concentration of [redacted] to [redacted] ng/ml.

3. Reproducibility -
 a. daily calibration of assay

<u>MEXITIL added to Plasma (ng/ml)</u>	<u>Coefficient of Variation</u>
[REDACTED]	9.14
[REDACTED]	11.2
[REDACTED]	12.0
[REDACTED]	18.7
[REDACTED]	10.1
[REDACTED]	51.2

b. long term accuracy and precision

	<u>MEXITIL Standard (ng/ml)</u>			
Accuracy (%)	-2.8	3.6	-3.8	7.2
Precision (%)	8.3	12.5	24	41

Plasma Data

The firm employed 4 subjects in this pilot study. Most of the subjects had plasma concentrations near the assay sensitivity limit especially for doses of 2 x 50 mg and 4 x 50 mg. Therefore, it is not possible to use these plasma concentrations to conclude if dose proportional within individual subject (See Fig. 2.1).

Urinary Data

The firm has also documented urinary levels. The drug concentrations in urine were higher than their plasma concentrations. The Division of Biopharmaceutics plotted the urinary excretion rates for these 4 subjects (See Fig. 2.2 - 2.5). It is apparent that there were zig-zag profiles. The 48 hour % cumulative urinary excretions for these subjects are shown as follows:

	<u>#1</u>	<u>#2</u>	<u>#3</u>	<u>#4</u>
2 x 50 mg Capsules	3.73	3.85	2.81	2.72
4 x 50 mg Capsules	4.15	6.80	4.79	2.42
8 x 50 mg Capsules	2.26	13.60	3.52	4.59
200 mg Solution	2.70	9.67	2.22	2.49

Figures 2.2-2.5 indicated that first order process might be involved from 18 hours to 36 hours post dose (See Fig. 2.2-2.5). It is difficult to envision the kinetics involved from 0 to 18 hours post dose.

The firm indicated that the percent excreted did not depend on treatment (See Table above) but did appear to increase as the pH of the urine decreased (See Fig. 2.6). The Division of Biopharmaceutics acknowledges the fact from the paper published by A.H. Beckett et al (Post graduate Medical Journal, 1977 53, 60-66) that urinary pH affects the cumulative urinary excretions. Yet the data that the firm presented in this pilot study had at least two variables: pH and dose strength, thus it is not justified to compare pH effect without considering the different dose strengths given.

Comments

1. The firm did not validate the specificity of the assay. All the major metabolites should be shown not to interfere with the assay of the parent compound.

III BIOAVAILABILITY STUDY (E 82-94)

Objective

To compare the relative rate and the extent of the absorption of Mexitil in plasma after administration of 2x200 mg capsules taken without food or with food and 400 mg reference oral solution in 24 normal male subjects.

Treatments

1. 2x200 mg capsules without food Batch PD-0309
 2. 2x200 mg capsules with food Batch PD-0309
 3. 1x400 mg oral solution Batch 90828
- Subjects fasted 10 hours pre-dose and 4.5 hours post-dose
Washout - 5 days

Investigator

Miguel Zinny, M.D.

Clinical Laboratory

Same as that in Pilot Bioavailability Study

Analytical Laboratory

Same as that in Pilot Bioavailability Study

Method

GC Method

RESULTS

Mean Data

Table 3.1 and Table 3.2 show the mean concentration of Mexiletine and AUCs, C_{max}, T_{max} following oral administration respectively. Fig. 3.1 describes the plasma profiles for 3 treatments.

Individual Data

Table 3.3 shows the individual AUCs, C_{max} & T_{max}

Table 3.4 shows AUCs ratios for capsules relative to solution.

Half Lives

The half-lives for all three treatments are shown in Table 3.5. The half-lives ranged from 4 to 22 hours.

75/75 Rule

1. AUCs Ratios - 29% of the 24 subjects studied were outside 75% to 125% range. (See table 3.4)
2. C_{max} Ratios - 13% and 17% of the 24 subjects studied were outside 75% to 125% range for treatment 2x200 mg capsules with food, and treatment 2x200 mg capsules without food respectively. (See Table 3.3)

Statistics

1. AUCs - The mean area under the curve for 2x200 mg capsules taken without food (11.4), and 2x200 mg capsules taken with food (12.2), were 89.1% and 95.3% of the reference solution (12.8). None of the formulation differed significantly from each other.

2. C_{max} - The mean peak concentration for 2x200 mg capsules taken without food (0.72) and 2x200 mg capsules taken with food (0.77) were 87.8% and 93.9% of the reference solution (0.82) respectively. The formulations did not significantly differ from each other, except that the Mexiletine 2x200 mg capsules taken without food had a significantly lower peak than the reference solution ($p=0.0141$).
3. T_{max} - The mean time to peak were 2.8 hours for Mexiletine 2x200 mg capsules taken without food, 2.9 hours for 2x200 mg capsules taken with food and 2.8 hours for the reference solution. There were no statistically significant differences in mean time to peak.
4. Power - There was more than 90% power at $\alpha = 0.05$ to detect 20% difference from the reference solution between AUCs or between C_{max} .

Comment

1. The bioavailability study is acceptable.
2. The bioavailability for the capsules (2x200 mg) with food was about 94% relative to solution without food.

IV Dose Proportionality Study

Investigators:

1. Stephen S. Steen, M.D. E78-419
2. Jeremy N. Ruskin, M.D. E78-415
3. Wilmer L. Thompson, Jr. J.D. E78-417

Procedures

Data of those patients who completed all phases (placebo, 200 mg tid, 300 mg tid, 400 mg tid) in the three dose ranging studies of Drs. Steen, Ruskin and Thompson were used to determine the dose proportionality of Mexiletine. In these studies, a total of 20 patients received all three doses of Mexiletine (200 mg tid, 300 mg tid, and 400 mg tid) for three days. On the third day of each dose, blood samples were taken prior to the morning dose and at 0.5, 1, 1.5, 2, 3, 4, 6, and 8 hours after the morning dose.

Results

1. Plasma Profiles

The Division of Biopharmaceutics plotted all the plasma profiles for the 20 patients studied (See Fig. 4.1 and Fig. 4.2). It was very apparent the profiles exhibited zig-zag patterns. The firm did not understand the reason for the phenomenon.

2. C_{max}

The individual C_{max}s are shown in Table 4.1. The mean values for 200 mg bid, 300 mg bid and 400 mg bid were 1305 ± 604 ng/ml, 2165 ± 878 ng/ml, and $2785 \pm$ ng/ml respectively. However, if we examined the individual C_{max} by 75/75 rule, we found that from 200 mg bid to 300 mg bid dosing, 35% of the subjects studied did not have a proportional C_{max} increase and from 200 mg bid to 300 mg bid dosing, 55% of the subjects studied did not have a proportional C_{max} increase and 35% had a ratios (C_{max} 400/C_{max} 200) higher than 2.9 (2.9-5.1). Since the concentrations for efficacy and side effects are close, the nonproportional increase in C_{max} as doses increase should be viewed with caution.

3. AUCs

It should be noted that some investigators failed to collect the plasma levels up to the end of dosing intervals. Using all the data available, it was found that 4 out of 6 patients of Ruskins', 1 out of 3 patients of Thompson's, 3 out of 11 patients of Steens's did not have proportional plasma profiles as doses changed from 200 mg bid to 400 mg bid. Overall, 40% of 20 patients had non-proportional plasma profiles (See Table 4.2).

These patients were:

#1102, #1103, #1105, #1111, #1201, #1301, #1306, #1313.

Almost all these patients (except #1102) had humps in their plasma profiles.

V Dissolution Study

See Table 5.1 - 5.4 for dissolutions of 4 strengths: 100 mg, 150 mg, 200 mg and 250 mg. Also, see Fig. 5.1 - 5.4 for dissolution profiles. The data (using USP Method II, 50 rpm in water) presented demonstrated that Mexiletine's dissolution characteristics were not altered by capsule size or weight of fill.

VI Formulations

See Table 6.1 for 4 formulations. All 4 formulations are composition proportional.

VII Metabolism

- Mexiletine (I) is extensively metabolized in man and is eliminated as unchanged drug and metabolites. The major metabolites are parahydroxy mexiletine (VI) hydroxymethylmexiletine (VII) and their corresponding alcohols VIII and IX, up to 20% (normal urinary pH). The minor metabolic routes are N-oxidation, Va and Vb (Total 1-2%); deamination to the ketone (III) and reduction to the alcohol. IV (up to 4 %) N-methylation (II) occurs to a very minor extent (< 0.5%). Conjugations of VI, VIII, IX as well as mexilitine also occurred.

	R1	R2	X
I	H	H	HNH ₂
II	H	H	HNHCH ₃
III	H	H	=O
IV	H	H	HOH
Va	H	H	HNOH
Vb	H	H	=NOH
VI	H	OH	HNH ₂
VII	OH	H	HOH
IX	OH	H	HOH

- The buccal absorption curves of mexiletine and metabolites can be divided into 3 classes:

Class 1 involves the amines, mexilitine and N-methylmexiletine whose absorptions show a rapid change with pH.

Class 2 contains the neutral ketone alcohol and oxime, with low and intermediate absorptions at acidic pH and showing little or no change within pH 5-8.

Class 3 contains the major basic metabolites (VI and VII), which have higher absorptions at acidic pH values and show no change upon varying the pH values when less than their pKa values, within the physiological range (pH 5-8).

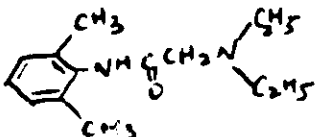
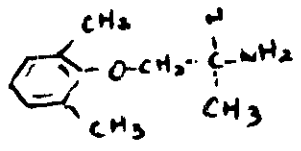
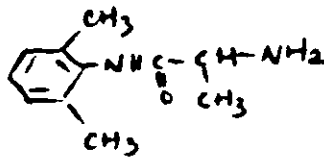
(See Fig. 7.1)

Although the pKa values of the major basic metabolites (VI and VII) are not too dissimilar from that of the parent amine, the differences in the renal reabsorption of the un-ionized forms can be explained in terms of their different rates of lipid partitioning upon varying the urinary pH.

- The plasma concentrations showed a more rapid decline under maintained acidic urine, than under normal urinary pH. The biological half-lives were reduced from mean values of 9 ± 2 hour (normal urinary pH) to $4 - 5 (\pm 1)$ hour (controlled acidic urine). The rapid decline of plasma mexiletine with acidic urine was reflected in its urinary excretion, 30-55% was excreted in 24 hours under this condition, whereas only 10-23% was excreted in the subjects studied, under conditions of normal urinary pH. (See post graduate Med. J. 1977 53 (Suppl. 1) 60-66).

COMMENTS

- Mexiletine is a Class I antiarrhythmic agent similar to lidocaine. The Division of Biopharmaceutics summarizes all the pharmacokinetics parameters for Lidocaine, Mexiletine and Tocainide as follows*:

	<u>Lidocaine</u>	<u>Mexiletine</u>	<u>Tocainide</u>
<u>Structure</u>			
<u>% Urinary excretion</u>	$2 \pm 50\%$	$7.5 \pm 41\%$	40
<u>% bound in plasma</u>	$51 \pm 16\%$	50-60	--
<u>CLT (ml/kg/min)</u>	$9.2 \pm 26\%$	7.0-13.0	$2.4 \pm 8\%$

<u>Vd (l/kg)</u>	1.1 ± 40%	5.5 ± 10%	2.6 ± 7%
<u>T 1/2 (hour)</u>	1.8 ± 25%	4 - 22	13 ± 18%
<u>F (%)</u>	35 ± 11%	88- 94	87 - 106

*Values are represented as mean ± C.V.

2. The 2x200 mg capsule is almost 90% bioavailable relative to oral solution. The mean time to peak is about 2.8 hours. Food has not affected bioavailability. The absolute bioavailability was 87%.
3. There was negligible first pass effect. The 7.5% of dose excreted as unchanged drug in the treatment of 2x200 mg capsules indicated that there was extensive metabolism. The negligible first pass, and high volume of distribution indicated high tissue distribution.
4. Metabolism of Mexiletine is as follows:
 - a. hydroxylation on the ring
 - b. N-oxidation
 - c. N-reduction
 - d. N-methylation
 - e. Conjugation
5. In the dose proportionality study (E78-419, E78-415 and E78-417), zig-zag patterns were noticed in plasma profiles. The reason for this phenomenon is not clear. It might be due to:
 - 1) assay methodology?
 - 2) enterohepatic recycling?
 - 3) renal reabsorption?

35% of the 20 patients studied did not have a proportional increase in C_{max}s or AUCs as doses were changed from 200mg bid to 300mg bid or 400 mg bid. Since the effective plasma level is close to plasma levels associated with side effects, the firm should explain as to the validity of the results of this study.

6. The labelling of mexiletine is requested by the division of Biopharmaceutics for a review.

DEFICIENCIES

1. The % of urinary excretion appears to be affected by urinary pH. The plasma concentrations showed a more rapid decline under maintained acidic urine, than under normal urinary pH, the biological half-lives were reduced from mean values of 9 ± 2 hour (normal urinary pH) to $4-5 (\pm 1)$ hour (controlled acidic urine). The rapid decline of plasma mexiletine with acidic urine was reflected in its urinary excretion, 30-55% was excreted in 24 hours under this condition, whereas only 10-23% was excreted in the subjects studied, under conditions of normal urinary pH. Since this drug can lead to stomach upset, antacids taken concomitantly might affect urinary pH and subsequently affect plasma levels. The firm should submit a study investigating this issue.
2. The firm needs to explain the zig-zag patterns in the dose-proportionality study. It should be noted that zig-zag patterns were not observed in single dose relative bioavailability study.
3. The firm should validate the assay specificity. The non-interference of major metabolites in the assay of the parent compound should be documented.
4. The firm should verify that the formulations used in a) V. Haselbarth et. al. study, b) relative bioavailability study (E-82-94) and c) dose-proportionality study (E-78-419, E78-415, E-78-417) the same as the final marketed formulation.

CONCLUSION - Application Deficient

The absolute bioavailability study (clin. Pharmacol Ther. June 1981 June 729) and bioavailability study (E 82-94) of NDA 18873 submitted on September 30, 1982 have been found acceptable by the Division of Biopharmaceutics with regard to bioavailability/bioequivalence requirement. The dose proportionality study (E 78-419, E78-415, and E 78 417) is deficient (see deficiency #2). The application is still deficient with regard to bioavailability/bioequivalence requirement (See deficiencies #1, #2 and #3).

The above recommendation as well as deficiencies should be forwarded to the firm.

M. Y. Huang 11/14/83

M. Y. Huang, Ph.D.
Pharmacokinetics Branch

R/D INITIALED BY CT/VISWANATHAN, Ph.D.
FT INITIALED BY CT/VISWANATHAN, Ph.D.

CT. Viswanathan

11/5/83-mstephens: [REDACTED]:cas:11-14-83

cc: NDA 18-873 Original, HFN-110, HFN-525 (Huang), Drug, Chron, Review,
and Division Files.

Table 1: Kinetic parameters of mexiletine after intravenous infusion

Parameter	Subject						$\bar{x} \pm SD$ (N = 6)
	1	2	3	4	5	6	
Weight (kg)	83.0	91.0	80.0	84.0	78.0	69.0	80.8 ± 7.3
Dose (mg)	198.51	196.56	197.05	201.30	199.75	196.80	198.34 ± 1.92
Distribution volumes*							
V _c (central) (l)							30.89 ± 8.8
V _s (tissue) (l)							275.0 ± 80.0
V _d (tissue) (l)							93.0 ± 78.5
V _{ss} (γ phase) (l/kg)							5.46 ± 0.54
t _{1/2} (hr)*							6.34 ± 1.48
AUC _{0-∞} (μg/ml/hr)							4.21 ± 1.45
Clearance*							
CL _R (ml/min)							845.56 ± 238.1
CL _T (ml/min/kg)							10.34 ± 2.30

* Values are also valid for the oral administrations.

Table 1: Kinetic parameters of mexiletine after intravenous infusion

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V _d (tissue) (l)							93.0 ± 78.5
V _{ss} (y phase) (l/kg)							5.46 ± 0.54
t _{1/2} (hr)*							6.34 ± 1.48
AUC _{0-∞} (μg/ml/hr)							4.21 ± 1.45
Clearance*							845.56 ± 238.1
CL _R (ml/min)							10.34 ± 2.30
CL _T (ml/min/kg)							

* Values are also valid for the oral administrations.

Table 1: Kinetic parameters of melitine after intravenous infusion

Parameter	Subject						$\bar{x} \pm SD$ (N = 6)
	1	2	3	4	5	6	
Weight (kg)	83.0	91.0	80.0	84.0	78.0	69.0	80.8 ± 7.3
Dose (mg)	198.51	196.56	197.05	201.30	199.75	196.80	198.34 ± 1.92
Distribution volumes*							
V _d (l ^{central}) (l)							30.89 ± 8.8
V _d (tissue) (l)							275.0 ± 80.0
V _d (tissue) (l)							93.0 ± 78.5
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Clearance*							845.56 ± 238.1
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*Values are also valid for the oral administration.

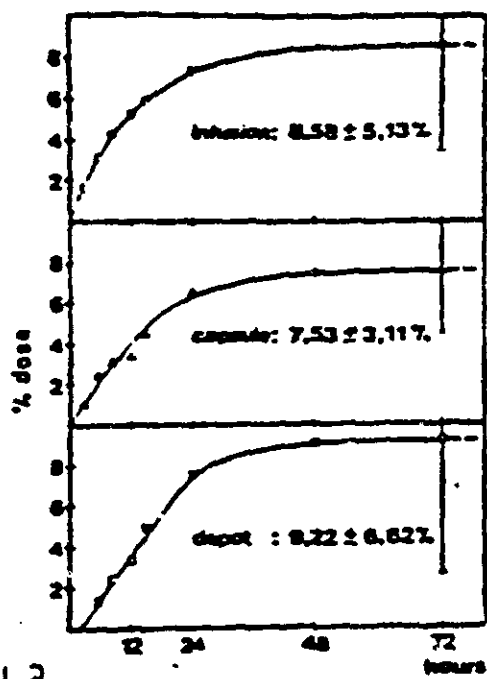
Table I: Kinetic parameters of mexiletine after intravenous infusion

Parameter	Subject						$\bar{x} \pm SD$ (N = 6)
	1	2	3	4	5	6	
Weight (kg)	83.0	91.0	80.0	84.0	78.0	69.0	80.8 ± 7.3
Dose (mg)	198.51	196.56	197.05	201.39	199.75	196.80	198.34 ± 1.92
Distribution volumes*							
V _c (central) (l)							30.89 ± 8.8
V _s (tissue) (l)							275.0 ± 80.0
V _d (tissue) (l)							93.0 ± 78.5
V _{dss} (y phase) (l/kg)							5.46 ± 0.54
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Clearance*							845.56 ± 238.1
Cl _r (ml/min)							10.34 ± 2.30
Cl _{cr} (ml/min/kg)							

*Values are also valid for the oral administrations.

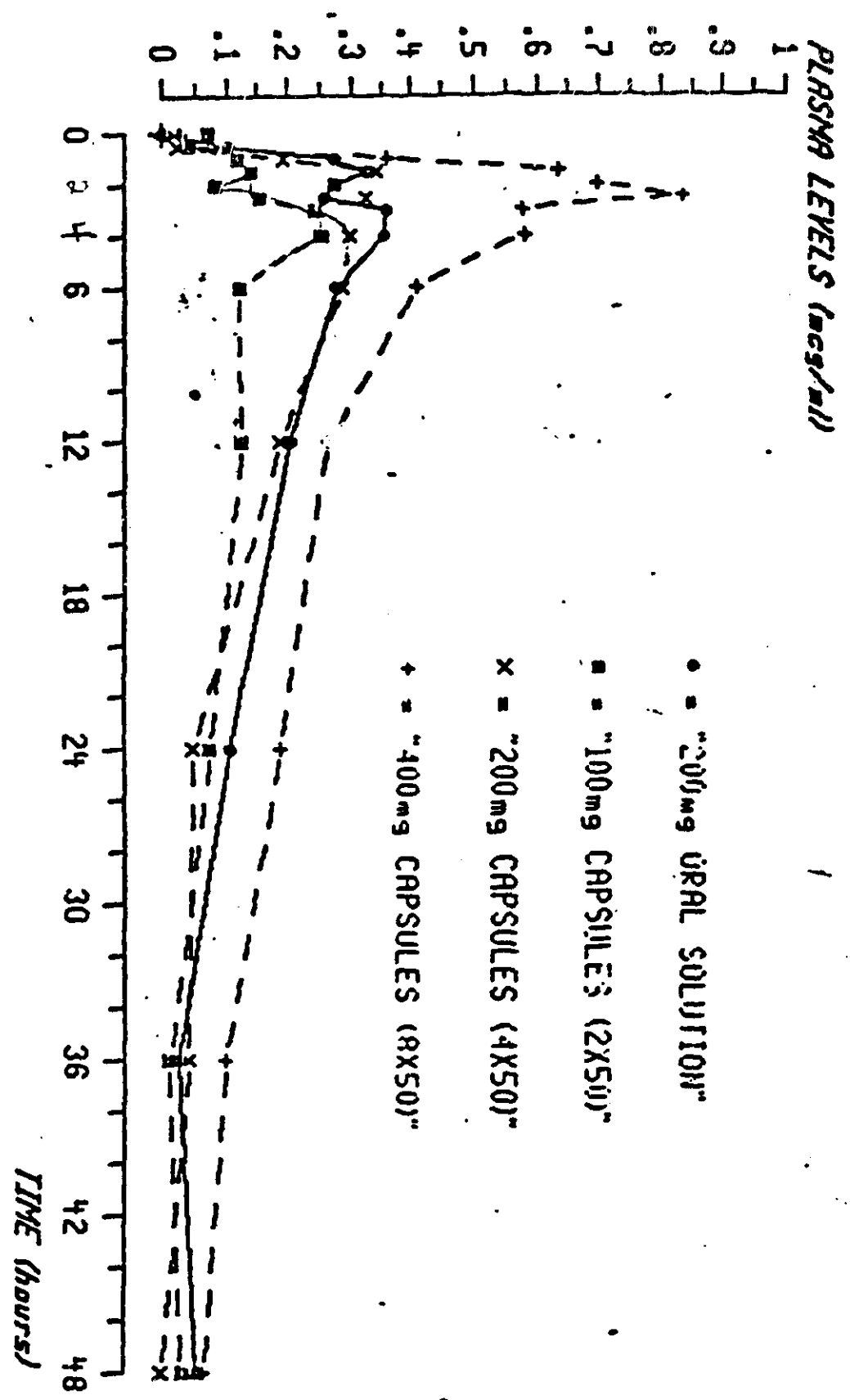
1 PAGE

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1.2
 Fig. 2. Cumulative renal excretion of mexiletine in a group of six subjects ($\bar{x} \pm SD$).

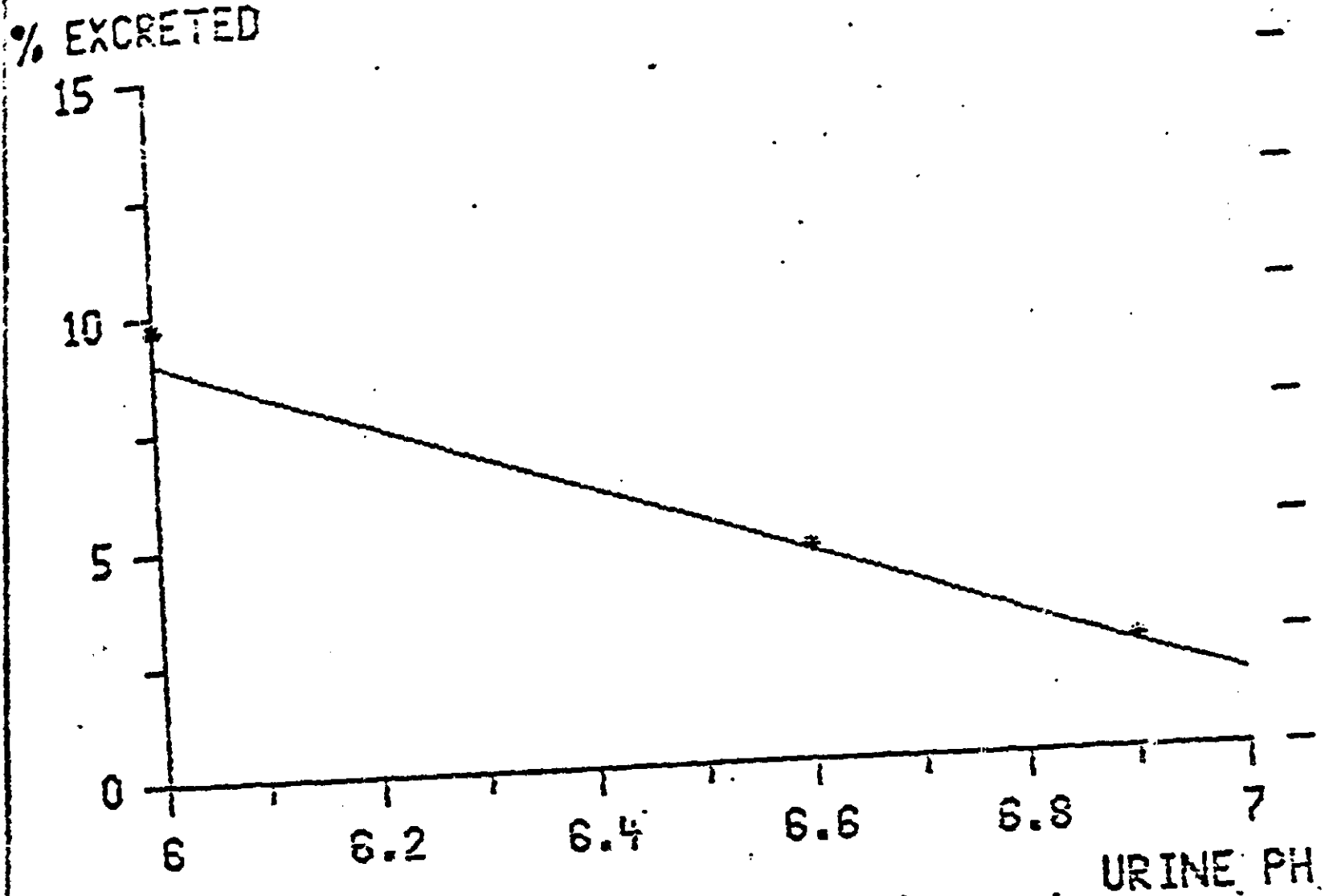
Figure 1. Mean plasma levels of mexiletine (N = 4).



4 pages

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Figure 2.6
EFFECT OF PH ON EXCRETION OF MEXITIL



POLYNOM OF DEGREE 1 VARIABILITY	df	SS	MS	s	c.o.d.	r	F-Value
TOTAL	15	144.93237	9.66215	3.10940			17.48
BETWEEN	1	80.48328	80.48328	2.14557	0.55531	0.74519	
WITHIN	14	64.44908	4.60350				

COEFFICIENTS OF REGRESSION				
I	b(I)	CONF. L. (55%)	T(CALC)	T(95%)
0	53.52148		4.18127	2.14478
1	-7.42465	3.80947		

TABLE 3.1
 Mean Concentration (mcg/ml) of Mexitil in Plasma
 of Mexitil Capsule Treatments Versus
 Reference Solution Following Oral Administration:
 Mean at Each Sampling Point^a

(Means^b of 24 Subjects)

Hour After Administration of the Dose (Hours)	400 mg Mexitil Reference Solution			Two 200 mg Mexitil Capsule Taken Without Food		Two 200 mg Mexitil Capsule Taken with Food	
	.5	0.24 ± 0.03			0.09 ± 0.01		0.09 ± 0.02
1	0.54 ± 0.03			0.37 ± 0.03		0.38 ± 0.04	
1.5	0.64 ± 0.03			0.57 ± 0.03		0.56 ± 0.02	
2	0.72 ± 0.04			0.62 ± 0.03		0.61 ± 0.03	
2.5	0.71 ± 0.04			0.64 ± 0.03		0.68 ± 0.05	
3	0.71 ± 0.02			0.60 ± 0.02		0.66 ± 0.05	
4	0.66 ± 0.03			0.59 ± 0.03		0.61 ± 0.03	
6	0.59 ± 0.03			0.51 ± 0.03		0.54 ± 0.03	
12	0.39 ± 0.03			0.34 ± 0.02		0.36 ± 0.03	
24	0.17 ± 0.02			0.19 ± 0.02		0.21 ± 0.02	
36	0.13 ± 0.02			0.11 ± 0.01		0.11 ± 0.01	
48	0.06 ± 0.01			0.04 ± 0.01		0.05 ± 0.01	

^aSource Data: Appendix AA
^bStandard Error of the Mean

TABLE 3.2

Plasma Hexitell Concentration (mcg/ml) of Hexitell
Capsule Treatments Versus Reference Solution
Following Oral Administration: Area Under the
48-Hour Curve; Peak Concentration; Time to Peak^a

(Means^b of 24 Subjects)

Parameter	400 mg Hexitell Oral Reference Solution	Two 200 mg Hexitell Capsule Taken Without Food	Percent of Oral Reference Solution	Two 200 mg Hexitell Capsule Taken With Food	Percent of Oral Reference Solution
Area Under The Curve (48 hrs; mcg-hrs/ml)	12.8 ± 0.7	11.4 ± 0.5	89.1	12.2 ± 0.7	95.3
Peak Concentration (mcg/ml)	0.82 ± 0.02	0.72 ± 0.02	87.8	0.77 ± 0.05	93.9
Time To Peak (In hours)	2.8 ± 0.2	2.8 ± 0.2	100.0	2.9 ± 0.2	103.4

^aSource Data: Appendix BB
Anova Tables: Appendix B
^b± Standard Error of the Mean

4 pages

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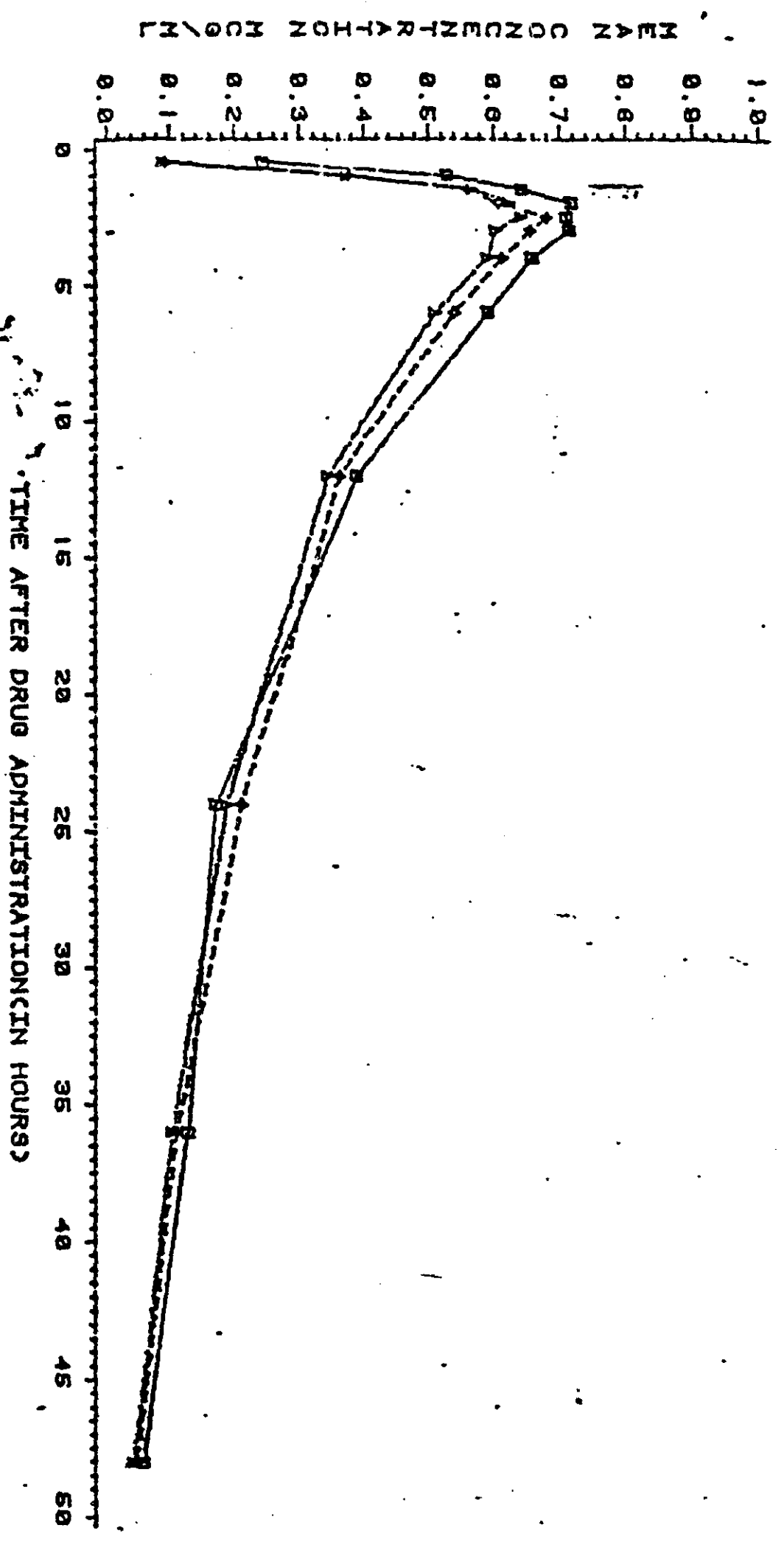
TABLE 3.5

Compilation of elimination half-lives for mexiletine

<u>Patient No</u>	<u>Solution No Food</u>	<u>2x200 Capsules No Food</u>	<u>2x200 Capsules With Food</u>	<u>Mean for 3 Weeks</u>
101				
102				
103				
104				
105				
106				
107				
108				
109				
110				
111				
113				
114				
115				
116				
117				
118				
119				
120				
122				
123				
124				
125				
126				
$\bar{x} \pm SD:$	10.2 $\pm$ 3.8	9.9 $\pm$ 3.7	10.8 $\pm$ 4.3	10.28 $\pm$ 3.1
Range:	(4.1-19.7)	(4.1-22.0)	(4.0-20.9)	(6.0-18.0)

N. 21447, N.O.
STUDY NO. E82-04

3.1 TIME PROFILE OF MEAN CONCENTRATION OF MEXITIL (MCG/ML) IN PLASMA BY TYPE OF ADMINISTRATION



LEGEND: SQUARE - 400 MG MEXITIL SOLUTION
TRIANGLE - 2 MEXITIL 200 MG CAPSULES TAKEN WITHOUT FOOD
DIAMOND - 2 MEXITIL 200 MG CAPSULES TAKEN WITH FOOD

E82-1678

2 pages

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Table 4.1

CONCENTRATION OF NEXITIL IN THE PLASMA:
 PEAK CONCENTRATION
 BY PATIENT AND DOSE

PATIENT	PEAK_200	PEAK_300	PEAK_400	PEAK_500
1102				
1103				
1105				
1106				
1107				
1111				
1301				
1303				
1305				
1306				
1308				
1309				
1312				
1313				
1314				
1316				
1317				
1201				
1213				
1216				
$\bar{x}$	1305	2165	2925	
SD	604	878	788	

Source Data: Appendix AA

2 pages

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Table 5.1

DISSOLUTION DATA

Mexitil^R Capsules 100 mg
FD-0088

<u>Time</u> <u>(Minutes)</u>	<u>Individual Values</u> <u>Σ Dissolved</u>	<u>Mean</u>	<u>Range</u>	<u>N</u>
15		92.8		6
30		97.1		12
45		93.4		6
60		97.7		12

Table 5.2

DISSOLUTION DATA

Mexitil^R Capsules 150 mg
PD-0321

<u>Time</u> <u>(Minutes)</u>	<u>Individual Values</u> <u>% Dissolved</u>	<u>Mean</u>	<u>Range</u>	<u>N</u>
15		85.8		6
30		96.7		12
45		94.8		6
60		99.2		12

Table 5.3 DISSOLUTION DATA
 Mexitil^R Capsules 200 mg
 PI-0309

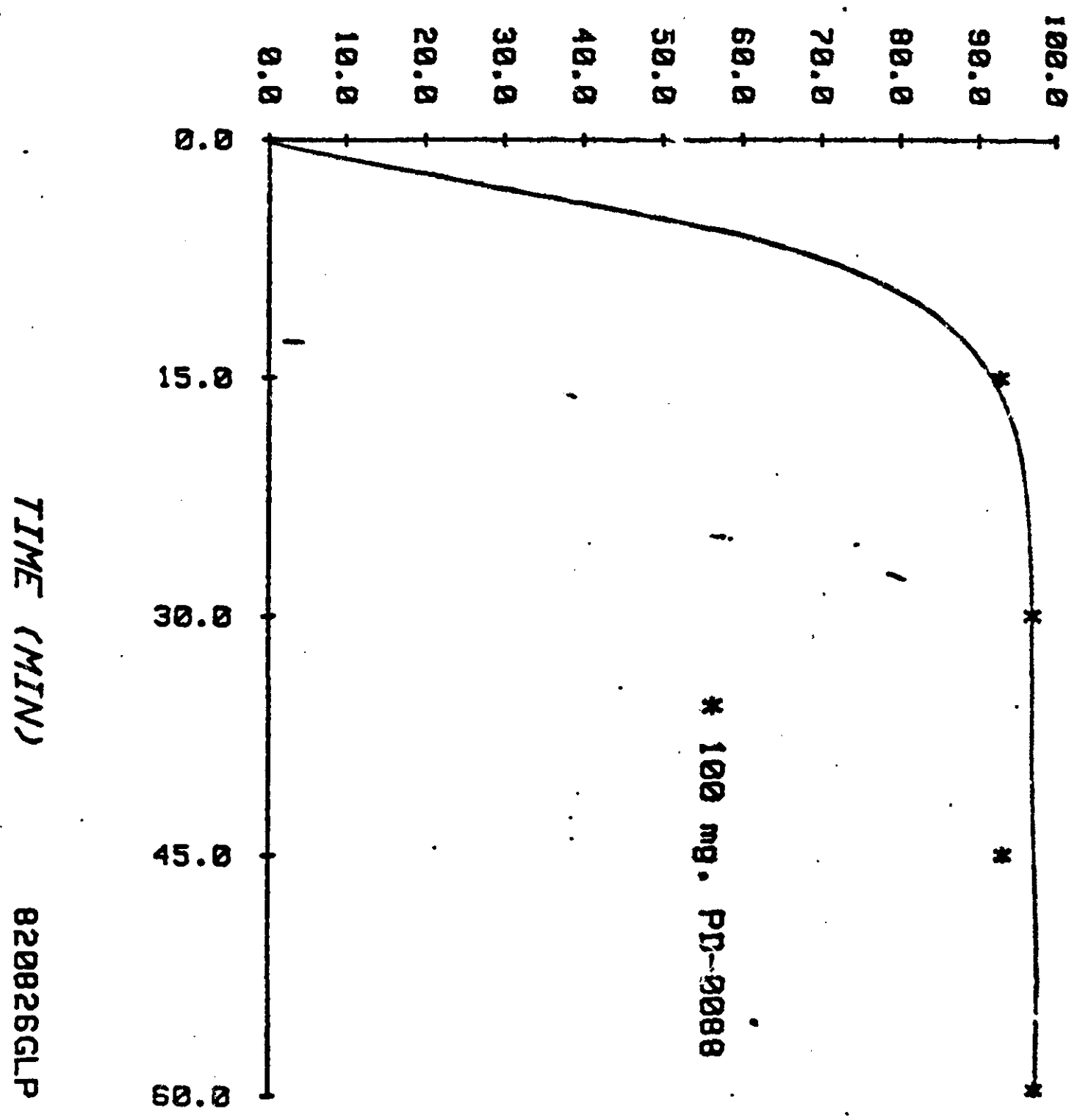
<u>Time</u> <u>(Minutes)</u>	<u>Individual Values</u> <u>% Dissolved</u>	<u>Mean</u>	<u>Range</u>	<u>N</u>
15		89.4		12
30		96.4		12
45		98.3		12
60		99.1		12

Table 5.4 DISSOLUTION DATA
 Mexitil^R Capsules 250 mg
 PD-0315

<u>Time</u> <u>(Minutes)</u>	<u>Individual Values</u> <u>% Dissolved</u>	<u>Mean</u>	<u>Range</u>	<u>N</u>
15		89.9		6
30		95.6		12
45		96.3		6
60		96.4		12

% DISSOLVED

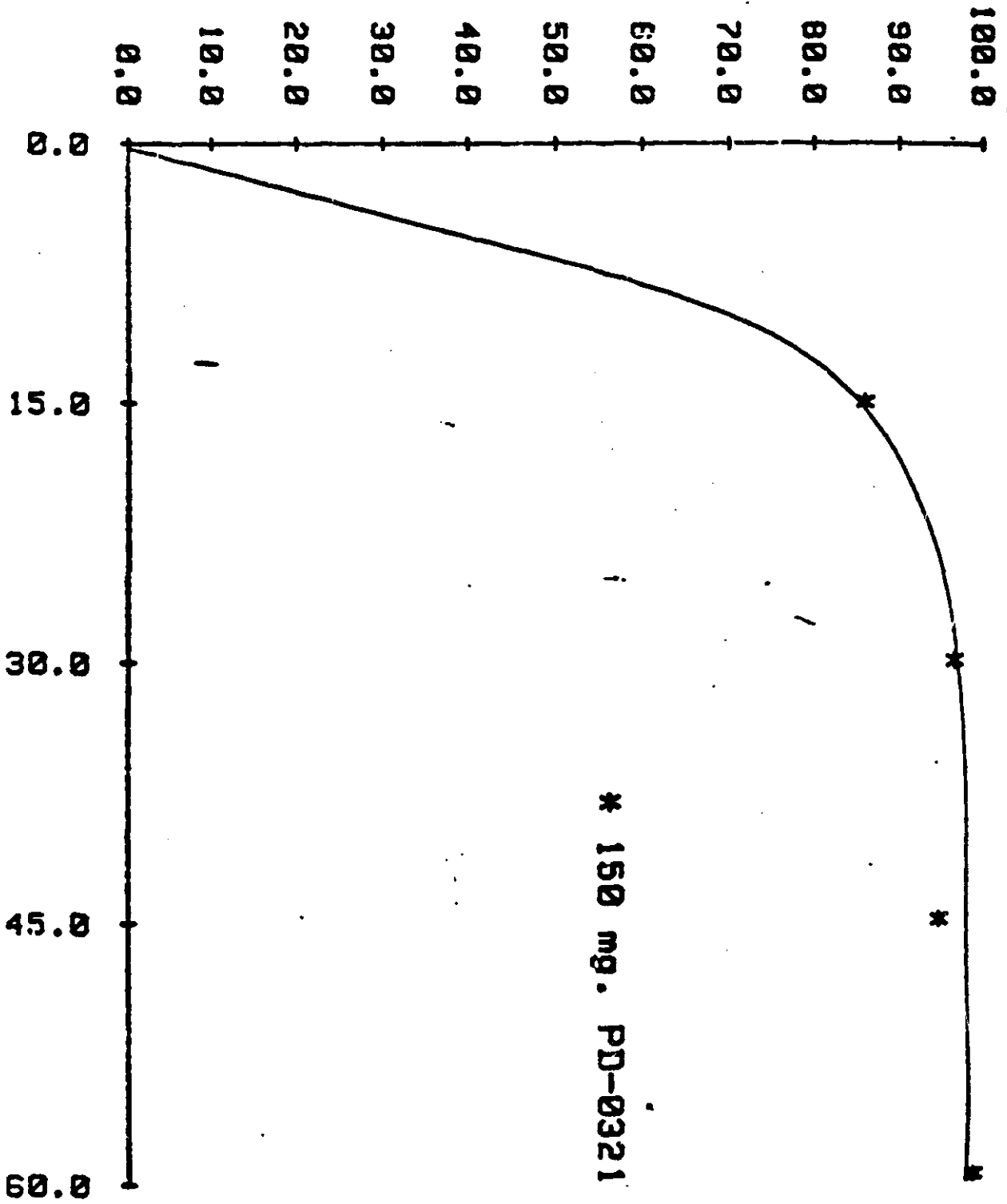
Fig 5.1 MEXITIL CAPSULE DISSOLUTION



TIME (MIN) 820026GLP

% DISSOLVED

Fig 5.2 MEXITIL CAPSULE DISSOLUTION



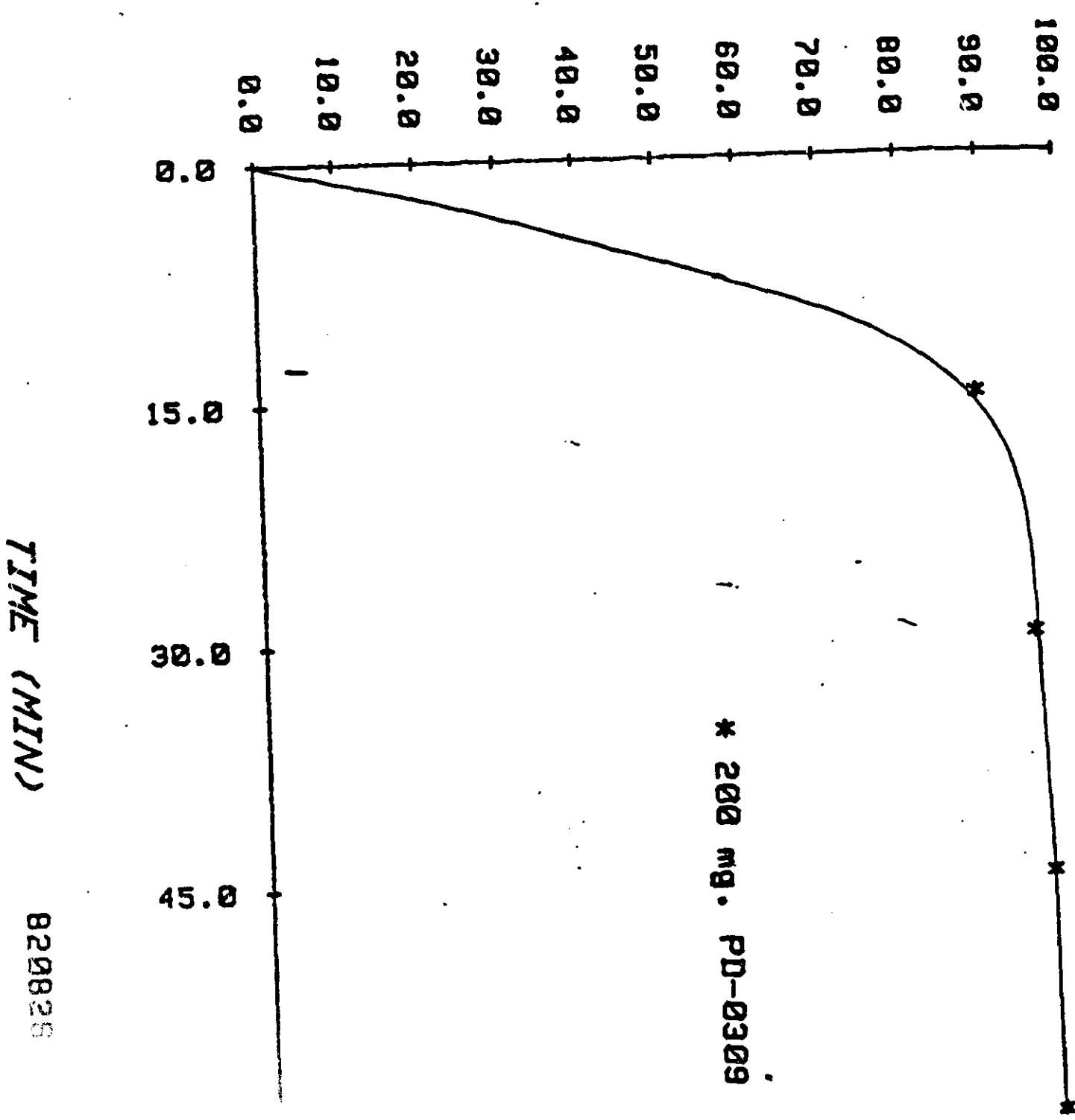
* 150 mg. PD-0321

TIME (MIN)

820826 GLP

% DISSOLVED

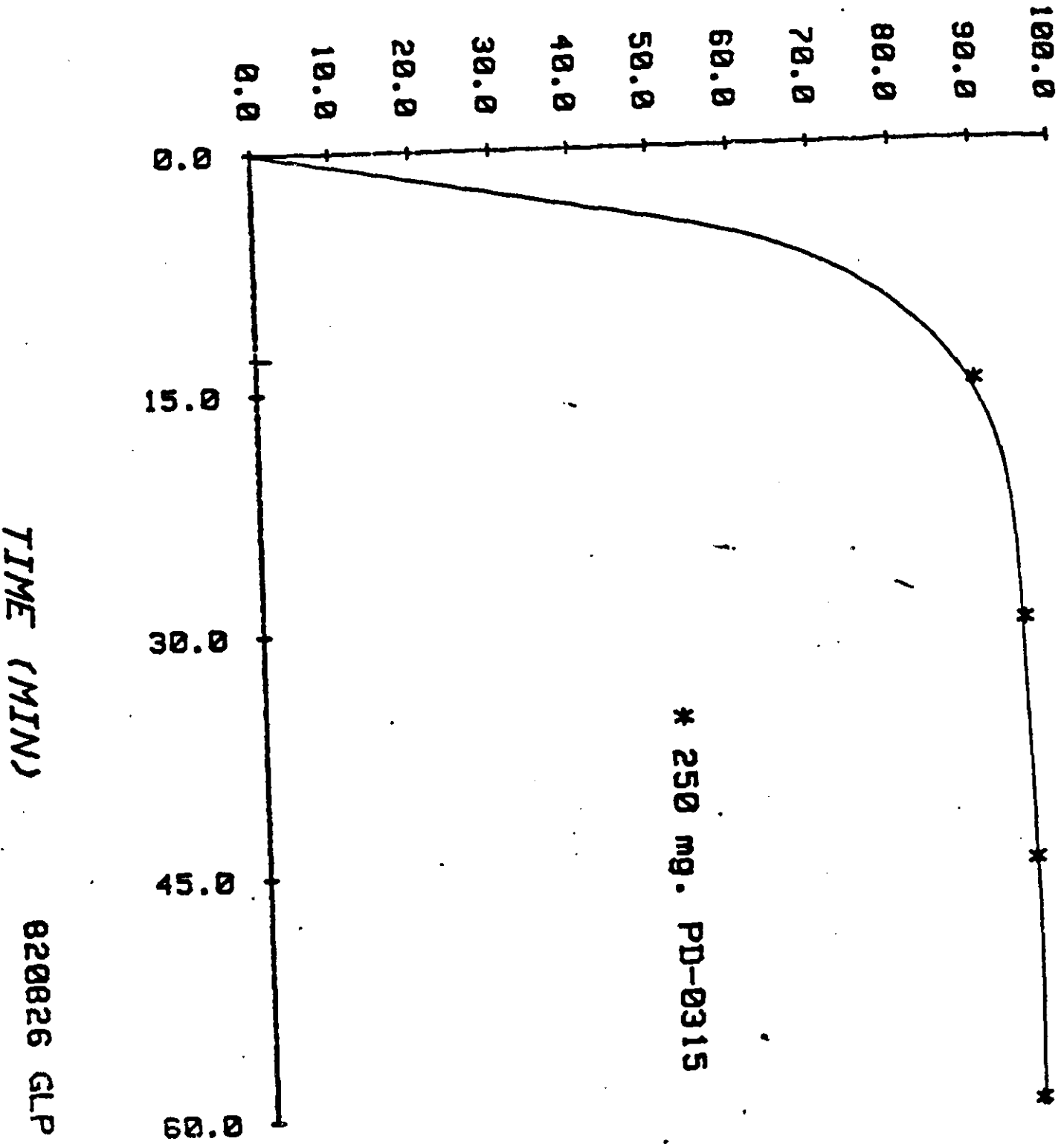
Fig 5.3 MEXITIL CAPSULE DISSOLUTION



TIME (MIN) 029825

% DISSOLVED

Fig 5.4 MEXITIL CAPSULE DISSOLUTION



% DISSOLVED

Fig 5.4 MEXITIL CAPSULE DISSOLUTION

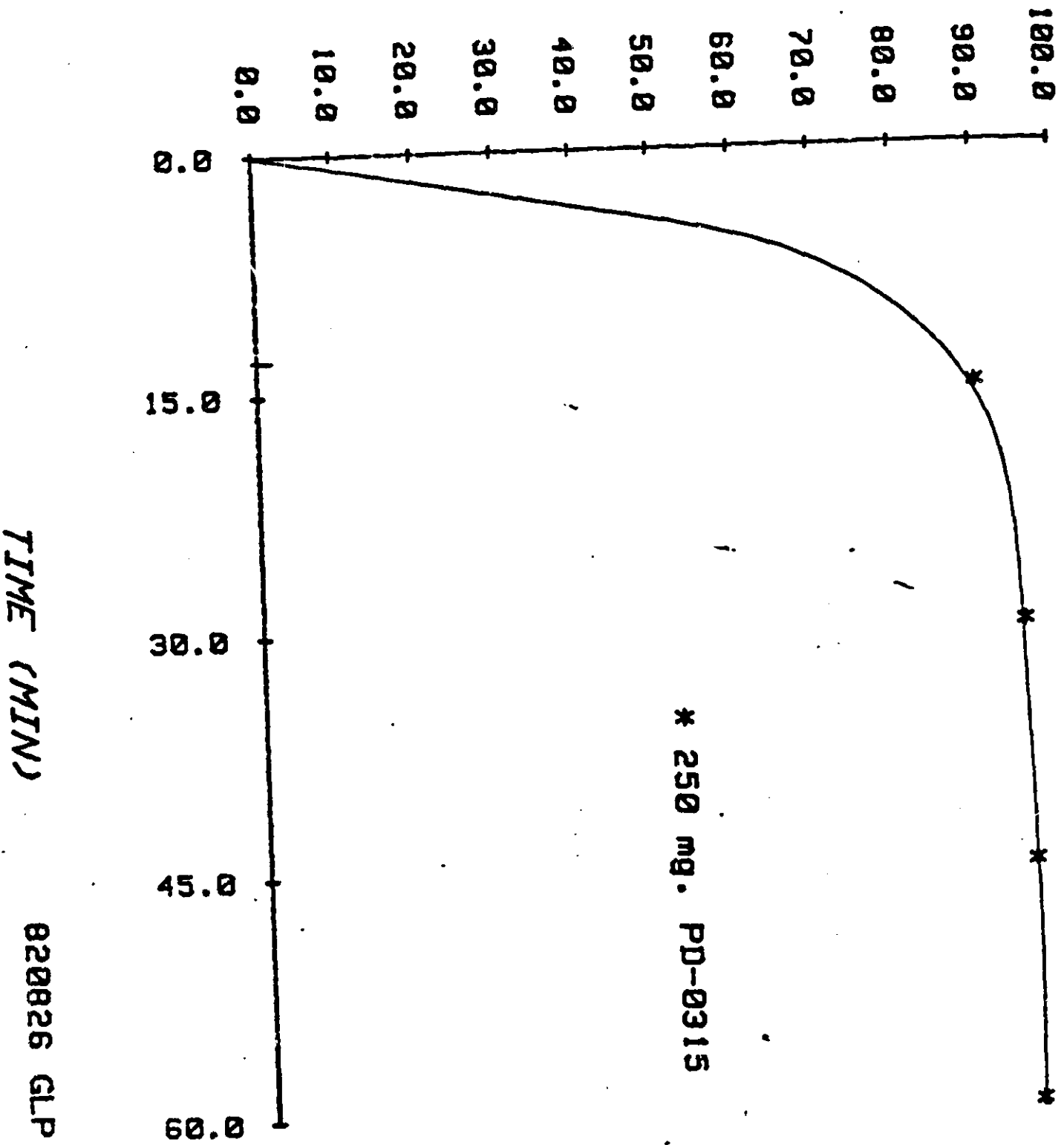


Table 6.1

COMPOSITION OF HEXITILE CAPSULES

Component	Proportion of Granulation %	Mg/Capsule			
		100 mg Capsule*	150 mg Capsule**	200 mg Capsule**	250 mg Capsule***
HEXILETINE HCl.	62.50	100.00	150.00	200.00	250.00
Corn Starch, NF	33.75	54.00	81.00	108.00	135.00
Colloidal Silicon Dioxide, NF	2.50	4.00	6.00	8.00	10.00
Magnesium Stearate, NF	1.25	2.00	3.00	4.00	5.00

*Size 2 hard gelatin capsule
 **Size 1 hard gelatin capsule
 ***Size 0 hard gelatin capsule

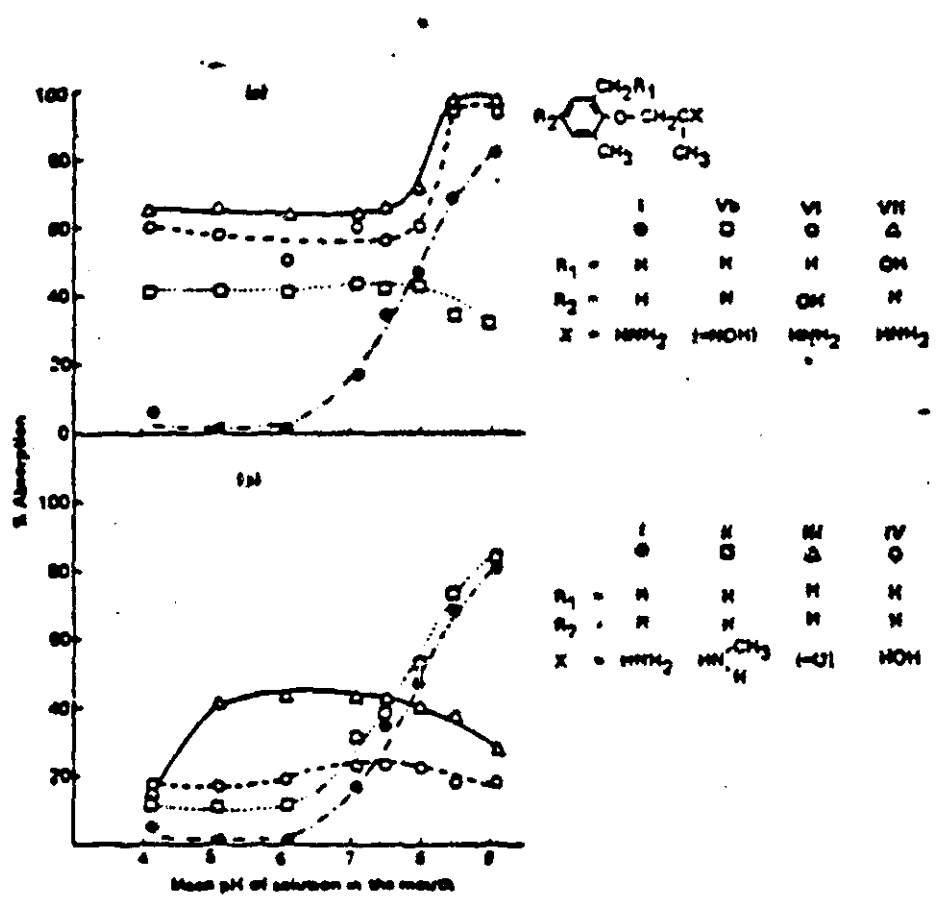


FIG. 7 (a) Buccal absorption of mexiletine (I) and its more polar metabolic basic products (Vb, VI & VII). (b) Buccal absorption of mexiletine (I) and metabolic products (II-IV) at different pH values.

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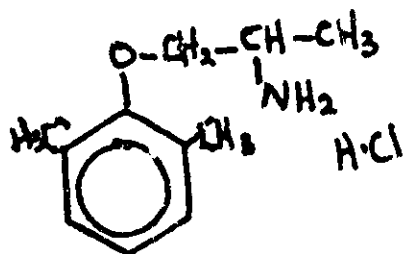
CF Review

NY 13 1985

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review and Evaluation of Manufacturing Controls Data
Chemist review #3

Date Completed: April 8, 1985

- A. 1. NDA#: NDA 18-873
Applicant: Boehringer Ingelheim
Address: 90 East Ridge
Ridgefield, Connecticut 06877
AF#: 43-827
2. Product Name(s):
Proprietary: MEXITIL
Nonproprietary: Mexiletine Hydrochloride
USAN: Mexiletine for base only
Compendium: None
Code Name and/or Number: Ko 1173 as hydrochloride
3. Dosage Form and Route of Administration:
Capsules: 50 mg purple/red body/cap 200 mg red/red body/cap
100 mg orange/red body cap 250 mg aqua green/red body/cap
150 mg caramel/red body/cap
Rx or OTC: Restricted to prescription use only.
4. Pharmacological Category and/or Principal Indications:
antiarrhythmic agent
5. Structural Formula and Chemical Name:
1-methyl-2-(2,6-xilyloxy) ethylamine hydrochloride
Empirical Formula: C₁₁ H₁₇ NO. HCl Molecular Weight: 215.712



- B. 1. Initial Submission: September 9, 1982
Resubmission October 3, 1984
2. Amendments: June 7, 1984 Not seen or reviewed
Revised mexitiline HCl
specifications
August 13, 1984-Manufacturing Controls
October 10, 1984-Manufacturing
controls-Stability
January 7, 1985-Medical and pharmacological
SBA
January 7, 1985-Revised Mexitil capsules
specifications
3. Supporting IND, NDA, DMFs, and Letters of Authorization:

C. Remarks:
Establishment Inspections- Not Quite Satisfactory

EIR requested October and November, 1982 for all facilities and received March 19, 1985. Boehringer Ingelheim KG, West Germany facilities used for synthesis of the new drug substance has not been inspected within the last two years. At the request of the applicant, the scheduled April 22, 23, 1985 inspection was postponed. EIR dated 7/82 is satisfactory.

Compliance memo dated March 28, 1985 approved the following facilities based on satisfactory inspections: Boehringer Ingelheim Ltd., Danbury, CN (EIR 3/83 drug product)

[REDACTED]

Page 3 NDA 18-873

Labels and Labeling- Not Quite Satisfactory

Request applicant to obtain a USAN name for mexitiline hydrochloride and use this official name on all labels and labeling. The USAN name mexitiline is for the base only.

Method Validation- Method Validation requested.

Manufacturing controls: Satisfactory with applicant commitment for the following:

Page 4 NDA 18-873

Conclusions and/or Recommendations:

Application is approvable from the standpoint of manufacturing control information upon receipt of applicant commitments to make the revisions or comments listed in section C Remarks. Applicant requested to respond to above comments on (March 19, 1985 telecon).

Kathleen E. Jongedky April 8, 1985
Reviewing Chemist

cc:
Orig:
✓ HFN-110
HFN-110/CSO
HFN-110/KJongedky 4/15/85
cb/4/15/85/0265v