Efficacy and Safety of Perhexiline Maleate in Refractory Angina

A Double-Blind Placebo-Controlled Clinical Trial of a Novel Antianginal Agent

Patricia L. Cole, MD, Andrew D. Beamer, MD, Noreen McGowan, RN, Catherine O. Cantillon, RN, Kathleen Benfell, RPh, Ralph A. Kelly, MD, L. Howard Hartley, MD, Thomas W. Smith, MD, and Elliott M. Antman, MD

Despite large gains in the medical and surgical treatment of angina pectoris in the past two decades, many patients are refractory to conventional medical therapy and are unsuitable for a first or, more commonly, repeat coronary revascularization procedure. We evaluated the efficacy of perhexiline maleate, a drug with an antianginal mechanism of action in humans that is as yet unknown, by using a randomized double-blind placebo-controlled crossover design in 17 patients with refractory angina who continued to receive maximal antianginal therapy, typically including nitrates, a β-blocker, and a calcium channel antagonist. In view of perhexiline’s potential for hepatic and neurological toxicity, plasma drug levels were monitored and maintained in the 150–600 ng/ml range. Sixty-three percent of patients were judged perhexiline responders by objective exercise testing criteria, as compared with 18% of patients on placebo (p<0.05). By blinded review of subjective measures of anginal frequency and severity, 65% of patients noted an improvement while on perhexiline, whereas no patient identified the placebo phase with improvement. Side effects observed in 29% of patients were minor and related to transient elevations of blood levels of more than 600 ng/ml; no patient suffered hemodynamic or cardiac conduction abnormalities attributable to perhexiline. With attention to the pharmacokinetics of perhexiline’s elimination in individual patients, this novel antianginal agent seems to be safe and effective and deserves further evaluation in patients already receiving maximal antianginal therapy who are not candidates for revascularization procedures. (Circulation 1990;81:1260–1270)

During the last 20 years, we have witnessed a dramatic increase in the range of therapeutic options, both medical and surgical, for the treatment of angina pectoris. The size of that subgroup of patients who remain refractory to conventional therapeutics progressively declined as each new class of antianginal drugs or surgical approach was introduced. Nevertheless, even now in the 1990s, most clinicians can identify in their practice patients who are not surgery or angioplasty candidates and whose frequency of anginal episodes is poorly controlled on maximal medical therapy. The reemergence of anginal symptoms in previously revascularized coronary artery bypass patients who are not candidates for a second or third operation suggests that this subgroup of patients will not decline but, rather, might increase in the future.

“Maximal medical management” for angina pectoris in contemporary practice consists of the judicious use of nitrates, β-adrenergic receptor blockers, and calcium channel blockers, in addition to an antiplatelet agent (usually aspirin) and, with a view to the long term, a lipid-lowering regimen. For patients with refractory symptoms or patients intolerant of one of these major classes of drugs, the therapeutic options, particularly in the United States, are limited. Ironically, a drug introduced in Europe nearly 20 years ago might provide a safe and effective adjunct to the modern treatment of angina.1

Perhexiline maleate gained a reputation for efficacy in the medical management of angina in the

From the Cardiovascular Division, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts.

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Address for correspondence: Elliott M. Antman, MD, Cardiovascular Division, Brigham and Women’s Hospital, 75 Francis Street, Boston, MA 02115.

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1970s and seemed to have no significant effect on myocardial contractility or on hemodynamics.\textsuperscript{2--11} It was also found, however, to cause infrequent but unpredictable serious hepatic and neurological toxicity.\textsuperscript{10--14} Despite its effectiveness, use of the drug had become limited in the early 1980s, in part because of its toxicity but also because of marketing decisions by its manufacturers. Originally labeled as a calcium antagonist although the experimental evidence was far from clear that this was its clinically relevant mechanism of action in humans, the incentive for marketing perhexiline declined as less toxic calcium channel blockers were developed.

Within the past decade, however, it has become evident that toxicity is directly related to perhexiline blood levels and that the drug has a saturable rate of hepatic metabolism that is genetically determined. A subset of patients demonstrates saturable clearance of the drug at standard therapeutic doses, in some cases leading to a dramatically lengthened elimination half-life.\textsuperscript{2,13,15} With the advent of straightforward and reliable methods for quantifying blood levels of perhexiline,\textsuperscript{16--18} individualization of dosing has led to a pronounced decrease in the incidence of serious side effects.\textsuperscript{15,17}

Therefore, to investigate rigorously the safety and efficacy of perhexiline, a prospective randomized double-blind placebo-controlled crossover trial was initiated. Its purposes were twofold, as follows: 1) to study the efficacy of perhexiline as an antianginal therapy when added to the existing medical regimen in patients whose symptoms were refractory to other therapeutic modalities, and 2) to determine whether drug-related side effects could be minimized and antianginal efficacy maintained when the dosage of perhexiline was adjusted to maintain plasma levels in the proposed therapeutic range of 150--600 ng/ml.\textsuperscript{15}

**Methods**

**Study Design**

This was a double-blind randomized crossover trial in which patients served as their own controls. Baseline measurements were made as described herein. Patients were then randomly assigned to receive either placebo or perhexiline for an initial 3-month period. At the conclusion of 3 months, end-point measurements were made, and the patient was crossed over to receive the alternative medication (perhexiline or placebo). One physician (E.M.A.) remained unblinded and used the results of the perhexiline assay to adjust drug dosage to maintain perhexiline blood levels in the therapeutic range (150--600 ng/ml) suggested by Horowitz et al.\textsuperscript{15} When it was necessary to adjust the dose of active drug, this physician "informed" the patient of the change through one of the blinded physicians or study nurses although placebo dosages were carefully adjusted in a similar manner so as to maintain the double-blind nature of drug administration.

**Entry Criteria**

The study population consisted of patients who were referred by cardiologists from the medical service, coronary care unit, or outpatient cardiology practice at Brigham and Women’s Hospital and who were suffering from refractory angina pectoris. All patients were required to have diagnostic evidence of significant coronary artery disease at coronary arteriography, a documented history of acute myocardial infarction (by electrocardiographic or enzyme criteria, or both), or both the diagnostic evidence and the documented history. Additionally, all patients had recurrent episodes of chest discomfort typical of myocardial ischemia (retrosternal or upper extremity discomfort, or both, relieved by sublingual nitrates) despite medical therapy with a combination of \( \beta \)-adrenergic receptor blockers, nitrates, and calcium channel blockers that, in the opinion of the treating cardiologist, had been advanced to the maximum-tolerated doses. Maximum-tolerated therapy was defined as the highest doses of \( \beta \)-blockers, nitrates, and calcium antagonists used in combination that did not produce symptomatic bradycardia, hypotension, or congestive heart failure. Patients also had coronary anatomy that rendered them unsuitable candidates for initial or repeat coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty.

**Exclusion Criteria**

Patients were excluded if one or more of the following conditions were present: suboptimal medical therapy; Q wave myocardial infarction during the preceding 3 months; severe left ventricular failure (New York Heart Association class III or IV); hemodynamically significant valvular disease, hypertension (systolic blood pressure, <85 mm Hg), or hypotension (systolic or diastolic pressures, >210 and >120 mm Hg, respectively); evidence of severe renal (creatinine, >2.5 mg/dl) or hepatic (SGOT, >50 units/l and bilirubin, >2.0 mg/dl) dysfunction, brittle insulin-dependent diabetes mellitus; or known peripheral neuropathy.

All patients were enrolled with the approval of their primary physician, and all patients signed an informed consent statement using the guidelines set forth by the hospital’s Committee for the Protection of Human Subjects.

**Study Protocol**

Before randomization, all patients underwent a detailed history and physical examination by one of the investigators (P.L.C. or A.D.B.), including a screening neurological exam. Baseline laboratory measurements included serum electrolytes, blood urea nitrogen, creatinine, glucose, liver function tests, uric acid, and a complete blood count. Additionally, a chest radiograph and electrocardiogram were performed.

All patients had previously undergone exercise tests and were familiar with the standard procedures
TABLE 1. Characteristics of Study Group

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>MI (n)</th>
<th>CAD (vessels)</th>
<th>EF (%)</th>
<th>CABG (n ops)</th>
<th>Grafts (n)</th>
<th>PTCA (n)</th>
<th>β-blk (mg/day)</th>
<th>TNG (mg/day)</th>
<th>CCBA 1 (mg/day)</th>
<th>CCBA 2 (mg/day)</th>
<th>Dig (mg/day)</th>
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<td>SD</td>
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<td>13.1</td>
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MI, myocardial infarction; CAD, coronary artery disease; EF, left ventricular ejection fraction; CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty; β-blk, β-blocker; TNG, calcium channel blocking agent; Dig, digoxin; A/C, anticoagulants; ops, operations; ISDN, isosorbide dinitrate; DZ, diltiazem; Warf, warfarin; Thy, thyroid; Aten, atenolol; NIF, nifedipine; Fur, furosemide; Dipy, diprydiamole; Prop, propranolol; Tr/HCTZ, triamterene/hydrochlorothiazide; ASA, aspirin; Mfopa, methyl dopa; Chlor, chlorpropamide; Nico, nicotinic acid; Metop, metoprolol; VER, verapamil; Tolb, tolbutamide; Capt, captopril; Cholest, cholestyramine.

in the exercise laboratory used during the trial. All patients underwent maximum symptom-limited graded exercise testing using a bicycle ergometer, except in one case where an arm ergometer was used. The initial exercise load for all tests was 5 W, and the load was increased by 10–20 W every 5 minutes. For each patient, the identical protocol was used during the baseline test, at the end of the 3-month perhexiline-phase exercise test, and at the end of the 3-month placebo-phase exercise test.

In addition to the above information, patients were asked to complete a specific-activity scale questionnaire that helped to quantify exercise capacity and activity level.18,19 Patients were also asked to keep a detailed diary of anginal episodes, including frequency and duration of angina, precipitating events, and consumption of sublingual nitroglycerin.

Drug Administration

After baseline data were collected, patients were randomly assigned by a research pharmacist (K.B.) to receive either perhexiline or placebo. The initial dose of perhexiline was 100 mg p.o. daily for 3 days and 100 mg p.o. twice daily thereafter. Placebo tablets identical to perhexiline were supplied by Merrell Dow Pharmaceuticals Inc. (Cincinnati, Ohio), and the placebo was dosed in a manner similar to active drug. Beginning at 1 week and then at approximately 2–4-week intervals, "study drug" blood levels were measured and dosage adjusted accordingly by the unblinded physician.

At the end of the initial 3-month period, a complete physical examination, including neurological evaluation, electrocardiogram, and the laboratory measurements previously noted, was repeated. Additionally, each patient underwent a repeat interview and assessment of subjective response, performed a repeat exercise tolerance test, and had a study drug blood level drawn. The groups were then cross-over to the other medication, dosing was initiated in a manner similar to the initial 3-month period, and serial blood level determinations were obtained. At the end of this second 3-month block, the physical examination, electrocardiogram, and laboratory measurements were repeated, and patients again underwent an assessment of subjective response, an exercise tolerance test, and a final drug level determination.

Assay

Perhexiline maleate levels in plasma or serum were measured using the technique described by Horowitz et al16 with minor modifications. Plasma samples spiked with hexadine HCl as an internal standard were extracted in hexane, dried, reconstituted in a sodium bicarbonate buffer, and derivatized with dansyl chloride exactly as previously described.16 Chromatography was performed in 3-μm reverse-phase Radial-Pak cartridges (Waters Chromatography Div., Millipore Corp., Milford, Massachusetts) using isocratic (100% methanol) conditions, with detection by a fluorescence detector using 360- and 510-nm excitation and emission filters. Perhexiline maleate
TABLE 1. Continued

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<th>Diuretics (dose/day)</th>
<th>Vasodil (dose 3/day)</th>
<th>A/C</th>
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<td>Thy USP</td>
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<td>Dipy, ASA</td>
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<tr>
<td></td>
<td>Capt37.5</td>
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<td>Insulin</td>
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</table>

standards and hexadiline HCl were donated by Merrell Dow Pharmaceuticals Inc. The limit of detection was 1 ng perhexiline/ml plasma. The coefficient of variation of perhexiline 250 ng/ml added to blank plasma samples and analyzed over a 1-month period was 9.4% (n=12), and that of replicate samples performed on the same day was 1.7% (n=5). The use of 3-μm radial compression cartridges allowed excellent resolution with rapid separation (12 minutes) at low column pressures.

Criteria for Antianginal Efficacy

Definitions of drug efficacy were established before initiation of the trial and included assessment of both objective and subjective responses. Objective evidence of drug efficacy was defined as the fulfillment of one or more of the following criteria as compared with baseline exercise testing: 1) the absence of angina at an equivalent workload; 2) the absence of angina at an equivalent exercise duration; 3) an increase of more than 20% in peak exercise workload; or 4) increase of more than 20% in peak exercise duration. If a patient met any of these criteria, he or she was classified as a responder. Categories 3 and 4 were deemed necessary criteria in case a patient did not have angina during baseline exercise testing.

Subjective criteria for efficacy were established by a review of angina diaries, nitroglycerin consumption assessments, and a specific-activity scale by both the patient and a study physician (P.L.C. or A.D.B.), each of whom remained blinded to the assigned sequence of therapies. A determination was made regarding which of the two 3-month periods, if either, resulted in a significant reduction in the frequency or severity, or frequency and severity, of angina and requirement for nitroglycerin. Patients were classified as responders based on subjective criteria if the blinded review identified a 3-month period that was clearly superior to the interval on the alternative medication.\textsuperscript{18,19}

Statistical Analyses

Statistical analyses were performed to compare the proportion of patients classified as responders based on the pretrial definitions of objective or subjective criteria for efficacy as noted previously during the various treatment phases. Because the drug responses in individual patients represented paired data measured on a nominal scale, the proportion of responders during the perhexiline phase and during the placebo phase were entered into a 2×2 contingency table and analyzed using the McNemar test with Yates' correction for continuity.\textsuperscript{20} The 95% confidence intervals (95% CI) for the proportion of patients responding during each treatment phase were determined from standard statistical tables of confidence limits of the binomial distribution.\textsuperscript{21} Group results for continuous variables are presented as mean±1 SD. Comparisons between group means were performed with a two-tailed paired \textit{t} test. Because of the crossover nature of the trial design, an analysis of variance (ANOVA) with repeated measures was performed to examine the effect of drug administration on exercise performance. Results of all analyses were considered statistically significant when \textit{p} values were less than 0.05.

Results

Clinical Characteristics of Study Group

A total of 19 patients (13 men and six women) were enrolled during an 18-month period (Table 1). Two patients initially enrolled did not complete the study, one because of an intercurrent myocardial infarction, and one because of a fractured leg (while on placebo) that precluded exercise testing. Seventeen patients completed the study and form the basis of this report. They had a mean age of 65±9.4 years (range, 43–81 years), and they had suffered a mean of 1.19±0.7 myocardial infarctions before enrollment. Sixteen of these 17 patients had undergone coronary arteriography, and 13 patients had undergone previous coronary artery bypass surgery (three of them twice). All patients were on combination antianginal therapy; 14 patients were on \textbeta-blockers, 15 were on long-acting nitrates, and 14 were on calcium channel blockers (three patients were on two calcium channel blockers). Other medications included digoxin (four patients); diuretics (eight patients); vasodilators (two patients); aspirin, dipyriramole, or both (11 patients); and insulin (three patients). Three patients were receiving lipid-lowering agents.
Objective Criteria for Drug Efficacy (Exercise Tolerance Testing)

All 17 patients completed each of the three exercise tests. In the case of patient 12, the baseline test was terminated after 540 seconds because of the development of progressive hypotension and fatigue. This was judged to be a result of having taken his maintenance antianginal medications within 30 minutes of exercise. During the perhexiline and placebo phases, peak exercise durations were 1,080 and 1,020 seconds, respectively, when the same antianginal medications were taken more than 2 hours before exercise testing. Because of the noncomparable clinical circumstances present during the three tests, this patient’s exercise data were excluded from analysis, although the results are reported in Table 2.

During baseline exercise testing, 10 of 16 patients experienced angina at an exercise load of 29±28 W (5–90 W), which developed at 520±312 seconds (range, 180–1,020 seconds) of exercise. The mean peak exercise load achieved by the group was 38±35 W at a peak exercise duration of 662±386 seconds. The six patients who did not experience angina in the baseline exercise test all had their test stopped because of fatigue.

During the exercise test performed at the conclusion of the perhexiline phase of treatment, seven of the 10 patients who experienced angina during the baseline exercise test were able to exercise to at least the same exercise load, duration, or both as during the baseline test without experiencing angina. As compared with the baseline exercise test, seven of 16 patients achieved at least a 20% increase in peak exercise duration. Based on the pretreatment definition of a positive exercise response, 10 of 16 patients (63%; 95% CI, 35–82%) were classified as responders to perhexiline. The peak exercise load achieved by the group was 42±35 W and peak exercise duration was 675±322 seconds (p=NS, as compared with baseline). One of the six nonresponders (patient 2 in Table 2) during the perhexiline phase had undetectable drug levels while on active treatment.

During the exercise test performed at the conclusion of the placebo phase of treatment, two of 16 patients were able to exercise to at least the same exercise load, duration, or both as during the baseline test without experiencing angina. Compared with the baseline exercise test, three of 16 patients achieved at least a 20% increase in peak exercise duration. Based on the pretreatment definition of a positive exercise response, three of 16 patients (18%; 95% CI, 5–43%) were classified as responders to placebo. The mean peak exercise load achieved by the group was 36±36 W, and peak exercise duration

### Table 2. Summary of Subjective and Objective Responses to Perhexiline and Placebo

<table>
<thead>
<tr>
<th>Patient</th>
<th>Drug order</th>
<th>Double-blind diary review</th>
<th>Baseline ETT</th>
<th>Perhex ETT</th>
<th>Plac ETT</th>
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<tbody>
<tr>
<td></td>
<td>Perhex</td>
<td>Plac</td>
<td>Onset of angina (W) (sec)</td>
<td>Peak exercise (W) (sec)</td>
<td>Onset of angina (W) (sec)</td>
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Drug order, number indicates which 3-month block was randomized to perhexiline.
Criteria for drug response as compared with baseline exercise testing, as follows: a, absence of angina at equivalent workload; b, absence of angina at equivalent exercise duration; c, increase of >20% in peak exercise workload; d, increase of >20% in peak exercise duration.
ETT, exercise tolerance test; Perhex, perhexiline; Plac, placebo.
*Undetectable drug levels while on active treatment. †Initial workload during test was 30 W.
was 577±316 seconds (p=NS, as compared with baseline).

To control for the effects of multiple exercise tests, the effects attributed to the natural history of the disease and the placebo effect, the exercise test responses during the perhexiline and placebo phases were each compared with the baseline exercise test (Figure 1). Applying the criteria of a positive exercise response as compared with baseline if no angina occurred at an equivalent exercise load or duration and/or a 20% increase in peak exercise load or duration was achieved, the proportion of individuals responding to perhexiline was significantly greater than that observed during placebo (p<0.05) (Figure 1). Restricting the definition of a positive exercise response as compared with baseline to the absence of angina at an equivalent exercise load or duration, the proportion of individuals responding to perhexiline was also significantly greater than observed during placebo (p<0.05). Restricting the definition of a positive exercise response as compared with baseline to at least a 20% increase in peak exercise load or duration, there was a trend toward a greater proportion of responders on perhexiline as compared with placebo, although this did not achieve statistical significance (p<0.25). The analysis of variance with repeated measures did not reveal any significant relation between the order of drug administration and any of the indices of exercise performance previously discussed. There was no statistically significant difference in the rate-pressure product at rest (before exercise) or at peak exercise duration among the baseline, perhexiline, and placebo exercise tests (p=NS, by ANOVA). Finally, there was no evidence of a period effect for either the objective or subjective responses, suggesting a lack of any significant alteration in the patients’ conditions attributable to the passage of time.  

Subjective criteria of efficacy. Based on a double-blind review of angina diaries, nitroglycerin consumption estimates, and the specific-activity scale, 11 of 17 (65%; 95% CI, 41–83%) were able to identify a treatment phase associated with subjective improvement, whereas six patients were unable to distinguish between the two treatments. In all 11 cases where definite subjective improvement occurred during one of the treatment phases, the patients were receiving perhexiline. Thus, no patients identified the placebo phase as the period during which they had subjective improvement. The proportion of responders based on subjective criteria was, therefore, significantly greater during the perhexiline phase as compared with the placebo phase (p<0.005) (Figure 1).

Side effects. Five of 17 (29%) patients developed side effects, as follows: Four patients developed transient ataxia; additionally, there were two episodes of temporary nausea, one episode of dizziness, and one patient developed Beau’s lines (horizontal streaking of the nailbed). All of these side effects were mild, occurred while under treatment with active drug, were associated with blood levels of drug transiently in excess of 600 ng/ml, and resolved in 2 weeks or less with reduction of the maintenance dose of perhexiline and the ensuing decrease in perhexiline blood levels. No patient developed other subjective side effects previously attributed to perhexiline such as anorexia, weakness, changes in visual acuity, rash, or weight loss. During the course of the study, no significant deviations from baseline measurements occurred in serum creatinine, blood urea nitrogen, alkaline phosphatase, bilirubin, glucose, or AST. During the course of the study, no patients developed symptomatic bradycardia, hypotension, decompensation of left ventricular function, or worsening of ventricular arrhythmias.

Pharmacokinetics of perhexiline in study group. All patients were started on a dose of perhexiline 100 mg p.o. daily for 3 days, followed thereafter by 100 mg p.o. twice daily. Sixteen of 17 patients (94%) required an alteration in the maintenance dose of
perhexiline during the 3-month period based on the results of blood level determinations. Thirteen patients required a lower maintenance dose to maintain perhexiline blood levels between 150–600 ng/ml; on average, the lowering of dosage occurred on day 27. Three patients required an increased dose to maintain blood levels in the desired range. The mean daily dose during the 3-month period of treatment with perhexiline was calculated for each patient, and ranged widely at 23–278 mg/day (mean, 135±79 mg/day) (Figure 2).

While monitoring for side effects or making adjustments to the maintenance dose of perhexiline, or both, sufficient specimens were obtained in 11 of 17 patients to permit estimation of the half-life of the terminal phase of drug elimination. The range of half-lives was 35–864 hours and exhibited a bimodal distribution. The terminal phase in all individuals, except patients 1 and 13, had a half-life of less than 144 hours; the terminal phase in the remaining two patients had half-lives of 402 and 864 hours, respectively (Figure 3).

Figure 4 illustrates the necessity for careful monitoring of perhexiline blood levels. The left panel depicts the results of serial perhexiline blood level determinations in patient 1 (a presumed poor metabolizer) who had a prompt rise in levels to nearly 2,500 ng/ml in less than 1 week of treatment. No further perhexiline was administered until study day 90 when the blood level had declined back to the desired range. The estimated terminal half-life of excretion of perhexiline calculated from the data between day 50 and day 100 was 864 hours. The right panel depicts the results of drug-level monitoring in patient 12 (a presumed extensive metabolizer) who received progressive increases in the daily dose of perhexiline to maintain blood levels of 150–600 ng/ml. Dosing with perhexiline was terminated on day 90 according to the protocol, allowing an estimation of the terminal half-life of excretion at about 36 hours. Neither patient experienced drug-related side effects during perhexiline treatment. Both cases demonstrate the value of therapeutic drug monitoring because the presence of initially unacceptably high or low levels and the slowly progressive rise in levels over time would not have been suspected clinically before the emergence of an adverse reaction.

Discussion

This report provides strong evidence that perhexiline maleate administration results in an incremental improvement in patients with refractory angina pectoris.
already receiving maximal medical therapy. Although there was little doubt of the drug’s efficacy in untreated or minimally treated angina patients based on studies performed in the 1970s, this is the only study using a double-blind placebo-controlled crossover design to document efficacy and safety when perhexiline was added to maximally tolerated doses of a conventionally prescribed contemporary drug regimen. The study population was treated more aggressively with standard antianginal therapeutic modalities than in any other previously reported clinical trial of perhexiline and included a number of patients who had already undergone one or more coronary artery bypass or angioplasty procedures.

Perhexiline was used with a negligible impact on the hemodynamic profile of individual patients. No exacerbations of congestive heart failure or conduction disturbances developed despite the fact that the drug was administered in conjunction with β-adrenergic receptor antagonists and calcium channel blocking drugs. The absence of any deleterious interaction with the latter class of drugs is particularly relevant, considering 70% of patients were receiving verapamil, diltiazem, or both, when prescribed perhexiline.

**Efficacy**

Although subjective evaluations of a drug’s antianginal effectiveness as compared with placebo can be reliable if both patient and examining clinician are blinded as in this study, we felt that an objective measure of perhexiline’s efficacy was necessary as well, particularly because the patients were also receiving a number of other antianginal medications concurrently. Based on the pretial criteria for establishing drug efficacy, 63% of the patients improved their bicycle ergometer performance while receiving active drug, as judged by a blinded investigator (P.L.C. or A.D.B.), as compared with just 18% in the placebo phase (p<0.05). The fact that there were no significant changes in the group means for exercise test performance during the perhexiline or placebo phase versus baseline testing seems to reflect the considerable interindividual variability in the response to exercise, as indicated by the magnitude of the standard deviations.

Criteria 1–4, noted in “Methods,” were selected as measurement end points for objective evidence of drug efficacy because the elimination of angina with exercise or the increase in workload tolerated during exercise are clinically meaningful drug responses. Other criteria, such as the rate-pressure products at onset of angina or 1 mm or more ST segment depression, were not selected as objective end points because previous drug trials with β-blockers and calcium antagonists failed to show a consistent drug-related increase in double product at the onset of ischemia. The majority of the drug benefit reported in these cases seemed to be related to an increase in working capacity before the development of ischemia. Because we anticipated that many patients who would meet the entry criteria for this trial would have an abnormal baseline electrocardiogram or be receiving medications that would obscure the interpretation of ST segment deviation with exercise, or both, the time to onset of 1 mm or more ST segment depression was also not selected as a measurement end point.

It is possible that a residual perhexiline effect after the crossover to placebo phase might have obscured a more pronounced perhexiline effect in patients who randomly received active drug first. We believe, however, this is unlikely for several reasons. Based on the estimated half-life of excretion of the drug, even individuals with the lowest clearance rates would have had undetectable perhexiline plasma levels within 3 months after crossover at the time of the final exercise test. All patients had undetectable perhexiline levels during the placebo phase. Furthermore, by ANOVA, there was no effect of the order of drug administration on exercise performance.

Using subjective measures of efficacy including angina diaries and estimates of sublingual nitroglyc-
Pharmacokinetics of cations when the dosage was 1,170 required any adjustment of line angina during the treatment of perhexiline consumption convincing. Sixty-five levels regimens sponded to able patients in the perhexiline phase, whereas none noted an improvement in symptoms during the placebo phase (\(p<0.005\)). No patient reported a worsening of baseline angina during the treatment phase that corresponded to therapy with perhexiline, and none required any adjustment of other antianginal medications during the active drug phase. This remarkable difference in the patients’ blinded subjective assessment of drug efficacy is noteworthy, considering the complexity and severity of most patients’ underlying coronary disease in this study and their intensive regimens of other concomitantly administered antianginal agents.

Safety

The results of the present investigation support the conclusions of Horowitz et al.\(^{15}\) based on evidence from an uncontrolled long-term study of a patient population similar to ours, that therapeutic efficacy can be maintained with a minimum of toxicity when dosage is adjusted to maintain plasma levels within a range of 150–600 ng/ml. In our study, side effects attributable to the drug were relatively minor, were related to transient elevations in plasma perhexiline levels to more than 1,000 ng/ml, and disappeared when the dosage was adjusted to bring plasma levels within the therapeutic range.

In the report by Horowitz et al\(^{15}\) concerning 18 patients with refractory angina given 50–400 ng of perhexiline daily with dose determined by relief of symptoms rather than by any arbitrary therapeutic range of plasma levels, 74% of patients either became asymptomatic or had a clear reduction in angina frequency but an unacceptable 47% developed hepatic or neurological toxicity. The average maximal perhexiline plasma level in these patients was 1,170 ng/ml overall, and 1,281 ng/ml in patients developing side effects. Importantly, no patient in this group developed side effects during as long as 27 months of drug therapy if plasma levels were below 700 ng/ml. When these investigators studied a second group of 19 patients whose plasma drug levels were maintained below 600 ng/ml, no clinical or biochemical evidence of toxicity attributable to perhexiline developed during durations of treatment lasting up to 42 months. Our study supports the recommendation of Horowitz et al\(^{15}\) that the therapeutic range be limited to 150–600 ng/ml.

Pharmacokinetics of Perhexiline Elimination

Perhexiline is rapidly absorbed from the gastrointestinal tract after oral administration and is excreted in urine and stool as the parent compound plus its more water-soluble metabolites, mono- and dihydroxyperhexiline. Bioavailability is variable, in the range of 52–95%.\(^{10}\) The elimination half-life of perhexiline has been reported to be in the range of 2–5 days for most patients, although the clearance rate is widely variable and nonlinear with respect to dosage.\(^{12}\) Importantly, hepatic metabolism has been demonstrated to be saturable at “therapeutic” doses of the drug. For a small subset of patients receiving perhexiline, nominally classified as “poor hydroxylators” who have a genetic defect in the metabolism of perhexiline and of other drugs, saturation of hepatic metabolism and a switch from first-order to zero-order elimination kinetics occurs at relatively low doses of the drug.\(^{12,17}\) These patients can have dramatically lengthened elimination half-lives once the hepatic metabolic threshold is exceeded, as illustrated by our patient 1 (Figure 4, left panel), in whom the perhexiline elimination half-life was longer than 5 weeks. These patients seem to be at greatest risk for toxicity.

Perhexiline undergoes classic “phase I” oxidative metabolism in the liver by a specific isoform of the cytochrome P-450 family of related enzymes. Knowledge of the molecular biology of the P-450 enzymes has rapidly expanded in the last several years and is the topic of several recent extensive reviews.\(^{27,29}\) The specific P-450 enzyme responsible for perhexiline metabolism is now known to be a member of the type II, class D family, denoted P-450\(_{1b1}\).\(^{30–32}\) The subscript “db1” refers to “debrisoquine type 1,” after the now rarely used sympatholytic antihypertensive drug that, in very low doses, serves as a useful agent to determine hydroxylator phenotype in humans.\(^{33–35}\)

This enzyme is also responsible for the initial metabolism of many other drugs, including many of the newer type Ic antiarrhythmics (e.g., encainide and flecainide), several \(\beta\)-blockers (e.g., timolol, metoprolol, and propranolol), and some tricyclic antidepressants.\(^{28,29}\) The poor hydroxylator phenotype is transmitted as an autosomal recessive trait with a prevalence of 5–10% among Caucasians, and is presumably because of inheritance of two mutant alleles for the P-450\(_{1b1}\) gene, recently localized to chromosome 22.\(^{31,32}\)

It would be useful if the poor hydroxylator patients could be identified before initiating therapy with perhexiline. This can be done by measuring, in the urine, the ratio of debrisoquine and its major P-450\(_{1b1}\) metabolite after a subtherapeutic oral dose, a relatively simple task for most laboratories with access to standards. Alternatively, a patient’s genotype can be established by identifying characteristic restriction fragment length polymorphisms on Southern analyses of genomic DNA. Although this sort of analysis would aid in establishing a safe therapeutic dose of perhexiline, it is not necessary for routine clinical practice and cannot replace plasma drug monitoring. It should be emphasized that 94% of patients in this study, not just the presumed two poor hydroxylators, required adjustment of the maintenance dose of perhexiline, reflecting the slow development of saturation of hepatic metabolism and the transition from first-order to zero-order elimination kinetics in many patients. Nevertheless, we believe...
that, with reasonable attention to therapeutic drug monitoring, only slightly more rigorously than is appropriate for digoxin or procainamide and which is less demanding than monitoring prothrombin times with warfarin therapy, perhexiline is a safe drug. The dose should be monitored at weekly intervals until a stable plasma drug level is achieved and, then, monthly or less frequently, as needed, thereafter.

**Perhexiline’s Mechanism of Action**

On an extensive review of the literature up to 1980, William E. Vaughan concluded that experimental pharmacologists in academia and industry had failed to elucidate the means by which perhexiline acted as an antianginal agent in humans. He concluded that the experimental evidence did not support the description of perhexiline as a coronary vasodilator but, rather, that its antianginal efficacy might be because of a change in myocardial metabolism, perhaps by altering the primary source of carbon and reducing equivalents for oxidative phosphorylation from fatty acids to glucose. There is evidence that the enhancement of carbohydrate uptake and metabolism could have protective effects during ischemia. This might be because there is an approximate 6% increase in ATP produced per O\textsubscript{2} consumed when glucose is used rather than fatty acids as substrate, thus providing a critical margin of increased efficiency when oxygen supply to the myocardium is limited by obstructive coronary artery disease. Within the past decade, other agents such as oxifene, an inhibitor of carnitine acyltransferase, and the adenosine derivative, N(6)-phenyl-N(6)-allyladenosine, both of which reduce fatty acid oxidation in favor of glucose oxidation, have been demonstrated to have protective effects in experimental models of ischemic myocardium without altering hemodynamics.

**Clinical Implications**

We have shown, in a double-blind prospective randomized study using a crossover design between treatment and placebo phases, that perhexiline maleate is effective in reducing the frequency and severity of anginal attacks and in increasing exercise tolerance in patients with refractory angina, many of whom had already undergone at least one coronary revascularization procedure. Perhexiline’s efficacy was superior to placebo despite the fact that patients were receiving maximally tolerated doses of the conventional antianginal regimen currently available in the United States. We also confirmed that the risk of potentially serious toxic effects of perhexiline can be greatly reduced, if not eliminated, by appropriate attention to plasma drug levels.

Although it is difficult to estimate the size of the relevant population, we believe that the number of refractory angina patients unsuitable for further revascularization or angioplasty will increase as the pool of patients who have already undergone one or more procedures age and their atherosclerosis progresses. Additionally, perhexiline might prove useful for those patients whose coronary disease is extensive and diffuse or inaccessible to surgery or to the angioplasty catheter. Finally, perhexiline has been used, in addition to conventional antianginal agents, in Europe, New Zealand, and Australia to reduce anginal symptoms in patients waiting for scarce semielective positions on cardiovascular surgery operative schedules.

Although perhexiline has been shown to be effective when given alone as single-drug antianginal therapy, we would not recommend its being used as a first-line drug for the treatment of angina because of its potential for serious toxicity. Nevertheless, the absence of clinically important hemodynamic or negative inotropic effects of the drug, or of known deleterious drug interactions with the many other medications these patients were receiving confirms the experience of Horowitz et al that, if dosed properly, perhexiline can be safely used in addition to other therapeutic modalities.

**Perhexiline’s Availability**

Perhexiline is unavailable in the United States, in large part, because of the fact that in recent years perhexiline has not had a strong advocate. The institutions that would normally perform that function, clinical investigators in academic medicine, and the pharmaceutical industry, have been reluctant to support the drug for several reasons. These reasons include the drug’s reputation for severe hepatic and neurological toxicity that developed before the genetics of its metabolism were understood and therapeutic drug monitoring became widely available. Another reason is the original marketing of the drug as a calcium antagonist, only to be superceded by effective and less toxic drugs of this class. Finally, the fact that patent rights have expired for this agent in many parts of the world (although not in the United States, where the drug has never been marketed). Although we were generously supplied with perhexiline maleate tablets and look-alike placebos, as well as standards for the high-performance liquid chromatography assay, this study received no funding, directly or indirectly, from the pharmaceutical industry.

Perhexiline remains commercially available in several European and South American countries, Australia, and New Zealand. Based on the average cost of perhexiline in these countries, an estimated monthly supply of the drug in U.S. funds would cost $10–20. The results of this report, when viewed in the context of other recent uncontrolled studies, support a more extensive examination of the safety and efficacy of perhexiline in patients with refractory angina.

**References**


Key Words: angina • myocardial ischemia • perhexiline maleate • clinical pharmacology • slow metabolizer • cytochrome P-450
Efficacy and safety of perhexiline maleate in refractory angina. A double-blind placebo-controlled clinical trial of a novel antianginal agent.
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