Long-Term Effect of Perhexiline Maleate on Ventricular Ectopic Activity

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SUMMARY
The effectiveness of perhexiline maleate in the suppression of ventricular ectopic activity has been studied in 10 patients after myocardial infarction. Before treatment all patients exhibited frequent ectopic beats, i.e., more than 8 per hour. Numerous Holter magnetic tape recordings were made over a 9-10-month period of treatment. During the entire period of monitoring significant suppression of ectopic activity was observed in 5 patients and transient suppression in 4, of whom 3 subsequently showed a transient increase. The drug was discontinued in 1 patient because of nausea, anorexia and weight loss. No other adverse effects were encountered.


Sudden death from ventricular fibrillation is the biggest and probably the most remediable of major public health problems. It is possible that with the use of beta-adrenergic blocking agents or other anti-arrhythmic drugs, a substantial proportion of coronary deaths may be prevented or postponed. A relationship between sudden death and the presence of ventricular ectopic activity has been claimed. Whether this relationship is specific, remains to be shown. The specificity and possible beneficial effect can only be evaluated properly by controlled long-term administration of a relatively safe and effective anti-arrhythmic drug. Up to now a study of this nature was unjustified, because of the ineffectiveness and hazards of the better-known anti-arrhythmic agents, e.g. quinidine, diphenylhydantoin and procainamide.

In this study we report on the effectiveness and side-effects of perhexiline maleate as a ventricular anti-arrhythmic agent in patients with frequent ventricular ectopic beats (VEB) after myocardial infarction.

PATIENTS AND METHODS
The anti-arrhythmic effects of perhexiline maleate were studied in 10 patients who exhibited frequent VEB, i.e., more than 8/h, on at least two 6-hour Holter tape recordings made 3 months apart. The patients were selected at random from a group of patients who had suffered myocardial infarction and who were evaluated regularly at the Military Medical Institute. Their ages ranged from 49 to 62 years (mean 55), and the study commenced 6.94 months (mean 29) after they had last suffered acute myocardial infarction.

None of the patients was on other anti-arrhythmic agents, but 5 were being treated for hypertension and 2 for angina pectoris, 1 of the latter also receiving digitalis for intermittent atrial fibrillation.

After control tapes had been obtained, perhexiline maleate was prescribed in a dose of 200 mg twice a day. Holter tape recordings, spanning 6 hours each, were then obtained monthly for the first 6 months, and again after 3-4 months. The tracings were always obtained on the same working day. At each visit a resting electrocardiogram (ECG) was recorded and fasting blood was collected for serum alanine aminotransferase, aspartate aminotransferase, urea nitrogen, uric acid, creatinine, cholesterol, triglyceride and thyroxine determinations.

The magnetic tapes were scanned on an Avionics electrocardioscanner, and the number of VEB per hour was calculated from the total observed over the 6-hour monitoring period. The resting heart rate on control ECGs was compared with the resting heart rate after 9-10 months' treatment. Changes in QRSTU patterns were evaluated. The results of the study were subjected to statistical analysis by applying Student's paired t test.

RESULTS
Seventy-one 6-hour Holter recordings were made while the patients were on treatment. The change in the number of VEB is given in Table 1. A statistically significant reduction in the number of VEB was seen after 4 weeks (P<0.0005), 8 weeks (P<0.05), 12 weeks (P<0.0005), and 36 weeks (P<0.05) of therapy. A statistically significant reduction at the other periods of testing was not reached because of a significant increase in frequency of VEB in patients 3, 9 and 10, despite an initial transient reduction in patients 3 and 10. Patient 1 discontinued the drug on his own initiative because of severe anorexia and weight loss of 7 kg. Patient 3 sustained a recurrent myocardial infarction 9 months after initiation of therapy, from which he recovered. The previously reported mild fluctuations in serum alanine aminotransferase and aspartate aminotransferase levels, in spite of constant drug dosage, were confirmed. A reduction in resting heart rate of 5-30 beats per minute (mean 12) was observed in all patients after 9-10 months of therapy. The T-wave amplitude decreased to some extent in all patients, especially in the praecordial leads and more particularly in V2 (mean 0.65 mm in V1, 1.65 mm in V2, 1.0 mm in V3, 0.45 mm in V4, 0.15 mm in V5 and 0.1 mm in V6). No other changes in the QRSTU complex were observed.

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DISCUSSION

Even though the change in the absolute number of VEB on anti-arrhythmic therapy constitutes an objective measurement, a possible placebo effect still requires consideration. While evaluating the antidyshrhythmic properties of disopyramide phosphate in 130 patients, Smith noted a 30% decrease in the number of VEB during the placebo phase of the trial. As a criterion for effective antidyshrhythmic properties of a drug, the complete abolition of ventricular couplets and tachycardia and a 75% reduction in VEB frequency were suggested. Notably, however, both couplets and ventricular tachycardia are found to be related to the absolute number of VEB present.

Studies from this Institute indicate that the number of VEB in patients with chronic ischaemic heart disease tends to remain stable for prolonged periods of time. This finding creates a useful model for the evaluation of the effectiveness of anti-arrhythmic agents, and the results of an open study may thus be taken into account when a statistically significant reduction in the number of VEB occurs in a patient known to manifest a stable number of VEB.

Perhexiline maleate was originally introduced for the treatment of angina pectoris, and was subsequently found to be potent and relatively free from side-effects. The drug's ability to suppress ventricular arrhythmias is of additional importance. In vivo electrophysiological studies demonstrated that perhexiline causes reduced automaticity of latent ventricular pacemakers and slows conduction in specialized ventricular conduction tissue. Anti-arrhythmic effects have been confirmed in human studies.

The present study demonstrates a reduction in ventricular ectopic activity of varying significance over a 9-10-month period, with a maximum reduction of 86% at 1 month, falling to 30% at 5 months and rising again to a 75% reduction at 9 months (Table 1). An almost ideal anti-arrhythmic response was obtained in 5 of the 10 patients studied and was sustained for the entire period of observation. After an initial good response in 3 patients, the frequency of VEB actually increased to well above the control level while the patients were on the drug. One of these patients (No. 3) subsequently developed a myocardial infarction. In 1 patient a reduction in VEB was seen only after 6 months' therapy. The drug was discontinued in 1 patient because of side-effects, viz. nausea and anorexia. If the dosage had been lowered, it would probably not have been necessary to discontinue treatment.

In accordance with previous reports, mild elevations in serum alanine aminotransferase and aspartate aminotransferase levels were noted in this study. This finding, especially fluctuations in serum transaminase levels while the patients were on a constant dosage, is at present unexplained. The possible mechanisms for the reduction in resting heart rate in patients on the drug are also unclear. Some workers did not observe a reduction in resting heart rate.
Other long-term studies for determining effective suppression of VEB are available for quinidine, procainamide, and diphenylhydantoin. These drugs were ineffective in the majority of patients studied, despite the fact that the dosage used was associated with toxicity in a high proportion of cases. This fact, and the fact that perhexiline maleate has been used for prolonged periods of time in patients with angina pectoris, without serious side-effects, suggest that a comparative study between these drugs and perhexiline is not indicated.

Although perhexiline maleate is a welcome addition to the family of anti-arrhythmic drugs, the actuarial problem of whether successful suppression of ventricular ectopic activity will result in longer survival remains to be elucidated.

REFERENCES

Maintenance Dialysis and Renal Transplantation Facilities in South Africa – 1977

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SUMMARY
A survey undertaken in July 1977 revealed that 27 hospital centres were treating 307 patients with chronic renal failure by maintenance haemodialysis and 22 patients by chronic peritoneal dialysis. An additional 28 patients were receiving home dialysis. Seven of the centres had transplantation programmes and were treating 271 survivors with functioning renal homografts.


The fifth annual survey of dialysis and transplantation facilities available in South Africa for patients suffering from chronic renal failure was undertaken in July 1977. The results are presented for comparison with those of previous surveys and to assess the growth and development of these facilities during the past year.

At the time of the survey 628 patients were reported to be receiving treatment (Fig. 1 and Table I). This represents an increase of 106 patients, or 20% more than were being treated 1 year previously. A total of 27 hospital centres participated in this service. Twenty-three hospitals had facilities for maintenance haemodialysis (Table II), 3 of these hospitals, i.e. J.G. Strijdom, Worcester and East London hospitals, having been established as haemodialysis centres during the past year. A total of 115 stations (bed-dialyser complexes) were available for the 307 patients receiving hospital haemodialysis, as compared with 107 stations and 258 patients on this form of treatment in 1976. The centre with the largest number of patients on haemodialysis was Baragwanath Hospital, where 52 patients were being treated with the aid of only 10 stations. The H.F.