

REPORTS ON THERAPY

Mexiletine: An Effective Antiarrhythmic Drug for Treatment of Ventricular Arrhythmias in Congenital Heart DiseaseJEFFREY P. MOAK, MD, FACC, RICHARD T. SMITH, MD, FACC,
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The use of antiarrhythmic drugs to suppress ventricular arrhythmias in pediatric patients with a structurally or hemodynamically abnormal heart appears to improve long-term prognosis. The previously successful use of phenytoin to treat serious ventricular arrhythmias led to the investigation for an alternative antiarrhythmic agent, in the same antiarrhythmic drug class, for those patients who develop side effects or become intolerant to phenytoin's antiarrhythmic effect. Forty-two children and young adults (age range 5 months to 34 years, mean 15.5 years) were treated with mexiletine. Arrhythmias treated were ventricular tachycardia (25), ventricular couplets (8), multiform ventricular premature beats (4) and frequent uniform ventricular premature beats (5). Anatomic diagnoses included congenital heart disease (postoperative in 26, unoperated in 2), cardiomyopathy (7), no heart disease (4) and other (3). Thirty-three patients had been previously treated with 1 to 5 (mean 1.6) antiarrhythmic drugs.

In the short term, ventricular arrhythmias were effectively suppressed in 30 (71%) of all 42 patients treated. During follow-up (ranging to 42 months, median 10.6), 18 (60%) of the 30 acute responders continued to have excellent control. Early suppression of ventricular arrhythmias was more effective in patients with congenital heart disease (89%) than in those with cardiomyopathy (29%) or no heart disease (43%) ($p < 0.01$). Initial complexity of ventricular ectopic activity had no effect on treatment results.

Of 25 patients previously treated with phenytoin, in whom alternative antiarrhythmic therapy was required, 40% had long-term arrhythmia control when treated with mexiletine. Mexiletine therapy was terminated for side effects in only five patients (12%). Mexiletine is recommended for young patients with congenital heart disease and serious ventricular arrhythmias.

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The successful control of ventricular arrhythmias has proved efficacious in decreasing the morbidity and mortality among children with heart disease (1). However, drug treatment of ventricular arrhythmias with many of the currently available antiarrhythmic agents may be complicated by impairment of myocardial function and side effects (2).

Many pediatric patients with ventricular arrhythmias have complicated congenital heart disease associated with myocardial dysfunction. Phenytoin has been previously demonstrated to be highly effective in the treatment of serious ventricular arrhythmias in patients with congenital heart disease and to cause few side effects (3,4). However, alternative antiarrhythmic therapy is needed for those patients

who develop phenytoin-induced side effects (rash or gingival hyperplasia) and young female patients desiring to become pregnant, in whom other antiarrhythmic drugs have been ineffective. Because phenytoin has been so effective, we sought to study an alternative antiarrhythmic drug, mexiletine, which has similar electrophysiologic properties (type Ib local anesthetic effect). Furthermore, mexiletine has been shown to be effective in the treatment of adult patients with ventricular arrhythmias and ischemic heart disease. But more important, there has been little evidence of impairment of myocardial function or only rare instances of arrhythmia aggravation secondary to its use (5-8). This report reviews the effectiveness and toxicity of mexiletine in treating serious ventricular arrhythmias in infants, children and young adults.

Methods

Study patients. The study group comprised 42 patients with clinically significant ventricular ectopic activity. Ven-

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tricular arrhythmias treated included isolated ventricular premature beats (uniform or multiform) with a frequency >30/h, ventricular couplets or ventricular tachycardia. Ventricular tachycardia was defined as the occurrence of three or more consecutive excitations originating from the ventricle at a rate ≥ 120 /min. Patients older than 18 years were included if they had congenital heart disease.

Mexiletine protocol. Each patient was admitted to the hospital for mexiletine treatment. All antiarrhythmic drugs, except digoxin, were discontinued 5 drug half-lives before commencing mexiletine therapy. Pretreatment laboratory work-up included: 15 lead electrocardiogram (ECG); continuous ambulatory electrocardiogram usually starting 36 to 48 hours before initiating therapy; chest X ray film; echocardiogram; treadmill test; complete blood count with differential and platelet count; blood urea nitrogen and creatinine determinations; and liver function tests.

After these baseline studies were obtained, oral mexiletine was initiated with a dose of 2.9 mg/kg every 8 hours. Seventy-two hours were allowed for a steady state to be reached. Although this time period exceeded 5 drug half-lives calculated using the average adult drug half-life of 12.1 hours (9), we chose it to ensure that a true steady state had been achieved. At this point, blood was drawn for determination of the serum concentration (trough level) and the continuous ECG was analyzed for effectiveness. If the drug was ineffective (see later) and there were no side effects, the dose of mexiletine was increased to 4.3 mg/kg every 8 hours and 72 hours were allowed to elapse at which point effectiveness was redetermined. At no time did any patient receive more than 5.0 mg/kg per dose. If at any dose mexiletine was effective but caused significant side effects,

the dosage was decreased by one-half and effectiveness was reevaluated.

Routine outpatient follow-up was scheduled at 1, 3 and 6 months and 1 year and then every 6 months after the start of treatment with mexiletine. Outpatient data included history, physical examination, 15 lead ECG, chest X ray film, 24 hour ambulatory ECG and repetition of all initial laboratory blood tests.

Criteria for drug efficacy. Mexiletine effectiveness was assessed on the basis of continuous electrocardiography. Treatment was considered successful for patients being treated for ventricular couplets or ventricular tachycardia (three or more consecutive ventricular premature beats) if there was complete elimination of the arrhythmia. In patients being treated for frequent uniform or multiform ventricular premature beats (frequency >30/h), therapy was considered successful if there was an 85% reduction in the number of ventricular premature beats during a 24 hour period (10,11).

In patients in whom ventricular tachycardia or couplets could be provoked during exercise, mexiletine was considered successful if on repeated treadmill exercise tests mexiletine prevented the reappearance of ventricular tachycardia or couplets.

Blood level assay. Mexiletine serum concentrations were determined by high pressure liquid chromatography by Boehringer Ingelheim, Ltd. A therapeutic concentration of mexiletine has been suggested to range between 0.5 and 2.0 mg/liter (9).

Statistical analysis. Analysis of variance (ANOVA) was performed for multigroup comparisons. If the ANOVA was statistically significant ($p < 0.05$), Bonferroni's modification of the *t* test was subsequently used for pairwise comparisons (12). Statistical significance was inferred if the probability of a difference occurring by chance was < 0.05 .

Table 1. Anatomic Diagnosis in 42 Patients

	No. of Patients
Congenital heart disease	
Tetralogy of Fallot/pulmonary atresia + ventricular septal defect	12
Aortic stenosis	4
Ventricular septal defect + pulmonary vascular obstructive disease	4
Truncus arteriosus	2
AV canal defect	2
D-transposition of great arteries + ventricular septal defect	2
L-transposition of great arteries + ventricular septal defect + pulmonary stenosis	1
Tricuspid atresia	1
Cardiomyopathy	7
Purkinje cell tumor	2
Status post AV node ablation	1
No heart disease	4

AV = atrioventricular.

Results

Clinical Features

Cardiac diagnoses (Table 1). All except 4 of the 42 patients enrolled in the study had an abnormal heart. The most common cardiac diagnosis was congenital heart disease, which was reported in 28 patients (67%). Of these 28 patients, 26 had had previous cardiac surgery and 2 had had no operation. The next most common cardiac condition treated was cardiomyopathy (in seven patients, three of whom had arrhythmogenic right ventricular dysplasia). Two patients had Purkinje cell tumors. One patient had previously undergone atrioventricular (AV) node ablation for incessant supraventricular tachycardia and had an associated dilated cardiomyopathy.

Age of onset, duration of therapy and dose. The patients ranged in age from 5 months to 34 years (mean 15.5 years) when mexiletine therapy was instituted. The duration

of therapy has ranged up to 42 months (mean 10.6). Seventy percent of patients in whom mexiletine was continued beyond the early drug testing stage had follow-up >6 months. The dose of mexiletine utilized ranged from 1.4 to 5.0 mg/kg (mean 3.3) every 8 hours.

Ventricular arrhythmias. All patients had frequent ventricular ectopic activity documented by ECG monitoring. Twenty-five patients had recurrent episodes of ventricular tachycardia, eight had ventricular couplets, four had multiform ventricular premature beats and five had uniform ventricular premature beats. Six patients had sustained, incessant ventricular tachycardia. The 19 patients with non-sustained ventricular tachycardia had a mean of 6.8 ± 3.7 beats/run and 70.9 ± 219.9 runs of ventricular tachycardia/24 h. Ventricular couplet frequency ranged from 2 to 48/24 h (mean 9.6 ± 16.5). The frequency of isolated uniform or multiformed ventricular premature beats was >30/h.

Previous therapy (Table 2). Thirty-three patients had been previously treated with 1 to 5 (mean 1.6) antiarrhythmic drugs. Phenytoin had been used in 25 patients (60%). All previous antiarrhythmic drugs were discontinued because of inadequate arrhythmia control or side effects.

Mexiletine Therapy

Effectiveness: overall. Shortly after the start of mexiletine therapy, ventricular arrhythmias were effectively suppressed in 30 (71%) of the 42 patients. Therapy was terminated early in the other 12 patients because of inadequate arrhythmia control. During follow-up, 18 (60%) of the 30 patients who continued on mexiletine treatment had excellent control of their arrhythmia. Mexiletine was discontinued in five patients because of side effects and in seven (23%) because of late arrhythmia recurrence.

Effectiveness: heart disease. Mexiletine was most effective in suppressing ventricular arrhythmias in patients with congenital heart disease (Fig. 1). In the 28 patients with congenital heart disease, complete arrhythmia control was achieved in 25 (89%) early after initiation of therapy. Fourteen (56%) of these 25 patients continued to have suc-

Table 2. Previous Antiarrhythmic Therapy in 42 Patients

	No. of Patients
Phenytoin	25
Propranolol	8
Quinidine	6
Atenolol	3
Procainamide	2
Disopyramide	2
Verapamil	2
Amiodarone	2
Flecainide	1

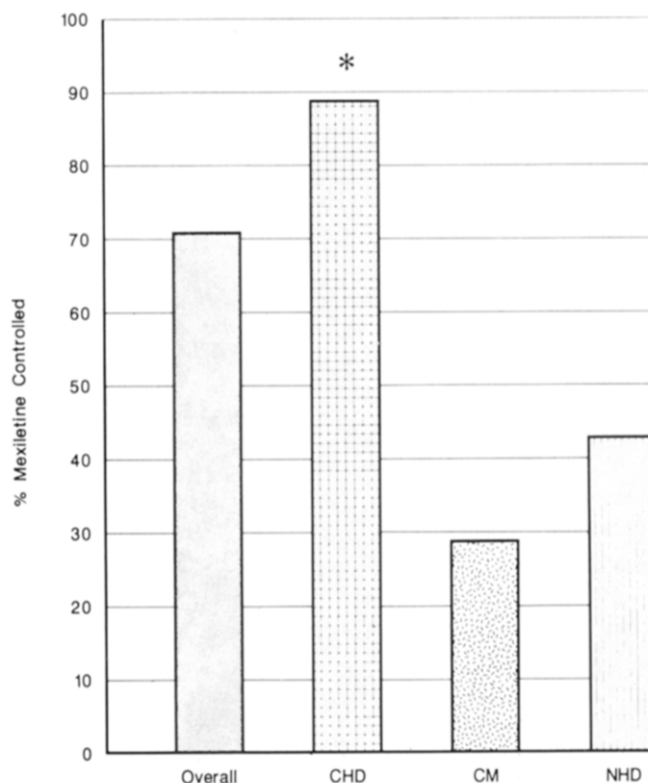


Figure 1. Arrhythmia control and type of associated heart disease. The analysis was performed by evaluating the percent of patients with specific types of heart disease who had effective control of arrhythmia early during therapy: all patients (overall) (n = 42), those with congenital heart disease (CHD), cardiomyopathy (CM) and no heart disease (NHD). Mexiletine therapy was most effective in the group with congenital heart disease (*p < 0.01).

cessful control of their arrhythmia during follow-up. Mexiletine was discontinued in four (16%) for drug-related side effects and in seven (28%) because of arrhythmia recurrence late after initiation of therapy. In the cardiomyopathy group (seven patients), mexiletine therapy was moderately effective, but less so than in the group with congenital heart disease. Long-term arrhythmia control occurred in two (29%) of the seven patients. The no heart disease group (four patients) and the two miscellaneous groups of Purkinje cell tumor (two patients) and AV node ablation (one patient) were analyzed collectively. Successful long-term arrhythmia suppression occurred in two (29%) of these seven patients; one had a Purkinje cell tumor and the other had had AV node ablation. Mexiletine therapy was least effective in the patient groups of cardiomyopathy and no heart disease.

Effectiveness: arrhythmia type. No significant differences were evident between the presenting arrhythmia type and the adequacy of long-term arrhythmia control (Fig. 2). Continued effective arrhythmia control was maintained in 12 (48%) of 25 patients with ventricular tachycardia, 3 (43%) of 7 patients with ventricular couplets and 3 (33%)

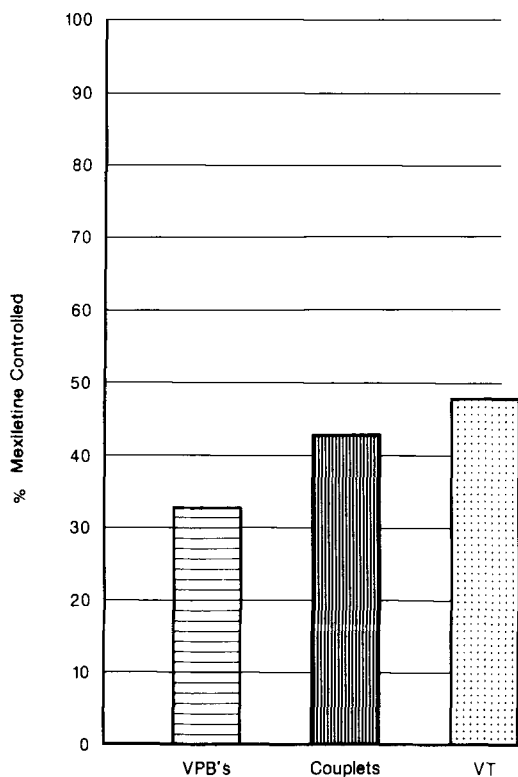


Figure 2. Arrhythmia control and complexity of ventricular arrhythmia. The analysis was performed by evaluating the percent of patients with specific grades of ventricular ectopic activity (frequent isolated ventricular premature beats [VPB's], couplets and ventricular tachycardia [VT]) who had effective long-term arrhythmia control. Mexiletine's efficacy was not significantly influenced by the complexity of the ventricular ectopic activity that was treated.

of 9 patients with either isolated frequent multiform or uniform ventricular premature beats.

Effectiveness: previous phenytoin failures. Of the 25 patients previously treated with phenytoin, therapy had been terminated because of inadequate arrhythmia control in 12, rash in 12 and gingival hyperplasia in 1 patient. Twenty-one (84%) of these patients had excellent arrhythmia control during the early phases of mexiletine therapy. Completely successful long-term arrhythmia control was achieved in 10 (48%) of these 21 patients. Mexiletine was stopped because of side effects in four and arrhythmia recurrence in seven patients.

Concomitant therapy. Mexiletine was used in combination with another antiarrhythmic agent in six patients. This included a beta-receptor blocker in four patients, procainamide in one and phenytoin in one. Concomitant phenytoin and mexiletine therapy was used in one patient who had fair arrhythmia control with phenytoin alone. Higher doses of phenytoin had produced central nervous system side effects. Phenytoin treatment was supplemented with mexi-

letine in the hope of improving arrhythmia control without causing significant side effects. Unfortunately, the combination produced little improvement in arrhythmia control. The concomitant use of additional antiarrhythmic agents in patients with fair arrhythmia control with mexiletine rarely enhanced therapeutic effectiveness. Only two (33%) of these six patients had long-term suppression of their arrhythmia.

Adverse effects. The incidence and type of side effects noted during therapy with mexiletine are listed in Table 3. Twenty-eight (67%) of the 42 patients had no side effects. The remaining 14 patients had side effects, but most of these were well tolerated and usually disappeared with a decrease in the dosage of mexiletine. Mexiletine was discontinued because of side effects in only five (12%) of the enrolled patients. The most common side effect, nausea, occurred in 11 patients. Administration of mexiletine with food usually abated this symptom. Nine patients had symptoms referable to the central nervous system. Headaches occurred in six; tremor and mood changes in three; vertigo in two; and paresthesias in one patient. A morbilliform rash erupted during mexiletine therapy in two patients. One patient with moderately impaired renal function (creatinine clearance not measured) experienced hypotension and sinus tachycardia after the first several doses of mexiletine. The hypotension resolved with cessation of therapy. Of particular importance was the fact that there was no exacerbation of congestive heart failure in any of the patients treated or an increase in the quantity of their ventricular ectopic activity.

The measured serum concentrations of mexiletine ranged from 0.3 to 1.9 mg/liter. No correlation was evident between therapeutic effectiveness or side effects and serum concentration of mexiletine. The serum concentration of patients with side effects was frequently in the "therapeutic range." Similarly, no relation between serum concentration and drug response could be demonstrated.

Table 3. Long-Term Mexiletine Side Effects in 14 Patients

Side Effect	No. of Patients
Gastrointestinal	11
Nausea	11
Neurologic	9
Headache	6
Tremor	3
Mood changes	3
Vertigo	2
Paresthesias	1
Dermatologic	2
Rash	2
Cardiovascular	1
Hypotension	1

Discussion

Mexiletine effectiveness. The results of this study demonstrate mexiletine to be highly effective in treating ventricular arrhythmias in children and young adults. After initiating therapy with mexiletine, 71% of all patients achieved early arrhythmia suppression as documented by continuous ECG monitoring. Early arrhythmia control was particularly high in the subgroup of patients with congenital heart disease (89%). Mexiletine effectively suppressed all grades of ventricular ectopic activity equally well.

Comparison with other antiarrhythmic drugs. Increasing awareness of the importance of ventricular arrhythmia control in pediatric patients with an abnormal heart (structural heart disease or cardiomyopathy) naturally brings to the foreground questions concerning antiarrhythmic drug efficacy (1,13). Few reports are available from which a comparative analysis of antiarrhythmic efficacy can be made (14). Most reported series contain small numbers of treated patients. Furthermore, the spectrum of antiarrhythmic drugs studied is limited. However, the largest antiarrhythmic experience reported to date has been with either phenytoin or amiodarone (3,4,15-18).

Previous investigators have noted favorable results with these agents (3,4,15-18). In using phenytoin to treat 51 patients with chronic ventricular arrhythmias, Garson and Gillette (3) observed successful arrhythmia control early after initiating therapy in 76% of patients. Satisfactory arrhythmia control was maintained in 57% of patients during a mean follow-up period of 15.2 months. The experience of Kavey et al. (4) in treating 19 patients with phenytoin was similar; 74% had effective arrhythmia control early during therapy. A favorable experience with amiodarone was noted by a number of investigators. In the two largest series reported (15,16), the observed early success rate was high, ranging from 70 to 86%; long-term success was achieved in 54% of patients on amiodarone therapy followed up by Garson et al. (16).

Our results with mexiletine compared quite favorably with the results using these two other agents. Early arrhythmia control occurred in 71% of all patients initially treated with mexiletine (89% of those with congenital heart disease); during long-term follow-up, arrhythmia control was maintained in 50% of patients with congenital heart disease.

Twenty-five of our patients had previously been treated with phenytoin. Excellent early arrhythmia control occurred in 84% of this subgroup, whereas 40% had effective long-term control. For those patients in whom phenytoin therapy must be discontinued because of side effects (rash, gingival hyperplasia or hirsutism), we recommend treatment with mexiletine. Because of phenytoin's known teratogenicity (19), one additional subgroup of patients in whom alternative antiarrhythmic therapy should be considered is young women desiring to become pregnant. To date, no reports have attributed a teratogenic effect to mexiletine.

Antiarrhythmic therapy—which agent to use? Before choosing an antiarrhythmic agent for a particular patient, consideration should be given to the type of underlying heart disease. Evidence is becoming available to suggest the important influence the type of underlying heart disease has in modifying the response to treatment. Ventricular arrhythmias in patients with congenital heart disease appear particularly sensitive to phenytoin and mexiletine (1,3,4). In the present study evaluating mexiletine and in a previous report (3) using phenytoin, arrhythmia control was best achieved in patients with congenital heart disease. Patients with congestive cardiomyopathy and subjects with no heart disease responded less well to therapy with these two agents. Although not advocating treatment of ventricular arrhythmias in children with no heart disease, we recognize its necessity in symptomatic patients and those with secondary impairment of cardiac function. Propranolol and quinidine have been reported to be efficacious in patients without heart disease (14,18,20). However, these two agents are therapeutically less effective than mexiletine or phenytoin in patients with congenital heart disease (1).

In deciding on an antiarrhythmic agent for patients with diminished cardiac function, serious thought should be given to its negative inotropic effects. The reported experience with mexiletine usage in adult patients with ischemic heart disease has been quite favorable (5-8). A review of studies by Shanks (21) found mexiletine nearly devoid of adverse hemodynamic effects when administered in a dosage that maintained "therapeutic" plasma concentrations. No exacerbation of congestive heart failure occurred in our patients. Hypotension developed in one patient who had renal failure. Marked impairment of renal function is known to diminish the clearance of mexiletine (9) and probably contributed to its accumulation in this patient, although a serum concentration was not available. Several local anesthetic agents, particularly disopyramide, quinidine and procainamide, have significant negative inotropic effects and should be avoided in patients with compromised cardiac function (2).

A frequently reported complication of local anesthetic antiarrhythmic drug usage is arrhythmia aggravation. Repeated documentation of this complication can be found in reports of patients with ischemic heart disease treated with local anesthetic agents (22,23). It has been reported (20,25) in the pediatric age group during quinidine administration. The true incidence of this side effect, however, is unknown. The reported incidence of proarrhythmic effects has been significantly lower with mexiletine treatment (5-8). In our series, we did not observe any exacerbation of ventricular arrhythmias.

Therapeutic effectiveness in pediatric patients: probable role of the underlying heart disease. Our results and those of previous studies (3,4) demonstrate that mexiletine and phenytoin have an enhanced therapeutic effectiveness in treating pediatric and young adult patients with congenital

heart disease, in contrast to the reported low effectiveness of these agents in adult patients with ischemic heart disease (5-8). Speculation regarding the basis for enhanced therapeutic effectiveness of phenytoin and mexiletine (type Ib local anesthetic agents) in pediatric and young adult patients may be directed toward either the patients' younger age or a difference in electrophysiologic substrate for the ventricular arrhythmias (congenital heart disease versus ischemic heart disease). We favor the latter hypothesis. Many of our patients (36%) were teenagers or young adults. In addition, recent studies by Spinelli and Rosen (26) provided further evidence against the age hypothesis. These investigators could not demonstrate any in vitro age-related differences in electrophysiologic effects of phenytoin on either normal or depressed canine cardiac Purkinje fibers. Collectively, these results suggest the importance of the type of underlying heart disease in explaining the high therapeutic effectiveness of type Ib antiarrhythmic agents in the "younger" age group.

Conclusions. Mexiletine is a useful agent for the long-term control of ventricular arrhythmias in patients with congenital heart disease. Successful arrhythmia control is independent of arrhythmia complexity. For patients with ventricular arrhythmias occurring in the setting of cardiomyopathy or no heart disease, mexiletine is not recommended. A high concordance rate of therapeutic success makes mexiletine an important alternative to phenytoin. Side effects are relatively infrequent and mild in nature.

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