# Mexiletine therapy in patients with chronic drug-resistant malignant ventricular arrhythmias

## Clinical efficacy, safety, and side effects[1]

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**The authors report their overall experience with 138 patients receiving mexiletine for chronic drug-resistant ventricular arrhythmias. Of these 138 patients, 26 (19%) were "early failures" (that is, experiencing refractory arrhythmias or intolerant to therapy prior to initial hospital discharge) and an additional 22 patients (16%) were "late failures" (that is, experiencing refractory arrhythmias or intolerant to therapy after hospital discharge). Chronic oral maintenance therapy was successful for 90 patients (65%). Nine (7%) arrhythmia-related deaths occurred. Side effects were common (28% initially and 52% during chronic maintenance therapy), but discontinuation of the drug was only required for 9 patients (7%). No significant biochemical abnormalities or electrocardiographic conduction disturbances were observed. Mexiletine appears to be a clinically useful and safe antiarrhythmic agent for the treatment of chronic drug-resistant ventricular arrhythmias.**

**Index terms:** Arrhythmia, drug therapy · Propylamines

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Mexiletine is an antiarrhythmic agent which became available in Europe for clinical trials in 1971.[1] It is still under clinical investigation in the United States for the treatment of ventricular arrhythmias. Although multiple reports have described the use of mexiletine for the treatment of acute and chronic ventricular arrhythmias,[1–19] its exact therapeutic role remains to be determined. For this reason, we report our experience involving the clinical efficacy, safety, and side effects of mexiletine given orally to a large group of patients with chronic malignant ventricular arrhythmias that could not be managed with conventional antiarrhythmic drugs.

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**Definitions Used**

| | |
|---|---|
| **Early Failure** | **Those patients not experiencing successful arrythmia control (as defined in protocol design) on maximally tolerated mexiletine dosage or suffering from intolerable side effects, occurring during initial hospitalization** |
| **Late Failure** | **As per "early failure," but occurring one to 30 months after hospital discharge** |
| **Sustained ventricular tachycardia (VT)** | **At least 11 repetitive ventricular beats or hemodynamic compromise occurring either spontaneously or induced during programmed electrical-stimulation testing** |
| **Nonsustained VT** | **Four to 10 repetitive ventricular beats occurring either spontaneously or induced during programmed electrical-stimulation testing** |
| **Repetitive ventricular ectopy** | **Three repetitive ventricular beats occurring spontaneously** |
| **Coronary artery disease** | **A well-documented transmural myocardial infarction and/or catheterization data confirming the presence of luminal obstruction (>50%) in one or more coronary arteries** |
| **Primary electrical disease** | **Ventricular arrhythmias occurring in the absence of identifiable structural cardiac disease** |

*Protocol design*

From August 1, 1980, to December 31, 1983, 158 patients at the Cleveland Clinic received mexiletine for the treatment of malignant ventricular arrhythmias refractory or intolerant to conventional antiarrhythmic drug therapy (procainamide, quinidine, disopyramide, diphenylhydantoin—alone or in combination). Twenty of these patients were excluded from this study (17 patients received combination therapy with mexiletine and never a trial of mexiletine alone, data involving 2 patients before mexiletine therapy were incomplete, and 1 patient was lost to follow-up). Thus, this report focuses on the remaining 138 patients. All these patients were hospitalized, and prior arrhythmia history and antiarrhythmic drug trials were evaluated carefully. When the clinical history, documented hospital transfer records, and plasma drug levels confirmed drug unresponsiveness or intolerance, a drug trial with the same antiarrhythmic agent was not repeated. However, if the arrhythmia diagnosis or drug responsiveness was uncertain, programmed ventricular stimulation in the electrophysiology laboratory, along with acute drug testing, was performed for confirmation.

Our electrophysiology study protocol has been previously described in detail.[20] Single- and double-programmed ventricular extrastimuli were first introduced into sinus rhythm and then into paced rhythms at one, two, or three cycle lengths (usually 600, 450, and 400 msec), scanning throughout diastole until ventricular refractoriness was reached or sustained ventricular tachycardia (VT) induced. If needed, burst ventricular pacing (5–10 repetitive extrastimuli) at cycle lengths of 350–240 msec was performed, followed by triple extrastimuli introduced at one or two paced cycle lengths (usually 450–400 msec). Finally, if necessary, the same procedure was then repeated at the right ventricular outflow tract.

All patients were aware of the experimental status of mexiletine and written consent was obtained prior to the initiation of therapy. The use of mexiletine was considered successful in patients with spontaneous recurrent sustained VT or ventricular fibrillation (VF) when clinical and electrographically documented elimination of these episodes was achieved. In patients with malignant arrhythmias in whom sustained VT was induced by programmed electrical stimulation, mexiletine was considered successful when the sustained VT could not be reinduced after therapy. In the population of symptomatic patients with nonsustained VT, arrhythmia control was considered successful with mexiletine when symptoms no longer occurred and multiple am-

**Table 1.** Description of anatomic classification vs. arrhythmia analysis in 138 patients receiving mexiletine

| Anatomic subset | Sustained ventricular tachycardia | Nonsustained ventricular trachycardia | Repetitive ventricular ectopy | Ventricular fibrillation |
|---|---|---|---|---|
| Coronary artery disease | 54 | 21 | 15 | 26 |
| Left ventricular aneurysm | 11 | 0 | 0 | 4 |
| Coronary artery bypass surgery | 18 | 8 | 11 | 6 |
| Primary myocardial disease | 12 | 9 | 4 | 5 |
| Mitral valve prolapse | 3 | 2 | 3 | 2 |
| Aortic valve disease | 1 | 1 | 0 | 0 |
| Mitral valve disease | 2 | 2 | 0 | 2 |
| Primary electrical disease | 5 | 2 | 2 | 2 |

bulatory electrocardiographic recordings failed to demonstrate the arrhythmia. In patients with repetitive ventricular ectopy, mexiletine was considered successful when symptoms improved and near complete suppression of couplets and triplets was achieved, as recorded on multiple ambulatory electrocardiographic recordings.

The initial mexiletine dosage in most patients was 200 mg and was given orally every eight hours. After an observation period of 24–48 hours, the dosage was gradually increased or decreased depending on arrhythmia control or side effects. Patients were subsequently monitored in the hospital using Holter monitoring and/or telemetry for an additional seven to 10 days. Follow-up was six to eight weeks after hospital discharge and every three months thereafter. At each outpatient visit, an electrocardiogram, urinalysis, complete blood count, SMA-17 chemistry profile, and anti-nuclear antibody titer were obtained. Chest radiographs were also obtained every six months or as indicated. During each visit, the patient was questioned regarding the occurrence of side effects, and a physical examination was performed.

Drug dosages and length of follow-up are reported as mean ± standard deviation.

*Holter monitoring*

For the purpose of assessing the suppressibility of ventricular ectopy, 24-hour electrocardiographic recordings were analyzed before and after drug administration in 109 patients. High-fidelity two-channel cassette recordings were made using Del Mar Avionics (Irvine, Calif.) Holter monitors. Recordings involving all antiarrhythmic agents before mexiletine use were obtained whenever possible. After mexiletine use, recordings were performed after the "dose-finding" period during initial hospitalization. Electrocardiographic analysis was performed using a technician-assisted computerized Del Mar Trendsetter (model #9040). Holter monitoring was analyzed for the presence of ventricular tachycardia (four or more beats), ventricular triplets and couplets, R on T phenomenon, and the total number of ventricular ectopy per 24 hours. All monitoring results were read over by a physician. Interobserver variation was tested and showed no variation in interpretation when Holter recordings were reread.

## Results

*Patient characteristics*

There were 138 patients (92 men, 46 women) receiving mexiletine (mean age, 51 ± 12 years; range, 27 to 81 years). The primary diagnoses included coronary artery disease (90 patients; 37 with prior coronary artery bypass surgery), primary myocardial disease (25 patients; 24 with idiopathic cardiomyopathy and 1 with arrhythmogenic right ventricular dysplasia), mitral valve abnormalities (12 patients), primary electrical disease (9 patients), and aortic valve disease (2 patients) (*Table 1*).

Mexiletine was used for the treatment of VT or VF in 114 patients (83%) (with sustained VT

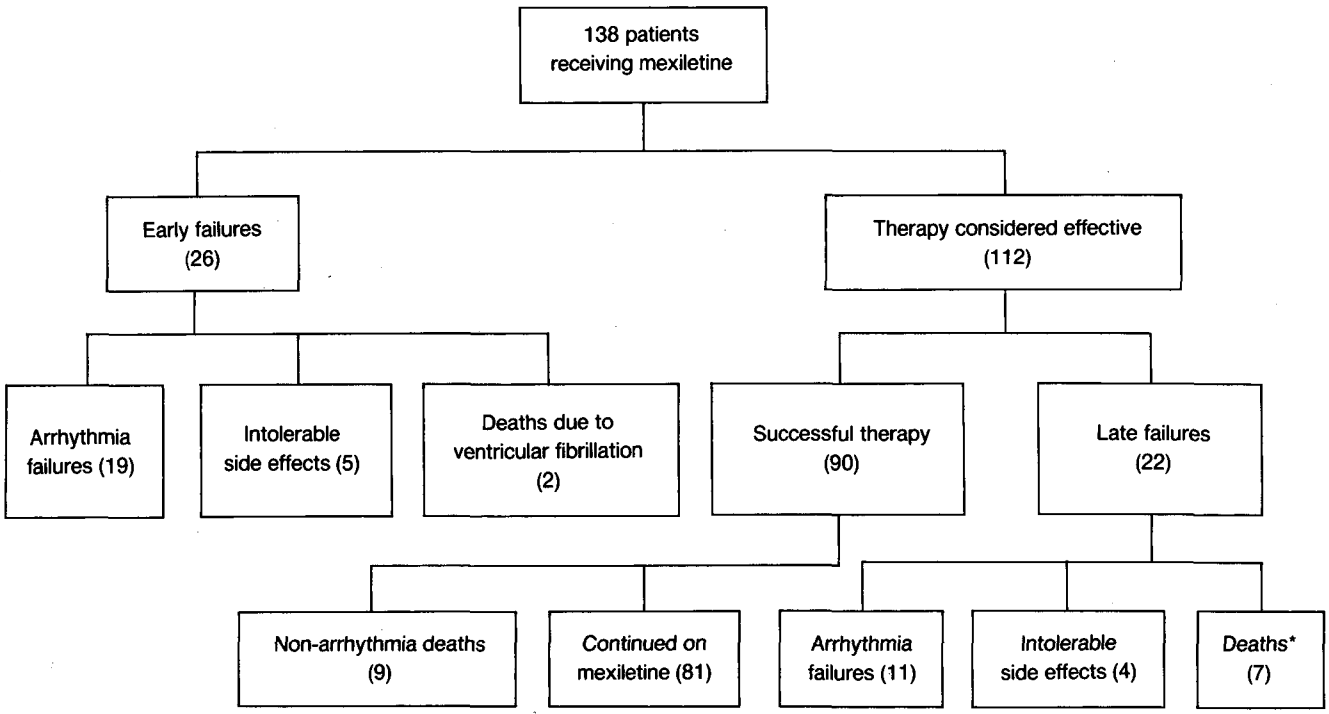


**Figure.** Outcome of 138 patients receiving mexiletine.
* The seven deaths included three that were the result of VF; four were sudden deaths occurring at home.

in 68% and nonsustained VT in 32%*) and symptomatic repetitive ventricular ectopy (triplets) in 24 patients (17%).

Before the mexiletine clinical trial, 113 patients had been treated unsuccessfully with procainamide (mean daily dose, 3.1 ± 1.0 g). A total of 107 patients had received quinidine (mean daily dose, 1.2 ± 0.38 g), and 59 patients had been given disopyramide (mean daily dose, 0.67 ± 0.26 g). In addition, 33 patients had received propranolol (mean daily dose, 0.12 ± 0.09 g) and 16 patients had received diphenylhydantoin (mean daily dose, 0.39 ± 0.09 g). Most patients received multiple antiarrhythmic drugs, either alone or in combination. The average number of drugs failed per person prior to the initiation of mexiletine therapy was 2.8. A drug failure was defined as a recurrence of the arrhythmia on maximally tolerated dosages or the occurrence of intolerable side effects.

* Of these 114 patients, 37 (32%) had experienced one or more episodes of VF.

**Table 2.** Description of nine nonarrhythmia-related deaths

| | No. of patients |
|---|---|
| Myocardial infarction | 2 |
| Congestive heart failure | 3 |
| Respiratory arrest | 1 |
| Pneumonia | 1 |
| Gastrointestinal infarction | 1 |
| Trauma | 1 |

*Electrophysiology testing*

Sixty-six patients underwent electrophysiology studies prior to receiving mexiletine; 45 patients (68%) had inducible ventricular tachycardia (31 sustained, 14 nonsustained). Programmed electrical stimulation was performed for 51 patients receiving mexiletine at a mean of 52 days (range, 2–585 days). Twenty-four patients had inducible VT (16 sustained, 8 nonsustained) at a mean dosage of 727 ± 189 mg (range, 300–1,200 mg) and 27 were noninducible at a mean dosage of 731 ± 256 mg (range, 150–1,200 mg).

*Holter monitor results*

Analysis of the Holter recordings in 109 pa-

tients, performed between two to 1,134 days after administration of mexiletine (mean, 180 ± 257), revealed that 38 patients (32%) were found to have successful premature ventricular contraction (PVC) suppression, defined as (*a*) ≥70% reduction in total PVC count, (*b*) ≥90% reduction in couplets, (*c*) ≥90% reduction in R on T phenomenon when present, and (*d*) 100% reduction in triplets and VT. Seventy-one patients (60%) had unsuccessful PVC suppression; 16 of these still had VT recorded.

*Clinical efficacy*

The results of the mexiletine therapy are summarized (*Figure*). One hundred twelve patients (81%) were considered effectively treated and were discharged from the hospital on mexiletine. The mean length of follow-up was 15 ± 12 months (range, 1 to 34 months). The daily dosage ranged between 150–1,800 mg (mean, 705 ± 293 mg). All but 5 patients received 300 mg or more daily. Therapy subsequently failed in 22 of these patients (*Figure*), including 4 with intolerable side effects, at a mean of 10 months (range, 1 to 34 months) and a mean daily dosage of 734 ± 366 mg (range 200–1,200 mg).

Ninety patients (65%) after hospital discharge achieved successful chronic oral maintenance therapy. Nine nonarrhythmia-related deaths occurred in this group (*Table 2*). Dosage adjustment was required in 5 patients who experienced one or more episodes of documented symptomatic spontaneous sustained VT (mean, 13 ± 10 months; range, 3–29 months) at a mean daily dose of 440 ± 238 mg (range, 150–750 mg). All 5 patients had a prior history of chronic recurrent sustained VT. Arrhythmia control was achieved in all 5 by increasing the daily mexiletine dosage. Three of these patients had either decreased or discontinued their medication because of side effects prior to the recurrence of VT.

*Early failures*

Twenty-six patients were considered early failures (*Figure*). The mean duration of treatment was nine days. Nineteen patients had refractory arrhythmias, despite maximally tolerated dosages (mean daily dose, 810 ± 220 mg). Five patients had the drug discontinued because of intolerable side effects, despite arrhythmia control in 4 of them. Two deaths resulted from VF, two days and four days after the initiation of mexiletine therapy, respectively.

*Comparative statistical analysis*

In comparing the early and late arrhythmia failure groups, there is no statistically significant difference ($P > 0.45$, $t$ test results) in mexiletine dosage. No statistically significant differences in age, sex, cardiac anatomy, or arrhythmia history were found when the 22 late failures were compared to the 90 successes ($t$ test and $\chi^2$ test; all $P$ values $>0.05$). Furthermore, there was no statistically significant difference found in length of follow-up when the group of nine nonarrhythmia-related deaths was compared to the seven late arrhythmia deaths.

*Table 1* describes the breakdown of arrhythmias according to anatomic classification. Clinical efficacy was determined in each subset population. Comparative statistical analysis between subsets was performed using the $\chi^2$ test for association. No statistically significant differences in clinical efficacy were found (all $P$ values $>0.05$).

*Mexiletine plus beta blocking agents*

Forty-two patients either received (23 patients) or continued (19 patients) beta blocking agents (mostly propranolol) for various reasons in combination with mexiletine during their course of therapy. Ten patients with neurological side effects (mostly tremors) received beta blocking agents, permitting a mean reduction in mexiletine dosage of 279 ± 166 mg and subsequent resolution of their symptoms. Altogether, therapy failed for 7 patients because of refractory arrhythmias. The clinical efficacy for these 42 patients receiving beta blockers is statistically significant when compared to those patients receiving mexiletine alone (83% vs. 57% mexiletine alone; $P = 0.001$). For the purposes of this study, those patients receiving mexiletine and beta blocking agents were considered as receiving mexiletine alone.

*Side effects*

Side effects are summarized (*Table 3*). Twenty-eight percent of the patients experienced side effects during the "dose-finding" period prior to hospital discharge and 52% experienced side effects during chronic maintenance therapy. Nausea and tremors were the most common side effects experienced. Dizziness and abdominal pain occurred less frequently. Although side effects were more apparent during chronic oral maintenance therapy, they generally subsided with time and could be reduced by taking the

**Table 3.** Mexiletine side effects

| Side effects | Initial hospitalization (N = 138) Patient number (%) | Chronic therapy (N = 116) Patient number (%) | Last follow-up visit (N = 116) Patient number (%) |
|---|---|---|---|
| Nausea | 22 (15.9) | 44 (37.9) | 18 (15.5) |
| Tremors | 16 (11.6) | 37 (31.9) | 13 (11.2) |
| Dizziness | 10 (7.2) | 13 (11.2) | 3 (2.5) |
| Abdominal pain | 5 (3.6) | 16 (14.0) | 3 (2.5) |
| Vomiting | 4 (2.9) | 7 (6.0) | 1 (0.8) |
| Ataxia | 4 (2.9) | 5 (4.3) | 0 (0) |
| Confusion | 4 (2.9) | 2 (1.7) | 0 (0) |
| Drowsiness | 2 (1.4) | 0 (0) | 0 (0) |
| Insomnia | 2 (1.4) | 0 (0) | 0 (0) |
| Anorexia | 2 (1.4) | 1 (0.8) | 0 (0) |
| Hiccoughs | 1 (0.7) | 1 (0.8) | 0 (0) |
| Dysgeusia | 1 (0.7) | 0 (0) | 0 (0) |
| Dysarthria | 1 (0.7) | 1 (0.8) | 1 (0.8) |
| Visual problems | 1 (0.7) | 1 (0.8) | 1 (0.8) |
| Hot flashes | 1 (0.7) | 0 (0) | 0 (0) |
| Nervousness | 1 (0.7) | 3 (2.5) | 0 (0) |
| Memory loss | 0 (0) | 2 (1.7) | 0 (0) |
| Nightmares | 0 (0) | 4 (3.4) | 2 (1.7) |
| Rash | 0 (0) | 2 (1.7) | 2 (1.7) |
| Diarrhea | 0 (0) | 4 (3.4) | 2 (1.7) |
| Paresthesias | 0 (0) | 4 (3.4) | 1 (0.8) |

drug with food. A diffuse skin rash developed on 2 patients 17 days and 12 months after the onset of mexiletine therapy, requiring their withdrawal from the drug trial. Both patients were receiving 1,200 mg daily.

*Drug safety*

Laboratory parameters were analyzed for evaluation of drug safety. Mexiletine appeared to have no detrimental effect on renal function, as determined by serial blood urea nitrogen (BUN) and serum creatinine levels. No patients had leukopenia ($\leq 2{,}500 \times 10^6$/L) or thrombocytopenia ($\leq 150{,}000 \times 10^6$/L) while on mexiletine. Mild abnormalities (<1.5 times normal) in serum alkaline phosphatase levels were noted in only 2 patients. In both instances, values returned toward normal while the patients continued mexiletine at a lower daily dosage. No abnormalities in serum lactic dehydrogenase, serum glutamic oxalate transaminase, or bilirubin levels were seen.

Positive antinuclear antibody (ANA) titers were observed in 5 asymptomatic patients. Only one titer >1:80 (1:160) was observed, which decreased to 1:80 during 23 months of follow-up. Prior to mexiletine, significant ANA titers ($\geq$1:80) were present in 5 patients (all previously receiving procainamide). These titers decreased or were nonreactive during mexiletine therapy. In only 1 asymptomatic patient did a previously reactive ANA titer of 1:40 increase to 1:80 during 37 months of chronic oral maintenance therapy.

There were no new electrocardiographic conduction disturbances in our patient population receiving mexiletine only during chronic oral maintenance therapy (PR interval [$P = 0.95$] and QRS duration [$P = 0.29$], paired $t$ test). However, 1 patient, a 49-year-old woman with no prior history of sinus-node dysfunction, experienced documented symptomatic 2.4-second sinoatrial pauses after three months on mexiletine (1,000 mg daily). The drug was reduced to 800 mg daily resulting in resolution of symptoms. Follow-up with multiple ambulatory electrocardiographic recordings did not reveal any further sinus-node dysfunction.

No clinical correlation was found between the use of mexiletine and worsening of left ventricular function in patients with left ventricular impairment. No patient deaths could be directly attributed to the use of this drug. Although mexiletine cannot be definitely excluded as a cause

of death in the 2 patients dying from VF, we believe death was a result of recurrent uncontrolled ventricular arrhythmias prior to achieving an adequate therapeutic drug level.

## Discussion

Although it is difficult to standardize drug therapy and make carefully controlled observations, our data suggest that mexiletine is a useful antiarrhythmic drug.

Conclusions regarding drug efficacy are dependent on the standard of measurement. Efficacy can be defined as (*a*) a percent reduction in PVCs, (*b*) a reduction in the episodes of nonsustained ventricular tachycardia, (*c*) a reduction in both asymptomatic and symptomatic sustained ventricular tachycardia, (*d*) patient survival, and (*e*) any combination of the preceding. When there are no adequate control groups for comparison, caution must be used when drawing conclusions about drug efficacy. In our mexiletine-responsive patients, clearly a reduction occurred in both nonsustained and sustained ventricular tachycardia as demonstrated by ambulatory Holter monitoring and clinical assessment by our criteria. However, we could demonstrate only a 32% successful PVC suppression on Holter analysis after the drug therapy. Clearly our clinical efficacy is much higher (65%).

### *Comparison with previous studies*

In comparing studies for drug efficacy, differences in success achieved appear to be the result of careful selection in patient population and definition of drug efficacy. Early studies of patients without drug-resistant ventricular arrhythmias report a better antiarrhythmic effect. Talbot et al[3] reported a 95% reduction in premature ventricular ectopy in 43 of 59 patients (72%) with acute and chronic ventricular arrhythmias. Campbell et al[9] reported complete abolition of ventricular arrhythmias in 19 of 24 patients (79%) and partial suppression (75% PVC reduction and no ventricular tachycardia) in an additional 4 patients. Other studies report similar efficacy in PVC suppression.[2,8,10,14,15,17]

Studies in patients with chronic drug-resistant ventricular arrhythmias (similar to our patient population) are more variable. Abinader and Cooper[1] reported a total abolition of chronic ventricular ectopy in 6 of 10 patients (60%) and a good response (75% PVC reduction and no ventricular tachycardia) in an additional 2 patients. From our patient population, only 32% achieved successful PVC suppression using similar criteria. However, Heger et al[12] found only 2 of 13 patients (15%) had successful PVC suppression (90% reduction) and suppression in the remaining 11 patients was unsuccessful (50% PVC reduction). Likewise, Flaker et al[16] reported successful arrhythmia control in only 6 of 22 patients (27%).

### *Sudden death*

A primary goal in the treatment of ventricular arrhythmias is the prevention of sudden cardiac death. Antiarrhythmic control of advanced grades of ventricular ectopy has been shown to markedly reduce the incidence of sudden death, compared to cases in which antiarrhythmic drugs were unsuccessful.[21] A recent double-blind, sudden-death-prevention trial performed in England failed to demonstrate a significant effect on mortality in patients treated with mexiletine (13% vs. a 12% placebo group).[22] We had a total of nine (7%) arrhythmia-related deaths in our study group. It is uncertain based on our results here whether a reduction in mortality or the prevention of sudden cardiac death can be achieved.

### *Side effects*

This study indicates that side effects are common during mexiletine therapy. Although side effects occurred in over one-half of the patients, the drug had to be discontinued in only 7%. The most common side effect was nausea. Tremor was the second most common side effect and was most often noted in the upper extremities. The types and frequency of side effects observed (*Table 3*) are similar to those reported in the literature.[2,8,10,14,16] Adverse neurological effects appeared to correlate with higher daily dosages of mexiletine. Our experience indicates that side effects can be managed by (*a*) decreasing the daily dosage, (*b*) administering the drug with food, (*c*) using smaller dosages administered more frequently throughout the day, and/or (*d*) using combination drug therapy. Although mexiletine has a long plasma half life of about 12 hours,[23] which may suggest a twice-daily administration, we prefer to administer the drug three times a day to minimize side effects. This dosing method has been shown to achieve therapeutic plasma drug levels.[3,23] In addition, we have found

that the use of beta blocking agents appears to decrease neurological side effects, especially tremors. Beta blockers and other antiarrhythmic agents permit a reduction in mexiletine dosage and may provide a synergistic antiarrhythmic effect. This has been observed by others.[24–27] In our experience, no irreversible side effects occurred as a result of mexiletine therapy.

*Drug safety*

Mexiletine appears to be a relatively safe antiarrhythmic drug. There were no irreversible biochemical abnormalities observed in our patient population. Although 5 patients had a new reactive ANA while on mexiletine, lupus-like reactions were not observed. The drug was also well tolerated in patients with severe left ventricular dysfunction. From our available data, we could not identify a worsening of ventricular arrhythmias or a pro-arrhythmic response, defined as (*a*) a fourfold increase in ventricular ectopy, (*b*) a tenfold increase in repetitive forms, and (*c*) a new emergence of sustained ventricular tachycardia.[28] However, it is conceivable that the deaths of the 2 patients from VF soon after the onset of mexiletine therapy could have been the result of such a response. However, we were unable to definitely incriminate mexiletine as the cause of death. Mexiletine has been reported to aggravate ventricular arrhythmias in 7.6% of the patients,[28] and one must be aware of this potential pro-arrhythmic response when using the drug. Although we did not observe worsening of conduction disturbances in our patients, caution should be exercised in those with severe conduction disturbances.[23]

## Summary

Mexiletine is useful for the treatment of drug-resistant malignant ventricular arrhythmias. In our study group, despite successful PVC suppression by Holter analysis in only 32%, clinical efficacy was achieved in 65%. As a result of the investigational status of mexiletine, our protocol demanded initiation of drug therapy in the hospital for careful observation and arrhythmia monitoring. The drug requires careful individual titration to optimize antiarrhythmic therapy and minimize serious side effects. Side effects were common during mexiletine therapy, but usually well tolerated and only occasionally required discontinuation due to intolerance. Combination therapy permitted lower dosages of mexiletine in some patients and reduced side effects and may improve antiarrhythmic control.

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