Clinical and Electrophysiologic Effects of Chronic Lorcanide Therapy in Refractory Ventricular Tachycardia

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Lorcainide is a class I antiarrhythmic drug currently under investigation in the United States. Initial reports (1-4) of its clinical efficacy in supraventricular and ventricular arrhythmias have been encouraging. However, its clinical efficacy in patients with recurrent ventricular tachycardia is being debated. Conflicting observations have been reported (5,6) regarding its ability to suppress induction of ventricular tachycardia during programmed electrical stimulation after intravenous administration. Lorcainide forms an active metabolite (nor-lorcainide), which accumulates after multiple drug doses and may reach a steady state over several days. This might imply that acute drug testing during programmed electrical stimulation may not predict chronic drug efficacy; however, chronic electrophysiologic and pharmacologic studies assessing lorcainide’s efficacy have not been performed. We evaluated the clinical, electrophysiologic and pharmacologic effects of chronic lorcainide therapy in recurrent refractory ventricular tachycardia associated with organic heart disease using programmed electrical stimulation.

Methods

Patient selection. Twelve patients (10 men and 2 women) ranging in age from 41 to 76 years (mean 63) with recurrent and refractory ventricular tachycardia were studied. Recurrent ventricular tachycardia was defined as three or more documented episodes of ventricular tachycardia and sustained tachycardia was defined as an arrhythmia of more than 30 seconds’ duration or requiring immediate pharmacologic or electrical termination for rapid hemodynamic deterioration in a shorter period of time. Before the study, all
patients had undergone serial electrophysiologic studies with acute and chronic drug testing with conventional agents. Acute drug testing was performed with intravenous lidocaine, procainamide and phenytoin, whereas chronic oral drug testing was performed with quinidine and disopyramide. The highest tolerated drug dose was administered in each instance, and therapeutic drug concentrations were documented at the time of electrophysiologic study.

**Failure to respond to a particular therapeutic agent was defined as the occurrence of any of the following:** 1) reinduction of sustained ventricular tachycardia during electrophysiologic study; 2) spontaneous episodes of sustained ventricular tachycardia with documented therapeutic drug concentrations; and 3) acceleration in rate or change in morphologic features of spontaneous or induced ventricular tachycardia.

All patients in this study had either failed to respond to all conventional agents as defined, or were intolerant of them. Recent acute myocardial injury was excluded in all patients by electrocardiographic and serum enzyme studies. The diagnosis of ventricular tachycardia was made using standard electrocardiographic criteria and proven by intracardiac recordings demonstrating absence of concordance between His and ventricular electrograms with HV intervals less than those in normal sinus rhythm (7). All patients also underwent cardiac catheterization and angiographic studies. Patients were excluded if they had significant hepatic dysfunction, high degree atrioventricular (AV) block or bifascicular block.

**Study design.** Complete history, physical and laboratory examinations were performed for each patient in the study. Antiarrhythmic therapy was discontinued for at least five drug half-lives before control electrophysiographic and electrophysiologic studies. After these studies, intravenous or oral lorcainide, or both, was administered. When intravenous lorcainide was administered as a loading dose, a dose of 200 mg was given at a rate not exceeding 10 mg/min. In one patient in whom oral therapy could not be instituted, intravenous lorcainide administration was continued up to a maximum of 600 mg/day in divided doses. All other patients were started on oral lorcainide therapy (200 to 400 mg/day in divided doses). Oral lorcainide was administered initially as 50 mg every 8 hours. The drug dose was increased up to 100 mg every 6 hours, or until cardiac monitoring demonstrated suppression of spontaneous sustained ventricular tachycardia for a 24 hour period. Oral lorcainide was administered in 11 of 12 patients for a minimal period of 48 hours and a maximal period of 240 hours (mean 106). In one patient, oral lorcainide therapy had to be discontinued because of sleep disturbances after 36 hours of drug administration. This patient was excluded from data analysis.

**Electrophysiologic techniques.** All patients underwent study in the nonsedated postabsorptive state. The initial study was performed in the absence of antiarrhythmic therapy for a period of five drug half-lives before study. With the use of standard venous and arterial catheterization techniques, three to four multipolar electrode catheters were placed in the right and left heart chambers. These were used for atrial and ventricular pacing and continuous monitoring of the His bundle electrogram. Additional electrode catheters were utilized for pacing and recording from other right and left ventricular sites. Femoral artery blood pressure was monitored in all studies utilizing an indwelling arterial cannula. All patients received intravenous heparin for anticoagulation after electrode catheter insertion. Intracardiac electrograms were usually monitored at the right atrium, AV junction at the His bundle location, right ventricle at the apex, septum or outflow tract, and left ventricle at the apex, septum or inferior or lateral wall. Three surface electrocardiographic leads (I, aVF, V1) were also recorded simultaneously with the intracardiac electrograms. The latter were filtered at 40 to 500 Hz and displayed on a multichannel display recorder (Electronics for Medicine VR 12). Data were stored on FM tape and hard copy recordings were obtained at paper speeds of 100 to 250 mm/s. Programmed electrical stimulation was performed utilizing a custom-made programmed stimulator (Bloom Associates, Ltd) that delivered rectangular pulses of 1 ms duration at twice diastolic threshold (0.4 to 2 mA).

The programmed electrical stimulation protocol used for induction of ventricular tachycardia included: 1) single premature atrial extrastimuli during sinus and atrial drive rhythms at two or more drive cycle lengths; 2) rapid atrial pacing with incremental rates until the Wenckebach phenomenon was observed; 3) single premature ventricular extrastimuli in sinus rhythm; 4) single and double premature ventricular extrastimuli in ventricular drive rhythm at two or more drive cycle lengths; 5) bursts of rapid ventricular pacing (15 seconds' duration) at cycle lengths ranging from 400 to 250 ms or up to ventricular refractory periods; and 6) triple and quadruple premature ventricular extrastimuli during ventricular drive rhythm.

**Single premature stimuli (S2)** were introduced at coupling intervals (S1S2) 20 ms shorter than the drive cycle length late in diastole and S1S2 was then progressively shortened by 10 to 20 ms decrements to the point of ventricular refractoriness. The effective refractory period of the right ventricle (VERP) was defined as the longest S1S2 interval that failed to elicit a ventricular response. It was determined at two ventricular pacing cycle lengths (range 400 to 600 ms) for each patient. Mean values of the right ventricular effective refractory period obtained at the two cycle lengths were used for statistical analysis. Subsequent premature stimuli (S1, S4, S6) were then introduced starting with coupling intervals (S1S3, S2S4, and S5S6) 50 ms longer than the shortest S1S2 interval, resulting in consistent capture at a constant drive cycle length (400 ms). These intervals were then de-
Increased by 10 ms until refractoriness was reached and the next premature stimulus was added.

During programmed ventricular stimulation, stimulation was initially performed at the right ventricular apex. If reproducible induction of arrhythmia was not achieved, alternate right ventricular sites were used and the entire stimulation protocol was repeated. If this failed to induce the arrhythmia, left ventricular stimulation from one or more left ventricular stimulation sites was performed using the same protocol. In this study, none of the patients needed pharmacologic agents, isoproterenol, for example, to assist in the induction of ventricular tachycardia. Stimulation protocols were continued until reproducible induction of sustained ventricular tachycardia was achieved.

Follow-up programmed electrical stimulation was performed on completion of oral lorcainide therapy. The entire stimulation protocol for the control study was repeated. The same pacing cycle lengths used in the control study were used in the follow-up electrophysiologic study for determinations of right ventricular effective refractory period. Follow-up programmed electrical stimulation was performed 4 to 6 hours after administration of the previous lorcainide dose. Plasma samples were obtained during the follow-up electrophysiologic study for determination of lorcainide and nor-lorcainide concentrations using previously described methods (8).

Cardiac monitoring. Continuous 24 hour cardiac monitoring (Physio Control CMS 600 telemetry unit) was performed in all patients from time of entry into the study protocol up to 48 to 72 hours after follow-up programmed electrical stimulation during treatment with lorcainide. Recordings were usually obtained during the rest state, but six patients were ambulatory during oral lorcainide treatment.

Noninvasive evaluation. In patients noted to have suppression of sustained ventricular tachycardia during cardiac monitoring and follow-up programmed electrical stimulation, a 24 hour ambulatory electrocardiogram and an exercise test were performed. A 24 hour Holter tape was recorded using the ICR series 7200 Holter recorder and scanning system and was scanned manually. Qualitative and semiquantitative analyses were performed for detection of single, paired or multiform premature ventricular complexes and ventricular tachycardia. A symptom-limited treadmill test was performed using a modified Bruce protocol.

Clinical follow-up. Patients on chronic oral lorcainide therapy were followed up in an outpatient arrhythmia clinic. Periodic cardiac monitoring using repeat ambulatory electrocardiographic recordings or transtelephonic transmitters to monitor arrhythmia recurrence was employed. Duration of follow-up has ranged from 2 to 12 months (mean 7).

Statistical analysis. Statistical comparisons of electrocardiographic intervals (RR, PR, QRS and QTc) and electrophysiologic variables (for example, right ventricular effective refractory period) were performed in 11 patients completing the study using the Student’s paired t test.

Results

Patient characteristics. Ten of the 12 patients in this study had coronary artery disease, and 2 had congestive cardiomyopathy. Six patients were in New York Heart Association functional class II, three were in class III and three in class IV. In the group with coronary artery disease, one patient had two vessel disease and nine patients had triple vessel disease. Left ventricular aneurysms were present in four patients. Left ventricular ejection fraction ranged from 10 to 40% (mean 31 ± 10). Left ventricular end-diastolic pressure ranged from 8 to 45 mm Hg (mean 22 ± 11). Spontaneous sustained ventricular tachycardia was documented in 10 patients, and nonsustained ventricular tachycardia in 2 patients. The duration of ventricular tachycardia in these patients ranged from 1 to 36 months. Ten patients had 5 to 25 episodes of sustained ventricular tachycardia, and nine patients had been resuscitated from one or more cardiac arrests.

Electrocardiographic intervals. Table 1 shows the changes in electrocardiographic intervals in individual patients after chronic lorcainide administration. There was a significant increase in PR interval (187 ± 55 to 219 ± 56 ms; probability [p] < 0.02), QRS duration (107 ± 10 to 127 ± 12 ms; p < 0.001) and QTc interval (404 ± 49 to 482 ± 58 ms; p < 0.005), with no significant change in RR interval (872 ± 147 versus 762 ± 126 ms; p > 0.2).

PR prolongation during treatment with lorcainide was noted both in patients with a normal PR interval and in those with significant first degree atrioventricular (AV) block. One patient had a markedly prolonged PR interval that showed further prolongation on drug therapy. There was no progression to higher degree AV block in any patient during lorcainide administration; however, one patient developed excessive QTc prolongation requiring reduction of the lorcainide dose.

Electrophysiologic observations. Right ventricular effective refractory period could be measured in nine patients before and after chronic lorcainide administration (Fig. 1).

| Table 1. Standard Electrocardiographic Intervals (mean ± 1 standard deviation in ms) During the Control State and After Chronic Lorcainide Therapy |
|-----------------------------------------------|----------------|----------------|----------------|
| Electrocardiographic Intervals               | Control        | Lorcainide     | p Value       |
| RR                                           | 872 ± 147      | 762 ± 126      | > 0.2         |
| PR                                           | 187 ± 55       | 219 ± 56       | < 0.02        |
| QRS                                          | 107 ± 10       | 127 ± 12       | < 0.001       |
| QTc                                          | 404 ± 49       | 482 ± 58       | < 0.005       |

p = probability.
had severe central nervous system side effects and withdrew from the study.

Eleven patients underwent follow-up programmed electrical stimulation after 48 to 240 hours (mean 106) of lorcaïnide therapy. Four patients had no inducible sustained ventricular tachycardia. In one patient, there were no repetitive ventricular responses and in three patients, three to five repetitive ventricular responses could be elicited. In three patients, sustained ventricular tachycardia could be induced with a stimulation protocol that was previously ineffective (fewer extrastimuli or ventricular pacing at slower cycle lengths), but the arrhythmia was significantly slower (mean increase in arrhythmia cycle length 70 ms). In four patients, there was no change from the control study in the arrhythmia cycle length or induction pattern. In all patients with inducible sustained ventricular tachycardia during follow-up studies, the pattern of arrhythmia was identical to that noted during control studies. There were no inducible additional or "nonclinical" patterns of ventricular tachycardia.

Figure 3 shows the response to programmed electrical stimulation during control and follow-up studies in one patient during lorcaïnide therapy. During the control study, three right ventricular extrastimuli induced sustained ventricular tachycardia with a right bundle branch block pattern and a cycle length of 250 ms (Fig. 3, top panel). After initiation of lorcaïnide therapy, three extrastimuli induced a maximum of five repetitive ventricular responses at a slower rate (Fig. 3, lower panel).

**Drug levels.** Plasma lorcaïnide concentration was determined in eight patients at the time of electrophysiologic study and ranged from 100 to 799 ng/ml (mean 310 ± 166). Simultaneous values for nor-lorcaïnide concentration ranged from 116 to 496 ng/ml (mean 256 ± 133) (Fig. 4). There were no significant differences between drug levels in responders and nonresponders.

**Clinical follow-up.** Continuous 24 hour cardiac monitoring during hospitalization demonstrated no recurrence of...
spontaneous ventricular tachycardia in the four patients who showed suppression of sustained ventricular tachycardia induction during follow-up programmed electrical stimulation studies. Two of the four patients were able to complete a treadmill exercise test and had no arrhythmia noted during the test. Lorcainide therapy was continued in these four patients, but one patient was unable to continue treatment after 7 days because of severe sleep disturbances. Periodic Holter monitoring in the remaining patients showed single ventricular premature depolarizations in one patient and multiform and paired premature depolarizations in two patients. These patients have remained arrhythmia-free on lorcainide therapy during a follow-up period of 2 to 12 months (mean 7). One patient with advanced renal failure died after 2 months of treatment.

Nine of the 12 patients entering the study required alternative therapy for their arrhythmia. This included administration of mexiletine (one patient) or amiodarone (six patients) and endocardial resection (two patients).

**Adverse effects.** Sleep disturbances, most commonly insomnia, were noted in five patients receiving oral lorcainide. Three of these patients also reported vivid dreams, and two patients with this side effect withdrew from the study, one after 36 hours and another after 7 days of drug administration. One patient developed marked confusion while on lorcainide therapy, which resolved after reduction in drug dosage.

**Discussion**

**Electrophysiologic effects.** Lorcainide is classified as a type I antiarrhythmic agent on the basis of its cellular electrophysiologic effects. It decreases the rate of rise of the action potential ($V_{max}$), reduces conduction velocity and prolongs the refractory period in a variety of animal tissues (9). It has no effect on slow channel-mediated electrical activity. In human studies (1,10), intravenous lorcainide (2 mg/kg) reduced sinus cycle length, had no effect on intraventricular conduction. Intravenous lorcainide also increased corrected sinus node recovery time, had no consistent effect on atrial effective refractory period, but may or may not have prolonged ventricular effective refractory period (1,10).
Ventriculoatrial conduction was abolished (O'Keefe DB, unpublished observations).

In our study, oral lorcaimide did prolong atrioventricular and intraventricular conduction and ventricular repolarization. In contrast to intravenous administration, chronic oral administration does not alter sinus cycle length and significantly prolongs ventricular effective refractory period. Oral effects may be due to accumulation either of the parent compound at the tissue level or of the active metabolite, nor-lorcaimide alone, or a combination of both effects. Nor-lorcaimide has been reported to have electrophysiologic effects comparable with those of the parent compound (11).

**Antiarrhythmic effects.** Intravenous and oral lorcaimide have been efficacious in suppression of ventricular premature depolarizations in uncontrolled and controlled studies (2–4, 12). The efficacy of lorcaimide in patients with recurrent ventricular tachycardia is unclear. Cocco and Strozzi (13) reported suppression of ventricular tachycardia in six of seven patients with recurrent ventricular tachycardia or fibrillation with oral doses of 200 to 300 mg/day. Somani and di Giorgi (2) reported a similar result in a single patient. Studies (5,6) on the efficacy of intravenous lorcaimide in suppression of induced ventricular tachycardia using programmed electrical stimulation have been in apparent conflict. Somberg et al. (5) found intravenous lorcaimide to be more effective than intravenous lidocaine and comparable with intravenous procainamide in suppression of electrically induced ventricular tachycardia. However, Sung and Somani (6) did not report any success in suppression of induced ventricular tachycardia in five patients with drug refractory ventricular tachycardia. These differences are probably related to patient selection in these studies, with more refractory arrhythmias in the latter study.

In our study, oral lorcaimide suppressed electrically induced ventricular tachycardia in 4 of 11 patients with refractory ventricular tachycardia. Oral administration results in substantially greater effects on ventricular refractoriness and this could explain the response in this patient group. It could also be explained by inability to attain sufficiently premature coupling intervals after lorcaimide to initiate ventricular tachycardia. Drug concentrations for both lorcaimide and nor-lorcaimide at the time of electrophysiologic study were in the therapeutic range reported for chronic oral therapy in other studies. However, the efficacy rate in refractory ventricular tachycardia was certainly not striking, and adverse effects resulted in further attrition in the number of patients able to continue long-term drug therapy.

Adverse effects were frequent and difficult to manage. We therefore conclude that chronic lorcaimide therapy may be effective in some patients with refractory ventricular tachycardia, but continued long-term therapy is severely limited by its adverse effects.

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**References**

