Comparison of the electrophysiologic effects of intravenous and oral lorcainide in patients with recurrent ventricular tachycardia

Debra S. Echt, M.D., L. Brent Mitchell, M.D.,* Robert E. Kates, Ph.D., and Roger A. Winkle, M.D.

ABSTRACT  The electrophysiologic effects of intravenous lorcainide (2.2 mg/kg) in 10 patients were compared with the electrophysiologic effects of oral lorcainide (mean dose 400 mg/day for 8 days) in 11 patients, all with recurrent ventricular tachycardia that could be induced with programmed stimulation. Intravenous and oral lorcainide resulted in similar prolongation of the QRS, QT, and HV intervals, but only oral lorcainide resulted in prolongation of the AH interval and atrial and ventricular effective refractory periods. After both oral and intravenous lorcainide, ventricular tachycardia could still be induced, but the arrhythmia was slower and better tolerated hemodynamically. The mean plasma lorcainide level during a maintenance intravenous infusion was 1254 ± 662 ng/ml compared with a lorcainide level of 562 ± 41 ng/ml and a norlorcainide level of 1212 ± 653 ng/ml after oral dosing. No norlorcainide was detected in plasma after intravenous lorcainide. These data suggest that the short-term electrophysiologic effects of intravenous lorcainide may be different from those of short-term therapy with the oral drug. These differences should be considered during short-term studies of lorcainide.


LORCAINIDE is a new antiarrhythmic drug that decreases the rate of rise of phase 0 of the cardiac intracellular action potential, and the conduction velocity, spontaneous activity, and effective refractory period in isolated dog Purkinje fibers, dog papillary muscles, and guinea pig auricles.1 Lorcainide is clinically effective in the treatment of premature ventricular contractions, reciprocating supraventricular tachycardia using an accessory pathway, and ventricular tachycardia.2-5 Previous studies have described the electrophysiologic effects of intravenous lorcainide in man, and several of these have included data on the effect of the drug on the inducibility of ventricular tachycardia.5-7 In contrast to the large amount of data available describing the electrophysiologic effects of intravenous lorcainide, there are only limited data on the oral drug. During long-term oral therapy a metabolite, norlorcainide, accumulates to plasma concentrations approximately two times those of lorcainide.3,8,9 Norlorcainide has been administered to a single patient and was found to suppress chronic premature ventricular complexes.10 In dogs, norlorcainide has electrophysiologic activity similar to that of lorcainide11; however, its effects in man are unknown. If the electrophysiologic effects of norlorcainide differ from those of lorcainide, as has been implied for encainide and its metabolites,12 this would have important implications regarding the therapeutic testing and management of patients on oral compared with those on intravenous lorcainide.

In this study, we have compared the clinical electrophysiologic effects of lorcainide during short-term intravenous administration with those observed during short-term oral therapy in two similar groups of patients with recurrent ventricular tachycardia.

Methods

Patient selection. Twenty-one patients with recurrent sustained ventricular tachycardia that required drugs or cardioversion for termination took part in this study. Treatment with multiple antiarrhythmic drugs had failed in all patients, failure being the result of clinical tachycardia recurrence, drug failure at electrophysiologic testing, drug contraindications, or adverse drug effects. Subjects received lorcainide under a compassionate-use protocol and with approval of the Human Subjects Com-
mittee. Written informed consent was obtained for both lorcainide use and electrophysiologic testing.

Electrophysiologic testing. All patients underwent a baseline electrophysiologic study for determination of electrophysiologic parameters and to document the inducibility of ventricular tachycardia with programmed stimulation. All antiarrhythmic agents except digoxin were withdrawn for a minimum of five half-lives before baseline electrophysiologic testing. The instrumentation and techniques used to perform programmed stimulation have been previously reported.13 The order in which induction modes were used was: rapid atrial pacing; single atrial premature beats during atrial drive (A2A2); single, double, and triple ventricular premature beats during spontaneous rhythm (V2V2V2, V2V2V2); single, double, and triple ventricular premature beats during ventricular drive (V1V2, V1V2V1, V1V2V2V2); and rapid ventricular bursts. If ventricular tachycardia was not induced by a ventricular drive rate just faster than the intrinsic sinus rate, the stimulation was repeated with ventricular drive cycle lengths of 700, 600, 500, 430, and 400 msec. Ventricular burst pacing was initiated at a cycle length of 400 msec and repeated at shorter cycle lengths until the pacing stimulus failed to result in 1:1 ventricular capture. Systemic arterial pressure was continuously monitored via a femoral artery catheter. Electrophysiographic measurements included the RR cycle length during spontaneous rhythm, and the QRS duration, QT interval, and QT interval corrected for heart rate [with the use of the formula QTc = QT (sec)/√RR (sec)] during atrial pacing of constant cycle length. All intervals measured were averaged over three cardiac cycles. Other baseline electrophysiologic parameters measured included the sinus node recovery time, Wenckebach cycle length, HV and AH intervals, right atrial effective refractory period during paced rhythm, atrioventricular node effective, relative, and functional refractory periods during constant atrial paced rhythm, and right ventricular effective refractory period during constant right ventricular paced rhythm.14

All patients underwent ventricular tachycardia induction by programmed stimulation, both before and while receiving lorcainide. During episodes of the induced ventricular tachycardia, morphologic characteristics, cycle length, and mean arterial pressure were determined.

Patient groups

Group A. Group A consisted of 10 patients who received intravenous lorcainide during the baseline electrophysiologic study. Lorcainide was administered as a 2.2 mg/kg loading dose over 20 min that was followed by a maintenance infusion of 0.55 mg/kg/min via Harvard pump and through a peripheral vein for 20 min. During the 20 min loading infusion RR, QRS, QT, HV, and AH intervals and arterial pressures were recorded and measured at 5 min intervals. During the maintenance infusion all electrophysiologic measurements were repeated at the same basic drive cycle lengths used in baseline testing, and a second attempt was made at ventricular tachycardia induction. None of the patients in group A were enrolled into group B.

Group B. Group B comprised 11 patients who underwent a control electrophysiologic study followed by a period of therapy with oral lorcainide. None of the patients in group B received intravenous lorcainide loading at any time. Oral lorcainide therapy was initiated a mean of 26.6 ± 41.6 days (range 0 to 153) after the control study was performed. A total daily dose of 400 mg was the therapeutic goal, but the dose was lowered in patients with electrophysiographic or clinical signs of lorcainide toxicity and raised in patients with persisting ventricular tachyarrhythmias. Patients underwent repeat electrophysiologic testing after 5 to 7 days on the initial lorcainide dosage regimen.

Lorcainide plasma concentrations. Blood samples for plasma drug concentrations were collected from group A patients at 5, 10, 15, and 20 min during the loading period and at 25, 30, and 40 min during maintenance infusion. In group B patients a single blood sample was collected at the completion of the electrophysiologic study. Blood samples were obtained from the intra-arterial catheter, centrifuged, frozen at −20°C, and later analyzed for lorcainide and norlorcainide concentrations with a high-pressure liquid chromatography assay.15

Statistical analysis. The mean baseline electrocardiographic and electrophysiologic data and ventricular tachycardia characteristics were compared for the two groups with the use of a nonpaired two-tailed t test. The significance of changes in measured parameters in each group after lorcainide was determined with the use of a two-tailed, paired t test for matched pairs.

Results

Comparability of groups A and B. There were no significant differences in the general clinical characteristics of patients in the two groups (table 1). The baseline electrophysiologic data for the groups were also analyzed for comparability. There was no statistical difference between groups in baseline QRS, QT, QTc, HV, or AH intervals or right atrial or ventricular effective refractory periods during paced rhythm. The characteristics of the induced ventricular tachycardias in the two groups before lorcainide differed in that the mean cycle length was longer (320 ± 61 vs 256 ± 56 msec) and the mean blood pressure higher (66 ± 26 vs 40 ± 14 mm Hg) in group A compared with in group B.

Drug dosing and plasma levels. Group A patients received a mean lorcainide loading dose of 146.7 ± 30.5 mg iv, and a mean maintenance infusion of 27.2 ± 7.4 mg iv. The plasma lorcainide level remained constant through the 40 min infusion, as depicted in figure 1. The mean plasma lorcainide concentration during the maintenance infusion was 1254 ± 662 ng/ml. No norlorcainide was present in any sample from group A. In group B the mean oral loading period

<table>
<thead>
<tr>
<th>n</th>
<th>10 men</th>
<th>11 men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>63 ± 5.3</td>
<td>62 ± 8.2</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Cardiomyopathy, nonischemic</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>NYHA classification (CHF symptoms)</td>
<td>2.3 ± 1.2</td>
<td>2.2 ± 0.6</td>
</tr>
<tr>
<td>Left ventricular function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular end-diastolic pressure (mm Hg)</td>
<td>15 ± 8.0</td>
<td>19 ± 7.1</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>30 ± 11</td>
<td>31 ± 13</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>2.2 ± 0.7</td>
<td>2.5 ± 0.9</td>
</tr>
<tr>
<td>No. of antiarrhythmic drugs previously failed</td>
<td>3.8 ± 0.8</td>
<td>5.3 ± 1.3</td>
</tr>
</tbody>
</table>

Values, where appropriate, are mean ± SD.
before restudy was 8.2 ± 1.3 days. The median dose on the day of restudy was 200 mg bid, with a range of from 100 to 400 mg bid, and the mean lorcanide plasma concentration was 562 ± 41 ng/ml. The mean norlorcanide level was 1212 ± 653 ng/ml.

Electrophysiologic measurements. In group A, during the 20 min lorcanide loading infusion QRS, QT, and HV intervals were each progressively and significantly prolonged (figure 2). The spontaneous RR cycle length, AH interval, and mean arterial pressure did not change significantly.

The electrophysiologic values before and after lorcanide for each group, the mean percentage change, and statistical significance are summarized in table 2. In both groups the QRS, QT, QTC, and HV intervals were prolonged with lorcanide. However, the AH interval and the atrial and ventricular effective refractory periods were prolonged significantly (by 22.6%, 13.2%, and 17.3%, respectively) only after the oral loading dose (figure 3). In the majority of patients, the atrioventricular effective refractory period could not be determined because it was equal to or exceeded by the atrial effective refractory period.

Ventricular tachycardia induction. In the baseline study sustained ventricular tachycardia could be induced in all patients in both groups and this effect was reproducible. One patient in group A had continuous ventricular tachycardia that was not terminated by an intravenous loading dose of lorcanide. After termination of the ventricular tachycardia with rapid pacing, tachycardia could not be reinduced. In all remaining patients in both groups, ventricular tachycardia remained inducible after lorcanide.

The ventricular tachycardia cycle length increased in nine of 10 patients after intravenous lorcanide infusion, and in 10 of 11 patients after oral lorcanide therapy (table 3). This slowing of ventricular rate was statistically significant, with a mean change from 320 ± 61 to 398 ± 73 msec in group A, and a mean change from 256 ± 56 to 401 ± 114 msec in group B. Slowing of ventricular tachycardia rate was associated with an increase in the mean arterial blood pressure, particularly in group B patients (figure 4). The mean arterial pressure increased from 66 ± 26 to 75 ± 30 mm Hg in group A patients and from 40 ± 14 to 76 ± 23 mm Hg in group B patients after lorcanide. Compared with baseline, the morphologic characteristics of induced ventricular tachycardia were unchanged in seven patients and changed in two patients in group A, while in group B it was the same in six and different in five patients.
Among individual patients the programmed stimulation mode required to induce ventricular tachycardia frequently changed slightly after lorcainide compared with baseline. However, there was no consistent trend toward making ventricular tachycardia either more difficult or easier to induce. Of note, however, was the observation that after lorcainide therapy ventricular tachycardia was induced by rapid atrial stimulation in five of the 21 patients. Tachycardia was not induced by this mode before lorcainide (figure 5). The ease of

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A (n = 10)</th>
<th>Group B (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous cycle length RR (msec)</td>
<td>649 ± 130 to 614 ± 92</td>
<td>↓ 5.4%</td>
</tr>
<tr>
<td>Mean BP (mm Hg)</td>
<td>96 ± 13 to 95 ± 14</td>
<td>↓ 1.5%</td>
</tr>
<tr>
<td>SNRT (msec)</td>
<td>1080 ± 483 to 1230 ± 1128</td>
<td>↑ 13.9%</td>
</tr>
<tr>
<td>WCL (msec)</td>
<td>384 ± 83 to 406 ± 58</td>
<td>↑ 3.7%</td>
</tr>
<tr>
<td>AVN-RRP (msec)</td>
<td>120 ± 32 to 153 ± 38</td>
<td>↑ 27.2%</td>
</tr>
<tr>
<td>QT (msec)</td>
<td>365 ± 39 to 388 ± 47</td>
<td>↑ 9.1%</td>
</tr>
<tr>
<td>QTc (msec)</td>
<td>486 ± 45 to 517 ± 60</td>
<td>↑ 6.4%</td>
</tr>
<tr>
<td>HV (msec)</td>
<td>46 ± 8 to 57 ± 13</td>
<td>↑ 25.1%</td>
</tr>
<tr>
<td>AH (msec)</td>
<td>104 ± 46 to 104 ± 38</td>
<td>0%</td>
</tr>
<tr>
<td>A-ERP (msec)</td>
<td>243 ± 41 to 247 ± 31</td>
<td>↑ 1.6%</td>
</tr>
<tr>
<td>V-ERP (msec)</td>
<td>241 ± 23 to 248 ± 14</td>
<td>↑ 2.9%</td>
</tr>
<tr>
<td>AVN-RPP (msec)</td>
<td>502 ± 80 to 491 ± 63</td>
<td>↓ 2.2%</td>
</tr>
<tr>
<td>AVN-FRP (msec)</td>
<td>415 ± 80 to 399 ± 76</td>
<td>↓ 3.8%</td>
</tr>
</tbody>
</table>

Values, where appropriate, are mean ± SD.
BP = blood pressure; SNRT = sinus node rhythm; WCL = Wenckebach cycle length; QTc = QT interval corrected for heart rate; A-ERP = right atrial effective refractory period during paced rhythm; V-ERP = right ventricular effective refractory period during paced rhythm; AVN-RPP = atrioventricular node relative refractory period; AVN-FRP = atrioventricular node functional refractory period.

TABLE 3
Ventricular tachycardia induction

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Cycle length RR (msec)</td>
<td>320 ± 61 to 398 ± 73</td>
<td>↑ 24.2%</td>
</tr>
<tr>
<td>Mean BP (mm Hg)</td>
<td>66 ± 26 to 75 ± 30</td>
<td>↑ 14.6%</td>
</tr>
</tbody>
</table>

Values, where appropriate, are mean ± SD.
BP = blood pressure.
ventricular tachycardia induction after drug was unrelated to the drug plasma levels attained.

Discussion

The findings of our study with regard to the electrophysiologic effects of intravenous lorcainide are in general agreement with those published by others. All studies have shown that intravenous lorcainide significantly slows His-Purkinje and intraventricular conduction, as measured by prolongation of the HV and QRS intervals. There is disagreement in the literature as to the effects of intravenous lorcainide on sinus and atrioventricular nodal electrophysiologic measurements. Sinus node function was unchanged in our study. However, in the studies by Kasper et al.\(^6\) and Ng et al.,\(^7\) the sinus cycle length decreased and sinus node recovery time increased. The AH interval was unchanged in our study, but was prolonged in two of three studies of intravenous drug by other authors. Somewhat inconsistent reports from study to study on the effects of sodium channel–blocking drugs on sinus or atrioventricular nodal functions are not uncommon since these structures are heavily influenced by changes in autonomic tone. The studies of intravenous lorcainide do not demonstrate a consistent effect on the atrial effective refractory period. Although the study by Ng et al.\(^7\) showed a small but significant increase in the atrial effective refractory period at a dose of 2.5 mg/kg, there was no significant increase at a dose of 1.25 mg/kg or when data from the low and high doses were combined. The results of Kasper et al.\(^6\) showed a significant increase in the ventricular effective refractory period, but the mean change was only 3.1%.

In our study, with administration of oral drug the QRS, QT, and HV intervals were prolonged to the same extent as after intravenous drug. However, in contrast to the findings after intravenous lorcainide, we also observed significant increases in the AH interval and in the atrial and ventricular effective refractory periods. The mean increases of 13.2% and 17.3% in atrial and ventricular effective refractory periods after oral drug were considerably greater than changes noted in any previous study (including the present one) after intravenous lorcainide. The different electrophysiologic effects of oral compared with intravenous drug was also recently reported for encainide.\(^12\) The changes noted were similar to those in our study, with atrial and ventricular refractoriness prolonged only after oral encainide. It has been hypothesized that active encainide metabolites formed principally after oral dosing are responsible for the differing electrophysiologic effects. This may also be true for lorcainide. Norlorcainide plasma levels far exceeded lorcainide levels after several days of oral loading doses,\(^9\) and perhaps the additional electrophysiologic effects reflect properties of norlorcainide in man. A discrepancy in electrophysiologic properties could cause variable responses to intravenous and oral preparations in a given patient. It is intriguing to speculate that the successful treatment with oral, but not intravenous, lorcainide of ventricular ectopy in two patients in another series\(^4\) was due to the differing electrophysiologic effects. However, in a canine study by Keefe et al.\(^11\) in which intravenous lorcainide and norlorcainide were administered as separate compounds no differences were found in electrophysiologic effects. Another possible explanation of the differences in electrophysiologic actions of oral and intravenous lorcainide could be a temporal alteration in lorcainide drug distribution and tissue saturation with a slower equilibration of drug effect on atrial and ventricular refractoriness compared with its other electrophysiologic effects.
A. BEFORE LORCAINIDE

![Electrocardiogram before lorcainide](image)

B. AFTER LORCAINIDE

![Electrocardiogram after lorcainide](image)

**FIGURE 4.** Ventricular tachycardia induction with programmed stimulation. Leads I, II, III, aVL, AVF, and V₁ refer to surface electrocardiogram recordings. Intracardiac electrocardiograms include recordings from the high right atrial (RA) region, the right ventricular (RV) apex, and the His position. BP refers to the systemic arterial blood pressure recording. S₁ is the ventricular drive pacing stimulus artifact and S₂, S₃, and S₄ are the extrastimuli. A. Before intravenous lorcainide infusion, ventricular tachycardia was induced with three extrastimuli in ventricular drive rhythm. The ventricular tachycardia cycle length was 250 msec and the mean aortic pressure was 40 mm Hg. B. After lorcainide administration, ventricular tachycardia was induced with two extrastimuli in ventricular drive rhythm. Ventricular tachycardia cycle length increased to 340 msec and mean aortic blood pressure increased to 60 mm Hg.

The mean lorcainide plasma level of 1254 ng/ml attained during maintenance infusion in our patients receiving intravenous drug is higher than the levels reported in patients in other series. The mean plasma lorcainide and norlorcainide concentrations of our patients receiving oral drug were also quite high compared with those in other series, a fact that in part reflects the higher drug doses used in these patients with refractory disease. The fact that higher lorcainide levels were observed in our patients after intravenous compared with after oral dosing eliminates the possibility that the additional electrophysiologic effects of oral lorcainide were a dose-dependent phenomenon.

In our study ventricular tachycardia could be induced with programmed stimulation in all but one patient after either oral or intravenous lorcainide therapy. Breithardt et al. reported that ventricular tachycardia could be induced in eight of 11 patients after intrave-
nous lorcanide loading, and in four of four patients on oral therapy. Bär et al. observed slowing of ventricu-
lar tachycardia rate followed by successful termination after intravenous lorcanide in four of five patients. The four patients successfully treated underwent pro-
grammed stimulation later and ventricular tachycardia could be induced again in three patients. In our study, the rates of the induced ventricular tachycardias were significantly slower, resulting in higher mean arterial pressures. The resultant hemodynamic stability during ventricular tachycardia has encouraged us to attempt long-term therapy in several patients with highly drug-refractory ventricular tachycardia despite persistence of inducible ventricular tachycardia.

The mode of stimulation required to induce ventricu-
lar tachycardia changed in many patients in our study, but there was no clear trend in terms of the number of ventricular extrastimuli needed for induction. These results are not exactly comparable to those of Bär et al. and Breithardt et al. since they used less aggressive protocols in which only one extrastimulus or two extrastimuli were used. In Breithardt’s study patients with plasma concentrations of lorcanide of greater than 660 ng/ml tended to require more aggressive stim-
ulation for ventricular tachycardia induction, but in our study this correlation was not present. It is noteworthy that in five of our patients ventricular tachycardia was induced with rapid atrial pacing after lorcanide ther-
apy. In our experience induction of ventricular tachycardia by this technique is quite uncommon at baseline so that the inducibility of tachycardia by this pacing mode after lorcanide seems to be a drug effect. Since we do not use this induction mode routinely after drug administration (it was used in this study as a means of measurement of sinus node recovery time), we cannot compare this effect of lorcanide to that of other drugs studied in our laboratory.

We conclude that potentially important electrophys-
ologic differences may exist between orally and intra-
venously administered lorcanide. In virtually all pa-
tients ventricular tachycardia could still be induced after drug administration, but the rhythm was slower and better tolerated hemodynamically.

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