ELECTROPHYSIOLOGICAL EFFECTS OF A NEW ANTIARRHYTHMIC AGENT, LORCAINIDE, ON THE ISOLATED CARDIAC MUSCLE FIBER AS COMPARED WITH DISOPYRAMIDE

KOKI SHIGENOBU,* HIDEKO ATODA (née TATSUNO),** TOSHIKO ASANO AND YUTAKA KASUYA

Department of Chemical Pharmacology, Faculty of Pharmaceutical Sciences, The University of Tokyo, Bunkyo-ku, Tokyo, 113, Japan

(Received May 23, 1980)

Electrophysiological effects of a new antiarrhythmic agent, lorcainide, were studied in the isolated guinea pig ventricular myocardium and were compared with those of disopyramide; some of the experiments were also made by using the canine ventricular myocardium. Both lorcainide and disopyramide selectively depressed the maximum rate of rise of the action potential with little effect on the resting and overshooting potential. The action potential duration tended to be shortened slightly, and the prolongation of the refractory period produced by these agents was only slight. Both agents did not produce the substantial modification of the slow response produced by isoproterenol in the depolarized muscle at the concentrations enough to depress the maximum rate of rise of the action potential. Both agents also produced the marked depression of the rate of rise of the action potential of the canine ventricular muscle, and the conduction velocity measured in the canine false tendon was markedly decreased by both agents. It was concluded that both lorcainide and disopyramide are typical Class I agents according to the classification proposed by Vaughan-Williams and that lorcainide is about 10 times (at least 3 times) more potent than disopyramide in this respect.

Keywords — antiarrhythmic agent; lorcainide; cardiac action potential; quinidined-like action; disopyramide; rate of rise of the action potential; conduction velocity

INTRODUCTION
Lorcainide hydrochloride or N-(4-chlorophenyl)-N[1-(1-methyl-ethyl)-4-piperidinyl]-benzeneacetamide mono-hydrochloride is a new antiarrhythmic agent and has been shown to be effective against various types of arrhythmias including post-infarction and ouabain-induced ventricular arrhythmias, and acetylcholine- and acenitine-induced arrial fibrillation.1) Its antiarrhythmic properties were also evaluated clinically.2) The purpose of the present paper is to examine the electrophysiological effects of lorcainide and to compare them with those of disopyramide which is widely used in this country.

METHODS AND MATERIALS
Male guinea pigs (250—300 g) were sacrificed by a sharp blow and beating hearts were quickly removed. After washing the blood in the ventricular cavity, the free wall of the right ventricle was dissected out for the microelectrode study. The preparation was placed in an organ bath containing 30 ml physiological salt solution and maintained at 37°. Bathing solution was continuously circulated with the bubbling gas mixture (95% O₂ and 5% CO₂). The mM composition of the physiological salt solution used was as follows: NaCl 135, KCl 3, CaCl₂ 2, MgCl₂ 1, NaHCO₃ 15 and glucose 5.5. Conventional
microelectrode penetrations were made into the endocardial surface using glass capillary micro-
pipettes filled with 3 M KCl. The action potentials were displayed on a Nihon Kohden dual beam oscilloscope Model VC-9 after passing through a microelectrode preamplifier (Nihon Kohden, Model MEZ 8101). The maximum rate of rise of the action potential and $dV/dt$ were measured in most experiments using a conventional R-C circuit for electronic differentiation. The preparations were driven by external electrical stimulation using bipolar platinum electrodes and rectangular current pulses (5 msec duration) at a constant frequency of 1 Hz.

For the measurement of the refractory period, test shocks were applied to the preparation through another unipolar external electrode placed closely to the recording electrode at various periods of the repolarization phase of the action potential. Current strength of the test shock was monitored and the strength-interval curve (excitability recovery curve in the refractory period) was obtained.

To examine the effects of the drugs on the slow channel system, slow response was produced by isoproterenol after inactivating the fast sodium channels by elevating the external potassium concentration to 30 mM. After the establishment of the stable slow response, test drugs were applied.

Since fibers running unidirectionally without branching are hardly obtainable in the guinea pig heart, canine hearts were used for the measurements of the conduction velocity. Young mongrel dogs (5–10 kg) were anesthetized with sodium pentobarbital; the heart was quickly removed and the ventricular cavity was washed thoroughly with physiological salt solution. False tendons were carefully examined in the right or left ventricular cavity. An appropriate single false tendon running freely from the endocardial surface without branching was carefully dissected with the attached small piece of endocardium (about 5 × 5 mm) at both ends of a single false tendon. The preparation was pinned down at the edge of the attached endocardium on the paraffine block in the organ bath. One end of the false tendon was stimulated by a bipolar external electrode at a constant frequency and the conducted action potentials were recorded at the other end of the false tendon with a glass microelectrode. Conduction velocity was calculated on the basis of the time lag from the stimulus at the one end to the rising phase of the action potential recorded at the other end and the length of the false tendon be-

![Diagram](image-url)

**FIG. 1. Typical Action Potential recorded from a Guinea Pig Ventricle and the Effect of Lorcaidine**

Records for 3 different doses of lorcainide are illustrated in each row. Left column: control action potential before lorcainide addition. Right column: action potentials obtained 6 min after the addition of lorcainide. A — B: $3 \times 10^{-6}$ M of lorcainide; C — D: $3 \times 10^{-5}$ M; E — F: $10^{-4}$ M. Time and voltage calibrations in F apply to all panels.
between the stimulating electrode and the recording microelectrode which was measured under a dissecting microscope with calibrated scale. Simultaneously obtained canine right ventricular free wall preparations were also used for the study of the effects of these agents on the rate of rise of the action potential; microelectrode penetrations were made into Purkinje fibers on the endocardial surface.

Lorcainide and disopyramide were generously supplied by Kyowa Hakko Kogyo Co. and Janssen Pharmaceutical Co., respectively.

RESULTS

1) Action Potential

Lorcainide did not produce drastic changes in the shape of the action potential, but the spike component was abolished especially at the high concentrations (Fig. 1). In Fig. 2 are shown the changes in the maximum rate of rise of the action potential and the amplitude produced by various concentrations of lorcainide as a function of time after the addition of the drug. As shown, the maximum rate of rise of the action potential ($+V_{\text{max}}$) was depressed with time and dose-dependently. However, the amplitude of the action potential did not change significantly even in the relatively high concentrations with the exception of $3 \times 10^{-4}$ M; at this highest concentration, the amplitude of the action potential diminished significantly at 5—10 min after the drug addition. The effects of disopyramide were qualitatively the same as those of lorcainide as shown in Figs. 3 and 4; it did not produce drastic changes in the shape of the action potential but produced a significant depression of the rate of rise without affecting the amplitude of the action potential. When comparing Figs. 2 and 4, the degree of the depression of $+V_{\text{max}}$ produced by $10^{-5}$ M lorcainide was roughly the same as that produced by $3 \times 10^{-5}$ or $10^{-4}$ M disopyramide. Therefore, the potency of lorcainide to produce the depression of

![Graph showing the effect of various doses of lorcainide on the maximum rate of rise (+$V_{\text{max}}$) and amplitude of the action potential.](image)

**FIG. 2. Effect of Various Doses of Lorcainide on the Maximum Rate of Rise (+$V_{\text{max}}$) and Amplitude of the Action Potential**

Solid line indicates the changes in $+V_{\text{max}}$ and the scale is at the left. Broken line indicates the changes in the amplitude and the scale is given at the right side. 3 plots are shown on each dose. C indicates the control value obtained before the addition of the drug. 1 and 5 indicate the values obtained from 1 to 5 min and 5 to 10 min after the addition of the drug, respectively.
\( +V_{\text{max}} \) is considered to be 3-10 times higher than that of disopyramide.

In Figs. 5 and 6 are shown the dose-response relationship with respect to the effects of lorcainide and disopyramide on the amplitude of the action potential, \(+V_{\text{max}}\) and the duration of the action potential. Each value is normalized and plotted as the percentage of the control value. It is also shown in these figures that both drugs selectively depressed the maximum rate of rise of the action potential without producing marked changes in the amplitude of the action potential, and that the depression of \(+V_{\text{max}}\) produced by \(10^{-8}\) M lorcainide was about the same as that produced by \(10^{-4}\) M disopyramide. The action potential duration (APD) tended to be shortened by both drugs, which was, however, not significant in the low concentrations.

Lorcainide showed a considerably strong negative chronotropic action in the guinea pig right atrial preparations, \(10^{-6}, 10^{-5}\), and \(3 \times 10^{-5}\) M lorcainide decreased the beating rate to 90%, 68% and 51% of the control rate, respectively (average of 4 experiments). In contrast, negative chronotropic action of disopyramide was less marked. \(10^{-6}, 10^{-5}\) and \(10^{-4}\) M disopyramide produced the reduction of the beating rate to 89%, 85%, and 84% of the control value, respectively (average of 4 experiments).

2) *Refractory Period*

The strength-interval curve was drawn in each experiment, and the absolute refractory period and the diastolic stimulus threshold were determined in each preparation. The results are listed in Table I. As shown, both lorcainide and disopyramide prolonged the absolute refractory period in all cases, but the degree of the prolongation was not so marked. The diastolic stimulus threshold was elevated by both drugs in many cases, but in some cases, they did not produce substantial changes in the diastolic stimulus threshold.

3) *Conduction Velocity*

After the conduction velocity in control condition was determined in each preparation, the drug was added cumulatively and the conduction velocity was determined 5 min after each dose. Mean control conduction velocity determined in the absence of the drug was 0.68±0.09 m/sec. Conduction velocity was decreased by both drugs dose-dependently as shown in Fig. 7. With respect to the activity to decrease the conduction velocity, lorcainide appeared to be about 10 times

![Diagram of action potentials](image)

**FIG. 3.** Effect of Disopyramide on the Shape of the Action Potential recorded from a Guinea Pig Ventricle illustrated in the Same Manner as in Fig. 1, except for the Dose of the Drug

\( A - B: 3 \times 10^{-3}\) M; \( C - D: 10^{-4}\) M; \( E - F: 3 \times 10^{-4}\) M.
FIG. 4. Effect of Disopyramide on $+ \dot{V}_{\text{max}}$ and the Amplitude of the Action Potential. Illustrations are exactly the same as in Fig. 2.

FIG. 5. Dose-response Relationship on the Effect of Lorcaainide on the Amplitude, Maximum Rate of Rise ($+ \dot{V}_{\text{max}}$), and the Duration of the Action Potential. Ordinate of each graph: % of control value before the drug addition. Broken line represents the value measured from 1 to 5 min after the addition of each dose, and the solid line 5 to 10 min. 50%, 70% and 90% duration means the time to repolarize to the level of 50, 70 and 90% of the total height of the action potential.
more potent than disopyramide; 50% reduction in the conduction velocity was obtained by about $10^{-5}$ M lorcainide and about $10^{-4}$ M disopyramide. In the presence of $3 \times 10^{-5}$ M lorcainide, the action potential did not propagate to the site of microelectrode penetration.

Since the main determinant of the conduction velocity is the rate of rise of the action potential, effects of both agents on the rate of rise of the action potential of canine Purkinje fiber were examined. As a result, lorcainide depressed the maximum rate of rise of the Purkinje action potential markedly. With respect to the depression of the maximum rate of rise, lorcainide was far more potent than disopyramide. 50% reduction in the rate of rise was achieved by about $10^{-5}$ M lorcainide and about $3 \times 10^{-4}$ M disopyramide; this result is in fairly good agreement with the result on the conduction velocity. The rising phase of the Purkinje action potential was extremely depressed in the presence of $3 \times 10^{-5}$ M lorcainide, indicating the highly progressed decremental conduction.

4) Slow Response
To determine the possible influence of lorcainide and disopyramide on the slow channel system, slow responses were produced by $10^{-7}$ M isoproterenol in the guinea pig ventricular muscle depolarized to about 40 mV by elevating the external potassium concentration to 30 mM. As shown in Fig. 8, both lorcainide and disopyramide did not produce substantial changes in the slow response at the concentration of $3 \times 10^{-4}$ M. However, at the concentration as high as $10^{-3}$ M, both agents produced the depression of the slow response.

---

**FIG. 6. Effects of Disopyramide: Dose-response Relationship**

Illustrations are made exactly in the same manner as in Fig. 5.
TABLE I. Changes in the Absolute Refractory Period and Diastolic Stimulus Threshold produced by Lorcanide and Disopyramide

<table>
<thead>
<tr>
<th>Experiment No.</th>
<th>ARD(^{90% APD}) × 100(^a) (Diastolic threshold, mA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before drug</td>
</tr>
<tr>
<td>1</td>
<td>82 (0.3)</td>
</tr>
<tr>
<td>2</td>
<td>77 (0.25)</td>
</tr>
<tr>
<td>3</td>
<td>73 (0.38)</td>
</tr>
<tr>
<td>4</td>
<td>75 (0.14)</td>
</tr>
<tr>
<td>5</td>
<td>61 (0.2)</td>
</tr>
<tr>
<td>6</td>
<td>81 (0.38)</td>
</tr>
<tr>
<td>7</td>
<td>80 (0.35)</td>
</tr>
<tr>
<td>8</td>
<td>55 (0.75)</td>
</tr>
<tr>
<td>9</td>
<td>66 (0.45)</td>
</tr>
<tr>
<td>10</td>
<td>73 (0.25)</td>
</tr>
<tr>
<td>11</td>
<td>82 (0.23)</td>
</tr>
<tr>
<td>12</td>
<td>100 (0.45)</td>
</tr>
<tr>
<td>13</td>
<td>80 (0.65)</td>
</tr>
<tr>
<td>14</td>
<td>80 (0.23)</td>
</tr>
<tr>
<td>15</td>
<td>70 (0.35)</td>
</tr>
<tr>
<td>16</td>
<td>80 (0.55)</td>
</tr>
</tbody>
</table>

\(^a\) Absolute refractory period relative to 90% duration of the action potential.

Absolute refractory period and the diastolic threshold (given in the parenthesis) are determined on the strength-interval curve.

FIG. 7. Changes in Maximum Rate of Rise (\(+\dot{V}_{\text{max}}\), A) and Conduction Velocity (B) produced by Lorcanide and Disopyramide

Condition velocity and maximum rate of rise were measured in the canine false tendon and terminal Purkinje fiber, respectively (see Methods). Drugs were given cumulatively and the measurements were made 5 min after each dose. Ordinate: Percent of the control value before the drug addition. Abscissa: Molar concentration of drugs. Microelectrode was held in the same cell before and after the drug addition in each experiment.
DISCUSSION

Present results clearly demonstrated that both lorca
inide and disopyramide are quinidine-like antia
rrhythmic agents. In other words, according to the classification proposed by Vaughan-Williams, these agents are classified to be Class I agents. They selectively depressed the rising phase of the action potential with little effect on the resting potential and the shape of the action potential. With respect to the depression of the maximum rate of rise, lorca
inide was about 10 times (at least 3 times) more potent than disopyramide. Since the amplitude of the action potential was not depressed significantly (indicating little or no changes in the resting and overshoot potential) at the concentrations which produced the significant reduction in maximum rate of rise, it would appear that the reduction in maximum rate of rise produced by both agents is mainly due to the depression of the fast sodium channels. A good correlation has been shown between fast sodium current and maximum rate of rise of the action potential.  

The other parameters we examined in relation to arrhythmias were the refractory period and conduction velocity. Both lorca
inide and disopyramide were tested at different concentrations to determine their effects on these parameters. As shown in the diagram, lorca
inide had a greater effect on the refractory period than disopyramide. The refractory period was significantly reduced by lorca
inide, whereas disopyramide had a lesser effect. The conduction velocity was also affected by both agents, with lorca
inide having a greater effect than disopyramide. The diagram clearly shows the differences in the effects of the two agents on the refractory period and conduction velocity.

**FIG. 8. Effect of Lorca
inide and Disopyramide on the Slow Response**

Slow response was produced by adding $10^{-7} \text{M}$ isoproterenol after inactivating the fast Na$^+$ channels by elevating the external K$^+$ concentration to 30mM. Isoproterenol-induced slow response was stable for at least 20 min; as shown in the upper row, the slow response recorded 7 min after the addition of isoproterenol is about the same as that recorded immediately after its appearance. Middle row: Effect of $3 \times 10^{-4} \text{M}$ disopyramide and lorca
inide on the slow response; as shown, the slow response was not significantly modified 4 min after the addition of the drugs. Bottom row: Effect of $10^{-3} \text{M}$ disopyramide and lorca
inide; at this high concentration, the slow response was markedly depressed by both agents. Superimposed photographs indicate the progress of the depression of the slow response.
Electrophysiology on Lorcaínide 685

Opyramide prolonged the refractory period. In addition, these agents also elevated the diastolic stimulus threshold in many cases. However, these changes were not marked and the APD was not prolonged, but rather shortened. Therefore, these agents have little characteristics as Class III antiarrhythmic agents.

Conduction velocity was decreased by both agents dose-dependently. With respect to this effect, lorcaínide was again about 10 times more potent than disopyramide. Both agents also depressed the rising phase of the action potential of canine Purkinje fibers, and the relative effectiveness of these agents to depress the maximum rate of rise was in fairly good agreement with their effects to depress the conduction velocity. In the presence of the highest concentration of lorcaínide we tested ($3 \times 10^{-5}$ M), the action potential did not propagate along the false tendon. The measurements of the maximum rate of rise of the action potential of the Purkinje fiber suggested that the highly progressed decremental conduction occurred at this high concentration. When comparing the effects on the guinea pig ventricular muscle with those on the canine Purkinje fiber, it appears that canine Purkinje fiber may be more sensitive to lorcaínide.

The action potential duration tended to decrease slightly by the application of these agents. The ionic mechanisms to produce this change are not known at present. Lorcaínide and disopyramide did not produce the substantial modification of the slow response produced by isoproterenol in the depolarized ventricular muscle at the concentrations sufficient to produce the significant depression in the rising phase of the action potential. Therefore, although these agents depressed the slow response at the highest concentration tested ($10^{-3}$ M), the inhibition of the slow inward current (Class IV action according to Vaughan-Williams) is unlikely to be involved in the mechanisms of the antiarrhythmic actions of these agents.

In conclusion, both lorcaínide and disopyramide were shown to affect various electrophysiological parameters related to arrhythmias. All of the changes produced by these agents, including the reduction in the maximum rate of rise, prolongation of the refractory period, elevated diastolic threshold and decrease in the conduction velocity, are considered to act antiarrhythmically. However, so-called quinidine-like action (Class I action according to Vaughan-Williams) must be the main mechanism of the antiarrhythmic action of these agents. In this respect, lorcaínide is about 10 times (at least 3 times) more potent than disopyramide.

REFERENCES
3) K.Shigenobu and N.Sperlakis: Calcium current channels induced by catecholamines in chick embryonic hearts whose fast sodium channels are blocked by tetrodotoxin or elevated potassium, Circulation Res., 31, 932–952 (1972).