Effects of Lidocaine and Droxicainide on Myocardial Necrosis: A Comparative Study

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Lidocaine has been shown to protect ischemic myocardium, but the degree of its effectiveness is not yet well established. Therefore, in this study, the effects of this drug on ultimate infarct size were examined quantitatively. Another member of the same class of drugs, droxicainide (ALS1249), DL-N-(2-hydroxyethyl)-pipecolinyl-2,6-dimethylanilide hydrochloride, is a new antiarrhythmic agent that has shown a good therapeutic index in the initial experimental studies. Accordingly, the effects of this drug on ultimate infarct size were examined and compared with those of lidocaine.

Coronary artery occlusion was performed on 29 dogs. One minute later, technetium-99m labeled microspheres were injected into the left atrium for assessment of the hypoperfused zone (the zone at risk of infarction). Fifteen minutes after occlusion, the dogs were randomized into three groups: 9 dogs served as a control group, 10 were given lidocaine and 10 were given the same dosage of droxicainide. Six hours after occlusion, the dogs were sacrificed and the hearts cut into 3 mm thick slices and incubated in triphenyltetrazolium chloride to delineate the area of myocardial damage. Autoradiography of the same slices provided images of the areas of myocardial hypoperfusion. Thereafter, in each dog, the percent of hypoperfused area that evolved to necrosis was calculated. In control dogs, it was 85.6 ± 2.0%; in lidocaine-treated dogs, 68.1 ± 4.1% (p < 0.01), a reduction of 20%; and in droxicainide-treated dogs, 50.1 ± 5.3%, a reduction of 41% (p < 0.001 versus control and p < 0.005 versus lidocaine).

Lidocaine is the antiarrhythmic agent most widely used in patients with acute myocardial infarction. Droxicainide is a new membrane-stabilizing agent about which only limited information exists. The initial experimental studies (1,2) reported that droxicainide appears to have a more potent antiarrhythmic activity and fewer side effects than lidocaine; however, these studies need further confirmation. Lidocaine has been reported to protect the ischemic myocardium (3–6), but these results are quantitatively controversial because of the technique employed to measure the extent of the protection. The protective effects of droxicainide on ischemic myocardium have not been tested.

The purpose of this study was to compare the effects of lidocaine and droxicainide—two drugs that have the same mechanism of action on arrhythmias—in the extent of myocardial ischemic injury. To accomplish this goal, the area of myocardial hypoperfusion (the zone at risk) was defined in all animals by the distribution of radioactive microspheres injected 1 minute after coronary artery occlusion. This permitted: 1) determination of the effectiveness of each drug separately, and 2) establishment of their relative efficacy.

Methods

Experimental preparation. Twenty-nine mongrel dogs (average weight, 18.0 ± 0.3 kg) were anesthetized with sodium thiamylal (25 mg/kg body weight, administered intravenously as a bolus). Respiration was maintained through an endotracheal tube with room air using a Harvard respirator. The heart was exposed through a left thoracotomy in the fifth intercostal space and suspended in a pericardial cradle. Polyethylene cannulas were used in the left carotid artery to monitor systemic arterial pressure in the jugular vein for administration of drugs and in the left atrium for injection of radiolabeled microspheres. Systemic arterial pressure and electrocardiographic lead aVF were recorded on a multichannel recorder (Gould Instruments). The left anterior descending coronary artery was dissected free from the adjacent tissue and permanently ligated with a silk su-
ature. One minute after coronary artery occlusion, $2 \times 10^6$ human albumin microspheres (mean diameter 20 $\mu$m, 3M Company) labeled with 8 mCi of technetium-99m were injected into the left atrium for the assessment of the zone of myocardial hypoperfusion. The injection of the microspheres lasted 15 seconds and was followed by an injection of 10ml of normal saline solution ("flush") over a period of 10 seconds. These injections of microspheres and their subsequent distribution in the myocardium, which define the areas of hypoperfusion, were done under the hemodynamic conditions occurring 1 minute after coronary artery occlusion; autoradiography, as reported later, was performed postmortem.

**Treatment groups.** Fifteen minutes after occlusion, the dogs were randomly assigned into three groups: 1) a control group of 9 dogs that received no drug; 2) a lidocaine-treated group of 10 dogs that received lidocaine hydrochloride; and 3) a droxicainide-treated group of 10 dogs that received droxicainide, DL-N-(2-hydroxyethyl)-pipecolinyl-2,6-dimethylanilide hydrochloride. (The drug was kindly supplied by G. Aberg, PhD, its inventor.) Both lidocaine and droxicainide were administered intravenously, 15 minutes after coronary artery occlusion in a dose of 2.5 mg/kg as a bolus and then as a continuous infusion for 6 hours (1.4 mg/kg). Six hours after occlusion, all dogs were sacrificed by intravenous administration of 20 mEq of potassium chloride.

**Postmortem preparation of left ventricle.** After sacrifice, the heart was excised. The distance from the origin of the coronary artery to the occlusion site was measured and the free wall of the right ventricle, atria, valves, great vessels and epicardial fat were removed from the left ventricle. The left ventricle was frozen to $-70^\circ$C and cut into 20 to 25 slices, 3 mm thick, parallel to the atrioventricular groove.

**Assessment of infarct size.** To assess the extent of myocardial necrosis (infarct size), all slices were incubated in a 1% solution of triphenyltetrazolium chloride for 10 minutes at 37°C, which stained the normal myocardium bright red and rendered the infarcted area yellow. Then the slices were immersed in a 10% solution of formaldehyde to enhance the difference in color between the normal and damaged myocardium. The tetrazolium staining technique (7,8) is based on depletion of dehydrogenases from the injured myocardium. The changes in color produced by the tetrazolium stain are closely related to the pathologic changes of myocardial necrosis. Recently, this technique was reviewed (9–11) and it was concluded that on the basis of both ultrastructural changes and light microscopy with hematoxylin-eosin, there is an excellent correlation between these techniques, which are the standards for myocardial infarction, and tetrazolium staining. The areas of necrosis observed in these experiments were contained within the areas of hypoperfusion and were traced onto transparent plastic sheets and measured with planimetry. Infarct size (IS) was expressed as a percent of the total area of the left ventricle.

To assess the extent of the hypoperfused zone of the myocardium, all the slices were then autoradiographed by placing them on X-ray film (Cronex 4, Dupont). The areas without blood flow were the "cold spots," whereas the areas with blood flow were the "hot spots." (12–14). "Soft" X-ray exposures (25 kVP, 100 mA) were made to delineate more accurately the perimeters of the slices. These were superimposed on the autoradiographs. In this manner, the otherwise invisible inner and outer arcs, the borders of the "cold spots," could be visualized (Fig. 1). The outlines of both areas were traced onto plastic sheets and measured with planimetry. The hypoperfused zone was then calculated as a percent of the total area of the left ventricle.

In each dog, the percent of the area at risk (that is, the hypoperfused zone) that evolved to necrosis was calculated by dividing the latter (IS) by the former (HZ) and multiplying by 100 (IS/HZ $\times$ 100). Use of this variable permitted assessment of whether the administration of a drug could reduce the extent of necrosis for a given zone at risk as compared with the percent of the hypoperfused zone that evolves to necrosis in an untreated (control) group of dogs.

**Hemodynamic studies.** In six additional dogs, the hemodynamic effects of droxicainide were studied. The dogs were anesthetized and the chest opened as in the previous groups. Left ventricular pressures were obtained through a catheter-tip pressure transducer (Millar Mikro-Tip pressure transducer catheter) with a built-in reference saline-filled catheter (model PC-480, Millar Instruments). Aortic pressures were obtained through a saline-filled catheter introduced into the left carotid artery. These pressures, as well as the electrocardiograms (lead aVF) and the first derivative of left ventricular pressure, were recorded on a polygraph (Brush, Gould Instruments). After instrumentation, the left anterior descending coronary artery was dissected free from the adjacent tissue and occluded. Fifteen minutes after occlusion, droxicainide was given in the same dosage as in the previous group. To evaluate the effects of the drug, all variables were compared at 15 minutes—that is, just before drug administration—and again in another 15 minutes.

**Statistical analysis.** The results were analyzed using one way analysis of variance. A paired t test compared hemodynamic changes in individual animals. All data were expressed as mean ± standard error of the mean (SEM) (15).

**Results**

Before randomization, the distance between the ostium of the left coronary artery and site of occlusion and the size of the hypoperfused zone were similar in all dogs. Hemodynamic variables measured before occlusion or just after occlusion (and therefore before randomization) were also
similar in dogs randomized into control and treated groups (Table 1).

Myocardial necrosis. There was a wide variation (from 8 to 42\% of the left ventricle) in the extent of the hypoperfused zones; however, the average in each of the three groups was similar. Thus, the hypoperfused zone (as a percent of the left ventricle) was 24.9 ± 3.4\% (n = 9) in the control group, 27.6 ± 3.2\% (n = 10, not significant [NS]) in the lidocaine-treated group and 24.9 ± 3.1\% (n = 10, NS) in the droxicainide-treated group. Infarct size (as a percent of the left ventricle) was 21.2 ± 3.0\% (n = 9) in the control group, 18.5 ± 2.3\% (n = 10, NS) in the lidocaine-treated group and 13.2 ± 2.2\% (n = 10, NS versus control and NS versus lidocaine) in the droxicainide-treated group. The percent of the hypoperfused zone that evolved to necrosis was 85.6 ± 2.0\% in the control group. This was reduced by 20\% in lidocaine-treated dogs (68.1 ± 4.1\%, p < 0.01) and 41\% in droxicainide-treated dogs (50.1 ± 5.3\%, p < 0.001 versus control, p < 0.005 versus lidocaine) (Fig. 2).

By using each dog as its own control, it was possible to calculate the percent of the hypoperfused zone (HZ) that evolved to necrosis. In each group, a good correlation was obtained between the percent of the left ventricle that was hypoperfused (at risk) and the amount of necrosis (IS). Thus, in the control group, the relation was IS = 0.86HZ - 0.06 (n = 9, correlation coefficient [r] = 0.98) (Fig. 3). In the treated group, the percent of the hypoperfused zone that evolved to infarction was significantly smaller, but the extent of the reduced infarction was still proportional to the initial extent of the zone of hypoperfusion. Thus, the relation was IS = 0.64 HZ + 0.72 (n = 10, r = 0.87) in the lidocaine-treated group, and IS = 0.67 HZ - 3.39 (n = 10, r = 0.91) (Fig. 3) in the droxicainide-treated group.

Hemodynamic variables. Coronary artery occlusion in the six additional dogs studied for hemodynamic status (Ta-

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**Table 1. Characteristics of 29 Randomized Dogs After Coronary Artery Occlusion and Before Administration of Drugs**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Lidocaine</th>
<th>Droxicainide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occlusion distance (cm)*</td>
<td>2.4 ± 0.2</td>
<td>1.7 ± 0.2</td>
<td>2.2 ± 0.3</td>
</tr>
<tr>
<td>Hypoperfused zone (% left ventricle)</td>
<td>24.9 ± 3.4</td>
<td>27.6 ± 3.2</td>
<td>24.9 ± 3.1</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>140 ± 5</td>
<td>166 ± 9</td>
<td>150 ± 8</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>97 ± 5</td>
<td>101 ± 10</td>
<td>85 ± 4</td>
</tr>
</tbody>
</table>

*Distance between ostium of left anterior descending coronary artery and site of occlusion.
Values are expressed as mean values ± standard error of the mean.
...monly used in patients with acute myocardial infarction, both to abolish arrhythmias and to provide prophylactic treatment (16–18). Protection of the ischemically injured myocardium with a resulting smaller infarction is an attempt to improve ventricular function (19–25), because anatomicopathologic and clinical studies have shown the relation between the extent of myocardial necrosis and cardiogenic shock (26–29).

An antiarrhythmic agent that could also protect ischemic myocardium would have great potential clinical usefulness. Accordingly, in this investigation we compared two antiarrhythmic agents: lidocaine, which is the drug most commonly used in patients with acute myocardial infarction, and droxicainide, which is also a membrane stabilizer that has been reported to have more potent antiarrhythmic effects than lidocaine and fewer neurologic side effects (1,2). Their relative effectiveness in protecting the ischemic myocardium was studied using a technique that permitted us to delineate the zone of hypoperfusion (that is, the zone at risk of infarcting) after coronary artery occlusion in vivo under the actual conditions of collateral flow, heart rate, intraventricular pressure and perfusion pressure (12–14). The extent of this zone of hypoperfusion is the major factor in determining the extent of myocardial necrosis.

In the control (untreated) dogs in this study, there was a close correlation between the extent of the zone of hypoperfusion and the resulting extent of the zone of necrosis (r = 0.98), which is in accordance with the close correlation obtained previously (13,14). Thus, with this technique it is possible to overcome the variability in the anatomy of coronary artery distribution and in the richness of collateral vessels to accurately determine the extent of the zone at risk of infarcting.

**Protective effect of lidocaine versus droxicainide.** Using this technique, we demonstrated that lidocaine had mild protective effects; it decreased the expected extent of damage by 20%. This reduction in damage, although statistically and probably biologically significant, was similar to that caused by hyaluronidase (13) and prostacyclins (30), but much less marked than that caused by other agents, such as certain beta-adrenergic blocking drugs (31) or calcium antagonists (32), which decrease damage by approximately 40%.

Previous studies on the protective effect of lidocaine on the ischemically injured myocardium (3–6,33) are in agreement about its beneficial effects. The electrocardiographic, electronmicroscopic, enzymatic and electrolytic variables used in these studies did not permit exact quantification of the reduction of the extent of myocardial damage. Nasser et al. (4), using pathologic techniques, demonstrated that lidocaine reduced infarct size markedly from 12.6 to 4.8 g. However, the infarcts in the nontreated dogs (12.6 g) were much smaller than those in the control dogs in the present study (18.4 g), which indicates that the zones of hypoper-

![Figure 3](https://example.com/figure3.png)

**Figure 3.** Relation between hypoperfused zone (on the abscissa) and infarct size (on the ordinate) in the control (circles) and droxicainide-treated (diamonds) dogs. Each symbol represents one dog. LV = left ventricle; other abbreviations as before.
fusion in that study were much smaller (lower coronary artery occlusion). We have recently demonstrated, with a calcium channel antagonist, that the efficacy of an agent in reducing infarct size depends on the size of the initial zone of hypoperfusion (14). Thus, when the zone of hypoperfusion is small and an effective drug is given, the decrease in infarct size is the most marked. This, therefore, can explain the apparent discrepancy between the two studies. Droxicainide reduced the expected infarct size by an average of 41%. This marked reduction was statistically significant in comparison not only with the control value but also with that obtained with lidocaine. The reduction in the expected infarct size with droxicainide was more pronounced in dogs with smaller than with larger zones of hypoperfusion, because the slope of regression lines was steeper (0.68) than the 0.49 that would have occurred if reduction in infarct size had been 41% with all hypoperfused zones. The good correlation coefficient (0.91) indicates that the alteration due to the influence of the extent of the hypoperfused zone was progressive and proportional.

Mechanisms of action. The mechanisms of action of lidocaine or droxicainide in protecting the ischemic myocardium are unknown; however, it seems that the hemodynamic changes, in most instances, cannot explain their effects. Thus, in the present study, preload, afterload and contractility did not change and heart rate decreased only slightly, which cannot explain the marked effect of droxicainide in reducing myocardial ischemic damage. The most accepted theory is that these drugs stabilize the cell membranes and thus preserve the integrity of the membranes, which may be of crucial importance in cell survival. The local anesthetic effect may be responsible for these beneficial effects (4), although the local anesthetic effects of other drugs such as d-propranolol are not effective in salvaging the ischemic myocardium (34).

Clinical implications. Extrapolation of these results to the clinical situation must be performed only with extreme caution because of species differences and limitations of the model. However, if droxicainide shows effects in patients similar to those exhibited in experimental dogs, this drug may be a substitute for lidocaine because of its more pronounced antiarrhythmic activity and its more marked protection of the ischemic myocardium.

**References**


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**Table 2. Hemodynamic Effects of Droxicainide in Six Dogs**

<table>
<thead>
<tr>
<th></th>
<th>Before Occlusion</th>
<th>p Value</th>
<th>15 Min After Occlusion</th>
<th>p Value</th>
<th>30 Min After Occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>140 ± 7.6</td>
<td></td>
<td>141 ± 8.2</td>
<td>&lt;0.005</td>
<td>134 ± 7.4</td>
</tr>
<tr>
<td>Systolic arterial pressure (mm Hg)</td>
<td>117 ± 3.7</td>
<td>&lt;0.05</td>
<td>104 ± 3.4</td>
<td></td>
<td>106 ± 3.0</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mm Hg)</td>
<td>95 ± 3.6</td>
<td>&lt;0.025</td>
<td>83 ± 3.1</td>
<td>&lt;0.05</td>
<td>85 ± 3.2</td>
</tr>
<tr>
<td>Left ventricular systolic pressure (mm Hg)</td>
<td>119 ± 3.6</td>
<td>&lt;0.05</td>
<td>108 ± 3.1</td>
<td>&lt;0.05</td>
<td>108 ± 4.0</td>
</tr>
<tr>
<td>Left ventricular end-diastolic pressure (mm Hg)</td>
<td>4 ± 0.8</td>
<td>&lt;0.05</td>
<td>6 ± 1.3</td>
<td></td>
<td>6 ± 1.4</td>
</tr>
<tr>
<td>Left ventricular dP/dt max (mm Hg/s)</td>
<td>2,656 ± 275</td>
<td>&lt;0.01</td>
<td>2,062 ± 200</td>
<td>&lt;0.005</td>
<td>2,040 ± 192</td>
</tr>
<tr>
<td>Left ventricular dP/dt0 (mm Hg/s)*</td>
<td>1,699 ± 237</td>
<td></td>
<td>1,567 ± 144</td>
<td></td>
<td>1,572 ± 145</td>
</tr>
</tbody>
</table>

*Measured at 40 mm Hg of developed pressure

$dP/dt =$ rate of rise in left ventricular pressure, $p =$ probability.
infarct size quantification: validation of the triphenyltetrazolium chloride tissue enzyme staining technique. Am Heart J 1981;101:593–600.


