Effects of Amiodarone on Refractory Ventricular Fibrillation in Acute Myocardial Infarction: Experimental Study

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Objectives. The aim of this study was to evaluate the efficacy of a single dose of intravenous amiodarone in facilitating defibrillation of ventricular fibrillation refractory to lidocaine and epinephrine plus direct current countershocks in experimental acute myocardial infarction.

Background. Amiodarone has been hailed as the most effective single antiarrhythmic drug for the treatment of ventricular arrhythmias. However, intravenous amiodarone has only sporadically been used in the defibrillation of ventricular fibrillation in acute myocardial infarction.

Methods. Acute myocardial infarction was induced in 60 dogs by ligation of the proximal left anterior descending coronary artery for 2 h. Animals that developed spontaneous ventricular fibrillation were treated with lidocaine and epinephrine plus five direct-current countershocks. Dogs with ventricular fibrillation refractory to this regimen were randomized to further treatment with additional intravenous administration of epinephrine and bolus lidocaine plus ≤15 direct-current countershocks (group I) or administration of amiodarone, 10 mg/kg body weight intravenously, followed by defibrillation with direct-current countershock (group II).

Results. Sixteen (27%) of the 60 dogs in which the protocol was attempted developed spontaneous ventricular fibrillation 21 min after ligation and were included in the study. Lidocaine and epinephrine plus five direct-current countershocks succeeded in converting ventricular fibrillation in one dog (6%). The other 15 dogs were randomized to group I (8 dogs) or group II (7 dogs). Defibrillation was achieved in one of the eight dogs in group I and in six of the seven dogs in group II (p < 0.005).

Conclusions. In an experimental model of acute ischemia, intravenous amiodarone (10 mg/kg) influences positively the response to defibrillation of ventricular fibrillation refractory to lidocaine and epinephrine plus direct current countershocks.

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descending coronary artery was dissected free and a lubricated umbilical tape tunneled underneath. The tape was then used to occlude the vessel for 2 h. A catheter was placed into the aortic arch and an arterial pressure line established for blood pressure monitoring throughout the experiment. Another catheter was placed into the left atrium for left atrial pressure recording. Adequate intravascular volume was maintained with lactated Ringer solution. All experiments conformed to the “Position of the American Heart Association on Research Animal Use” adopted by the Association in November 1984 (30).

Arrhythmia treatment protocol. All dogs were treated prophylactically with lidocaine 1.5 mg/kg bolus and continuous infusion of 1 mg/min throughout the experiment. Dogs that developed ventricular fibrillation during the 2 h of coronary artery ligation first received “standard treatment” (Fig. 1). First, a direct-current countershock of 50 J was delivered by two, 8-cm diameter, spoon-shaped electrodes secured to the heart. If sinus rhythm was not restored, a second direct-current impulse of 50 J was delivered. If ventricular fibrillation persisted, intravenous sodium bicarbonate was used to maintain blood at pH ≥ 7.3. During ventricular fibrillation ventilation was provided by the volume ventilator, which was adjusted to the levels maintained before the onset of ventricular fibrillation. A third direct-current countershock of 50 J was then delivered. Epinephrine (1.0 mg) was given intravenously and direct cardiac massage was performed for 1 to 2 min before a fourth direct-current impulse of 50 J was delivered. A fifth defibrillation attempt was made before ventricular fibrillation was characterized as refractory. Cardiac massage was instituted to maintain circulation during fibrillation. The dogs were then randomized into two groups (Fig. 2). In group 1, up to 15 defibrillation attempts with direct-current countershocks of 50 J each were allowed if defibrillation was not obtained while the dog was receiving conventional therapy (additional intravenous administration of bicarbonate, epinephrine and bolus lidocaine). In group II, intravenous amiodarone (10 mg/kg) was first administered to the animals over 30 s because of the emergency situation, then cardiac massage was performed for 1 min and followed by attempted defibrillation with direct-current countershocks. Dogs that did not develop spontaneous ventricular fibrillation during the 2 h of coronary artery ligation continued on protocols of myocardial salvage by reperfusion in combination with intraaortic balloon pump assistance (unpublished data).

Heart rate and hemodynamic variables. Heart rate, intraarterial blood pressure and left atrial pressure were recorded.

Amiodarone assay. Blood samples drawn within 30 min after amiodarone bolus administration and defibrillation of refractory ventricular fibrillation were centrifuged, plasma-separated and frozen. Samples were assayed for amiodarone by high pressure liquid chromatography (16) using n-hexane extracts of serum and the 2-ethyl,3-(4-dimethylaminoethoxy,3,5-diodo,benzoyl) as internal standard and an Amino-sil-x-1 column (Perkin-Elmer).

A standard curve of free drug serum containing 0.5, 1.0 and 2 mg/liter of amiodarone was prepared and used to calculate the concentration of the drug in the unknown samples. The reproducibility within 1 day was estimated by extracting 10 replicate serum samples containing 0.5, 1 and 2 mg/liter of amiodarone. The coefficient of variation of concentration ratio of amiodarone:internal standard was < 4%, whereas the lower limit of quantitation was 0.1 mg/liter. These findings were consistent with previous results (16).

Tissue samples of amiodarone from both infarcted and...
Figure 2. Standard treatment (up to five attempts) for defibrillation of ventricular fibrillation. Conventional therapy includes additional epinephrine and bolus lidocaine in addition to up to 15 defibrillation attempts. *p < 0.005 versus group I.

noninfarcted myocardium were also obtained at the termination of the experiment, frozen, homogenated with methanol and further extracted with n-hexane as described previously (31). Amiodarone concentration was then determined under the same conditions as for serum analysis (16).

Analysis of data. Heart rate and hemodynamic variables were averaged and presented as mean value ± SD. A paired t test was used to assess differences among the data sets for changes in variables (after amiodarone administration and defibrillation versus control stage [before ventricular fibrillation occurred]). The Fisher exact test was used to detect differences between groups. Significance was claimed at a level of p < 0.05 for two-tailed hypotheses.

Results

The protocol was attempted in 60 dogs. The mean heart rate for all dogs at baseline before artery ligation was 164 ± 38 beats/min; systolic blood pressure and left atrial pressure were 140 ± 25 and 9 ± 4.3 mm Hg, respectively. Spontaneous ventricular fibrillation occurred in 16 dogs (27%) within 21 ± 17 min (range 1 to 31) after coronary artery ligation. Sinus rhythm was restored with direct-current countershocks in one dog. In 15 dogs, ventricular fibrillation persisted even after the fifth defibrillation attempt despite administration of "standard treatment": additional epinephrine and bolus lidocaine and up to 15 defibrillation attempts with direct-current countershocks of 50 J each. Conversion to sinus rhythm occurred in one of the eight dogs in group I versus six of the seven dogs in group II (p < 0.005, Fig. 2). Of the seven dogs in group II, 6 had successful defibrillation with 1 to 3 direct-current countershocks; the dog that did not have conversion to sinus rhythm received up to 15 direct-current countershocks. The time elapsed between the onset of ventricular fibrillation and the time of successful defibrillation in the preceding experiments was estimated to be approximately 10 min.

Defibrillation of refractory ventricular fibrillation. The 15 dogs with refractory ventricular fibrillation were randomly allocated as described. Group I (eight dogs) received "conventional therapy": additional epinephrine and bolus lidocaine and up to 15 defibrillation attempts with direct-current countershocks of 50 J each. Conversion to sinus rhythm occurred in one of the eight dogs in group I versus six of the seven dogs in group II (p < 0.005, Fig. 2). Of the seven dogs in group II, 6 had successful defibrillation with 1 to 3 direct-current countershocks; the dog that did not have conversion to sinus rhythm received up to 15 direct-current countershocks. The time elapsed between the onset of ventricular fibrillation and the time of successful defibrillation in the preceding experiments was estimated to be approximately 10 min.

Heart rate and hemodynamic response (Table I). After amiodarone administration and successful defibrillation, the 6 dogs with refractory ventricular fibrillation had a significant decrease in blood pressure and heart rate and a significant increase in left atrial pressure. However, all dogs required epinephrine infusion to maintain heart rate and blood pressure.

Amiodarone plasma and myocardial concentration. At 23 ± 13 min after conversion of refractory ventricular fibrillation to sinus rhythm, mean plasma concentration of amiodarone was 2.53 ± 1.88 μg/ml (range 0.8 to 4.1 [n = 4]). Myocardial concentration at the infarcted area was
Table 1. Hemodynamic Variables After Successful Defibrillation in Group II (dogs treated with amiodarone)  

<table>
<thead>
<tr>
<th></th>
<th>Control Period</th>
<th>After Defibrillation</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>217 ± 18</td>
<td>143 ± 53</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Systolic aortic pressure (mm Hg)</td>
<td>149 ± 24</td>
<td>115 ± 31</td>
<td>&lt; 0.1</td>
</tr>
<tr>
<td>Left atrial pressure (mm Hg)</td>
<td>12 ± 3</td>
<td>31 ± 16</td>
<td>&lt; 0.05</td>
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* Mean 12 ± 3 min after defibrillation.

73.3 ± 35.1 μg per g of myocardial tissue and at the noninfarcted area 120.2 ± 20.6 μg per g of tissue (p < 0.03, n = 5). The myocardial/plasma concentration ratio at 23 ± 13 min after amiodarone administration was 28.97 at the infarcted area and 47.51 at the noninfarcted area.

Discussion

This study evaluated the efficacy of amiodarone in facilitating defibrillation of spontaneous ventricular fibrillation refractory to lidocaine and epinephrine plus direct-current countershocks in experimental acute myocardial infarction (32). In this setting amiodarone administered intravenously at a dose of 10 mg/kg influenced beneficially the response of refractory ventricular fibrillation to defibrillation. Thus, six (86%) of the seven dogs with refractory ventricular fibrillation versus one (13%) of the eight given conventional therapy had conversion to sinus rhythm. The high incidence of refractory ventricular fibrillation observed may be explained by the prophylactic use of lidocaine and the large extent of myocardial ischemia obtained. Thus, the ischemic area of the myocardium calculated using gentian violet, which separates the nonischemic from ischemic area of the left ventricle, in 22 dogs that completed the other protocols (unpublished data) was found to be 36 ± 10% of the left ventricle. Furthermore, six more dogs died of electromechanical dissociation.

Effects of amiodarone on ventricular arrhythmias. Oral amiodarone has been found to be effective in a wide array of supraventricular and ventricular tachyarrhythmias. The actual incidence of successful amiodarone therapy in preventing recurrent ventricular tachycardia and recurrent ventricular fibrillation was 52 ± 7% at 12 months and 28 ± 6% at 24 months in a study of 77 patients (13). In another study (15), 55% (34 of 62) of patients with these arrhythmias were treated successfully with amiodarone over an average of approximately 1 year of follow-up (15). However, the prolonged time to maximal clinical efficacy of oral amiodarone has important implications for some patients, such as those with frequent recurrence of life-threatening arrhythmias unresponsive to direct countershock.

In contrast to oral amiodarone, intravenously administered amiodarone showed rapid efficacy (0 to 64 h) in 58.5% of patients with recurrent ventricular tachycardia and ventricular fibrillation refractory to other drugs (5). It was also used safely and effectively for the termination of sustained ventricular tachycardia (9). However, close supervision and continuous monitoring not only of the ECG but also of blood pressure are recommended during intravenous amiodarone administration as hypotension may occur. Intravenous amiodarone used in a canine reperfusion arrhythmia model rapidly suppressed sustained ventricular tachycardia or ventricular fibrillation (24). This effect of amiodarone is significant because reperfusion arrhythmias have become increasingly important now that a variety of acute interventions are utilized to prevent myocardial infarction or limit infarct size by restoring myocardial blood flow after a period of ischemia. Although many reports are available on the efficacy of intravenous amiodarone to prevent recurrent ventricular tachycardia/ventricular fibrillation, the drug has been used only sporadically to facilitate defibrillation of ventricular fibrillation.

Thus, Maheswaran et al. (29) described a patient with intractable ventricular fibrillation after a digoxin overdose who was successfully treated with intravenous amiodarone. In another report (28), sinus rhythm was restored by direct-current countershock after intravenous administration of amiodarone (200 mg for 30 s) in a patient who had persistent ventricular fibrillation after 75 min of attempted resuscitation and 15 defibrillation attempts. More recently, Williams and associates (27) reported on 14 patients given intravenously administered amiodarone during prolonged in-hospital resuscitation from refractory cardiac arrest due to ventricular tachycardia or ventricular fibrillation. Eleven patients survived the prolonged cardiac arrest after receiving intravenous amiodarone. In 4 of the 11 survivors, sustained sinus rhythm was restored by a single cardioversion or defibrillation attempt administered several minutes after amiodarone administration. In our experimental study, the underlying cause of ventricular fibrillation was acute myocardial infarction. Our findings support previous data (27-29) that amiodarone given intravenously facilitates the defibrillation of ventricular fibrillation.

Mechanisms of action of amiodarone. Amiodarone may produce its antiarrhythmic and antifibrillatory actions by decreasing dispersion of refractoriness and restoring homogeneous patterns of conduction (33). Intravenous amiodarone exerts immediate effects on fast channel activity (34), blocks slow channel conductance (35) and possesses acute alpha- and beta-blocking properties (36).

Experimental data from a feline model of acute ischemia (37) demonstrated that ventricular tachycardia/fibrillation occurred in all animals that underwent left stellate ganglion stimulation superimposed on transient left anterior descending coronary artery occlusion but in none pretreated with intravenous amiodarone. The investigators concluded that amiodarone's most important protective electrophysiologic action in this model was acute onset of antiadrenergic activity.

Procainamide and bretylium for defibrillation of ventricular fibrillation. Procainamide (38) and bretylium (39-41) have both been used in successful defibrillation of ventricu-
lur fibrillation. Moreover, amiodarone was found more effective than bretylium (24) in suppressing reperfusion arrhythmias in dogs. However, no experimental data regarding procainamide and bretylium in facilitating defibrillation of refractory to lidocaine and epinephrine plus direct-current countershocks ventricular fibrillation are available for comparison with our findings.

Hemodynamic effects of amiodarone. Although in our experiments amiodarone influenced positively the response of refractory ventricular fibrillation to defibrillation, the dogs were hemodynamically unstable after defibrillation and required epinephrine infusion to maintain heart rate and blood pressure within acceptable values. Amiodarone may cause hypotension, presumably because of vasodilation and negative inotropic effect (33). However, the worsening of the hemodynamic variables after defibrillation compared with pre-fibrillation data may have been a result of the large ischemic area and the prolonged resuscitation period rather than a direct adverse effect of intravenous amiodarone.

Myocardial and plasma concentrations of amiodarone. Myocardial amiodarone concentration at the infarcted area after defibrillation was 30 times higher than that observed in plasma at the same time interval. Amiodarone was detected in the nonperfused myocardium at a concentration of 73.3 ± 35.1 µg per g of myocardial tissue. Detection of amiodarone in the nonperfused myocardium may be explained by retrograde perfusion of the area during direct heart massage. Other drugs, such as lidocaine (42,43) and procainamide (44), have also been shown to be distributed in ischemic areas of myocardium. The mechanisms speculated to explain drug accumulation were local properties of ischemic myocardium, binding of the drug to molecules such as phospholipids or altered metabolism of the drug in the infarct area. Myocardial and plasma amiodarone concentrations were within those reported by Latini et al. (31).

Limitations of the study. The results of our study should be extrapolated to the clinical setting only with great caution. Clinical determinants of ventricular fibrillation are undoubtedly more complex than those in the experimental model.

Conclusions. We conclude that intravenous amiodarone influences positively the response to defibrillation attempts of ventricular fibrillation refractory to lidocaine and epinephrine plus direct current countershocks in a canine model of experimental acute ischemia. Because clinical outcome may be adversely affected by a prolonged period of resuscitation, these data suggest the use of intravenous amiodarone in humans with refractory ventricular fibrillation complicating acute myocardial infarction who require cardiopulmonary resuscitation and multiple direct-current countershocks.

References


