EXPERIMENTAL STUDIES

Lidocaine Causes a Reversible, Concentration-Dependent Increase in Defibrillation Energy Requirements

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To investigate the influence of lidocaine on the energy requirements for internal defibrillation, lidocaine (n = 8) or saline solution (n = 12) was administered by intravenous infusion to 20 pentobarbital-anesthetized dogs, and the likelihood of successful defibrillation was examined at various shock energy levels before and after treatment. After lidocaine administration to a mean steady state concentration of 5.6 ± 2.7 \( \mu \text{g/ml} \), the mean energy required to achieve 50 and 90% success in defibrillation \( (E_{s0} \text{ and } E_{s90}) \) increased by 61.1 ± 34.1% \( (\text{mean } \pm \text{SD}, p < 0.005) \) and 47.1 ± 28.6% \( (p < 0.005) \), respectively. The steady state log lidocaine concentration correlated positively with the observed increase in \( E_{s0} \) \( (r = 0.887, p < 0.01) \) over a concentration range from 1.95 to 9.8 \( \mu \text{g/ml} \). In a related experiment, lidocaine infusion was administered to five dogs and then abruptly discontinued. At energy levels achieving a mean 90.0 ± 10.0% success in defibrillation before treatment, only 43.3 ± 23.4% success was achieved after 60 minutes of the lidocaine infusion \( (p < 0.01) \) at a mean plasma concentration of 8.4 ± 2.1 \( \mu \text{g/ml} \). The percent of successful defibrillations returned to baseline value \( (92.0 ± 18.0\%, p < 0.01) \) after drug washout at a time when mean lidocaine concentration had declined to 1.8 ± 0.5 \( \mu \text{g/ml} \).

Lidocaine causes a reversible, concentration-dependent increase in the energy requirements for successful defibrillation; recommendations to administer lidocaine to patients with ventricular fibrillation resistant to defibrillation may need to be reviewed.

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The development of clinically applicable systems for internal defibrillation and the increased availability of defibrillation for cardiac arrest occurring in the community has stimulated interest in the factors influencing cardiac defibrillation (1-6). The effect of clinical variables and therapeutic interventions on the amount of electrical energy required for successful defibrillation is also relevant to the use of automatic internal defibrillators, which deliver an electrical discharge of preset energy in response to ventricular tachycardia or fibrillation (4,7).

Patients at risk for ventricular fibrillation are often treated with lidocaine, because this drug increases the threshold for the induction of ventricular fibrillation (8,9) and is advocated, among other indications, for the treatment of ventricular fibrillation resistant to electrical defibrillation (10,11). Although lidocaine may effectively prevent primary ventricular fibrillation in acute myocardial infarction (12), it may also have deleterious effects on the energy requirements for defibrillation (13). It has been found to increase the "defibrillation threshold" for transthoracic shocks (13); however, the energy requirements for defibrillation using internal electrodes have not been studied. It was recently shown (14) that no single "threshold" energy value can be defined below which defibrillation is uniformly unsuccessful and above which it is uniformly successful; rather, the probability of successful defibrillation increases as the energy delivered increases according to a sigmoid "dose-response curve." In this study we explored the effect of lidocaine on the relation between shock energy and the probability of successful defibrillation using a system of electrodes suitable for implantation.

Methods

Experimental protocol. Twenty-five mongrel dogs (22 ± 3.2 kg) were anesthetized with sodium pentobarbital,
25 mg/kg body weight, intravenously followed by 2 to 3 mg/kg per h as necessary; they were maintained on humidified room air with a Harvard model 613 respirator, with adjustments based on hourly measurements of arterial blood gases. Normal saline solution was infused at 2 cc/kg per h throughout the experiment, and normothermia was maintained with a heating blanket. Through a left thoracotomy, the heart was exposed and suspended in a pericardial cradle. A 13.5 cm² titanium mesh patch identical to that used in patients in conjunction with the AICD automatic implantable defibrillator (Intec Systems, Inc.) was sutured to the anterolateral left ventricle; a titanium spring lead with about 10 cm² surface area was inserted into the right atrium through the atrial appendage and secured with a suture. A bipolar platinum-iridium electrode embedded in an acrylic button was sutured to the right ventricular epicardium. Drug (or saline solution) was infused into a femoral vein through a Harvard model 941 syringe pump. Surface electrocardiographic leads II and aVL and femoral artery blood pressure were continuously monitored on a Beckman model E108 oscilloscope and recorded on a paper recorder (Honeywell model 941 Visicorder) at 2.5 to 250 mm/s.

**Ventricular fibrillation was induced** with 60 Hz fully rectified current through the right ventricular electrodes; after 15 seconds of fibrillation, defibrillation shocks were applied across the ventricular patch and right atrial spring electrodes, with the patch acting as the cathode. The waveform used was a truncated exponential with 60% tilt, and the initial voltage was varied to deliver a 7 ms pulse into a 50 Ω load for all energies. The pulses were delivered by a battery-operated device with energy variable from 1 to 40 J. Pulse waveforms were recorded on a Tektronix model 7623A storage oscilloscope, and initial and final current and pulse duration were recorded.

**Defibrillation curve measurements.** Fibrillation-defibrillation trials were carried out every 3 minutes as follows: six energy levels in 1 to 2 J increments were chosen, which were expected to span the range from uniform failure to uniform success in defibrillation. Six shocks (one at each energy level) were then applied in random order, and a similar series of six randomly ordered shocks was repeated five times to establish a baseline energy versus percent success curve. Saline solution (n = 12) (control dogs) or lidocaine (n = 8), in a 3 or 5 mg/kg loading infusion over 10 minutes followed by 50 or 100 μg/kg per min maintenance infusion, was then administered. After 80 minutes, a second set of defibrillatory shocks, at four energy levels chosen to fall in the middle of the percent success versus energy curve, were applied to determine a second defibrillation curve. If any first attempt at defibrillation was unsuccessful, a 16 to 20 J rescue shock was applied within 10 seconds; only the initial shocks were used for analysis. Arterial blood was drawn for lidocaine plasma concentration analysis just before and at 30 and 60 minutes after the start of the second set of shocks. Ventricular refractory periods were measured at a constant drive cycle length using standard methods, before and after each defibrillation curve determination.

**Single energy defibrillation.** In a second set of experiments (n = 5), a single energy level with 80 to 100% successful defibrillation was established in 5 to 10 trials. Sequences of five trials at this energy level were repeated 30 and 60 minutes after the start of lidocaine infusion, and 45 minutes after discontinuation of the drug. Lidocaine plasma concentrations were measured after 30 and 60 minutes of infusion and 45 minutes after stopping the drug, using an enzyme-linked immunoassay (EMIT, Syva Corp.). Because only slight positive correlations between the estimated energy required for 50% success and body weight (r = 0.65) and heart weight (r = 0.66) (p < 0.06, NS) were observed, results are expressed in joules, not corrected for weight.

**Statistical analysis.** The relation between energy and percent of successful defibrillations for each dog was fit to a sigmoidal “dose-response” curve using logistic regression techniques. The energy levels associated with predicted 50 and 90% success (E₅₀ and E₉₀, respectively) were calculated, and comparison between pretreatment and posttreatment periods was made using paired t tests, and between saline-treated and lidocaine-treated dogs using unpaired t tests. Systematic variations in the likelihood of success at a given energy level over time were assessed with multiple logistic regression. The relation between lidocaine concentration and change in defibrillation energy requirement (E₅₀) was analyzed by linear regression. A probability (p) value less than 0.05 was considered statistically significant for all analyses.

**Results**

**Defibrillation curves.** For all dogs, both before and after lidocaine infusion, a range of energy levels associated with an increasing probability of successful defibrillation was found, with a mean ratio of 2.04 ± 0.53 between energy levels associated with an 80 to 100% and a 0 to 20% likelihood of success, respectively. The probability of success at any given energy level during the entire experiment for control dogs and during either the baseline or the postinfusion period for lidocaine-treated dogs, when analyzed by

<table>
<thead>
<tr>
<th>Table 1. Mean E₅₀ and E₉₀ Values Before and After Treatment in 12 Control Dogs</th>
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<tr>
<td>--------------------</td>
</tr>
<tr>
<td>E₅₀ (J)</td>
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<tr>
<td>Saline</td>
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<td>lP = NS</td>
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</tbody>
</table>

E₅₀ and E₉₀ = energy levels required for 50 and 90% success of defibrillation, respectively (values in joules). NS = not significant.
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Figure 1. Relation between percent successful defibrillation and energy before (closed circles) and after (open circles) lidocaine administration in order of increasing steady state plasma concentration (upper left corner, μg/ml).

Multiple logistic regression, did not vary significantly with time. Similarly, among the 12 control animals, the percent success-energy curve was not significantly affected by saline infusion (Table 1) and the energy levels associated with 50 (E50) and 90% (E90) success remained relatively constant. The relation between delivered current and percent success was qualitatively similar to that for energy. The relation between current and success cannot be shown graphically because each shock is associated with a unique current value.

The relation between the energy level and the likelihood of successful defibrillation in the first set of experiments is shown in Figure 1. At baseline, the lidocaine-treated group had a success-energy relation similar to that of the control animals; mean E50 and E90 values were not significantly different between control and treated dogs at baseline (Tables I and 2). After administration of lidocaine, there was a marked decrease in the percent of successful defibrillations for most energy levels, expressed as a rightward shift in the percent success versus energy curve (Fig. 1). The mean E50 was increased after lidocaine administration by 61.1 ± 34%, from 5.3 ± 1.4 to 8.7 ± 3.2 J (p < 0.005), and the mean E90 was increased by 47.1 ± 28.6%, from 7.5 ± 1.7 to 11.3 ± 4.0 J (p < 0.005). Figure 2 shows the baseline and postdrug fitted curves for a representative dog; in this dog only 40% of shocks were successful in defibrillation at the highest energy levels, which had been uniformly (100%) successful before lidocaine administration.

Lidocaine concentration-response relation. Figure 3 shows the relation between log steady-state lidocaine concentrations and changes in energy levels associated with 50% success rate (E50). There is a linear increase in defibrillation energy requirement with increasing drug concentrations, with a significant positive correlation between log lidocaine concentration and proportional increase in E50 (r = 0.887, p < 0.01). Similarly, in each animal the energy level associated with an estimated 90% success rate before lidocaine administration had only an estimated 32.0 ± 32.0% success rate after drug administration, with a positive correlation between log lidocaine concentration and the fall in success rate (r = 0.812, p < 0.01).

Table 2. E50 and E90 Values Before and After Lidocaine Treatment in Eight Study Dogs

<table>
<thead>
<tr>
<th>Case</th>
<th>E50</th>
<th>E90</th>
<th>Lidocaine Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td>Post</td>
<td>%</td>
<td>Pre</td>
</tr>
<tr>
<td>1</td>
<td>4.31</td>
<td>5.55</td>
<td>+ 28.8</td>
</tr>
<tr>
<td>2</td>
<td>7.40</td>
<td>12.69</td>
<td>+ 71.5</td>
</tr>
<tr>
<td>3</td>
<td>5.45</td>
<td>5.78</td>
<td>+ 6.1</td>
</tr>
<tr>
<td>4</td>
<td>6.63</td>
<td>10.98</td>
<td>+ 65.6</td>
</tr>
<tr>
<td>5</td>
<td>2.89</td>
<td>4.02</td>
<td>+ 39.1</td>
</tr>
<tr>
<td>6</td>
<td>6.25</td>
<td>11.47</td>
<td>+ 83.5</td>
</tr>
<tr>
<td>7</td>
<td>4.53</td>
<td>9.54</td>
<td>+ 110.6</td>
</tr>
<tr>
<td>8</td>
<td>5.29</td>
<td>9.72</td>
<td>+ 83.7</td>
</tr>
<tr>
<td>Mean</td>
<td>5.34</td>
<td>8.72</td>
<td>+ 61.1</td>
</tr>
<tr>
<td>±SD</td>
<td>± 1.44</td>
<td>± 3.18</td>
<td>± 34.1</td>
</tr>
</tbody>
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All values are in joules. Lidocaine concentration = steady state lidocaine concentration in μg/ml. Post = value after lidocaine administration; Pre = baseline value before lidocaine administration; Δ% = value after lidocaine baseline value — 1. Other abbreviations as in Table 1.
Figure 2. Percent successful defibrillation (DF) versus energy curves fitted by logistic regression analysis and raw data points before (solid curve, closed circles) and after (dashed curve, open circles) lidocaine administration in a representative dog. C_p = lidocaine concentration (µg/ml) steady state; E_50 and E_90 = the estimated energies required for 50 and 90% success, respectively.

Single energy defibrillation. To establish whether the effect of lidocaine was reversible, five animals were studied at a single energy level before, during and after lidocaine administration. Figure 4 shows the mean percent success in defibrillation during this experiment and the corresponding lidocaine concentrations. The mean percent success decreased from 90 ± 10% at baseline to 76 ± 26% at 30 minutes (p = NS) and to 43 ± 23% at 60 minutes (p < 0.01). The mean plasma lidocaine concentrations at 30 (7.3 ± 1.3 µg/ml) and 60 minutes (8.4 ± 2.1 µg/ml) were not significantly different. After drug washout, 45 minutes after the infusion was discontinued, the mean proportion of successful defibrillations had risen to 92 ± 18% (p < 0.05) at a time when mean plasma lidocaine concentration had declined to 1.8 ± 0.5 µg/ml. Heart rate, blood pressure and ventricular refractoriness were not altered by lidocaine. However, to produce ventricular fibrillation, the fibrillating pulse had to be applied for considerably longer periods after lidocaine treatment, suggesting that the threshold for fibrillation was, as expected, elevated in our experiment.

Discussion

Experimental effects of lidocaine in defibrillation. The most commonly measured determinant of the energy requirement for defibrillation is the “defibrillation threshold” (3,15–17). A single “threshold” value for energy (or current) is identified, usually by gradually increasing levels of shock energy until successful defibrillation occurs, or by progressively decreasing energy levels until a shock fails to defibrillate. Using such methods in pentobarbital-anesthetized dogs, Babbs et al. (13) found a maximal increase of 48% in the defibrillation energy “threshold” for transthoracic shocks after a 3 mg/kg intravenous bolus of lidocaine, and an increase of 99% after an 80 minute infusion of 0.5 mg/kg per minute. Lidocaine plasma concentrations were not measured in that study; Kerber et al. (18) found a 60% increase in transthoracic “defibrillation threshold” at 2 hours after a loading and maintenance infusion of lidocaine in pentobarbital-anesthetized dogs, which occurred at mean concentrations of both 6.2 and 15.0 µg/ml.

Measurement of defibrillation energy requirements. As we have previously reported (14) and as illustrated in Figures 1 and 2, the distinction between inadequate and sufficient energy for defibrillation is not a sharp one, and a relatively wide range of energy levels with intermediate probabilities of success can be identified. After infusion of lidocaine, the percent success-energy was shifted rightward in all dogs, and four of eight had 40% or fewer successes at energy levels that were 100% successful before treatment. The high correlation between lidocaine plasma concentra-
tions. Although the choice of the energy levels associated with 50% success (E\textsubscript{50}) or 90% success (E\textsubscript{90}) as measures of energy requirement for defibrillation are arbitrary, the logistic curve fit allows the calculation of the estimated probability of success at any energy level (Fig. 3). The construction of such curves allows a more precise analysis of the effects of interventions on the electrical "dose" for defibrillation.

The results for animals studied at a single energy level (Fig. 4) demonstrate that the lidocaine-induced increase in energy requirements for defibrillation are fully reversible, and that the residual small concentrations (1.8 ± 0.5 \( \mu \)g/ml) of lidocaine seem to have no effect. The maximal fall in success rate was observed at 60 minutes after the start of drug infusion; four of five animals showed a progressive decrease in percent success from 30 to 60 minutes after drug administration, during a time when plasma concentrations were stable. The fact that multiple logistic regression analysis showed no significant change in the results over time during the postlidocaine curve determinations in the first set of experiments suggests that the maximal effect may be achieved within 80 minutes after drug administration. Other reports also note an apparent delay in maximal drug effect (13,18). Because the antiarrhythmic effect of lidocaine has a rapid onset after administration (8,9,19), and because lidocaine shows rapid distribution kinetics (20), this delay in maximal effect suggests a discrepancy between the antiarrhythmic actions of lidocaine and its influence on defibrillation energy requirements.

**Lidocaine and external defibrillation.** The limited information available in humans does not confirm a clinically important effect of lidocaine on defibrillation in the setting of cardiac arrest. In a prospective observational study, Kerber et al. (21) found no difference in the rate of successful defibrillation between patients receiving lidocaine before their arrhythmia and those not receiving the drug; Babbs et al. (22) found no effect of lidocaine on defibrillation in patients undergoing cardiac surgery. The effect of lidocaine in patients with ventricular fibrillation resistant to defibrillation has not been well studied. In a nonrandomized comparison of lidocaine treatment with no antiarrhythmic treatment for patients with ventricular fibrillation refractory to countershock (23), no significant differences were found, with a low proportion of patients (21 and 17%, respectively) admitted to the coronary care unit. Whether lidocaine is therapeutic or potentially harmful in this setting is not known. It is, however, no more effective than bretylium in established cardiac arrest (24), and its routine use in the prevention of ventricular fibrillation has been questioned (25).

**Effect of antiarrhythmic drugs on internal defibrillation.** Quinidine, at concentrations usually achieved in clinical use, has no effect on defibrillation energy require-

ments for internal defibrillation (26); similarly, procainamide and digoxin have no effect (27). Although bretylium was reported to decrease energy requirements for transthoracic shocks (28), it likewise was without significant effect in dogs tested with an internal electrode system (26).

Encainide and its metabolite ODE (o-demethyl encainide), but not its MODE (3-methoxy-o-demethyl encainide) metabolite, lead to large increases in energy requirements, consistent with the drug-toxic arrhythmias resistant to defibrillation occasionally seen after encainide therapy (29). Amiodarone, given intravenously to dogs with implanted electrodes, leads to a decrease in defibrillation energy, and long-term oral amiodarone has no effect (30), although limited clinical information (31) suggests that amiodarone-treated patients may require higher energy levels than those not taking the drug.

**Limitations of the study.** Our study has several limitations. The relation between the occurrence of a ventricular fibrillation and defibrillation in anesthetized healthy dogs and its occurrence in patients with cardiac disease is not known; however, the "defibrillation threshold" is not significantly different in awake and pentobarbital-anesthetized dogs (32). Because the energy requirements are so much smaller for intracardiac defibrillation than for transthoracic shocks, the large relative changes after lidocaine administration observed in this study cannot be directly extrapolated to energy requirements for external defibrillation. However, they suggest that the use of lidocaine and lidocaine-like drugs should be reassessed in patients in whom internal or external defibrillation is difficult.

**Conclusion.** Lidocaine causes a reversible, concentration-dependent increase in the energy requirements for successful defibrillation; recommendations to administer lidocaine in the setting of ventricular fibrillation resistant to defibrillation may need to be reviewed.

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**References**

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10. Standards and guidelines of cardiopulmonary resuscitation (CPR) and emergency cardiac care (ECC). JAMA 1980;244(suppl):453–509.


