Evaluation of Antiarrhythmic Drugs on Defibrillation Energy Requirements in Dogs
Sodium Channel Block and Action Potential Prolongation

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D. Robertson Coxe, and Elizabeth Cato

Antiarrhythmic drugs have been reported to produce variable effects on defibrillation energy requirements. However, the relation between the in vitro electrophysiologic effects of these agents and the changes in defibrillation energy requirements have not been systematically examined. Therefore, we evaluated the effects of the sodium channel blocking drugs lidocaine and procainamide, the action potential prolonging drugs N-acetyl procainamide and clofilium, and the potassium current blocker cesium in acute canine models with the same internal spring and epicardial patch electrodes used in humans for ventricular defibrillation testing. Ten series of experiments were performed in 78 dogs. Nonlinear regression was used to derive curves of energy dose versus percent successful defibrillation attempts and the 50% and 90% effective energy dose for each experimental condition. Saline control experiments indicated that the preparation was stable throughout the 6-hour duration of the experiments. Lidocaine doubled the defibrillation energy requirement ($p<0.001$) at a mean plasma concentration of 8.2 $\mu$g/ml. The effect of lidocaine on defibrillation energy was reversible, present at therapeutic plasma concentrations, linearly related to plasma concentration ($r=0.69$, $p<0.002$), and present even after only 5-second episodes of ventricular fibrillation. In contrast, procainamide had no effect on defibrillation energy at mean plasma concentrations of 8.5 and 13 $\mu$g/ml, even after prolonged (30-second) episodes of ventricular fibrillation, whereas N-acetyl procainamide, clofilium, and cesium all decreased the energy requirement for defibrillation by 13–27%. Moreover, with the addition of N-acetyl procainamide, there was a trend toward diminishing the increase in defibrillation energy requirement caused by lidocaine. All agents prolonged the mean ventricular fibrillation cycle length. Lidocaine shortened the QT interval, whereas all other agents increased the QT ($p<0.05$). The major electrophysiologic effect of lidocaine is of sodium channel blockade, whereas, N-acetyl procainamide, clofilium, and cesium predominantly increase the action potential duration, and procainamide exerts both effects. Thus, these data indicate that sodium channel block and action potential prolongation exert significant and antagonistic modulating effects on defibrillation energy requirements. (Circulation 1989; 79:1106–1117)

External defibrillation and antiarrhythmic drug administration are the primary emergency treatments for patients experiencing ventricular fibrillation. Recently, the automatic implantable cardioverter-defibrillator device has become available for the long-term management of patients surviving cardiac arrests. More than two thirds of patients treated with this device also receive antiarrhythmic drug therapy, usually to prevent frequent discharges by the device. However, data from a range of canine studies and anecdotal reports of patients indicate that concomitant treatment with some drugs may increase defibrillation energy requirements.

Previous studies of antiarrhythmic drug effects on defibrillation in dogs have used varying methodologies, have had conflicting results, and have not yielded insight into mechanisms. In this study, we evaluated a potential mechanism by comparing...
in a uniform fashion the effects of a series of antiarrhythmic agents with varying electrophysiologic actions on ventricular defibrillation. The purpose of this study was to test our hypothesis that the electrophysiologic effects of antiarrhythmic drugs upon ionic channel currents determines their effects on ventricular defibrillation. We selected for testing two agents whose predominant effects are believed to be due to block of the fast inward sodium current, lidocaine and procainamide, and two agents whose predominant effects are due to prolongation of repolarization without depressing sodium current, N-acetyl procainamide (the major metabolite of procainamide)\textsuperscript{21} and clofilium.\textsuperscript{22} The latter action has been attributed to block of outward potassium current(s). To further assess the role of potassium current(s) on defibrillation, we also tested the effect of cesium, a blocker of several potassium currents in the heart.\textsuperscript{23,24} Sodium channel blocking drugs are now recognized to have use-dependent actions.\textsuperscript{25–27}

We took advantage of these known electrophysiologic effects to assess the interactions of drugs and ventricular fibrillation duration. Finally, we assessed the interaction of drugs with opposing effects on defibrillation energy requirements by evaluating the combination of effects of N-acetyl procainamide and lidocaine.

Methods

Animal Preparation

Studies were performed in adult mongrel dogs in accordance with the guiding principles of the American Physiologic Society. General anesthesia was administered with 30 mg/kg i.v. sodium pentobarbital, followed by intubation with endotrachealuffed tube and mechanical respiration with supplemental oxygen. Defibrillation electrodes were then implanted, and these consisted of a transvenous spring-coil electrode and an epicardial patch electrode (Cardiac Pacemakers, St. Paul, Minnesota) identical to those used in patients and illustrated in Figure 1. The transvenous spring-coil electrode, 10 cm\textsuperscript{2} surface area, was introduced into a jugular vein and advanced to the midtrium under fluoroscopic guidance. The 14-cm\textsuperscript{2} patch electrode was sutured to the left venricular apex through a left lateral thoracotomy. A transvenous bipolar pacing and recording catheter with 1-cm interelectrode spacing was introduced into the other jugular vein and advanced to the right ventricular apex under fluoroscopic guidance. The chest wall incision was then closed, and the chest tube was drained by constant suction.

Defibrillation Testing Protocol

Defibrillation was accomplished with the patch electrode as cathode and spring-coil electrode as anode. The induction of ventricular fibrillation was accomplished by stimulating across the bipolar pair at the catheter tip, that is, separate from the high-output electrodes. Stimulation was delivered to the catheter from a current-limited (maximum 20 mA) 120 Hz rectified alternating current pulse. Defibrillation was accomplished by electrode connections to a specialized external cardioverter defibrillator unit (ECD, Cardiac Pacemakers), which delivered a truncated exponential waveform of 60% tilt (60% exponential decrease in amplitude from leading to trailing edge) and variable pulse duration. Delivered energies between 1 and 40 J could be selected in 1–2 J increments. The defibrillation test energy was delivered 10 seconds after initiation of defibrillation except in the experiments designed to examine other ventricular fibrillation durations. If the test energy level was unsuccessful in defibrillation, high energy was delivered immediately either internally or externally across large skin electrode pads (R-2, Morton Grove, Illinois). Only the first defibrillation attempt was analyzed after each induction of fibrillation. Test energy determinations were separated by a minimum of 3 minutes to assure restoration of heart rate and blood pressure.

To quantify defibrillation energy requirements, we used the dose-response approach described by Davy et al.\textsuperscript{28} Four or five fibrillation and defibrillation sequences, at varying defibrillation energies, were first used to estimate defibrillation energy requirements. Four energy levels, ranging from 8 J below and to 8 J above the estimate were selected and delivered in random order five times each and analyzed as described below. To determine the defibrillation energy requirement under each given experimental condition, a total of 20 energy tests for data points and four or five estimate energy tests were performed during 75 minutes.

Other Measurements

The bipolar right ventricular electrogram, the transcardiac electrogram between the spring-coil

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Diagram of placement of internal defibrillating electrodes (spring-coil and patch) and bipolar pacing and recording catheter.}
\end{figure}
and patch, three surface electrograms (leads I, aV_{F}, and V_{1}), and intra-arterial pressure were monitored throughout the study and recorded on photographic paper (Honeywell Electronics for Medicine, White Plains, New York). Surface electrocardiogram intervals during sinus rhythm were averaged for five complexes. The right ventricular effective refractory period (RV-ERP) was determined for each experimental condition with constant ventricular pacing of cycle length 280 msec at twice diastolic threshold for eight beats followed by a single premature extrastimulus and a 2-second pause between drive trains. The extrastimulus interval was decreased by 2 msec until reaching ventricular refractoriness with the RV-ERP defined as the longest coupling interval failing to result in capture. The ventricular fibrillation cycle length, defined as the mean interval between discrete electrogram deflections during ventricular fibrillation, was determined from the right ventricular endocardial electrogram by averaging the ventricular activation interval during the 2 seconds just before defibrillation. Because the cycle length measured from a single electrogram may not be representative of other sites, only the relative changes in cycle length with drugs were considered in the interpretation of the data. Arterial blood gases were determined every 30 minutes during each study, and adjustments were made to maintain the pH between 7.35 and 7.45 and the P_{O_{2}} greater than 90 torr. Serum electrolytes were determined during each experimental condition in the control and cesium experiments.

**Overall Experimental Protocol**

Ten series of experiments were performed as described below. Each acute study comprised two to four sequential experimental conditions referred to as phases A–D, with baseline predrug testing performed in the first phase (A). Each animal served as its own control and was sacrificed at the end of the experimental protocol. In each phase, defibrillation energy requirements were determined with the energy dose and response approach described above. Except for cesium and clofilium (see below), drugs were administered as loading infusions for 15 minutes and followed by maintenance infusions to permit stable plasma concentrations during the measurement periods (pseudo steady state). Testing was begun during the drug maintenance infusion, 45 minutes after the start of the loading infusion. Higher drug concentrations were then assessed by administering follow-up loading and maintenance sequences to attain higher pseudo steady-state values.

**Series 1. Control experiments.** In these experiments, measurements were obtained during baseline conditions in all three phases (A, B, and C) to determine the stability of the preparation over time. Saline infusions were administered between phases to simulate the drug infusion protocols. A total of 11 experiments were performed with six experiments performed consecutively before the experiments in series 2–10, whereas the remaining five experiments were performed at intermittent intervals throughout the study period to reassess the stability of the animal preparation.

**Series 2. Lidocaine effect and reversibility.** These experiments were designed to evaluate the action of lidocaine on ventricular defibrillation energy and assess whether the effect was reversible. After baseline testing, lidocaine at high dosage was administered (9.2 mg/kg load and 285 μg/kg/min maintenance). After testing on lidocaine, drug infusion was discontinued for 1 hour, and only two selected defibrillation energy values were retested. No attempt was made to test after complete elimination of lidocaine, which would have required a further 6–8 hours.

**Series 3. Lidocaine concentration dependence.** These experiments were performed to determine whether or not lidocaine had an effect on defibrillation energy at lower, more usual therapeutic dosages, and to assess the relationship between plasma lidocaine concentration and effect. After baseline testing, three sequential lidocaine loading (3, 6, and 9 mg/kg) and maintenance (100, 200, and 400 μg/kg/min) infusions resulting in pseudo steady-state plasma concentrations were administered to each animal, and testing was repeated at each level.

**Series 4. Lidocaine and ventricular fibrillation duration.** These experiments were designed to evaluate whether or not the magnitude of the lidocaine effect was dependent upon the duration of ventricular fibrillation. Because prolonged ventricular fibrillation may itself alter defibrillation energy requirements, the duration of fibrillation was controlled. Ventricular fibrillation durations of 5 and 15 seconds were selected for testing. The 5- and 15-second episodes of ventricular fibrillation were tested in alternating sequence in phase A and repeated in phase B during lidocaine administration (9.2 mg/kg loading and 285 μg/kg/min maintenance infusions).

**Series 5. Procainamide effect.** These experiments were designed to assess the effects of intravenous procainamide on defibrillation energy. After baseline testing, two loading (15 mg/kg followed by an additional 5 mg/kg) and maintenance (2 and 3 mg/min) infusion sequences were used to achieve two pseudo steady-state procainamide plasma concentrations to evaluate mid and high therapeutic levels.

**Series 6. Procainamide and ventricular fibrillation duration.** These experiments were designed to assess whether or not procainamide would show an effect on defibrillation dependent upon the duration of fibrillation. Because of the results found in series 5 experiments, 5 and 30 seconds of ventricular fibrillation were selected for testing before and during procainamide (15 mg/kg loading and 2.5 mg/kg maintenance infusions).

**Series 7. N-Acetyl procainamide effect and concentration dependence.** These experiments were designed to evaluate the effect of N-acetyl procain-
amide on defibrillation energy. After baseline testing, N-acetyl procainamide was infused to two pseudo steady-state levels in five experiments and to three levels in six experiments, as described by Jaillon and Winkle\(^3\) using sequential loading (range, 8.5–68 mg/kg) and maintenance (range, 50–400 μg/kg/min) infusions.

**Series 8. Clofilium effect.** Testing was performed at baseline and after each of two 30-minute loading infusions of 0.3 mg/kg. Clofilium’s long half-life\(^3\) eliminated the need for a maintenance infusion during the 75-minute testing periods.

**Series 9. Cesium effect.** These experiments were designed to evaluate the effect of block of potassium current(s) on defibrillation energy. Testing was performed at baseline and during each of two constant cesium chloride infusions (0.017±0.008 and 0.024±0.008 mM/kg/min). Cesium infusion was initiated a minimum of 45 minutes before testing and adjusted in some instances, increased because of lack of QT interval prolongation, or decreased due to low arterial pH.

**Series 10. Lidocaine and N-acetyl procainamide interactions.** These experiments were designed to assess the effects of combining antiarrhythmic agents that showed contrasting effects on defibrillation energy. After baseline testing in phase A, testing was performed during lidocaine administration (7.5 mg/kg load and 225 μg/kg/min maintenance) in phase B. The lidocaine maintenance infusion was then continued, N-acetyl procainamide loading (25.5 mg/kg) and maintenance (150 μg/kg/min) infusions added, and the defibrillation energy requirement retested on both lidocaine and N-acetyl procainamide in phase C.

**Drug Concentrations**

Samples for plasma drug concentrations were obtained at the end of each drug-loading period and at three regular intervals during maintenance infusions in each phase. Plasma lidocaine, procainamide, and N-acetyl procainamide levels were determined with fluorescent immunoassay techniques. Serum cesium levels were determined with atomic absorption spectroscopy. An assay for plasma clofilium concentrations was not available.

**Data Analysis**

The defibrillation energy responses for each test condition were determined from the relation of energy level and the percent successful defibrillation attempts. Nonlinear regression\(^3\) was used to derive the best fit to the function: \(y = e^x / (1 + e^x)\), where \(y\) is the proportion of successes at the energy level \(ED_x\), \(x\) is \([\ln(ED - ED_{90})]/(ED_{90} - ED_{50})\), \(ED\) is the energy dose (Joules), \(ED_{90}\) is 50% effective energy dose, and \(ED_{50}\) is the energy dose associated with 90% effective defibrillation. By parameterizing the logistic relation in this way, estimates of \(ED_{90}\) and of \(ED_{50}\) were obtained directly rather than by interpolation. The defibrillation energy values corrected for animal weight and heart weight were also analyzed.

Analysis of the data was performed with two-way analysis of variance (ANOVA). Experiments evaluating the effects of ventricular fibrillation duration and drug on defibrillation energy requirements were analyzed with ANOVA with repeated measures. All other experiments were analyzed with two-way ANOVA by single test. Only if analysis of variance indicated a difference among means was a pairwise test (Duncan’s multiple range test for two-way ANOVA, Student-Newman-Keuls Test for ANOVA with repeated measures) used to compare individual data sets. Linear regression analysis was used to analyze drug plasma concentration-effect relations. All results are expressed as mean±SD.

**Results**

Of 94 dogs surgically prepared for these experiments, nine dogs expired or became unstable during experimentation, and seven dogs had unstable lidocaine plasma concentrations. Results are from the remaining 78 studies in 10 series of experimental protocols. Examples of dose-response curves derived from the logistic model are illustrated in Figure 2. At baseline, the defibrillation energy requirements varied markedly among dogs. In 66 dogs (excluding series 4 and 6 where the duration of fibrillation was other than 10 seconds), the mean 90% effective energy dose was 13±6 J (range, 4–35 J). Interindividual variations in animal weight (21±3 kg; range, 16–30 kg) and heart weight (162±32 g; range, 99–275 g) were also present. Defibrillation energy requirements were linearly related to animal

![Figure 2. Curves derived with logistic regression of the relation between energy and percent successful defibrillation attempts from one experiment. Panel A: Curves derived from baseline testing, which indicate higher energy needs after 30 seconds of ventricular fibrillation (ED\(_{90}\) of 9 J, ED\(_{90}\) of 11 J) than after 5 seconds (ED\(_{90}\) of 5 J, ED\(_{90}\) of 7 J). Panel B: Curves derived during procainamide testing at a mean plasma concentration of 9.5 μg/ml with results similar to those at baseline (30 seconds, ED\(_{90}\) of 9 J, ED\(_{90}\) of 11 J; 5 seconds, ED\(_{90}\) of 4 J and ED\(_{90}\) of 5 J).](image-url)
weight \( (r=0.49, p<0.001) \) and heart weight \( (r=0.26, p=0.04) \). However, because these correlations were not strong and because each animal served as its own control, the results are presented without weight adjustment.

Lidocaine increased the defibrillation energy requirements, whereas saline controls and procainamide had no effect, and \( N \)-acetyl procainamide, clofilium, and cesium all decreased the defibrillation energy requirements (Figure 3). The corrected QT interval was shortened by lidocaine administration, and it was prolonged by procainamide, \( N \)-acetyl procainamide, clofilium, and cesium (Figure 4). Results of each series are detailed below.

**Series 1. Control Experiments**

Results from eleven control experiments listed in Table 1 indicate that the preparation was quite stable over time. The 50% and 90% effective energy doses were not found to change between phases A, B, and C. The RR interval decreased in phase C, and the right ventricular effective refractory period increased in phase B. No significant changes were found in arterial blood gases, arterial pressure, other electrocardiographic intervals, the mean ventricular fibrillation cycle length, or serum electrolytes. The serum potassium concentration was 3.6±0.4 meq/l in phase A, 3.8±0.3 meq/l in phase B, and 3.8±0.4 meq/l in phase C.

**Series 2. Lidocaine Effect and Reversibility**

In six experiments, high lidocaine concentrations \( (8.2±1.2 \, \mu g/ml) \) increased the 50% effective energy dose from 8±4 to 16±6 J \( (p<0.001) \) and the 90% effective energy dose from 11±5 to 24±12 J \( (p<0.05) \). The ventricular fibrillation cycle length increased from 96±3 to 129±20 msec \( (p<0.01) \). Defibrillation energy values previously effective before and ineffective during lidocaine infusions were again effective after 1 hour of lidocaine washout at which time the mean plasma concentration was 1.9±0.3 \( \mu g/ml \).

**Series 3. Lidocaine Concentration Dependence**

Results of defibrillation testing in six experiments are listed in Table 1. Not only did high lidocaine concentrations increase defibrillation energy requirements, but lidocaine also increased the defibrillation energy at therapeutic plasma concentrations. Moreover, a linear relation was found between lidocaine and 50% effective energy dose \( (r=0.78, p<0.001) \) and 90% effective energy dose \( (r=0.69, p<0.002) \) as well as mean ventricular fibrillation cycle length \( (r=0.59, p=0.002) \). The corrected QT interval shortened as the lidocaine plasma concentration increased. The morphology of the ventricular fibrillation in the right ventricular electrogam became more uniform as the lidocaine concentration was increased (Figure 5).

**Series 4. Lidocaine and Ventricular Fibrillation Duration**

Results of six experiments are summarized in Table 2. At baseline, no significant differences were found in the defibrillation energy requirements after 5 and 15 seconds of ventricular fibrillation. Lidocaine increased the defibrillation energy after even 5 seconds of fibrillation. Ventricular fibrillation durations of 5 and 15 seconds did not alter the effect of lidocaine on defibrillation energy requirements. The mean ventricular fibrillation cycle length shortened with the longer ventricular fibrillation duration (both
**Table 1. Effects of Antiarrhythmic Drugs**

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<tr>
<th>Phase</th>
<th>Condition</th>
<th>ED90 (J)</th>
<th>ED50 (J)</th>
<th>VFCL (msec)</th>
<th>RV-ERP (msec)</th>
<th>RR (msec)</th>
<th>QRS (msec)</th>
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Series 3. Lidocaine concentration dependence (n=6)

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Series 4. Procainamide effect (n=6)

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Series 6. N-Acetyl procainamide (NAPA) effect (n=11)**

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Series 7. Clofibrate effect (n=6)

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Series 8. Cesium effect (n=11)

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Series 9. Lidocaine and N-acetyl procainamide interaction (n=9)

<table>
<thead>
<tr>
<th>Phase</th>
<th>Condition</th>
<th>μg/ml</th>
<th>ED90 (J)</th>
<th>ED50 (J)</th>
<th>VFCL (msec)</th>
<th>RV-ERP (msec)</th>
<th>QRS (msec)</th>
<th>RR (msec)</th>
<th>QTc</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Baseline</td>
<td>8±4</td>
<td>12±6</td>
<td>112±15</td>
<td>162±13</td>
<td>50±6</td>
<td>439±77</td>
<td>376±27</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Lidocaine</td>
<td>7.4±2.9</td>
<td>16±10*</td>
<td>21±13*</td>
<td>142±24*</td>
<td>183±20</td>
<td>57±6*</td>
<td>501±80*</td>
<td>362±32*</td>
</tr>
<tr>
<td>C</td>
<td>Lidocaine with NAPA</td>
<td>7.1±2.7</td>
<td>13±7</td>
<td>17±8</td>
<td>163±37‡</td>
<td>236±43‡</td>
<td>59±7‡</td>
<td>560±92‡</td>
<td>406±44‡</td>
</tr>
</tbody>
</table>

**Values are mean±SD.**

ED90, 50% effective energy defibrillation energy dose; ED50, 90% effective defibrillation energy dose; VFCL, ventricular fibrillation cycle length; RV-ERP, right ventricular effective refractory period.

*p<0.05, **p<0.01 (compared with phase A, two-way ANOVA); †p<0.01, ‡p<0.05 (compared with all previous phases, two-way ANOVA); §p<0.01, $p<0.05 (compared with all previous phases except C, two-way ANOVA); ††p<0.01 (compared with phase B, paired t test); **n=6 for phase D.

at baseline and during drug treatment) and lengthened with lidocaine administration.

**Series 5. Procainamide Effect**

Results from six experiments are listed in Table 1. No change in defibrillation energy was found despite attaining a mean plasma procainamide concentration of 8.5 μg/ml in phase B and 13.0 μg/ml in phase C. Despite the lack of change in defibrillation energy, procainamide did alter other electrophysiological variables including increasing mean ventricular fibrillation cycle length, RR interval, QRS interval, corrected QT interval, and right ventricular effective refractory period. No N-acetyl procainamide was detected at the end of the experiments. Figure 6 illustrates that the slowing of ventricular fibrillation cycle length during procainamide administration was associated with the morphology in the
right ventricular electrogram becoming more uniform as in the lidocaine experiments.

**Series 6. Procainamide and Ventricular Fibrillation Duration**

As anticipated, 29 30 seconds of ventricular fibrillation was associated with higher defibrillation energy requirements compared with 5 seconds of ventricular fibrillation both at baseline and during procainamide administration in all six experiments (Table 2). However, procainamide infusion did not result in an additional effect on defibrillation energy, even after 30 seconds of ventricular fibrillation with a mean plasma procainamide concentration of 11.9±3.6 μg/ml. An example from one experiment is shown in Figure 2. As in the case of lidocaine, administration of procainamide and testing after 30 seconds had opposing effects on the ventricular cycle length.

**Table 2. Effects of Ventricular Fibrillation Duration**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Condition</th>
<th>µg/ml</th>
<th>ED50 (J)</th>
<th>ED90 (J)</th>
<th>VFCL (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5 sec</td>
<td>15 sec</td>
<td>5 sec</td>
<td>15 sec</td>
</tr>
<tr>
<td>A</td>
<td>Baseline</td>
<td>...</td>
<td>7±3</td>
<td>9±4</td>
<td>11±5</td>
</tr>
<tr>
<td></td>
<td>Lidocaine</td>
<td>8.6±1.9</td>
<td>15±4†</td>
<td>18±4*†</td>
<td>22±3†</td>
</tr>
</tbody>
</table>

**Series 6. Procainamide and ventricular fibrillation duration (n=6)**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Condition</th>
<th>µg/ml</th>
<th>ED50 (J)</th>
<th>ED90 (J)</th>
<th>VFCL (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5 sec</td>
<td>30 sec</td>
<td>5 sec</td>
<td>30 sec</td>
</tr>
<tr>
<td>A</td>
<td>Baseline</td>
<td>...</td>
<td>6±2</td>
<td>10±3‡</td>
<td>9±4</td>
</tr>
<tr>
<td></td>
<td>Procainamide</td>
<td>11.9±3.6</td>
<td>8±4</td>
<td>11±5‡</td>
<td>10±5</td>
</tr>
</tbody>
</table>

Data are mean±SD.

ED50, 50% effective defibrillation energy dose; ED90, 90% effective defibrillation energy dose; VFCL, ventricular fibrillation cycle length.

*µp<0.05, *µp<0.01 (compared with 5 sec, ANOVA with repeated measures); †µp<0.01 (compared with baseline, ANOVA with repeated measures).
fibrillation cycle length. Mean ventricular fibrillation cycle length at baseline was decreased by 12 msec after 30 seconds compared with 5 seconds of ventricular fibrillation. Procainamide increased the mean ventricular fibrillation cycle length by 17 msec at both 5 and 10 seconds.

**Series 7. N-Acetyl Procainamide Effect**

The effects of N-acetyl procainamide infusions in 11 dogs are summarized in Table 1. Unlike experiments with saline controls, lidocaine, or procainamide, N-acetyl procainamide administration resulted in a significant reduction in the defibrillation energy required. However, the percent change in defibrillation energy did not correlate with plasma N-acetyl procainamide. In fact, the 90% effective energy dose increased in phase C compared with that in phases B and D. Mean ventricular fibrillation cycle length, right ventricular effective refractory period, and corrected QT interval all increased with N-acetyl procainamide, whereas no changes were found in the QRS and RR intervals. The mean ventricular fibrillation cycle length and right ventricular effective refractory period further increased at high doses (phase D), but the corrected QT interval did not.

**Series 8. Clofilium Effect**

The effects of clofilium in six dogs, summarized in Table 1, were qualitatively similar to those of N-acetyl procainamide, but clofilium administration resulted in a significant decrease in only the 50% effective energy dose. Clofilium increased the mean ventricular fibrillation cycle length, right ventricular effective refractory period, RR interval, and corrected QT interval, and administration of a second clofilium dose in phase C did not result in further change in these parameters.

**Series 9. Cesium Effect**

Like N-acetyl procainamide and clofilium, cesium chloride administration decreased the defibrillation energy requirement in 11 experiments (see Table 1). Higher serum cesium concentrations were not associated with a greater effect on defibrillation energy, despite evidence for a greater effect on mean ventricular fibrillation cycle length, right ventricular effective refractory period, and RR and corrected QT intervals. The serum cesium concentrations were not correlated with the percent change in defibrillation energy. Serum electrolyte values were measured, and the serum potassium was found to moderately increase in phase C (5.2±2.0 meq/l, p<0.05) compared with phase A (3.9±0.6 meq/l) and phase B (4.1±1.0 meq/l).

**Series 10. Lidocaine and N-Acetyl Procainamide Interaction**

As in previous lidocaine experiments, the administration of lidocaine increased the defibrillation energy requirement in these nine experiments. The addition of N-acetyl procainamide tended to lower the defibrillation energy (Table 1) to an extent similar to when administered alone, but the reduction was not statistically significant. Similarly, the combined effects of lidocaine and N-acetyl procainamide were additive for mean ventricular fibrillation cycle length, right ventricular effective refractory period, RR interval, and corrected QT interval.

**Discussion**

In this study, we have shown 1) the stability of this methodology for evaluating the defibrillation energy requirements in dogs, 2) that the acute administration of lidocaine increases defibrillation energy, whereas procainamide shows no effect, and 3) N-acetyl procainamide and clofilium lower the defibrillation energy requirement, 3) that administration of a known potassium channel blocker, cesium, lowers the defibrillation energy requirement, 4) that N-acetyl procainamide administration is associated with a trend toward lowering defibrillation energy requirements raised by lidocaine, and 5) that despite differing effects on defibrillation, all the antiarrhythmic agents tested prolong the mean ventricular fibrillation cycle length. The results are compatible with our hypothesis that the electrophysiologic actions of antiarrhythmic drugs upon ionic currents determines their effects on ventricular defibrillation.

**Models for the Acute Testing of Defibrillation Energy**

Many canine studies have previously evaluated the effects of antiarrhythmic agents. However, studies have varied in the use of internal and external defibrillation; the methodology for determining the defibrillation energy was frequently based on only a small number of determinations; antiarrhythmic drugs were usually not administered to permit study at stable plasma concentrations, and other electrocardiographic and electrophysiologic parameters were often not measured. The methodology developed by Davy et al. to analyze defibrillation energy requirements with the logistic model and used in our studies, and the use of loading and maintenance infusions to maintain stable plasma concentrations have allowed us to avoid these shortcomings.

**Effects of Sodium Channel Blocking Drugs on Defibrillation Energy**

In vitro, the extent of sodium current reduction by sodium channel blocking drugs is dependent on a number of factors including drug concentration, heart rate, and time at any rate (use dependence), transmembrane potential, and pH. Several investigators have successfully manipulated these variables in vivo, for example, showed drug-dependent changes in QRS duration as a function of stimulus frequency. Our results with lidocaine testing revealed a reversible, concentration-dependent effect on increasing defibrillation energy requirements. This lidocaine effect was evident
even after only 5 seconds of ventricular fibrillation as would be predicted because lidocaine binds to and dissociates from the sodium channel very rapidly, with a time constant for dissociation of 80–200 msec in vitro. In contrast, no effect on defibrillation was found with procainamide. The lack of effect is not explained by slower kinetics of interaction between the sodium channel and procainamide (recovery time constant of 2–6 seconds). Although procainamide may require greater than 10 seconds to reach its full sodium channel blocking activity, we were still unable to show any effect at 30 seconds compared with 5 seconds of ventricular fibrillation except for increases in defibrillation energy attributable to the prolonged duration of ventricular fibrillation. Other evidence of electrophysiologic action was present including increases in QRS, QTc, and ventricular effective refractory period. The potential confounding influence of N-acetyl procainamide generation was absent because it was not detected in plasma. Thus, the data with procainamide and lidocaine indicate that although both block sodium channels, their effects on defibrillation energy were divergent. Of note, lidocaine and procainamide also showed divergent effects on the corrected QT interval.

Action potential duration can itself influence the extent of sodium channel block by antiarrhythmic drugs. In addition, the effective refractory period is dependent on both sodium channel block (by shifting inactivation) and on action potential duration. A selective sodium channel blocking agent (such as tetrodotoxin) shortens action potential duration as a direct result of reducing sodium current. Lidocaine shortens action potential duration, and we showed significant shortening of the QT interval in our experiments. The action potential shortening by lidocaine may be due to increasing the potassium current or reducing sodium current or both. In contrast, procainamide prolonged the QT interval in our studies. Fain et al. found that 3-methoxy-O-desmethyl encaïnide (MODE), an active metabolite of encaïnide, did not affect defibrillation energy, although both encaïnide and the active metabolite O-desmethyl encaïnide (ODE) raised the defibrillation energy requirement in dogs. The QT interval changes were not reported, but MODE prolonged the ventricular effective refractory period to a greater extent than did the other drugs in their study. We have found that MODE, but not encaïnide or ODE, prolongs the JT interval in humans. Thus, our data and those of others strongly support our hypothesis that sodium channel blocking drugs that shorten action potential duration also increase defibrillation energy (lidocaine, phenytoin, encaïnide, ODE, whereas those that prolong action potential duration do not (procainamide, MODE)).

The only potent sodium channel blocking agent evaluated previously in which defibrillation testing results are not uniformly consistent with our hypothesi

esis is quinidine. Of four reported studies, the defibrillation energy was increased in the two earlier ones in which the quinidine doses were very high, approximately 14–28 mg/kg and 50 mg/kg. In the two more recent reports in which the defibrillation energy requirements were unchanged, the quinidine doses were 10 mg/kg and 10–14 mg/kg. In the latter study, two loading and maintenance infusions were used and mean plasma quinidine concentrations of 2.4 and 3.0 µg/ml were attained, which is similar to clinically therapeutic plasma levels. The effects of the very large quinidine boluses were likely confounded by the dramatic hemodynamic changes that quinidine produces when administered in this way. None of the studies reported QT intervals, and only one study reported plasma quinidine concentrations. Quinidine prolongs action potential duration in Purkinje fibers as a result of directly reducing I_k. However, at very high quinidine concentrations and rapid stimulation rates, action potential shortening has been found, which is consistent with frequency-dependent sodium channel blockade. Therefore, the increase in defibrillation energy may have been due to toxic quinidine levels or sodium channel effects overwhelming the potassium channel effects.

**Effects of Action Potential–Prolonging Agents on Defibrillation Energy**

Prolongation of action potential duration is an important effect of some antiarrhythmic drugs and may be an important factor in ventricular defibrillation. The plateau phase and phase 3 of the action potential is the net transmembrane potential resulting from declining inward sodium and calcium currents and increasing outward potassium currents. The agents we tested that prolong action potential duration, N-acetyl procainamide and clofibrate, both prolonged the QT interval and decreased the defibrillation energy required. These results agree with a preliminary study of d-sotalol and clofibrate. The action potential prolonging drug bretylium has been shown to decrease or have no effect on defibrillation energy. The effects of bretylium may be confounded by adrenergic blockade, which increase defibrillation energy requirements. Studies evaluating amiodarone have suggested increased defibrillation energy requirements or no effect. It would be difficult to attempt to predict the ultimate effect of amiodarone on defibrillation because it exhibits Class I, II, III, and IV activity.

Although changes in multiple currents may increase action potential duration, one frequently invoked mechanism for antiarrhythmic drugs is block of outward potassium channel currents. Recent findings from in vitro studies indicate clofibrate, sotalol, amiodarone, and quinidine prolong action potential duration by reducing the delayed rectifier potassium current I_K. We found that administration of cesium, a known potassium channel blocker, exerted similar effects. This indicates that
these antiarrhythmic drug effects on defibrillation energy may be a consequence of their net effects on potassium channels.

Unlike lidocaine, increasing doses of N-acetyl procainamide, clofilium, and cesium did not result in a greater effect on defibrillation energy. A number of explanations are possible: 1) the dose-response relation may be flat in the dose range we studied, 2) there may be variable drug uptake and concentrations at some critical myocardial site not in equilibrium with plasma, 3) the high dosages used to show concentration dependence may have had some additional toxic myocardial effect, and 4) ancillary properties, such as sodium channel blockade at very high N-acetyl procainamide concentrations, may have contributed to the net defibrillation energy requirement. However, even high N-acetyl procainamide concentrations did not increase the QRS interval. Finally, it is conceivable that the effects on defibrillation energy are due to a specific potassium current. For example, in Purkinje tissue, cesium has been shown to block the pacemaker current, \( I_P \), at 1–3 mM, the delayed rectifier, \( I_{Ks} \), at 5–10 mM, and the inward rectifier, \( I_{Kw} \), at 10 mM. Mean serum cesium levels in this study (6.5–8.6 mM) correlated with those of \( I_{Kw} \) block. Thus, one could speculate that \( I_{Kw} \) block lowers defibrillation energy and that block of other potassium channels has no effect on the energy required for defibrillation.

Thus, we provide evidence that the ultimate effect of an antiarrhythmic agent on defibrillation energy requirements may be the resultant of its ionic channel blocking activities. A "pure" sodium channel blocking agent would increase defibrillation energy requirements, whereas a "pure" action potential prolonging agent would decrease defibrillation energy requirements. Agents with both properties, for example, procainamide, quinidine, and MODE, may have little overall effect due to cancellation of opposing effects.

**Ventricular Fibrillation Cycle Length**

Transvenous low-energy cardioversion is more effective in terminating ventricular tachycardia when the rate is slow. Because recent experimental evidence suggests that reentrant activity also occurs during ventricular fibrillation, one might predict that slowing of ventricular fibrillation could reduce the defibrillation energy needs. However, in our study, all antiarrhythmic drugs tested prolonged the ventricular fibrillation cycle length and made the morphology more uniform, although their effects on defibrillation energy differed. Several explanations could account for these findings. First, the electrophysiologic mechanisms involved in ventricular tachycardia and ventricular fibrillation are probably different. Second, the mechanisms whereby drugs slow ventricular fibrillation may differ (slowing conduction vs. increasing refractoriness). Third, ventricular fibrillation cycle length prolongation by drugs is probably inherently dissimilar from fibrillation with a spontaneously slower rate.

**Potential Limitations**

Our control series used only three experimental phases, whereas the lidocaine and N-acetyl procainamide concentration-dependent experiments used four phases. Although no control exists for phase D, the interpretation of the data is not dependent upon phase D.

Although sodium pentobarbital increases sympathethic tone to the heart, Babbs found that pentobarbital anesthesia did not change the ventricular defibrillation energy requirements in acute dog experiments. Wang and Dorian found differences in defibrillation energy requirements in dogs receiving pentobarbital, enflurane, and fentanyl, but there was no control group for comparison. In these studies, the anesthesia administration and timing was similar among the experimental series.

We selected for testing, antiarrhythmic agents that have predominant effects on sodium or potassium ionic currents. However, no antiarrhythmic drug is totally selective for a single ionic channel. As mentioned previously, lidocaine may increase the potassium current in addition to blocking sodium channel activity. N-Acetyl procainamide is devoid of sodium channel blocking activity at concentrations less than 40 \( \mu \)g/ml; we did attain higher plasma concentrations in phase D of our experiments. Clofilium may also interact with the calcium channel at high concentrations.

These types of studies cannot determine the mechanism(s) by which ionic channel activity modulates defibrillation energy needs. Because the basic mechanism(s) responsible for defibrillation are not known, speculating on potential mechanisms is difficult. One hypothesis proposed by Babbs is that ventricular defibrillation occurs when myocardial cells are instantaneously excited and, thus, simultaneously rendered inexcitable. Antiarrhythmic drugs may affect defibrillation energy by altering potassium and sodium conductance and the strength of the stimulus required for excitation. Mechanisms other than effects on specific ion channels may be important. For instance, lidocaine may inhibit cardiac sympathetic activity. By using multiple drugs as probes, monitoring blood pressure, and evaluating electrocardiogram intervals, the likelihood of other drug effects such as hemodynamic or autonomic effects have been largely excluded. It is possible that ventricular defibrillation occurs by direct current depolarization or hyperpolarization and does not use ion channels. It is also conceivable that each individual agent has a distinct effect on defibrillation, independent of any other electrophysiologic properties. Further investigation is needed to more fully understand the mechanisms involved in ventricular defibrillation.
Clinical Implications

These results cannot be directly extrapolated to humans in that data were obtained in anesthetized dogs without structural heart disease in the setting of acute lead implantation. Clinical data regarding the effects of antiarrhythmic drugs on defibrillation has been limited to anecdotal and retrospective data regarding amiodarone, encainide, and mexiletine. Information on the effects of lidocaine, procainamide, N-acetyl procainamide, and clofibrate on defibrillation energy in humans is not available. However, animal data strongly support increased defibrillation energy requirements due to lidocaine. These data indicate the possibility that, in patients, administration of procainamide or a purer action potential prolonging agent may be preferable to lidocaine during the emergency treatment of ventricular fibrillation. Similar considerations may be relevant for patients with automatic implantable defibrillator devices.

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