Effects of encainide and its metabolites on energy requirements for defibrillation

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ABSTRACT Encainide, a class IC antiarrhythmic agent, has been associated with proarrhythmic responses of ventricular tachycardia and fibrillation requiring defibrillation in patients. We examined the short-term effects of intravenous encainide and its two major metabolites, O-demethyl-encainide (ODE) and 3-methoxy-ODE (MODE), on the energy requirements for successful defibrillation in 25 pentobarbital-anesthetized, open-chest dogs. Truncated exponential (60% tilt) defibrillation shocks were administered through right atrial spring and left ventricular epicardial patch electrodes identical to those used in man with the automatic implantable defibrillator. At baseline multiple shocks of varying energy were applied to construct curves of percent successful defibrillation as a function of energy (DF curves) for each animal. Encainide, ODE, or MODE was then infused in loading and maintenance doses to achieve QRS widening of 20% to 50%. Saline was administered to animals serving as controls. Determination of the DF curve was repeated, after which the infusion was discontinued. After 1 hr washout period, an additional DF curve was constructed. The data were analyzed by logistic regression, and the energies required for 50% successful defibrillation (E50) were compared. No significant differences existed between the four groups in body or heart weight, extent of QRS widening, or baseline E50 values. After administration of encainide and ODE, the E50 increased by 129 ± 43% (p < .001) and 76 ± 34% (p < .005), respectively. Return of E50 toward baseline was observed after the washout periods in both groups (p < .025), demonstrating the reversibility of the drugs' effects. No significant increase in E50 was observed after administration of MODE, and the results were not statistically different from those in the control group. We conclude that both encainide and ODE greatly increase the energy required for successful defibrillation, while MODE does not exert a significant effect. Also, their effect on defibrillation cannot be predicted by plasma drug concentration, extent of QRS widening, or increase in ventricular refractoriness.

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Encainide is a potent class IC antiarrhythmic drug that is effective in the treatment of ventricular ectopy and ventricular tachycardia refractory to conventional drug therapy. When administered by short-term infusions to anesthetized dogs and man, encainide prolongs His-Purkinje system and intraventricular conduction, while not significantly altering atrioventricular nodal function or ventricular refractory periods. During long-term oral therapy, encainide is metabolized to two major metabolites, O-demethyl encainide (ODE) and 3-methoxy-O-demethyl encainide (MODE), which accumulate in the plasma to steady-state concentrations fivefold higher than those of the parent drug. The electrophysiologic effects of long-term oral therapy differ from those observed after short-term intravenous administration in that atrioventricular nodal, His-Purkinje, and intraventricular conduction are depressed and atrial and ventricular refractoriness are increased after long-term oral encainide. These differences are thought to be due to the accumulation of ODE and MODE, which are also believed to be responsible in part for encainide's antiarrhythmic action.

Alteration of energy requirements for successful defibrillation by antiarrhythmic drugs has become increasingly important with the introduction and success.
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of the automatic implantable cardioverter/defibrillator, since the majority of patients receiving this device will undergo concurrent drug therapy for control of their arrhythmias. Past studies have shown that antiarrhythmic drugs such as lidocaine, quinidine, clofilium, brettylum, propranolol, and procanimide have differing effects on defibrillation, with some increasing, some decreasing, and others having no significant effect on energy requirements.17-21 The defibrillator has the capacity to deliver only a limited amount of energy, and a drug that has the potential to cause the maximum available energy to be unsuccessful in defibrillating the patient could be responsible for the ultimate failure of the device, while agents decreasing energy requirements would improve its effectiveness. Encainide has been associated with an arrhythmic response of sustained ventricular tachycardia or ventricular fibrillation in a significant number of patients.4, 7-10, 22-24 Many of these tachyarrhythmias have been difficult to terminate by electrical defibrillation. Therefore, we attempted to determine the effects of encainide, ODE, and MODE on defibrillation with an internal lead system identical to that used with the automatic implantable cardioverter/defibrillator.

Materials and methods

Animal preparation. The experiments were conducted in 25 mongrel dogs of both sexes weighing 16.6 to 28.2 kg (mean 21.8 ± 2.9) that were premedicated with 2 mg/kg body weight intramuscular morphine and anesthetized with 20 to 25 mg/kg body weight intravenous sodium pentobarbital. Additional doses of approximately 100 mg/hr were administered as required to maintain a level of surgical anesthesia. Previous work by Babbs25 has demonstrated that the ventricular defibrillation "threshold" is not significantly affected by anesthesia with sodium pentobarbital. The dogs were ventilated with humidified room air by a Harvard respirator pump. Normal saline was infused at a rate of 2 to 5 ml/kg/hr to prevent volume depletion. A polyethylene catheter in the femoral artery allowed continuous monitoring of systemic arterial pressure and blood sampling. The femoral vein of each dog was cannulated for the infusion of drug or placebo (saline). Arterial blood gases (pH, O2, and CO2 tension) were determined every 30 min by a Corning 165 pH/blood gas analyzer and the rate and volume of respiration was adjusted to maintain oxygen tension greater than 85 mm Hg and pH between 7.36 and 7.44. Sodium bicarbonate was administered when necessary. Electrocardiographic leads I, II, and aVF were monitored and displayed along with systemic pressure on a Beckman Instruments oscilloscope. Intravenous succinylcholine (Anectine, 20 mg/ml), 1 mg/kg, was given before opening the chest cavity. A left thoracotomy was performed through the fourth intercostal space, and the heart was suspended in a pericardial cradle. The internal defibrillating lead system, identical to the type used with the Intec Systems AID-B, was then implanted. A 13.5 cm2 titanium mesh patch electrode (cathode) was sutured directly to the epicardial surface of the left ventricle. A titanium spring lead (anode) with approximately 10 cm2 surface area was inserted into the right atrium via the right atrial appendage. The stimulating/fibrillating electrode consisted of two 1.5 mm diameter 80% platinum, 20% iridium electrodes embedded 1 cm apart in acrylic, and was sutured to the right ventricular epicardium.

Measurements. All ventricular fibrillation/defibrillation trials were recorded on a Gould ES 1000 Electrostatic Recorder at paper speeds of 5 to 25 mm/sec. QRS intervals from surface electrocardiographic leads were measured at 250 mm/sec. After 2 min of constant right ventricular pacing at a basic cycle length of 300 to 400 msec, programmed premature extrasystoles (S2) at twice late diastolic threshold were introduced after every eighth paced beat (S1). The longest S1-S2 interval (to the nearest 2 msec) at which S2 consistently failed to capture the ventricle was considered the ventricular effective refractory period (VERP). At the conclusion of the experiment the heart was removed and its weight was recorded.

Fibrillation/defibrillation trials. Fibrillation was induced by a 1 to 2 sec train of rectified 60 Hz electrical current of 10 to 15 V via the right ventricular epicardial electrode. The internal lead system was connected to a battery-operated external cardioverter-defibrillator (Intec Systems, Pittsburgh, PA) that could be preset to deliver an amount of energy variable from 1 to 40 J in 1 to 2 J increments. The defibrillating pulse was a truncated exponential with 60% tilt. The shock was delivered through a 0.25 Ω resistor in series with the internal lead system and the waveform was displayed on a Tektronix 7623A storage oscilloscope. The peak current, end current, and duration of the pulse were recorded for each trial to allow calculation of delivered energy. The heart was allowed to fibrillate for a total of 15 sec before the defibrillating shock was given. When defibrillation was unsuccessful a rescue shock of higher energy (up to 30 J) followed in less than 10 sec. A backup Hewlett-Packard 7802C defibrillator with a capacity to deliver up to 400 J through 5 cm paddles applied directly to the heart was used if necessary. Fibrillation/defibrillation trials were performed every 3 min during each phase, and only the first shock was used for analysis.

Protocol. The experiment was divided into three phases.

Baseline phase. Five energy levels in 1 to 2 J increments were chosen based on the animal’s weight and our past experience. Each of these five energy levels was tested five times in balanced random order by referring to a standard table of random numbers.26

Drug phase. A drug or saline loading dose was given over 20 min, immediately followed by a maintenance infusion that was administered until completion of the drug phase. Four of the five energy levels used in the baseline phase, which optimally defined the baseline percent successful defibrillation vs energy curve, were chosen to be tested in this phase of the experiment. After the loading dose and 10 min of the maintenance infusion, each of these energies was applied five times in balanced random order for a total of 20 trials. The drug phase was terminated prematurely if twice during the drug infusion the heart could not be defibrillated with repeated rescue shocks of up to 30 J and higher energy shocks (50 to 100 J) via the direct heart defibrillating paddles of the backup defibrillator were required.

Washout phase. At the conclusion of the drug phase the maintenance infusion was discontinued and no shocks were administered. After 60 min three of the four energy levels used in the drug phase were each administered five times in balanced random order for a total of 15 trials (in two dogs receiving encainide only two energy levels were used).

Drug infusions. Initial estimation of encainide, ODE, and MODE dosages was based on previous pharmacokinetic and electrophysiological studies27 and were titrated as needed to achieve a QRS interval increase of 20% to 50%. The drugs were administered at the following infusion rates (loading and main-
Plasma drug concentration. Blood samples of 5 ml were drawn into heparinized tubes from the femoral artery and replaced by an equal volume of saline after the beginning, middle, and before the end of the administration of shocks during the drug phase. Two additional samples were taken after the beginning and before the conclusion of the shocks given during the washout period. The blood samples were centrifuged and the plasma portion was separated and stored frozen until it was analyzed. The plasma was analyzed by high-pressure liquid chromatography for levels of encaainide, ODE, and MODE, as well as for other minor metabolites of encaainide such as N-dimethyl encaainide (NDE).

Statistical analysis. A curve relating energy to percent successful defibrillation for each of the three phases in each dog was generated by computer with a logistic regression model to fit the raw data to a sigmoidal dose-response curve. Changes in the likelihood of successful defibrillation within the same group of animals were analyzed by paired t tests comparing the predicted energies associated with 50% success (E50) and 80% success (E80). Comparisons between different groups of animals were performed by unpaired t tests at the same levels of success. In a few instances logistic curves could not be generated because all of the energies studied during the drug phase had 0% success or all of the energies examined during the washout phase were 100% successful. For the purpose of analysis in these cases, when the effects were the strongest and most convincing, E50 and E80 values were assigned that represented the minimums of the possible extents of change from the previous phase. Variation of the results with respect to time was assessed by multiple logistic regression. One-way analysis of variance was used to assess differences between three or more means. Other relationships were analyzed by standard linear regression. Results are reported as mean ± 1 SD and p < .05 was considered indicative of statistically significant differences in all analyses.

Results

Plasma drug concentrations. In dogs administered encaainide the mean plasma concentration during the drug phase reached 1983.6 ± 565.2 ng/ml and ranged from 1292.7 to 3090.0 ng/ml. These concentrations fell sharply after the infusion of drug was discontinued to a mean plasma concentration of 724.8 ± 356.7 ng/ml during the washout phase. In addition, measurable levels of two metabolites, ODE and NDE, presumably formed from the parent compound, were also detected. All dogs produced ODE, which reached a mean plasma concentration of 170.5 ± 43.6 ng/ml during the drug phase and declined to a mean of 117.3 ± 47.5 ng/ml after the washout period. Six of the seven dogs produced NDE, achieving a mean plasma concentration of 22.3 ± 14.8 ng/ml that increased to 89.6 ± 52.9 ng/ml during the drug and washout phases, respectively.

Dogs receiving ODE infusion had a mean plasma concentration of 524.7 ± 242.5 ng/ml (range 246.7 to 950.0) during the drug phase that subsequently declined to 69.2 ± 39.5 ng/ml in the washout phase. Animals given MODE had mean plasma concentrations equal to 850.4 ± 205.6 ng/ml (range 594.0 to 1132.7) during the drug infusion, which then decreased to a level of 230.8 ± 69.0 ng/ml in the washout phase. No additional metabolites were detected in either of these sets of animals.

QRS interval duration. The animals infused with saline showed no significant changes in the QRS interval over the course of the experiment (−1.5 ± 5.0%). On the other hand, a significant increase in the duration of the QRS interval from that measured during the baseline phase was observed in animals given encaainide (+34.7 ± 13.8%; p < .001), ODE (+36.85 ± 10.4%; p < .001), and MODE (+36.63 ± 6.9%; p < .001). A one-way analysis of variance showed that differences between the three groups in the magnitude of the increase were not statistically significant. There was also a significant decrease in the QRS duration after the washout period in animals treated with these same drugs: encaainide −12.9 ± 8.4% (p < .025), ODE −26.6 ± 9.2 (p < .001), and MODE −24.0 ± 5.8 (p < .001). Despite this decrease, the QRS intervals remained significantly prolonged relative to the baseline phase in all three sets of dogs, and therefore, the effect was not completely reversible within the time period studied.

VERP. Changes in VERP were analyzed after completion of the loading dose and 10 min of the maintenance infusion as well as after 60 min of washout. Significant differences were not observed after either encaainide (+2.4 ± 4.8%) or saline (+0.9 ± 4.8%) infusions. However, animals receiving ODE or MODE infusions had significant increases in VERP of 10.3 ± 5.6% (p < .01) and 15.8 ± 10.3% (p < .05), respectively, after administration of the drug. These increases were also significant when compared with the slight increase that was observed in the control animals (p < .025), but were not significantly different from each other. The decreases in VERP that were seen 60 min after discontinuing the drug infusions were not significant in either group of animals. Therefore, as was the case with QRS duration, the effects of ODE and MODE on VERP were not completely reversible within this time period.

Defibrillation energy requirement. The raw data along with the fitted curves generated by logistic regression for a single animal given encaainide are shown in figure 1. Figure 2 shows the mean E50 and E80 values, generated by logistic regression, for the baseline, drug, and washout phases of the experiment in the four groups of animals administered saline (control), en-
cainide, ODE, or MODE. A one-way analysis of variance demonstrated that differences between the control, cainide, ODE, and MODE groups in body weight (22.0 ± 1.9, 21.0 ± 3.1, 22.4 ± 1.9, and 21.9 ± 4.6 kg, respectively), heart weight (151.4 ± 14.9, 155.2 ± 26.0, 166.5 ± 27, and 174.6 ± 31.9 g, respectively), and baseline phase E50 (4.22 ± 1.07, 4.45 ± 2.39, 5.10 ± 1.76, and 5.98 ± 1.85 J, respectively) and E80 (5.51 ± 1.31, 5.82 ± 3.26, 7.08 ± 1.90, and 7.65 ± 2.44 J, respectively) values were not statistically significant.

The control animals (n = 6) (figure 2, A), which received saline, showed a small but significant decrease in the energy required for defibrillation throughout the course of the experiment. The E50 decreased by 15.2 ± 6.2% (p < .01) after the saline infusion and by a total of 21.6 ± 13.2% (p < .02) from the baseline measurements to the washout phase. The E80 value also decreased throughout the experiment, but these changes were not statistically significant.

Enca
dine (n = 7) (figures 1 and 2, B) had a profound effect on the energy required for successful defibrillation. After administration of drug, the E50 was increased by 128.9 ± 42.5% (p < .001) and the E80 increased by 103.8 ± 52.9% (p < .001). The lowest energy achieving 100% successful defibrillations during the baseline phase produced only a mean of 11.4 ± 22.7% success after administration of enca
dine. Figure 1 graphically shows this rightward shift of the fitted curves and the marked increase in E50 and E80 in a representative animal. There was a significant decrease in the E50 (p < .025) observed in the washout phase after discontinuing the drug, but both the E50 and E80 remained significantly elevated from their baseline phase values (p < .02 and p < .05, respectively). Animals given ODE (n = 6) (figure 2, C) also required much higher energies to achieve the same level of success when compared with their baseline phase values. The E50 was increased 75.9 ± 34.2% (p < .005) and the E80 increased 46.0 ± 26.6% (p < .005)
.01) after the drug was infused. After the 60 min washout period, both the E50 and E80 decreased significantly from the drug phase to the final phase (p < .02), but as was the case with encainide, the E50 of the washout phase remained significantly greater than its baseline phase value (p < .05). The washout phase E80, however, was not significantly different from its baseline value. Four of the 13 dogs given either encainide or ODE had to have the drug prematurely terminated because they could not be defibrillated with the internal lead system or with shocks of up to 100 J given by the direct heart paddles of the backup defibrillator; they eventually became asystolic and were resuscitated by cardiac massage. An additional animal given encaainide (figure 1) went into intractable ventricular fibrillation after single extrastimuli were applied to assess the VERP after completion of the drug phase; a stable blood pressure could not be restored and the animal died. The relative changes in E50 after administration of drug correlated poorly with the extent of QRS widening for the groups administered either encainide (r = .433) or ODE (r = .260). In addition, changes in E50 did not correlate significantly with log plasma encaainide (r = .573) or ODE (r = .754) concentration.

The action of MODE (n = 6) was quite different from that seen with either encainide or ODE (figure 2, D). No significant changes in either the E50 or E80 occurred after administration of drug. Also, the slight increase in E50 and small decrease in E80 were not significantly different from the changes observed in the control animals after infusion of the saline. There was a significant decrease in E50 and E80 (p < .01) when the washout phase values are compared with those during the baseline phase; however, this decrease was not statistically different from that seen in the control group.

For each animal, logistic regression analysis was also performed to analyze the relationship between current and percent success. As was expected, because the delivered energy is proportional to the square of the peak current, qualitative changes in energy requirements were paralleled by similar changes in current in all cases.

Analysis by multiple logistic regression did not show significant variation of the results with respect to time in any group.

Additional observations. During the course of the experiments, we observed episodes of sustained and non-sustained ventricular tachycardia, as well as a few in-

FIGURE 2. Mean energy associated with E50 (solid circles) and E80 (open circles) during the baseline, drug, and washout phases of the experiment for each group of dogs: A, control (saline); B, encainide; C, ODE; D, MODE. Statistically significant change from the previous phase is denoted by asterisk; see text for level of significance.
stances of severe bradycardia and heart block in animals administered encainide or ODE. None of these arrhythmias were associated with MODE treatment. We also observed that the administration of either encainide or ODE made it much more difficult to fibrillate the heart, and that this action was reversed after the washout period. This observation is in agreement with previous work that showed that the ventricular fibrillation threshold is increased after encainide therapy, but not with a recent study that showed ODE to lower the ventricular fibrillation threshold in ischemic hearts. In addition, there were some instances during administration of encainide or ODE when episodes of electrically induced fibrillation spontaneously reverted to normal sinus rhythm.

Discussion

We have previously demonstrated that the concept of defibrillation cannot be adequately defined by a single value, the so-called “defibrillation threshold.” Instead, defibrillation is best described by a curve of percent successful defibrillation versus energy, since a wide range of energies is associated with intermediate levels of success between 0% and 100%. Therefore, in this study we observed how encainide and its two major metabolites, ODE and MODE, affected the position of the defibrillation curve. Since the results resembled those seen in standard dose-response experiments, the data were analyzed by logistic regression and fit to a smooth curve. Rightward or leftward shifts in these defibrillation curves, indicating changes in the energy required for successful defibrillation, could then be analyzed for significance. The energies required to achieve 50% success (E50) and 80% success (E80) were chosen as the points for analysis because the E50 is traditionally used to describe dose-response curves, and the E80 is an energy level associated with a high degree of success.

The effects of encainide and its metabolites on the efficacy of defibrillation were striking. The energy requirements for successful defibrillation were greatly increased by the administration of encainide and ODE. On the other hand, no significant changes in the energy requirements were observed after MODE was given. What contributions the metabolites ODE and NDE, which reached plasma concentrations of 8.6% and 1.1%, respectively, of that of the parent drug in animals given encainide, made to producing the observed changes is not known. NDE probably had no effect, since the plasma NDE concentration was highest during the washout phase, the same period during which the effect on defibrillation was partially reversed. The effect of newly formed ODE is not as clear. The mean ODE concentration achieved in these dogs during the encainide drug phase was approximately a third of the concentration achieved when ODE was infused directly. Therefore, it is probable that the amount of ODE formed by metabolism of the parent compound contributed to the changes observed in energy requirements, but the extent of this contribution is not known. Also, because of this, nothing can be concluded about the relative potencies of these two compounds. However, it is clear that both drugs have deleterious effects on defibrillation, while MODE does not significantly influence the energy requirements for success.

These results were surprising. The electrophysiologic changes observed after drug administration were consistent with those reported by others using short-term infusions. Encainide, ODE, and MODE equally prolonged conduction as measured by QRS duration, while ODE and MODE also increased ventricular refractoriness to extents that were not statistically significant. The accumulation of these metabolites is thought to be responsible for the increase in VERP seen in patients undergoing long-term oral encainide therapy. Past studies have also shown the two metabolites to have very similar electrophysiologic effects. Therefore, these two structurally similar agents, which had nearly identical electrophysiologic properties, had extremely different effects on defibrillation.

We have also reported a significant increase in defibrillation energy requirements after infusion of the lidocaine. Besides having a much greater quantitative effect, encainide and ODE also exhibited a qualitative difference in their action. Even at toxic levels of lidocaine (> 20 ng/ml), the animals were always successfully defibrillated, although at times two or three rescue shocks of up to 20 J had to be given. This did not hold true for dogs administered encainide or ODE. Five of these 13 dogs (38.5%), including the animal that developed intractable ventricular fibrillation while assessing the VERP, could not be defibrillated by high-energy rescue shock via either the internal lead system or the direct heart paddles of the backup defibrillator. Clinical reports of similar experiences occurring in patients are numerous. The animals were resuscitated only by the performance of cardiac massage for several minutes. In the first four cases the drug phase was prematurely terminated, any pH abnormalities were corrected, and the animals recovered completely during the 60 min washout period to give results in the washout phase close to control values and demonstrating reversibility of the drugs’ effect. In the
last case a stable blood pressure could not be restored, and the animal died. Therefore, in some cases the effect of the drugs could not be overcome by just increasing the shock energy and would have probably resulted uniformly in death if the chest had not been open to allow cardiac massage.

The antiarrhythmic activity of infused encainide and ODE, as well as of oral encainide, has been shown to be strongly correlated with the degree of QRS prolongation. A similar relationship between the increase in E50 and QRS prolongation was not observed with the administration of either of these compounds. In fact, of the four animals that required cardiopulmonary massage, three had QRS increases of less than 27%. Clinical studies have also shown that the occurrence of proarrhythmic responses to encainide therapy could not be predicted by the extent of QRS widening. Plasma drug concentration also failed to correlate significantly with changes in energy requirements for successful defibrillation. In addition, the minimum plasma encainide and metabolite concentrations associated with effective antiarrhythmic activity vary widely among patients. Therefore, it would not be possible to define blood levels or extent of QRS prolongation under which effective antiarrhythmic therapy could be achieved without causing detrimental alterations in the energy required for successful defibrillation.

These results have important implications. Our study suggests that either early or late in the course of encainide therapy, when concentrations of encainide, ODE, or both are high, patients who experience ventricular fibrillation either as a primary event or secondary to acceleration of ventricular tachycardia will require much higher energy shocks to terminate their arrhythmia and are at risk of not being successfully resuscitated. Although our experiments were carried out in healthy dogs, the results correlate well with clinical reports of difficulty in defibrillating patients treated with oral encainide. Similar problems have also been observed in dogs administered intravenous ODE.

The plasma concentrations of infused encainide, ODE, and MODE were attained as a result of titrating the dosages to achieve a QRS interval prolongation of 20% to 50%. This extent of widening is comparable to that seen in clinical studies examining the effects of short-term intravenous and long-term oral encainide. In addition, this increase is thought to be associated with effective suppression of arrhythmias in man and is well tolerated over long periods of time.

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electrical activity, which when altered, influences the ease with which the fibrillating heart can be restored to a normal sinus rhythm.

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