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ELEVATION OF VENTRICULAR DEFIBRILLATION THRESHOLD IN DOGS BY ANTIARRHYTHMIC DRUGS

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Abstract

Effects of antiarrhythmic drugs upon the threshold delivered energy (TDE) and threshold peak current (TPC) for electrical ventricular defibrillation by damped sinusoidal shocks were investigated in 25 pentobarbital-anesthetized dogs. TDE and TPC were increased by the three antiarrhythmic drugs tested. Bolus injections produced a transient rise, and continuous infusions produced a steady rise in defibrillation threshold. The maximal percent elevations in mean defibrillation threshold during the 60 minutes after intravenous drug treatment in groups of n = 5 dogs were:

Treatment	% increase in TDE	% increase in TPC
Lidocaine bolus (3 mg/kg)	48	26
Lidocaine (0.5 mg/Kg/min)	99	45
Quinidine bolus (50 mg/Kg)	172	70
Diphenylhydantoin (1 mg/Kg/min)	83	35
Controls	1	4

Accordingly, individuals receiving antiarrhythmic drugs whose hearts nonetheless fibrillate may require greater electric shock strength for defibrillation.

Key words: ACLS, advanced cardiac life support, cardiac arrest, fibrillation, resuscitation

Introduction

The minimum electrical "dose" in terms of either current or energy required to defibrillate the ventricles is defined as the ventricular defibrillation threshold. Although there are many reports of the influence of antiarrhythmic drugs on fibrillation threshold, there are no quantitative studies that have shown the effects of such drugs on the minimum energy or current required to defibrillate the ventricles. This paper describes a new phenomenon, the elevation of ventricular defibrillation threshold by three antiarrhythmic drugs.

Drug effects upon defibrillation threshold are of potential clinical importance because patients who fibrillate may have been placed on maintenance antiarrhythmic drug therapy or admitted to coronary care units where antiarrhythmic drugs may be given routinely. A population of patients especially prone to sudden death may be identified [1, 2], for whom some authors have proposed prophylactic treatment with procaine amide or related drugs in selected cases [3, 4]. Intravenous lidocaine by bolus injection or continuous infusion is currently recommended for hospitalized patients following acute myocardial infarction in order to prevent ventricular fibrillation [5, 6]. Nonetheless, the ventricles of patients receiving lidocaine may still fibrillate [7]. During cardiopulmonary resuscitation a variety of drugs may be given prior to defibrillation.

Since some authors have indicated that present commercial defibrillators, which store 400 Watt-seconds of energy, may have marginal or inadequate output for heavyweight patients [8, 9], the question of whether antiarrhythmic drugs alter the electrical dose required for defibrillation becomes especially pertinent. Accordingly, the present study was conducted to determine if antiarrhythmic drugs alter ventricular defibrillation threshold in a stable animal model.

Methods

Twenty-five mongrel dogs, weighing 6 to 12 kilograms, and anesthetized with pentobarbital sodium (30 mg/kg, intravenously) served as subjects. This anesthetic was chosen because we have previously shown that it does not alter the defibrillation threshold [10]. The details of anesthesia and monitoring have been described previously [11]. In brief, fibrillation was induced by 60 Hz electrical stimulation of the right ventricle via an intracardiac catheter-electrode. Defibrillation threshold was determined by repeated trials of fibrillation and transchest defibrillation, with successive shocks from a damped sinusoidal defibrillator (Capacitance 16 microfarads; inductance 44 millihenrys; internal resistance 7 ohms) each shock of peak current amplitude 10 percent less than the amplitude of the preceding shock. The lowest shock intensity able to achieve defibrillation, and differing no more than 10 percent in amplitude from an intensity that did not defibrillate, was defined as threshold.

The ventricles never were permitted to fibrillate more than 30 seconds prior to defibrillation and never were refibrillated until arterial blood pressure had returned to a stable level. The peak voltage and peak current for each shock were recorded on a storage oscilloscope. Only data from the first shocks applied after the onset of ventricular fibrillation were used in the calculation of threshold. Delivered energy was calculated from the product of peak voltage, peak current, and

defibrillator constants as previously described [12]. The antiarrhythmic drugs used in this study were quinidine gluconate injection, U.S.P. (Lilly), 80 mg/ml; lidocaine hydrochloride injection (Astra), 20 mg/ml, pH 6-7; and 5-5 diphenylhydantoin sodium salt (Sigma Chemical Co., St. Louis, Mo.). A freshly prepared, alkaline solution of diphenylhydantoin in water was used because the usual commercial diluent has been shown to alter the threshold for electrical stimulation of cardiac tissue [13]. Quinidine was given as a single intravenous bolus (50 mg/kg) to five dogs. Lidocaine was given as single intravenous bolus (3 mg/kg) to five dogs and as a constant infusion (0.5 mg/kg/min) to another five dogs. Diphenylhydantoin was given as a' continuous infusion (1 mg/kg/min) to an additional five dogs. These antiarrhythmic drug doses are in the range of 0.7 to 7 times the recommended therapeutic doses for dogs [14]. Five dogs in a control group received no drug other than pentobarbital to determine the effect of repetitive trials on the defibrillation threshold.

In all groups ventricular defibrillation threshold was determined at 15 minute intervals before and after drug treatment. The mean of three pre-drug threshold values for each animal was defined as 100 per cent of control and served as the reference for drug effect.

Results

Figure 1 shows the dramatic elevation of the threshold current and energy caused by an intravenous bolus of quinidine gluconate (50 mg quinidine base/kg) in five dogs. The data points in Figure 1 represent mean threshold energy and current ratios, which were calculated by dividing the individual threshold values by the average reference value for each animal. The period of negative time on the abscissa represents this control period. Quinidine increased threshold peak current by 70 per cent and threshold delivered energy by 172 per cent. The dose of quinidine was sufficient to cause blood pressure to fall initially from average values (systolic/mean/ diastolic) of 170/140/128 mmHg (high control blood pressures characteristic of dogs anesthetized with pentobarbital) to 95/73/60 mmHg. Thereafter the magnitude of blood pressure depression gradually diminished at approximately the same rate as the magnitude of defibrillation threshold elevation.
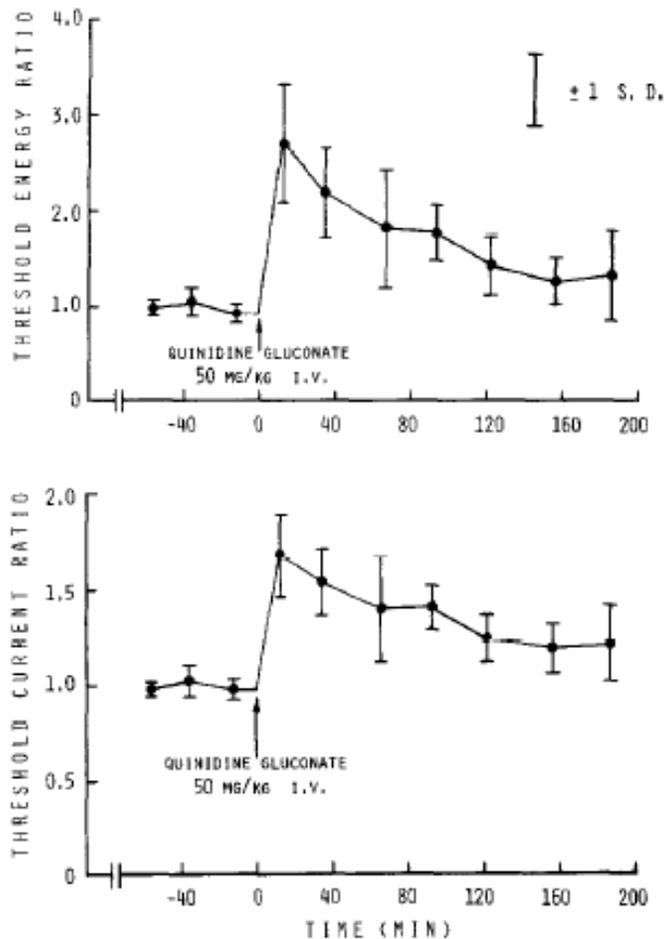
Figure 1. Effect of intravenous quinidine on ventricular defibrillation threshold in five dogs. The absolute threshold values corresponding to 1.00 on the vertical axes were 0.94 Watt-sec/Kg and 1.21 A/Kg. All threshold elevations after quinidine injection are statistically significant (U < 11, p < 0.01) except the final data point at 187 minutes. Because of the difference in the standard deviations of pre-drug and post-drug data, the Mann-Whitney U-test of significance was used to compare post-drug values with the aggregate pre-drug control values in this and subsequent figures.

Figure 2 illustrates a similar elevation of defibrillation threshold by an intravenous bolus of lidocaine (3 mg/kg). The maximal elevation of threshold current was 26 percent and the maximal elevation of threshold energy was 48 percent. The peak effect of lidocaine appeared later than the peak effect of quinidine. Administration of lidocaine by continuous intravenous infusion (0.5 mg/kg/min) also caused threshold to increase steadily in another group of five dogs (Figure 3) to a maximum of 199 percent of control energy and 145 percent of control current after 80 minutes. Blood pressure fell from 158/137/117 mmHg at the beginning to 137/119/103 mmHg at the end of the lidocaine infusion.

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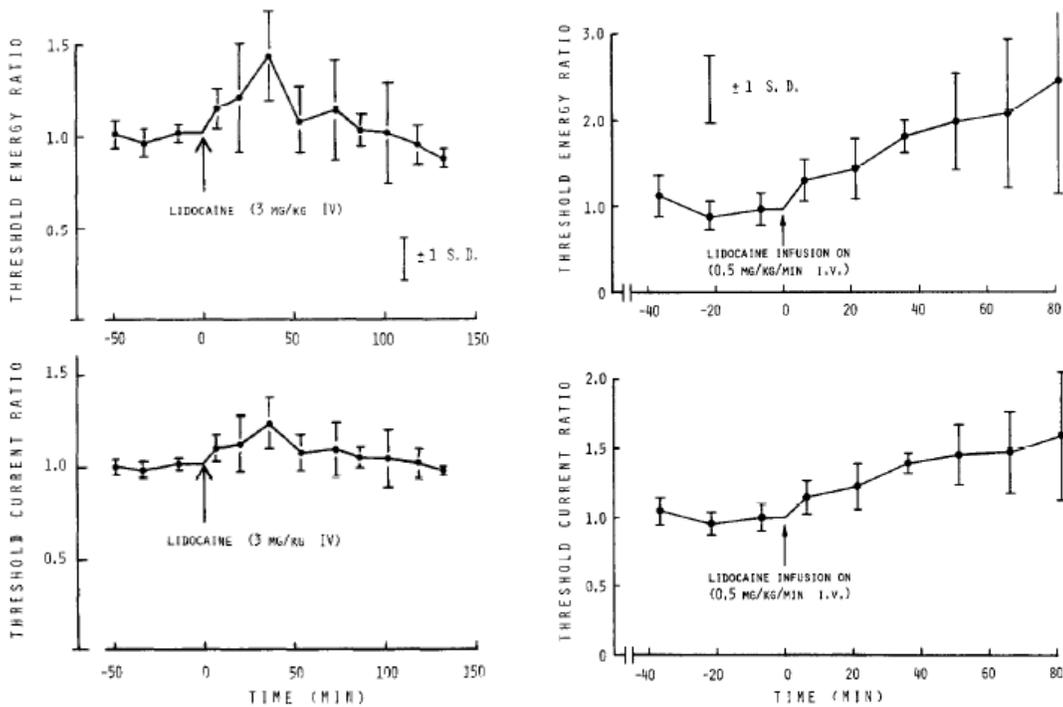
Figure 2 (left). Effect of intravenous lidocaine on ventricular defibrillation threshold in five dogs. The absolute threshold values corresponding to 1.00 on the vertical axes were 0.83 Watt-sec/Kg and 1.16 A/Kg. The peak elevation in defibrillation threshold is statistically significant (U < 11, p < 0.01).
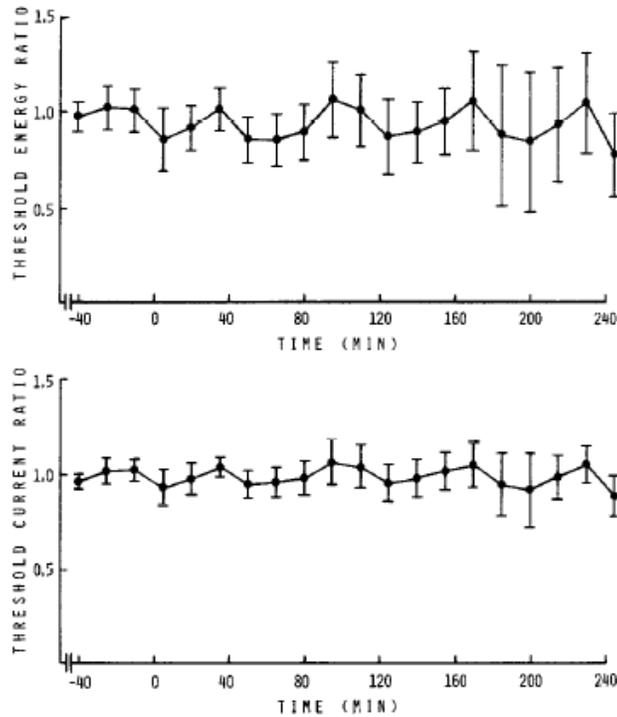

Figure. 3 (right). Effect of lidocaine infusion on ventricular defibrillation threshold in five dogs. The absolute threshold values corresponding to 1.00 on the vertical axes were 0.67 Watt-sec/Kg and 1.00 A/Kg. All threshold elevations after onset of the infusion are statistically significant (U < 14, p < 0.05). After 30 minutes of infusion threshold elevations are highly significant (U < 11, p < 0.01).

The effect of a continuous infusion of diphenylhydantoin (DPH) (1.0 mg/kg/min) is shown in Figure 4. This agent also caused the defibrillation threshold to increase. The increase in threshold was accompanied by a decrease in systolic, mean, and diastolic blood pressures from 185/160/132 mmHg (characteristic of pentobarbital anesthesia) to 112/87/60 mmHg during the DPH infusion.
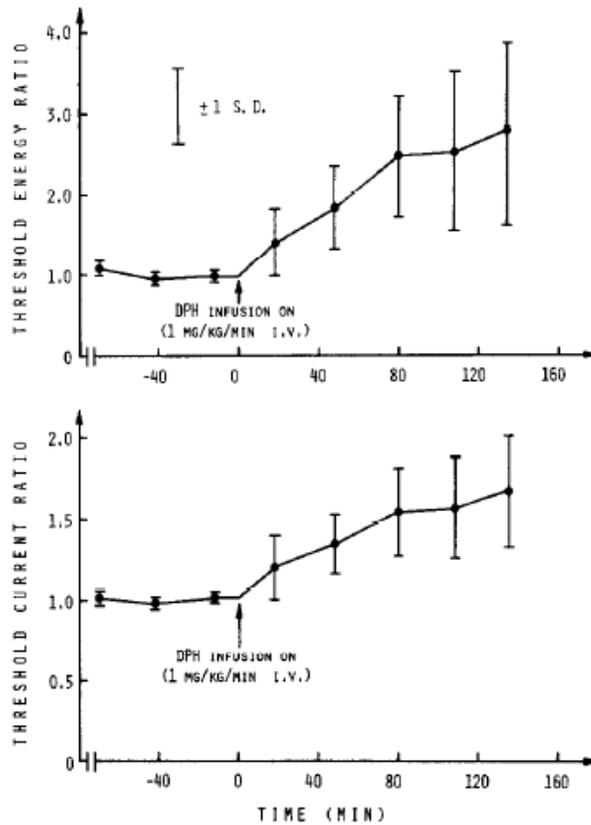
Figure 4. Effect of diphenylhydantoin (DPH) infusion on ventricular defibrillation threshold in five dogs. The absolute threshold values corresponding to 1.00 on the vertical axes were 0.76 Watt-sec/Kg and 1.01 A/Kg. All threshold elevations after onset of the infusion are statistically significant (U < 11, p < 0.01).

Figure 5 illustrates mean threshold energy and current in the control animals that received only pentobarbital. These animals were studied for a longer period of time than any drug treatment group to evaluate the stability of the preparation. In these animals threshold energy decreased by about 10 percent during the first hour of testing and thereafter remained stable. Threshold current did not change over a period of 280 minutes, and blood pressure remained stable, indicating little effect of the repeated episodes of fibrillation, circulatory arrest, and defibrillation upon the dependent variables of this study.

Figure 5. Effect of pentobarbital anesthesia only on ventricular defibrillation threshold in five dogs. The absolute threshold values corresponding to 1.00 on the vertical axes were 0.89 Watt-sec/Kg and 1.12 A/Kg. These animals served as controls. The slight, periodic variations in these threshold data were not reproducible in other control series.

Discussion

The objective of the present studies was to establish the direction of changes in ventricular defibrillation threshold produced by antiarrhythmic drugs. Some individuals might believe, *a priori*, that drugs given clinically to prevent fibrillation would also make defibrillation of the heart easier. Others might speculate that since most antiarrhythmic drugs reduce the excitability of cardiac muscle, and since defibrillation is caused by depolarization of cardiac muscle, most antiarrhythmic drugs would elevate the defibrillation threshold. The only previous report of the influence of an antiarrhythmic drug upon ventricular defibrillation is that of Woolfolk and associates [15] who found that quinidine (10 to 60 mg/kg, intravenously) decreased the likelihood of successful ventricular defibrillation in dogs given transchest shocks of 30, 40, or 50 Watt-seconds. The present studies confirm Woolfolk and colleagues' conclusion and also demonstrate that failure to defibrillate in the presence of quinidine may be reversed by the use of increased electric shock strength.

In the present study, relatively large doses of three antiarrhythmic drugs were used to demonstrate the phenomenon that antiarrhythmic drugs may raise the defibrillation threshold. The doses employed, however, did not cause mean blood pressure to fall below 70 mmHg and in this sense were pharmacologic rather than toxic doses. Plasma levels of quinidine, lidocaine, and diphenylhydantoin were not obtained in this initial study; since the pharmacokinetics of animals subjected to repeated ventricular fibrillation and defibrillation are complex, and equilibration of drug between plasma and tissue compartments could not be assumed. Under the conditions in which the experiments were performed it is likely that any plasma drug levels that might have been obtained would have been falsely high or grossly out of phase with the physiologic response. Indeed, the peak elevation of defibrillation threshold after an intravenous bolus of lidocaine occurred 40 minutes after injection in intact dogs, although peak plasma levels must have been established within seconds. Nonetheless, the present study points toward the potential, practical importance of drug induced elevations in ventricular defibrillation threshold in situations when defibrillator output is marginal.

Pantridge and associates [7], Tacker and colleagues [8], and Collins and coworkers [9] have reported that in patients weighing over 100 kilograms ventricular fibrillation often is not abolished by maximal (400 stored Watt-second) shocks from typical clinical defibrillators. In comparably heavyweight animals, shocks in excess of 400 Watt-seconds increased the percent success in defibrillation [16]. Presumably, the defibrillation thresholds of heavyweight patients are already close to the shock strength provided by 400 stored Watt-seconds. In such individuals drug induced elevations of defibrillation threshold could be lethal.

There is at present controversy about the appropriate shock strength for human ventricular defibrillation. The shock strength required for a given percent success reported by Adgey and colleagues [17] and by Crampton and coworkers [18] for out-of-hospital ventricular defibrillation is considerably less than the shock strengths reported by Tacker and associates [8] for a population of hospitalized patients. One possible explanation for the discrepancy between these studies may be more intensive antiarrhythmic drug therapy in the hospitalized patient

group. Accordingly, closer attention to drug treatment is warranted in future studies of human ventricular defibrillation.

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