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W A. Tacker

M.J. Niebauer

Charles F. Babbs

Purdue University, babbs@purdue.edu

W.J. Combs

B M. Hahn

See next page for additional authors

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Authors

W A. Tacker, M J. Niebauer, Charles F. Babbs, W J. Combs, B M. Hahn, M A. Barker, J F. Seipel, J D. Bourland, and L A. Geddes

The effect of newer antiarrhythmic drugs on defibrillation threshold

W. A. TACKER, MD, PhD; M. J. NIEBAUER, MS; C. F. BABBS, MD, PhD; W. J. COMBS;
B. M. HAHN; M. A. BARKER; J. F. SEIPEL; J. D. BOURLAND, PhD; L. A. GEDDES, PhD

Biomedical Engineering Center, Purdue University, West Lafayette, Indiana, USA

ABSTRACT

This study was conducted to determine the effects of clofilium phosphate and bretylium tosylate on ventricular defibrillation threshold. Dogs were anesthetized with pentobarbital and subjected to repeated fibrillation-defibrillation episodes. Defibrillation thresholds were determined at 15-min intervals using underdamped 5-6 msec sinusoidal current shocks, from 30 min before drug injection to 120 min after injection. Eight dogs were given clofilium phosphate (0.34 mg/kg, iv). Another 10 dogs were given bretylium tosylate (10.0 mg/kg, iv). Both drugs lowered defibrillation threshold from 15-90 min after injection. The maximum clofilium effect was a 31% decrease in threshold current and a 54% decrease in threshold energy. The greatest decrease in defibrillation threshold produced by bretylium was 16% for current and 31% for energy. These drug induced changes in defibrillation threshold are of potential clinical benefit, if they occur in human subjects at doses that are effective for control of ventricular arrhythmias.

Key words: ACD, AICD, arrhythmia, automatic implantable defibrillator-cardioverter, defibrillation, ventricular fibrillation, sudden cardiac death

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INTRODUCTION

The authors have shown recently that three major antiarrhythmic drugs (quinidine, phenytoin, and lidocaine) increase the threshold shock strength required for ventricular defibrillation in dogs.¹ This effect presents a potential clinical problem, because fibrillation may still occur after these antifibrillatory drugs have been given, and immediate electrical defibrillation is required. In particular, fibrillation may often occur after administration of lidocaine in the coronary care unit.²

An experimental drug, clofilium, developed by Eli Lilly and Company, seems to be the first member of a new class of antiarrhythmic drugs with a mechanism of action quite different from either quinidine, phenytoin, or lidocaine. This new compound probably blocks outward potassium current through the cell membrane and has been shown to produce chemical defibrillation in the absence of a defibrillator countershock.³ Such spontaneous defibrillation is tantamount to decreasing electrical defibrillation threshold to zero.

Bretylum tosylate has recently been approved for use as an antiarrhythmic in the United States and also has different pharmacological properties than the drugs mentioned previously.⁴ Bretylum, like clofilium, has been reported to produce chemical defibrillation in the absence of a defibrillator countershock.⁵ Because of the apparent ability of these two agents to make defibrillation easier, and because of their unique pharmacological characteristics, the authors have investigated the effects of intravenous clofilium phosphate and bretylum tosylate on ventricular defibrillation threshold in dogs.

METHODS

Eighteen mongrel dogs weighing from 9 to 22 kg were studied. Each dog was anesthetized with pentobarbital sodium (30 mg/kg, iv) and intubated to maintain a patent airway. Pentobarbital anesthesia was selected because it does not itself alter the defibrillation threshold.⁶ Lead II ECG was monitored using subdermal pin electrodes. A femoral vein was catheterized for administration of additional doses of pentobarbital to maintain anesthesia, as well as for administration of the antiarrhythmic drugs. A femoral artery was catheterized for direct measurement of blood pressure. A bipolar stimulating electrode mounted on a catheter was passed from the right jugular vein into the right ventricle to initiate fibrillation. Low resistance electrolytic gel and 10-cm diameter electrodes for external defibrillation were applied to the shaved right and left chest walls and the electrodes sutured in place. The defibrillator used in this study produced a slightly underdamped sinusoidal current waveform.⁷ The duration of the current pulse was maintained between 5-6 msec for each dog by varying the capacitance of the defibrillator from 20-40 microfarads. The inductance was set at 63 millihenrys, and the internal resistance of the defibrillator was 3.5 ohms. Voltage and current were displayed on a dual trace storage oscilloscope (Tectronix Inc., Beaverton, OR). The apparent impedance of the chest was calculated as the ratio of peak voltage to peak current. Stored energy, W_s , was calculated from the capacitance and initial voltage on the capacitor as;

$$W_s = (1/2)CE^2$$

where; C = capacitance, and E = voltage applied to the capacitor. Delivered energy was calculated using the equation

$$W_d = W_s[Z_a/(Z_a + R_i)]$$

where W_d = delivered energy, W_s = stored energy, R_i = internal resistance of the defibrillator, Z_a = apparent impedance of the subject.

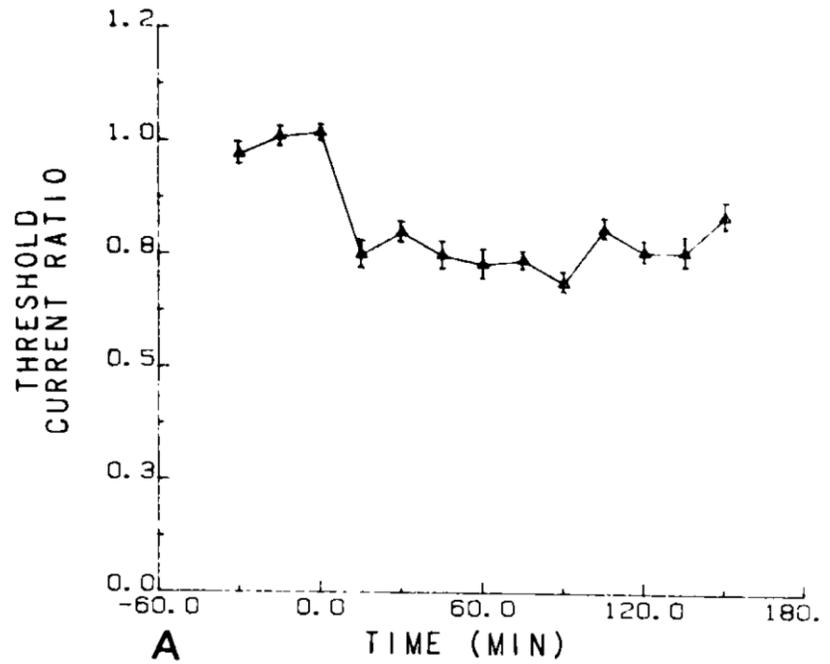
Ventricular fibrillation was produced by 60 Hz electrical stimulation through the transjugular stimulating electrode, and confirmed by the ECG and by the loss of arterial blood pressure pulses. Test shocks from the defibrillator were delivered at end-expiration and within 30 sec of the onset of ventricular fibrillation. If the test shock failed to defibrillate, a backup shock of approximately 2 amp/kg body weight was applied to achieve defibrillation. Following defibrillation, blood pressure was allowed to return to prefibrillation levels before the next fibrillation-defibrillation trial. A defibrillation threshold value was defined as a current intensity which defibrillated, but was no more than 10% greater than a current that did not defibrillate. Only test shocks (and not backup shocks) were used to establish threshold values.

Defibrillation threshold values were determined at 15-min intervals for 30 min before and 120 min after administration of test drugs. After measurement of three predrug thresholds, 0.34 mg/kg (1.0 μ mole/kg) clofilium phosphate (Eli Lilly and Co.) was administered to 8 dogs as an intravenous bolus via the femoral vein. Similarly, in another 10 dogs 10.0 mg/kg bretylium tosylate (Bretylol; Arnar-Stone Laboratories Inc.) was administered as an intravenous bolus and defibrillation threshold was monitored. These doses were selected because they are effective in preventing ventricular fibrillation in dogs. The three predrug threshold determinations for each dog were averaged and the mean values equated to 100% of control for each dog. Individual postdrug values were expressed relative to these predrug control values. The resulting normalized data from all of the animals were then averaged and the Mann-Whitney statistic calculated to test the null hypothesis that the various postdrug thresholds were the same as the predrug control thresholds.

RESULTS

Clofilium phosphate and bretylium tosylate clearly depressed the current (Figs. 1A and 1B) and energy (Figs. 2A and 2B) thresholds for ventricular defibrillation when given before the onset of fibrillation. Energy requirements for defibrillation dropped 54% after clofilium and 31% after bretylium. The onset of action was rapid with both drugs, producing near maximal depression of threshold 15 min after injection. In addition to the effect upon threshold, the authors observed that in some subjects that the time required for blood pressure to recover was prolonged after administration of bretylium. After clofilium administration, the authors did not observe slow blood pressure recovery after defibrillation.

FIG. 1. A. Effect of intravenous clofilium phosphate (0.34 mg/kg, given at $t = 0$) on current threshold for ventricular defibrillation in 8 dogs (mean \pm SEM). The absolute current threshold value corresponding to 1.00 on the vertical axis was 1.15 A/kg. All threshold depressions after drug injection are statistically significant ($U < 25$, $p < 0.001$). Because of the difference in the standard deviations of predrug and postdrug data, the Mann-Whitney U-test of significance was used to compare postdrug values with the predrug values in this and subsequent figures.



B. Effect of intravenous bretylium tosylate (10.0 mg/kg, given at $t = 0$) on current threshold for ventricular defibrillation in 10 dogs (mean \pm SEM). The absolute current threshold value corresponding to 1.00 on the vertical axis was 0.97 A/kg. All threshold depressions after bretylium injection are statistically significant ($U < 93$, $p < 0.05$) except the data point at 90 min postinjection.

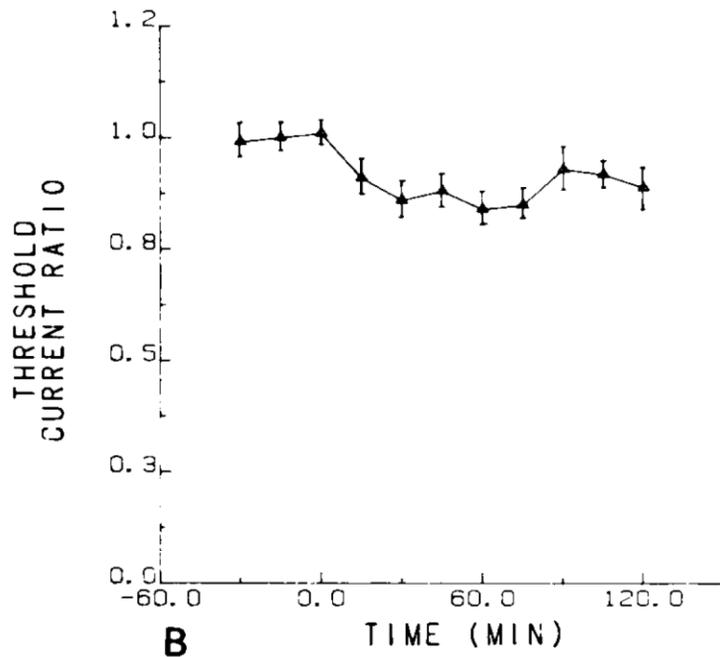
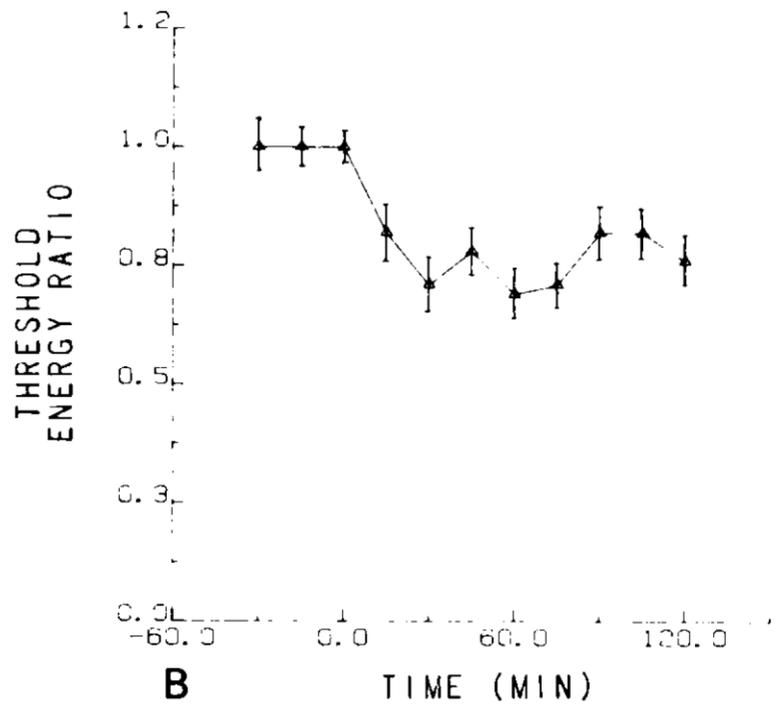
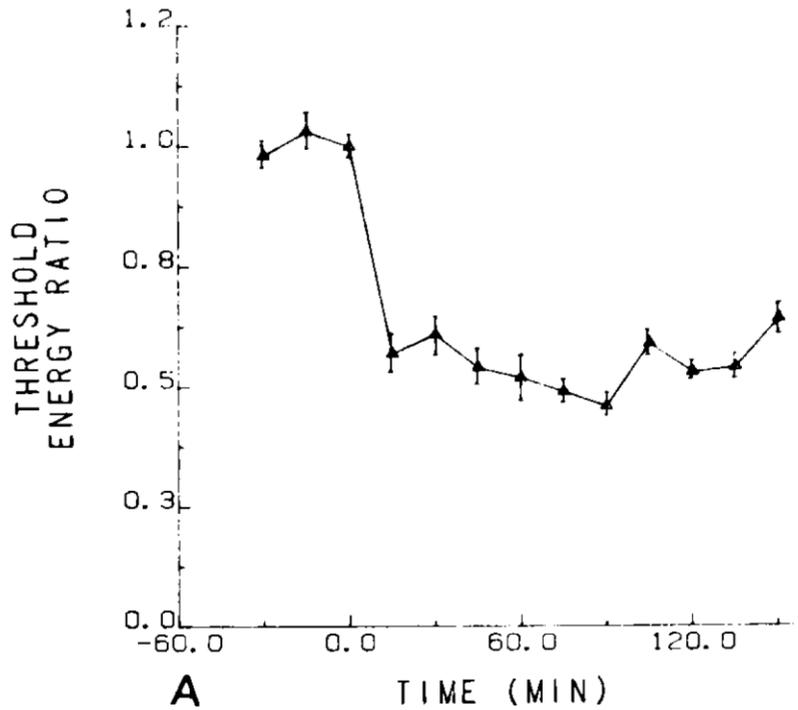


FIG. 2. A. Effect of intravenous clofilium phosphate (0.34 mg/kg. given at $t = 0$) on energy threshold for ventricular defibrillation in 8 dogs (mean \pm SEM). The absolute threshold value corresponding to 1.00 on the vertical axis was 2.59 J/kg. All threshold depressions after drug injection are statistically significant ($U < 18$, $p < 0.0003$).

B. Effect of intravenous bretylium tosylate (10.0 mg/kg, given at $t = 0$) on energy threshold for ventricular defibrillation in 10 dogs (mean \pm SEM). The absolute threshold value corresponding to 1.00 on the vertical axis was 1.77 J/kg. All threshold depressions after bretylium injection are statistically significant ($U < 75$, $p < 0.01$).



DISCUSSION

This report is the first to describe depression of defibrillation threshold by antiarrhythmic drugs. This effect is in direct contrast to the effects of quinidine, phenytoin, and lidocaine, all of which increase defibrillation threshold when given before the onset of fibrillation.¹ The apparent advantage of bretylium to decrease defibrillation threshold must be balanced against the apparent loss of hemodynamic recovery that we observed after it was given. Bretylium possesses antiadrenergic and hypotensive actions associated with depletion of norepinephrine from peripheral adrenergic nerve endings.⁴ In accordance with this known mechanism, some subjects treated with bretylium may not be able to recover as well from fibrillation-defibrillation episodes because of less effective autonomic reflexes. In a clinical study, however, Haynes et al.⁸ found no differences in resuscitative results (short term or long term survival) for patients after use of bretylium as compared to lidocaine.

The 0.34 mg/kg dose of clofilium decreased the energy threshold for defibrillation by 50%, but did not seem to adversely affect cardiovascular function. To the knowledge of the authors, this ability to depress defibrillation threshold without toxic side-effects is a unique property of clofilium. The digitalis glycoside, ouabain, may produce a similar (up to 50%) depression of defibrillation threshold,⁹ but only at doses approaching the LD50. Likewise, profound hyperkalemia (8-13 mEq/liter) can depress defibrillation threshold,¹⁰ but only in conjunction with severe cardiac dysrhythmias and weakening of cardiac contractility.

The elevation of defibrillation threshold by standard antiarrhythmic drugs¹ may explain, in part, the lower defibrillation success rate for in-hospital versus out-of-hospital patients.¹¹⁻¹⁵ The contrasting depression of defibrillation threshold by the newer antiarrhythmic drugs in this study may be of clinical benefit if it occurs in human subjects at doses that are effective for control of ventricular arrhythmias.

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