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Authors

Tobis, JM
Aronow, WS

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Cardiotoxicity of amitriptyline and doxepin

The cardiotoxicity of the tricyclic antidepressants amitriptyline and doxepin were compared in an animal with acute overdose. The mean repetitive extrasystole threshold (RET) decreased 71.5% with amitriptyline and 27.5% with doxepin (mean blood levels 933 ng/ml and 1889 ng/ml). Physostigmine reversed these effects. Sodium bicarbonate had a variable effect on the lowered RET. The toxic arrhythmogenic effects of the tricyclic antidepressants can be measured by RET and are partly reversed by autonomic tone manipulation. In the same blood level range, doxepin is less toxic than amitriptyline.

Jonathan M. Tobis, M.D., and Wilbert S. Aronow, M.D. *Irvine, Calif.*

Department of Medicine, University of California

There is controversy over the relative cardiotoxicity of various tricyclic antidepressant drugs.⁵ Some believe that doxepin is less cardiotoxic than amitriptyline or imipramine.⁸ On the other hand, there are several reports of fatal intoxication from doxepin alone.⁴ Vohra et al.⁸ studied the effects on bundle of His conduction of several tricyclic antidepressants in overdose victims.⁸ They found prolonged HV conduction time in seven of eight patients who had taken nortriptyline, amitriptyline, or imipramine but normal bundle of His studies in six patients after doxepin. Most of the deaths from tricyclic antidepressant overdose are from ventricular tachycardia that develops into ventricular fibrillation. Conduction abnormalities demonstrated by His studies suggest that electrical vulnerability to ventricular tachycardia may be a distinct characteristic. We therefore examined the effect of amitriptyline and doxepin on electrical instability.

Because of the life-threatening effects of overdose in humans, we were limited to the animal model to analyze the effect of amitriptyline and doxepin overdose on repetitive extrasystole threshold (RET). We chose a dog with acute drug overdose and constantly infused drug to maintain blood levels at toxic concentration. Electrical vulnerability was tested by measuring ventricular fibrillation threshold directly or by measuring the current required to produce a repetitive extrasystole. Matta et al.⁶ found that the RET is a good marker of the ventricular fibrillation threshold in 91% of the dogs they studied; single repetitive extrasystoles occurred when 66% of the fibrillation current was delivered and multiple extrasystoles at 82% of the fibrillation current. In those animals with a significant fall in RET (taken arbitrarily as >50% reduction in RET from baseline), several potential antidotes to the cardiotoxicity of tricyclic antidepressants were tested. We have reported on the effect of amitriptyline on RET and its reversibility with sodium bicarbonate, physostigmine, propranolol, or left stellate ganglionectomy.⁷ We report here on our comparison of the effect of doxepin on electrical

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Reprint requests to: Jonathan M. Tobis, M.D., University of California, Irvine, 101 City Dr. South, Orange, CA 92668.

Fig. 1. Comparison of amitriptyline and doxepin on RET.

vulnerability and the results of sodium bicarbonate or physostigmine to reverse the cardiotoxic effects.

Methods

We used 26 healthy mongrel dogs weighing 16 to 27 kg. Anesthesia was introduced intravenously with sodium thiamylal 4 mg/kg and alpha chloralose 40 to 80 mg/kg at a concentration of 5 mg/ml dissolved in heated normal saline. Additional alpha chloralose 20 to 50 mg/kg was given during the experiment if necessary to maintain anesthesia. The dogs were intubated and ventilated with a Harvard pump using a mixture of room air and 100% oxygen. The ventilator was adjusted to stabilize the arterial blood pH at 7.30 to 7.45. Lights were used to maintain body temperature. A 16-gauge polyethylene catheter was inserted

Table I. Effect of doxepin on RET and doxepin blood levels

RET control (mA)	RET after doxepin (mA)	Doxepin blood level (ng/ml)
Group A*		
33.3 ± 4.7	31.4 ± 7.2	1,614 ± 785
Group B†		
33.0 ± 4.5	6.8 ± 3.9‡	2,379 ± 921§

*RET after doxepin was not lowered more than 50% of control RET.

†RET after doxepin was lowered more than 50% of control RET.

‡p < 0.01 RET before and after doxepin in group B.

§p < 0.05 Doxepin blood level reached in group B compared with group A.

into the right femoral vein for injection of drugs. The left femoral artery was cannulated with a 16-gauge polyethylene catheter and used to measure systemic blood pressure and to obtain arterial blood samples. A Statham P23 Dc transducer and a Grass Polygraph recorder, Model 7, were used to record systemic blood pressure. An electrocardiogram was recorded on the Grass Polygraph using a standard limb lead.

Electrical testing of the heart was performed as follows. The chest was opened by a thoracotomy on the right. Two Cordis sutureless epicardial electrodes, Model 324-856, were placed 2 cm apart on the right ventricle midway between the apex and the atrioventricular groove. The electrodes were connected through a stimulus isolation unit (Grass SIU-5A) and a constant current unit (Grass CCU-1A) to a Grass S-44 square-wave pulse generator. The output of this assembly was calibrated with an oscilloscope. A separate pacemaker was placed in line with the Grass stimulator and was set at 200 beats per min to overcome any tachycardia induced by the anticholinergic effect of tricyclic antidepressants. The heart was paced at 2 mA with a 2-msec impulse. The pulse generator was able to deliver a premature impulse with variable delay after the last paced beat. The pacemaker would then shut off for 3 sec, during which the effect of the premature extrastimulus was observed on the electrocardiogram.

The RET was obtained in the manner de-

scribed by Matta et al.⁶ Electrical diastole was scanned in 5-msec decrements, beginning at the end of the T wave and ending at the border of the strength interval curve, i.e., where no depolarization could be induced with the extrasystole. The current of the extrasystole impulses was set at 2 mA and was increased in increments of 1 or 2 mA. The T wave was scanned at each successive current until a repetitive extrasystole was obtained. The RET was defined as the current required to induce at least one extra depolarization after the premature electrical input. The RET was verified by obtaining extrasystoles in at least two of three trials. The maximum output of our generator was 40 mA.

Experimental interventions. After the baseline RET was obtained and reproduced 15 to 30 min later, amitriptyline or doxepin was infused. Each animal received only one of the drugs. Doxepin was given at a rate of 10 to 15 mg/kg over 30 min, followed by a constant infusion of 0.01 to 0.03 mg/kg/min. Amitriptyline was given as an initial intravenous bolus of 3 to 10 mg/kg over 30 min, followed by constant infusion of 0.015 to 0.025 mg/kg/min. A constant infusion was used to maintain blood levels. The RET was obtained 15 min after the initial bolus and was verified as stable up to 60 min later. If the RET did not change significantly after the initial bolus, a second or even a third 10-mg/kg dose of drug was given. Blood levels of amitriptyline or doxepin were obtained at the time RET was established. Blood levels were analyzed by gas chromatography at Bio-Science Laboratories (Van Nuys, Calif.)

The methods and results of administering potential antidotes to amitriptyline have been reported.⁷ Ten dogs received doxepin. In those animals where the RET fell more than 50%, 44 mEq sodium bicarbonate was given intravenously, and the RET was reperformed within 10 min. Arterial pH was measured before and after bicarbonate. In four dogs equilibrium was established after bicarbonate treatment (as determined by return of RET and pH to values before bicarbonate therapy). Two milligrams physostigmine was then injected intravenously over 2 min, and RET was repeated at 10 to 20 min.

Fig. 2. Comparison of amitriptyline and doxepin on RET and effect of sodium bicarbonate in cases where fixed doses of drug decreased RET.

Statistical analyses were by Student's t test for paired or independent means.

Results

Three animals were tested for up to 3 hr for control levels and stability of the RET. The baseline RET was 31 ± 1 mA and remained at 30 ± 3 mA up to 3 hr later, with measurements taken every 30 to 60 min. After the control values were established in these three animals, 2 mg physostigmine was given intravenously. The repeat mean RET was 30.6 ± 5.4 mA (control not significantly different). For the control animals and at various stages during the intervention experiments, the ventricular fibrillation threshold (VFT) was compared with the RET. The RET was 90.8% of the VFT. However, during 1.5% of the trials the VFT occurred at the same current level as the RET.

Fig. 1 shows the RET in 10 dogs given doxepin and in 16 dogs given amitriptyline. There was no significant difference between mean RET control levels of the two groups. For the 16 dogs given amitriptyline, $\bar{x}$ RET ± 1 SD was

Fig. 3. Comparison of amitriptyline and doxepin on RET and effect of physostigmine in cases in which fixed doses of drug decreased RET.

28.8 ± 7.9 mA during the control period and 8.2 ± 5.3 mA after drug ($p < 0.001$). The average blood level at the time of RET determination was 933 ± 562 ng/ml. For the 10 dogs given doxepin, $\bar{x}$ RET ± 1 SD was 31.6 ± 5.3 mA during the control period and 22.9 ± 13.8 mA after drug ($p < 0.01$). The average blood level of doxepin at the time of RET determination was 1889 ± 899 ng/ml. All 16 dogs had more than a 50% reduction in RET after amitriptyline, whereas it occurred in only 4 of 10 dogs after doxepin (Chi square = 12.48, $p < 0.005$).

Because the RET did not consistently fall after doxepin, the results are divided into those of experiments in which the RET did and did not lower the RET more than 50% of control values (Table I). The mean blood level was $1,614 \pm 785$ ng/ml in the group with no response to doxepin and $2,379 \pm 921$ ng/ml in the group in which RET fell more than 50% in response to doxepin ($p < 0.05$).

Fig. 2 shows the RET in four dogs given amitriptyline and five dogs given doxepin in which RET was lowered and which were subsequently given sodium bicarbonate. Mean RET was 33.6 ± 4.8 mA before doxepin, 8.4 ± 7.3 mA after doxepin ($p < 0.01$) and 11.1 ± 5.1

mA after bicarbonate (not significant). Mean arterial pH was 7.31 ± 0.08 before bicarbonate and 7.37 ± 0.06 after 44 mEq sodium bicarbonate. Mean RET was 25.3 ± 4 mA before amitriptyline, 5.8 ± 3.3 mA after amitriptyline ($p < 0.01$), and 21.3 ± 16 mA after sodium bicarbonate (change not significant). Mean arterial pH was 7.26 ± 0.08 before bicarbonate and 7.39 ± 0.08 after an average dose of 44 mEq sodium bicarbonate. Table II compares the effect of bicarbonate on the RET after amitriptyline or doxepin.

Fig. 3 depicts the RET before and after physostigmine in six dogs given amitriptyline and in 4 dogs given doxepin, which responded with more than 50% reduction in RET. The mean RET was 23.5 ± 5.7 mA before amitriptyline, 9.8 ± 6 mA after amitriptyline ($p < 0.001$), and 26.7 ± 6.8 mA after physostigmine (difference not significant). Mean RET was 34.6 ± 4.8 mA before doxepin, 5.6 ± 4.1 mA after doxepin ($p < 0.01$), and 19.8 ± 8.6 mA after physostigmine (difference not significant). Doxepin blood levels before and after physostigmine were not significantly different ($2,533 \pm 1,261$ ng/ml and $1,633 \pm 504$ ng/ml).

Discussion

Our data demonstrate that both amitriptyline and doxepin can reduce the RET in the anesthetized dog paced at a constant rate. The lowered RET is consistent with the clinical finding that severe tricyclic antidepressant overdoses predispose to ventricular tachycardia and fibrillation.

It is important to note the apparent differences in toxicity between amitriptyline and doxepin. Amitriptyline consistently lowered the RET levels in each of 16 dogs tested. The mean blood level was 933 ± 562 ng/ml. Doxepin lowered RET in only four of 10 dogs, and the mean blood level of $2,379 \pm 921$ ng/ml is more than 2 times the mean level needed with amitriptyline. The doses chosen for our study were targeted for 1,000 ng/ml, which is consistent with life-threatening overdose in humans.¹ It appears that doxepin is less toxic than amitriptyline in its ability to lower ventricular vulnerability despite higher blood levels of doxe-

Table II. *Effect of bicarbonate on RET after doxepin or amitriptyline*

	Control RET (mA)	After drug (mA)	After drug and after bicarbonate (mA)
Amitriptyline	25.3 ± 4.0	5.8 ± 3.3*	21.3 ± 16.0
Doxepin	33.6 ± 4.8	8.4 ± 7.3*	11.1 ± 15.1†

*p < 0.01 Compared with control level.

†p < 0.05 Compared with control level.

pin, but doxepin also has the same potential for inducing ventricular fibrillation if the dose is high enough in susceptible animals.

We found the response of amitriptyline and doxepin to sodium bicarbonate to be very variable. Brown et al.³ showed that the tricyclic antidepressants have increased protein binding at higher pH values.³ They described several cases in humans and in animal experiments in which sodium bicarbonate reversed ventricular arrhythmias and contracted the widened QRS induced by tricyclic antidepressants. Our data were not clear. There were several instances of amitriptyline and doxepin effects in which bicarbonate restored the RET to control levels, but there were just as many cases in which the RET remained the same or even fell after bicarbonate despite an average dose of 2 mEq/kg.

The results with physostigmine as an antidote were more consistent in our animal model. When the RET was lowered with either amitriptyline or doxepin, physostigmine was able to restore the RET to control levels. There was one instance of doxepin effect in which the RET improved less dramatically (from 2 to 8 mA) after physostigmine, but ventricular fibrillation could not be induced after physostigmine despite scanning the T wave with our maximum current of 40 mA.

The control testing studies demonstrate that the baseline RET can be expected to be stable and reproducible for at least 3 hr (which was the duration of most of our experiments). Physostigmine did not alter the control RET. Therefore its effect on RET after treatment with toxic levels of amitriptyline or doxepin suggests that it is a direct effect of physostigmine interference with the cardiotoxicity of tricyclic antidepressants.

From these experiments in dogs, we conclude that the cardiotoxicity of amitriptyline and

doxepin can be experimentally measured by lowering RET. This occurs partly through an imbalance of autonomic tone caused by the anticholinergic effect of tricyclic antidepressants and their effect on the reuptake of catecholamines. Our earlier studies demonstrated that propranolol, physostigmine, and left stellate ganglionectomy can reverse the toxic effect of amitriptyline on RET.⁷ Matta et al.⁶ described the effect of practolol on control RET levels. They found that, consistent with its antiarrhythmic action, practolol elevated the baseline RET by 50%. Thus the effect that propranolol has on reversing tricyclic cardiotoxicity may not be specific. Left stellate ganglionectomy does not raise the baseline RET, yet it does reverse the effects of amitriptyline on RET. This implies that autonomic tone is altered by the tricyclics and that the toxicity is partially mediated through this imbalance. It appears from the comparison of amitriptyline and doxepin that both can act in the same way to lower RET or VFT in dogs. At the same blood levels, doxepin has significantly less effect on RET.

There are some who believe that the toxicity of tricyclic antidepressants is being exaggerated.^{1,2} Our clinical experience also suggests that most persons who overdose with tricyclic antidepressants achieve inadequate blood levels (by the time they reach medical care and undergo gastric lavage) to develop life-threatening cardiac arrhythmias. There is, however, a sizable minority who absorb large amounts of tricyclic antidepressant and for whom an antidote is desirable. Although there should be caution in extending laboratory data to the clinical setting, our data support the use of physostigmine and possibly sodium bicarbonate in tricyclic antidepressant poisoning. The data from our study also suggest

that doxepin is less cardiotoxic than amitriptyline at similar blood levels.

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