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### Authors

Tobis, Jonathan M  
Aronow, Wilbert S

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## Effect of amitriptyline antidotes on repetitive extrasystole threshold

*The effect of amitriptyline that leads to ventricular tachycardia was evaluated by the repetitive extrasystole threshold (RET) technique in 18 dogs. The RET was  $28.8 \pm 7.9$  mamp before and  $8.2 \pm 5.3$  mamp after amitriptyline,  $p < 0.001$ . Physostigmine, propranolol, sodium bicarbonate, and left stellate ganglionectomy reversed the effect of amitriptyline on RET. We conclude that amitriptyline overdose predisposes to sudden death by lowering the ventricular fibrillation threshold. This cardiotoxic effect is mediated partly through the central nervous system and can be inhibited by increased plasma binding (bicarbonate), cholinergic stimulation (physostigmine), beta adrenergic blockade (propranolol), and sympathetic denervation (left stellate ganglionectomy).*

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

*Cardiology Section and Medical Service, University of California, Irvine, and Long Beach Veterans Administration Medical Center*

The mechanism of tricyclic antidepressant action is not established. The cardiotoxic properties have been established.<sup>6, 11, 14</sup> The most common serious clinical arrhythmia is ventricular tachycardia.<sup>7</sup> Several antidotes have been reported as successful in reversing the central nervous system and cardiac manifestations of tricyclic antidepressant overdose, i.e., physostigmine, propranolol, and sodium bicarbonate,<sup>3-5, 10, 12, 13</sup> but there is no agreement on their mechanism of action or efficacy.<sup>1, 2</sup>

We investigated some of the cardiotoxic properties of amitriptyline. Because of the life-threatening effects of an overdose in humans, we thought we were limited to the animal model to analyze the effect of an overdose of amitrip-

tyline on the repetitive extrasystole threshold (RET). Matta et al.<sup>9</sup> have shown that the RET was a good marker of the ventricular fibrillation threshold in 91% of the animals they studied. A single repetitive extrasystole occurred when 66% of the fibrillation current was delivered, and repeated extrasystoles were induced at 82% of the fibrillation current.

We then explored the effect of several potential antidotes. To elucidate the mechanism of action of the tricyclics, we manipulated sympathetic and parasympathetic nervous system activity with physostigmine and propranolol and by cutting the left stellate ganglion. We also studied the effect of sodium bicarbonate.

### Methods

Eighteen healthy mongrel dogs of both sexes, weighing 16 to 27 kg, were used. Anesthesia was induced intravenously with sodium thiamylal 4 mg/kg and alpha chloralose 40 to 80 mg/kg at a concentration of 5 mg/ml in heated

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

normal saline. Additional alpha chloralose 20 to 50 mg/kg was given if required during the experiment to maintain anesthesia. The dogs were intubated and ventilated with a Harvard pump with a mixture of room air and 100% oxygen. The ventilator was adjusted to stabilize the arterial blood pH at 7.30 to 7.45. Overhead lights were used to maintain body temperature. A 16 F polyethylene catheter was inserted percutaneously into the right femoral vein for drug administration. The left femoral artery was cannulated percutaneously with a 16 F polyethylene catheter and used to measure systemic blood pressure and obtain arterial blood samples. A Statham D 23 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 cavity was opened by right thoracotomy. A midline sternotomy was performed in the series of left stellate ganglionectomy experiments. 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-2A) to a Grass S-44 square-wave pulse generator. The output of this assembly was calibrated with an oscilloscope. The pulse generator was set at 200 bpm to overcome any tachycardia induced by the anticholinergic effect of amitriptyline. The heart was paced with a 2-msec impulse. The pulse generator had the ability to deliver a premature impulse with variable delay after the last paced beat. The pulse generator would then shut off for 3 sec, during which the effect of the premature extrastimulus could be observed on the electrocardiogram.

The RET was obtained in the manner described by Matta et al.<sup>9</sup> 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 impulse was set at 2 mamp and was increased in incre-

ments of 1 or 2 mamp until there was a repetitive extrasystole. 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 2 of 3 trials. The maximum output of our generator was 40 mamp.

**Experimental interventions.** After the baseline RET was obtained and reproduced 15 to 30 min later, amitriptyline was given as a bolus infusion of 10 to 20 mg/kg over 30 min in 9 dogs. In 7 other dogs an amitriptyline bolus of 3 to 10 mg/kg was injected intravenously and followed by a constant infusion of 0.015 to 0.025 mg/kg/min. The RET was obtained 15 min after the initial bolus of amitriptyline and was verified as stable up to 60 min later.

In 6 dogs physostigmine was given intravenously as a 2-mg bolus 30 to 45 min after the amitriptyline bolus or during continuous amitriptyline infusion. Another RET was obtained 10 to 15 min after physostigmine.

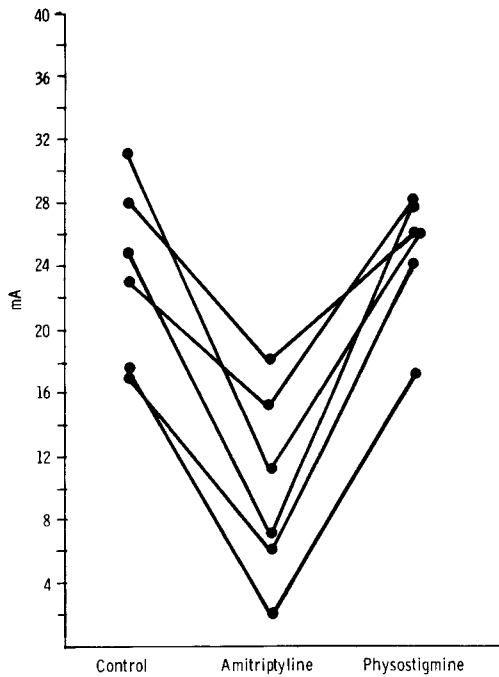
In 5 dogs propranolol 2 mg was given intravenously 30 to 45 min after the amitriptyline bolus or during continuous amitriptyline infusion. The RET was determined 10 to 15 min after propranolol.

In 5 dogs a midline sternotomy was performed. The RET was determined at baseline and then during an amitriptyline infusion of 0.015 to 0.025 mg/kg/min after an initial intravenous bolus of 3 to 10 mg/kg. A left stellate ganglionectomy was performed through the sternotomy incision. During constant infusion of amitriptyline the RET was again obtained.

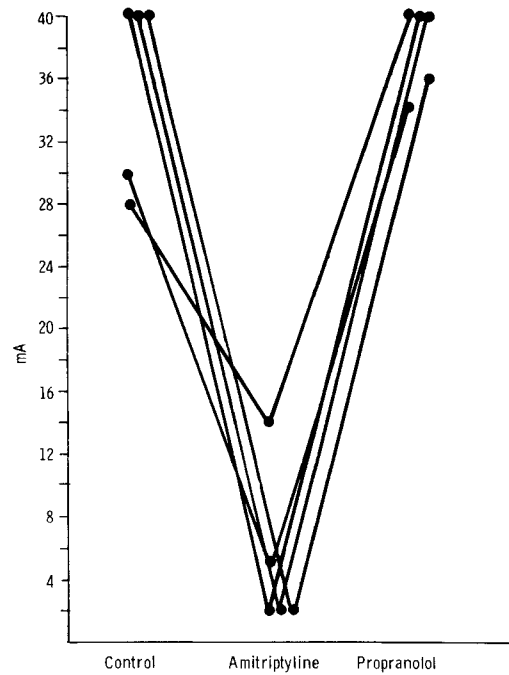
In 2 dogs sternotomy was performed, followed by baseline determination of RET. These dogs then had a left stellate ganglionectomy prior to any drug administration. After the postganglionectomy RET was performed, an amitriptyline bolus of 15 mg/kg was followed by a 0.015- or 0.025-mg/kg/min infusion intravenously, and RET was repeated.

In 4 dogs RET was determined before and during intravenous amitriptyline infusion. RET was repeated after 44 mEq sodium bicarbonate was given intravenously over 5 min. Arterial pH was determined before and after bicarbonate while RET was being determined.

Several amitriptyline blood samples were



**Fig. 1.** Repetitive extrasystole threshold before amitriptyline, after amitriptyline, and after physostigmine. mA, Milliampere (mamp).



**Fig. 2.** Repetitive extrasystole threshold before amitriptyline, after amitriptyline, and after propranolol. mA, Milliampere (mamp).

drawn during each experiment to ensure adequate toxic blood levels. Amitriptyline and nortriptyline plasma levels were determined by Bio-Science Laboratories.

### Results

For the entire group of 16 dogs RET  $\pm 1$  SD was  $28.8 \pm 7.9$  mamp during the control period and  $8.2 \pm 5.3$  mamp after amitriptyline,  $p < 0.001$ . Average blood level at the time of RET determination was  $933 \pm 562$  ng/ml.

Fig. 1 shows RET in the 6 dogs given amitriptyline followed by physostigmine. Mean RET was  $23.5 \pm 5.7$  mamp before and  $9.8 \pm 6.0$  ma after amitriptyline,  $p < 0.001$ , and  $26.7 \pm 6.8$  mamp after physostigmine (control not significantly different).

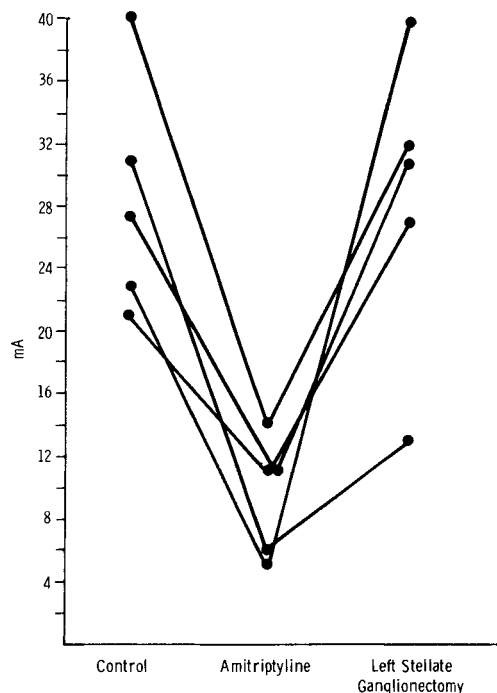
Fig. 2 shows RET in the 5 dogs given amitriptyline followed by propranolol. Mean RET was  $35.6 \pm 6.1$  mamp before and  $5.0 \pm 5.2$  mamp after amitriptyline,  $p < 0.001$ , and  $38.0 \pm 2.8$  mamp after propranolol (control not significantly different).

Fig. 3 shows RET in the 5 dogs given ami-

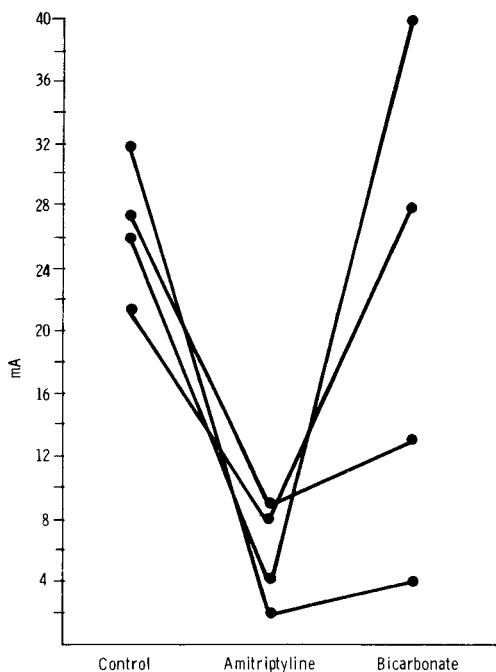
triptyline followed by left stellate ganglionectomy. Mean RET was  $28.4 \pm 7.5$  mamp before and  $9.4 \pm 3.8$  mamp after amitriptyline,  $p < 0.005$ , and  $27.6 \pm 9.8$  mamp after left stellate ganglionectomy (control not significantly different).

Fig. 4 shows RET in the 4 dogs given amitriptyline followed by sodium bicarbonate. Mean RET was  $25.3 \pm 4.0$  mamp before and  $5.8 \pm 3.3$  mamp after amitriptyline,  $p < 0.01$ , and  $21.3 \pm 16.0$  mamp after sodium bicarbonate (control not significantly different). Mean arterial pH was  $7.26 \pm 0.08$  before and  $7.39 \pm 0.08$  after an average dose of 44 mEq sodium bicarbonate.

In the 2 dogs with left stellate ganglionectomy before amitriptyline infusion, the ventricular fibrillation threshold (VFT) was measured directly rather than RET, because ventricular fibrillation developed in the control periods during RET measurement. Control VFT was  $33.0 \pm 7.5$  mamp before and  $37.0 \pm 0.0$  mamp after left stellate ganglionectomy ( $p$  not significant) and  $37.8 \pm 4.5$  mamp after amitrip-



**Fig. 3.** Repetitive extrasystole threshold before amitriptyline, after amitriptyline, and after left stellate ganglionectomy. mA, Milliampere (mamp).



**Fig. 4.** Repetitive extrasystole threshold before amitriptyline, after amitriptyline, and after sodium bicarbonate. mA, Milliampere (mamp).

tyline (p not significant). At the time of VFT the mean level of amitriptyline was  $971 \pm 526$  ng/ml.

### Discussion

Our data demonstrated that amitriptyline consistently reduced RET in anesthetized dogs. These dogs were given alpha chloralose to diminish the effects of anesthesia on myocardial electrical properties. The lowered RET is consistent with the clinical finding that tricyclic antidepressant overdoses predispose to ventricular tachycardia. This effect on RET was countered by physostigmine, propranolol, and left stellate ganglionectomy.

Clinical manifestations in victims of tricyclic antidepressant overdose suggest that there are 4 major mechanisms of action.<sup>15</sup> (1) There are early signs of anticholinergic effects, e.g., mydriasis, diminished secretions, tachycardia, decreased gastrointestinal tract motility, and urinary retention. (2) Tricyclic antidepressants have been shown to block the re-uptake of catecholamines at neuromuscular junctions,

which leads to early excess of catecholamines with resultant hypertension and tachycardia. (3) With continued blockage of catechol uptake there is catecholamine depletion with subsequent hypotension and bradycardia. (4) There may also be direct myocardial depression by tricyclic antidepressants, perhaps accounting for decreased contractility and heart block.

The most common serious arrhythmia that tricyclic antidepressant overdose victims develop is sinus tachycardia, often with a broad QRS, followed by ventricular tachycardia. One of the questions we sought to answer was whether this cardiotoxic effect is a direct action of tricyclic antidepressants on myocardial cells or whether there is some indirect action through the central nervous system.

Our hypothesis is that tricyclic antidepressant cardiotoxicity is the result of imbalance of autonomic tone to the myocardium, which induces dispersion of repolarization (evidenced by prolonged QT interval) and predisposes to ventricular tachycardia and ventricular fibrillation. Thus, antidotes to tricyclic antidepressant poisoning

may work if they reestablish normal autonomic tone.

Because tricyclic antidepressants have an anticholinergic action, physostigmine may counteract cardiotoxic manifestations by increasing cholinergic tone, and propranolol may block unopposed sympathetic tone to equalize the neural input of the myocardium and thereby counteract the cardiotoxic effect of tricyclics. The data from our experiments indicate that both physostigmine and propranolol counteract the effect of amitriptyline on RET.

The experiments with left stellate ganglionectomy suggest that the cardiotoxic properties of amitriptyline are centrally mediated. The partial sympathectomy reversed the toxic effects of amitriptyline on RET. When amitriptyline was given after left stellate ganglionectomy, there was no RET decrease despite toxic blood levels of amitriptyline ( $\bar{x}$  = 971 ng/ml). This blood level of amitriptyline consistently lowered RET before left stellate ganglionectomy. These blood levels of amitriptyline are associated clinically with severe overdoses with frequent episodes of ventricular tachycardia.<sup>2</sup>

The question arose as to whether physostigmine, propranolol, and left stellate ganglionectomy are nonspecific for counteracting tricyclic antidepressant toxicity and will tend to raise RET under any circumstance. We showed that there is no increase in baseline RET when left stellate ganglionectomy is performed before amitriptyline.

Sodium bicarbonate has been shown to increase the plasma binding of tricyclics by raising arterial pH. There are case reports of its clinical efficacy. In 2 dogs there was a dramatic increase in RET after 44 mEq sodium bicarbonate. In 2 other dogs RET did not increase despite adequate elevation of arterial pH. There are not enough clinical reports to suggest the frequency with which sodium bicarbonate is effective in reversing toxic tricyclic antidepressant properties.

In the clinical application of experiments, caution must be exercised in extending results from laboratory animals to humans. Data from our study suggest a rationale to pharmacologic intervention in humans with life-threatening arrhythmias resulting from amitriptyline. We recommend the cautious use of physostigmine,

propranolol, and sodium bicarbonate in the treatment of severe tricyclic antidepressant overdose.

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