Frequency-dependent effects of amitriptyline on ventricular conduction and cardiac rhythm in dogs

Stanley Nattel, M.D.

ABSTRACT Although overdoses of tricyclic antidepressant are known to produce both sinus tachycardia and ventricular tachyarrhythmias in man, these have been assumed to occur by independent mechanisms. This study was designed to evaluate the relationship of ventricular activation frequency to the cardiotoxic effects of amitriptyline. When amitriptyline was infused into dogs with formalin-induced atroventricular (AV) block to evaluate a broad range of pacing frequencies, the drug produced dose-related QRS prolongation that was markedly frequency dependent. Similar frequency-dependent depression of the maximum rate of depolarization (V_max) was noted for canine Purkinje fibers superfused with amitriptyline in vitro. The time constant of recovery from amitriptyline-induced block was dose independent and averaged 228 msec in vivo and 216 msec in vitro. When amitriptyline was infused into dogs with intact AV conduction, sinus tachycardia occurred within 15 min, followed by progressive QRS prolongation and ventricular tachyarrhythmias after an average of 29 min. Slowing of sinus rate by vagal stimulation (seven dogs) or intravenous metoprolol (five dogs) reproducibly reversed the QRS prolongation and ventricular tachyarrhythmias caused by amitriptyline. These studies show that amitriptyline produces frequency-related depression of ventricular conduction in vivo, with a time dependence similar to effects on the maximum rate of depolarization in vitro. Interventions that slow heart rate reverse the adverse effects of amitriptyline on ventricular conduction and cardiac rhythm.


LOCAL ANESTHETIC drugs have been shown to have important frequency-dependent effects on the maximum rate of depolarization (V_max) and the inward sodium current of mammalian cardiac tissues.¹ These observations have been incorporated into powerful new models of the interaction between antiarrhythmic drugs and cardiac sodium channels.²⁻³ Although these models have important potential clinical implications,⁴ there is relatively little information available about the occurrence in vivo and clinical relevance of frequency-dependent drug effects on ventricular conduction.

The tricyclic antidepressants are local anesthetic drugs⁵⁻⁷ with potentially useful antiarrhythmic effects.⁸ Overdoses of tricyclic antidepressants produce slowing of ventricular conduction and tachyarrhythmias.⁹⁻¹² The relative role of local anesthetic properties, anticholinergic actions, and blockade of norepinephrine uptake in producing tricyclic-induced ventricular tachyarrhythmias has been debated.¹³ We have shown that amitriptyline infusion predictably results in sinus tachycardia at low doses, followed by QRS prolongation and ventricular tachyarrhythmias at higher doses.¹⁴⁻¹⁵ These findings correspond to clinical observations suggesting that anticholinergic actions of the tricyclics are not directly responsible for ventricular arrhythmogenesis and that ventricular conduction slowing may play an important role in arrhythmia production as originally suggested by Vohra et al.¹⁶

The possibility that sinus tachycardia caused by tricyclic antidepressant overdose plays a permissive role in slowing of ventricular conduction, and in arrhythmogenesis has not been considered. Observations supporting this idea include the anecdotaly described reversal of amitriptyline-induced ventricular arrhythmias and conduction slowing by physostigmine in man¹⁷ and by physostigmine, neostigmine, and practolol in puppies.¹⁸

This investigation was designed to evaluate the frequency dependence of the effects of amitriptyline on
ventricular conduction in vivo and to relate these frequency-dependent effects to changes in $V_{\text{max}}$ of canine cardiac Purkinje fibers in vitro and to amitriptyline-induced ventricular arrhythmias in intact dogs. Preliminary results of these studies have been presented in abstract form.\(^1\)

**Methods**

**General.** Mongrel dogs of either sex were used for all experiments. For experiments in vivo, dogs were anesthetized with morphine (2 mg/kg im) and alphachloralose (100 mg/kg iv). This form of anesthesia was chosen because it results in baseline cardiovascular variables and effects of amitriptyline similar to those found in the awake, nonsedated dog.\(^1\)\(^4\)\(^5\) Catheters were inserted into the left femoral artery and both femoral veins and kept patent with heparinized saline solution (0.9%). A Statham P23 1D transducer (Statham Medical Instruments, Los Angeles) and electrophysiologic amplifiers and a paper recorder (Grass Instruments Co.) were used to monitor blood pressure, electrocardiographic leads II and aVR, and a right atrial electrogram or stimulus artifacts. All dogs were ventilated via an endotracheal tube at a rate of 10/min with a tidal volume obtained from a nomogram. The control heart rate of these dogs averaged 58 ± 8 beats/min and blood pressure averaged 153 ± 22/100 ± 20 mm Hg.

Tissues for studies in vitro were obtained from dogs anesthetized with sodium pentobarbital (30 mg/kg iv). Free-running false tendons were dissected from either ventricle along with subjacent muscle and attached to the paraffin-coated bottom of a Lucite tissue chamber. The preparation was stimulated with 2 msec square-wave pulses of twice diastolic threshold current via bipolar Teflon-coated platinum electrodes. A digital timing unit and stimulus isolator (Bloom Instruments, Flying Hills, PA) were used to control stimulus delivery. The tissue was superfused with modified Tyrode’s solution oxygenated with 95% O\(_2\)/5% CO\(_2\) and containing the following constituents: Na\(^+\), 141 mM; HCO\(_3\)^-; 22 mM; dextrose, 5.5 mM; K\(^+\), 4 mM; Mg\(^{2+}\), 0.5 mM; H\(_2\)PO\(_4\)^-; 0.9 mM; Ca\(^{2+}\), 2 mM; and Cl\(^-\), 125 mM. Temperature of the solution was kept at 37° ± 0.2° C by a heating element under negative feedback control from a thermost in the tissue bath (Hanna Instruments, Philadelphia). Glass microelectrodes filled with 3M KCl solution and with resistances of 8 to 20 megohm were coupled via a Ag-AgCl junction to a microelectrode amplifier (WPI Model KS-700). Transmembrane potential was displayed on a Tektronix 5115 storage oscilloscope and was differentiated electronically (differentiation linear over 20 to 1000 V/sec). Transmembrane potentials were converted into digital form with a 100 kHz analog-to-digital converter (Teclarm, Inc.) and analyzed with an IBM personal computer and custom-made software routines (Bascorn Consultants Inc., Montreal, Quebec).

**Frequency-dependent effects of amitriptyline on conduction in vivo.** A right thoracotomy was performed and complete atrioventricular (AV) block was produced by injection of small quantities (average 0.15 ml) of formalin.\(^2\) A bipolar, Teflon-coated, stainless steel electrode inserted into the right ventricle was used to stimulate the heart with 4 msec square-wave pulses of twice diastolic threshold current. Electrocardiographic recordings were obtained at 100 mm/sec paper speed during sustained stimulation at basic cycle lengths of 300 and 1000 msec and in the presence of premature beats and pauses. Single premature beats were initiated after every eight basic complexes at 1 Hz, and pauses were introduced after 18 basic activations at 2.5 to 3.3 Hz. Effective refractory period, defined as the longest premature coupling interval at which ventricular activation failed, was measured by the extrastimulus technique. Spontaneous escape intervals were measured by temporarily interrupting stimulation after at least 30 sec of continuous pacing at a selected frequency.

Induction of arrhythmia was attempted in some experiments with up to two extrastimuli and burst pacing. Ventricular tachycardia was defined as three or more successive broad QRS complexes at a rate greater than the underlying sinus or paced rate with evidence of AV dissociation.

The effects of amitriptyline were studied by a multiple infusion system developed during preliminary investigations. Stable drug effects were observed for over 20 min during continuous infusions of amitriptyline that had been preceded by 15 min loading infusions at 50% greater rate. Results were obtained during infusion at rates of 0.17, 0.33, and 0.67 mg/kg/min, which paralleled the range over which amitriptyline cardio toxicity in the dog resembles the drug’s toxic effects in man.\(^1\)\(^4\)\(^5\) Plasma amitriptyline concentrations were measured by previously developed high-pressure liquid chromatographic techniques.\(^1\)\(^4\)

**Frequency-dependent effects of amitriptyline on $V_{\text{max}}$ in vitro.** After a 1 hr stabilization period, control action potential characteristics were measured at basic cycle lengths of 300 and 1000 msec. Amitriptyline was then added to the superfusate at concentrations of 0.2 or 1 mg/liter, and measurements were repeated after 30 and 60 min. After 1 hr of drug superfusion, the effects of changes in basic stimulation frequency and of premature and delayed activation were evaluated. Premature or delayed action potentials with a take-off potential more than 2 mV different from basic action potentials were not included in analyses of changes in $V_{\text{max}}$. Results presented are for experiments in which continued impalement of the same cell was maintained during both control and drug superfusion periods. The concentration range selected was based on estimates of the range of free plasma concentrations associated with significant electrophysiologic effects in previous experiments.\(^1\)\(^4\)

The voltage dependence of $V_{\text{max}}$ was studied by increasing superfusate potassium concentration to 14 mM by the addition of potassium chloride. The resulting $V_{\text{max}}$ inactivation curves were fitted to an equation based on the observations of Weidmann.\(^2\)\(^1\) Nonlinear curve fitting techniques were used to obtain the transmembrane potential for 50% inactivation of $V_{\text{max}}$ ($V_{50}$) and the slope factor (S), which characterize the inactivation curve. Only curves that were reproducible upon potassium washout were used. Results were obtained first under control conditions, then after 1 hr of amitriptyline infusion at one cycle length, and finally during continued amitriptyline infusion at a second basic cycle length. The cycle lengths studied were 1000 and 300 msec (or the shortest cycle length greater than 300 msec at which sustained capture was obtained). Five experiments were performed to study the effects of 0.2 mg/liter amitriptyline and five with 1 mg/liter amitriptyline.

**Effects of amitriptyline, vagal stimulation, and metoprolol.** Amitriptyline was infused via the right femoral vein of closed-chest, anesthetized dogs at 0.5 mg/kg/min for 30 min followed by 1 mg/kg/min for up to 30 min. When ventricular tachycardia occurred, the infusion rate was reduced by one-third and the infusion was continued. We have shown that this protocol results in ventricular tachycardias in most dogs and that the effects of amitriptyline are constant for at least 30 min after the dose reduction.\(^1\) The vagi were isolated from the carotid sheaths in the neck but not decentralized and were stimulated with supramaximal voltage, square-wave bipolar pulses of 0.2 msec duration and 12 Hz frequency. To produce appreciable vagal effects in the presence of amitriptyline, it was necessary to administer an acetylcholinesterase inhibitor. We used a single dose of neostigmine (2.5 mg iv) given 1 min after...
the reduction in infusion rate. In experiments studying metoprolol, 2.5 mg of metoprolol (approximately 0.15 mg/kg) was administered intravenously 1 min after the onset of ventricular arrhythmia.

Statistical analysis. Group data are presented as mean ± SD. Comparisons between group means were made by two-way analysis of variance with Scheffe’s test.22

The frequency dependence of drug effects in vitro was determined by calculating an F ratio for interaction effects.22 Raw data and two-tailed tests were used for all statistical comparisons. A probability of 5% or less was taken to indicate statistical significance. Linear and nonlinear curve fitting was performed by least squares regression.

Results

Frequency-dependent effects of amitriptyline on ventricular conduction in vivo. Infusion of amitriptyline resulted in QRS prolongation that depended on both the frequency of activation and the drug infusion rate (table 1). Overall QRS morphology was not altered by the drug, but the slope of all portions of the QRS was decreased. Measurements of QRS duration were made from corresponding points at the first rapid voltage deflection to the last rapid deflection, with use of the same lead for both control and drug infusion periods. QT intervals at a basic cycle length of 1000 msec were decreased by amitriptyline, but at a basic cycle length of 300 msec large doses of amitriptyline increased the QT interval by increasing the QRS duration. Refractory periods decreased at the smaller infusion rates and increased at the largest infusion rate. Escape intervals varied greatly between dogs and were increased by amitriptyline. In three animals escape intervals were studied at four basic cycle lengths between 300 and 1000 msec and were increased by the drug at all frequencies.

Amitriptyline-induced QRS prolongation could be eliminated by pauses in the pacing protocol. Figure 1 shows the effect of an 8 sec pause interrupting stimulation at a basic cycle length of 350 msec during infusion of amitriptyline at 0.67 mg/kg/min. Within four complexes after the resumption of stimulation, the QRS returned to prepause values. Over 90% of steady-state change in QRS duration was obtained within 1 sec after a pause in all animals.

To quantitate the time dependence of QRS prolongation in the presence of amitriptyline, the response to variations in diastolic interval was studied. Diastolic interval was altered by introducing a premature stimulus (S2) after a train of eight basic stimuli (S1) at 1 Hz. The increase in QRS duration of premature complexes compared with the QRS duration of the last complex of the basic train was a log-linear function of the S1S2 coupling interval (figure 2). Similar results were obtained in each experiment by means of either premature stimuli or pauses to vary the S1S2 interval. Pauses were introduced after 18 basic complexes at a cycle length of 300 to 350 msec. The time constant of recovery from amitriptyline-induced QRS prolongation was obtained from the relationship between changes in QRS duration and S1S2 interval in each experiment.

Changes in QRS duration that were large enough to measure the time constant accurately were observed in all experiments at the two higher infusion rates. The time constants for QRS prolongation averaged 229 ± 34 and 226 ± 7 msec for the 0.33 and 0.67 mg/kg/min infusion rates, respectively.

Frequency-dependent effects of amitriptyline on Vmax in vitro. Amitriptyline decreased action potential duration and Vmax of canine Purkinje fibers. Under control conditions, Vmax was not significantly changed by decreas-

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<tr>
<td>Changes in electrophysiologic variables produced by infusion of amitriptyline into six dogs with complete AV block</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>QRS (msec)</th>
<th>QT (msec)</th>
<th>ERP (msec)</th>
<th>Esc. Int. (sec)</th>
<th>Ami. Conc. (mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BCL 1000</td>
<td>BCL 300</td>
<td>BCL 1000</td>
<td>BCL 300</td>
<td>BCL 1000</td>
</tr>
<tr>
<td>Control</td>
<td>94 ± 13</td>
<td>94 ± 13</td>
<td>288 ± 24</td>
<td>235 ± 17</td>
<td>221 ± 12</td>
</tr>
<tr>
<td>Amitriptyline (mg/kg/min)</td>
<td>0.17</td>
<td>95 ± 12</td>
<td>110 ± 8\8</td>
<td>265 ± 19\C</td>
<td>237 ± 23\D</td>
</tr>
<tr>
<td></td>
<td>0.33</td>
<td>102 ± 13</td>
<td>146 ± 9\D</td>
<td>261 ± 26\C</td>
<td>269 ± 29\D</td>
</tr>
<tr>
<td></td>
<td>0.67A</td>
<td>107 ± 14\C</td>
<td>186 ± 22\D</td>
<td>270 ± 18\B</td>
<td>308 ± 33\D</td>
</tr>
</tbody>
</table>

ERP = effective refractory period; Esc. Int. = pause before spontaneous ventricular escape after interrupting a 30 sec period of pacing; Ami. Conc. = plasma amitriptyline concentration immediately before (prestudy) and after (poststudy) measurement of electrophysiologic variables during a given drug infusion; BCL 1000, BCL 300 = measurements made at a paced basic cycle length of 1000 and 300 msec.

Amitriptyline was frequently impossible to maintain pacing at a cycle length of 300 msec during the 0.67 mg/kg/min infusion of amitriptyline. Measurements during this infusion were made at the shortest cycle length permitting sustained capture, averaging 350 msec.

Statistical comparisons (vs control at the same cycle length, by analysis of variance with Scheffe’s test): \( p < .05 \); \( \delta p < .01 \); \( \delta p < .001 \).
Amitriptyline shifted the voltage dependence of $V_{\text{max}}$ to more negative membrane potentials (figure 3). Decreasing the basic cycle length shifted the curve downward without any further rightward shift on the voltage axis. Nonlinear curve fitting of the experimental data showed that amitriptyline produced a concentration-related change in the voltage dependence of $V_{\text{max}}$, and that changes in frequency did not alter the voltage dependence of $V_{\text{max}}$ at a given amitriptyline concentration (table 2B).

Effects of changes in spontaneous rate on amitriptyline-induced conduction slowing and arrhythmia. Amitriptyline was infused into 13 closed-chest dogs with intact AV conduction, and ventricular tachyarrhythmias occurred in 12. Amitriptyline increased sinus rate from 57 ± 12 beats/min (control) to a maximum of 173 ± 37 beats/min after 15 min of infusion. QRS duration was altered more slowly by amitriptyline, increasing from 58 ± 8 msec (control) to 75 ± 18 msec after 15 min of drug infusion and then to a maximum of 127 ± 23 msec immediately before the onset of ventricular tachyarrhythmia after an average of 29 min of infusion.

Neostigmine transiently reversed ventricular tachyarrhythmias in one of seven dogs, without altering the cardiac rhythm among the other six. In all seven dogs, vagal stimulation resulted in complete abolition of ventricular tachycardia, slowing of heart rate, and decreases in QRS duration (figure 4). After vagal stimulation was stopped, heart rate gradually increased to previous values, QRS complexes widened, and ventricular tachycardia recurred. Vagal stimulation was then repeated, resulting in sinus rhythm with narrowed QRS complexes. This sequence could be reproduced repeatedly for 30 min after the initial occurrence of ventricular tachyarrhythmia.

Metoprolol was administered to five dogs with ventricular tachyarrhythmia and restored sinus rhythm at a slower rate in all. Although metoprolol was slightly less effective than vagal stimulation, its effects on RR intervals and QRS duration were qualitatively similar (table 3). Vagal stimulation did not significantly alter blood pressure compared with prearrhythmia values, but metoprolol often produced profound and progressive hypotension, sometimes leading to death.

Spontaneous ventricular tachyarrhythmias did not occur among any dogs with complete AV block. Pro-

$V_{\text{max}}$ was measured in five fibers exposed to 1 mg/liter of the drug and averaged 216 ± 32 msec. Changes in $V_{\text{max}}$ resulting from 0.2 mg/liter amitriptyline were much smaller, making accurate quantitation of the time constant at the lower concentration difficult.

Vagal stimulation, premature stimuli produced reductions in $V_{\text{max}}$ that were log-linearly related to the premature coupling interval (figure 2). The time constant for recovery from amitriptyline-induced block of
grammed electrical stimulation was applied in seven dogs and reproducibly resulted in ventricular tachyarrhythmias along with marked conduction slowing in six. Ventricular tachyarrhythmias consisted of ventricular tachycardia in five dogs and ventricular fibrillation in one.

**Discussion**

We have demonstrated that amitriptyline has frequency-dependent effects on ventricular conduction in vivo, with a similar time dependency to the drug’s depressant effects on $V_{max}$ in vitro. Furthermore, interventions that slow heart rate (including vagal stimulation, metoprolol, and AV block) reverse or prevent both conduction slowing and ventricular tachyarrhythmias caused by infusion of amitriptyline. In contrast to the extensive information about frequency-dependent effect of drugs on cardiac tissue in vitro, little has been published about corresponding effects in vivo. Lidocaine has been shown to produce time-dependent conduction slowing in intact hearts, but the time dependency was not quantified. A major restriction in studying rate-dependent drug effects in vivo is the often-limited range of frequencies that can be evaluated because of interference from supraventricular pacemakers. This problem can be avoided by using animals with complete AV block, as described in this study.

We used $V_{max}$ as an index of amitriptyline’s effects on cardiac sodium channels in vitro. The limitations of this approach are well recognized. It is nevertheless
TABLE 2A
Effects of amitriptyline on action potential characteristics of canine cardiac Purkinje fibers

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Amitriptyline (0.2 mg/l)</th>
<th>Amitriptyline (1 mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BCL 1000</td>
<td>BCL 300</td>
<td>BCL 1000</td>
</tr>
<tr>
<td>MAP (mV)</td>
<td>-86 ± 2</td>
<td>-90 ± 2</td>
<td>-85 ± 1</td>
</tr>
<tr>
<td>APA (mV)</td>
<td>128 ± 3</td>
<td>132 ± 2</td>
<td>126 ± 4</td>
</tr>
<tr>
<td>APD90 (msec)</td>
<td>213 ± 30</td>
<td>121 ± 8</td>
<td>116 ± 17E</td>
</tr>
<tr>
<td>Vmax (V/sec)</td>
<td>718 ± 104</td>
<td>683 ± 107</td>
<td>681 ± 107</td>
</tr>
</tbody>
</table>

BCL = basic cycle length; MAP = transmembrane potential at the time of activation; APA = action potential amplitude; APD90, APD50 = action potential duration to 50% and 90% of repolarization; P手段 = statistical significance of the interaction between pacing cycle length and drug effects, by F test for interaction.

*Results are from five experiments studying amitriptyline at 0.2 mg/l and 10 experiments at 1 mg/l.

Sustained capture could not always be maintained at a cycle length of 300 msec at this amitriptyline concentration. The shortest possible cycle length over 300 msec was then used, and the average cycle length studied was 350 msec.

Statistical comparisons (vs control at the same basic cycle length): 3p < .05; 4p < .01; 5p < .001.

TABLE 2B
Effects of amitriptyline on the voltage dependence of Vmax in canine cardiac Purkinje fibers

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Amitriptyline (0.2 mg/l)</th>
<th>Amitriptyline (1 mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>V50 (mV)</td>
<td>-66.7 ± 1.4</td>
<td>-71.6 ± 2.2c</td>
<td>-72.2 ± 1.9c</td>
</tr>
<tr>
<td>S</td>
<td>3.90 ± 0.62</td>
<td>3.52 ± 0.47</td>
<td>3.69 ± 0.78</td>
</tr>
</tbody>
</table>

V50 = transmembrane potential at which 50% reduction of Vmax was achieved; S = slope factor. Both values were obtained from nonlinear curve fitting of the K+-depolarized MAP - Vmax relationship to the equation: (Vmax) = (Vmax0)/(1 + exp(V50 - MAP)/S), where (V50) = (Vmax) of the test action potential, (Vmax)0 = Vmax before K+ depolarization, and MAP = activation potential of the test action potential. The mean correlation coefficient for the fits obtained was .99. Results were obtained from five experiments at each amitriptyline concentration.

Statistical comparisons (vs control): 3p < .05; 4p < .01; 5p < .001.

FIGURE 3. Effect of amitriptyline (Ami) on the relationship between Vmax and activation potential. The Vmax of action potentials was measured as a function of transmembrane potential at the onset of activation. Membrane potential was altered by increasing superfusate potassium concentration to 14 mM and then returning to control Tyrode’s solution. Under control conditions, changes in frequency did not alter membrane responsiveness. This figure shows the changes in membrane responsiveness in typical experiments after 1 hr of superfusion with 0.2 mg/liter of amitriptyline (left) and 1 mg/liter of amitriptyline (right). Amitriptyline produced a concentration-dependent rightward shift of the membrane responsiveness curve. Decreasing the cycle length in the presence of amitriptyline resulted in a downward shift of the curve, without changing its voltage dependence. BCL = basic cycle length (msec).
of the blocking actions of various drugs.\textsuperscript{24-28} Amitriptyline and imipramine have similar chemical structures and molecular weights, but our data suggest a more rapid time course for amitriptyline-induced block than has been shown for imipramine in vitro.\textsuperscript{25} The differences may be caused by differences in the experimental preparations used or by differences in rate of block, which can occur even with relatively small modifications of drug structure.\textsuperscript{26, 27}

The mechanism of frequency-dependent drug effects on cardiac sodium channels is an area of major ongoing investigation. Suggested mechanisms include drug-receptor association and dissociation rates that depend on the state of the sodium channel\textsuperscript{2} and access to the sodium channel that depends on the drug’s biophysical properties and the state of the channel.\textsuperscript{3} Those models predict that the block produced by tertiary amine local anesthetics (like amitriptyline) may be enhanced by depolarization and that recovery from depolarization-induced block is time dependent. The observed shifts in the voltage dependence of $V_{\text{max}}$ and the frequency dependence of $V_{\text{max}}$ depression caused by amitriptyline are therefore typical of drug effects described in these models. Furthermore, changes in QRS duration in the presence of amitriptyline in vivo follow a similar pattern and can be explained in terms of the models. With each activation, amitriptyline binds to sodium channels and begins to unbind during diastole. If diastole is sufficiently long, sodium channels become completely unblocked between activations and conduction is unaltered. As heart rate is increased, the diastolic period is shortened and there is insufficient time for complete drug unbinding between beats.

TABLE 3

Changes in electrocardiographic intervals produced by amitriptyline, and effects of vagal stimulation and metoprolol during continued infusion

<table>
<thead>
<tr>
<th></th>
<th>Amitriptyline Control</th>
<th>Prearrhythmia</th>
<th>Vagal stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (sec)</td>
<td>1.02 ± 0.36</td>
<td>0.34 ± 0.08\textsuperscript{c}</td>
<td>0.56 ± 0.14\textsuperscript{a}</td>
</tr>
<tr>
<td>QRS (sec)</td>
<td>0.055 ± 0.005</td>
<td>0.131 ± 0.019\textsuperscript{c}</td>
<td>0.079 ± 0.019\textsuperscript{a}</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Amitriptyline Control</th>
<th>Prearrhythmia</th>
<th>After metoprolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>0.95 ± 0.29</td>
<td>0.33 ± 0.05\textsuperscript{c}</td>
<td>0.49 ± 0.05\textsuperscript{b}</td>
</tr>
<tr>
<td>QRS</td>
<td>0.060 ± 0.009</td>
<td>0.135 ± 0.023\textsuperscript{c}</td>
<td>0.099 ± 0.016\textsuperscript{c}</td>
</tr>
</tbody>
</table>

All measurements were made during sinus rhythm, including those immediately before arrhythmia and after conversion to sinus rhythm by vagal stimulation (studied in seven dogs) or metoprolol (in five dogs). Statistical comparisons (vs corresponding control value, by two-way analysis of variance with Scheffé's test): \textsuperscript{c}$p < .05$; \textsuperscript{b}$p < .01$; \textsuperscript{a}$p < .001$. 

A well-characterized and standard method to study the cellular effects of antiarrhythmic drugs. Its advantages include simplicity and the ability to study tissues at physiologic temperatures and with superfusates that mimic the normal extracellular milieu. Much of our current understanding of cellular mechanisms of antiarrhythmic drug action depends on the use of $V_{\text{max}}$ as an index of maximum sodium permeability,\textsuperscript{1} although more direct measurements of sodium current will certainly provide important improvements in the understanding of drug mechanisms.

Considerable work has been done to characterize the biophysical properties that determine the time course
presence of persistent drug-associated (blocked) sodium channels reduces maximum sodium current and conduction velocity, resulting in QRS prolongation. Marked QRS prolongation is associated with the appearance of ventricular tachyarrhythmias. Slowing the underlying rate in the presence of amitriptyline allows greater diastolic time for drug unbinding from sodium channels, which reduces the degree of sodium channel block, improves ventricular conduction, and eliminates ventricular arrhythmias.

Amitriptyline slowed conduction with variable effects on refractory periods. At lower concentrations, refractoriness was decreased or unaltered by amitriptyline. At high concentrations, refractory periods were increased, presumably because of interval dependent inactivation of sodium channels. Sinus tachycardia in the presence of amitriptyline would favor reentry by increasing rate-dependent conduction slowing. If the heart rate was sufficiently rapid that ventricular activation occurred during phase 3 of the preceding action potential, further voltage-dependent conduction slowing would result. The establishment of reentry circuits would depend on the balance between changes in conduction and refractoriness caused by amitriptyline. The inducibility of arrhythmia by programmed stimulation in the presence of amitriptyline favors a reentrant type of arrhythmic mechanism. We found no evidence that amitriptyline enhances automaticity, either by measuring escape intervals in this study or by monitoring spontaneous intraventricular rate in previous work. The lack of overdrive enhancement of escape intervals is evidence against the possibility that amitriptyline causes ventricular tachyarrhythmias by inducing triggered automaticity.

Reversal of conduction slowing might be expected to abolish the conditions permitting reentrant arrhythmias in the presence of amitriptyline. This could explain the antiarrhythmic effects of vagal stimulation and metoprolol in this study and could account for the beneficial effects of alkalinization (the clinical treatment of choice) on arrhythmias caused by amitriptyline. Increases in pH have been shown to accelerate the recovery of sodium channels blocked by weakly basic local anesthetics, presumably by decreasing protonation of the drug-receptor complex. Amitriptyline has a pKa of 9.4, implying that its ionized drug fraction should be sensitive to pH changes over the physiologic range. Increasing the proportion of amitriptyline that is ionized would presumably facilitate egress of the drug from the sodium channel, possibly accounting for the improvements in conduction and reversal of arrhythmia that have been observed.

Amitriptyline is believed to cause sinus tachycardia by an anticholinergic mechanism. Ventricular tachyarrhythmias are thought to result from conduction slowing caused by amitriptyline’s direct actions on sodium channels. The experiments described here suggest that amitriptyline-induced sinus tachycardia and ventricular tachyarrhythmias are not merely coincidental in occurrence but also that sinus tachycardia contributes importantly to ventricular arrhythmogenesis by enhancing the frequency-dependent depressant effects of amitriptyline. This constitutes, to our knowledge, the clearest demonstration to date of a clinically relevant consequence of the frequency-dependent effects of local anesthetic drugs on the heart.

I would like to thank Steven Nuara and Carol Matthews for their excellent technical assistance and Merck-Frosst Pharmaceuticals of Montreal, Canada, for providing purified amitriptyline to standardize the HPLC assay. Dr. Sanfacon of Louis-H. Lafontaine Hospital provided invaluable advice regarding the technique for measurement of amitriptyline concentration.

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Frequency-dependent effects of amitriptyline on ventricular conduction and cardiac rhythm in dogs.
S Nattel

Circulation. 1985;72:898-906
doi: 10.1161/01.CIR.72.4.898

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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