Rate-Dependent Effects of Diltiazem on Human Atrioventricular Nodal Properties

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Background. Tachycardia enhances the channel-blocking effects of antiarrhythmic drugs. In contrast to the extensive data regarding the rate-dependent effects of sodium channel blockers in humans, little is known about the frequency-dependent effects of calcium channel blockers on human atrioventricular (AV) nodal properties. Accordingly, the purpose of this study was to evaluate the importance of heart rate in modulating the electrophysiological effects of diltiazem in humans.

Methods and Results. Electrophysiological studies were performed in 25 patients. Sinus node, atrial, and AV nodal function were evaluated at multiple atrial rates under control conditions and after administration of one of three intravenous doses of diltiazem designed to produce low, intermediate, and high stable plasma concentrations (designated doses 1, 2, and 3, respectively). Results were analyzed in terms of the longest and shortest cycle lengths obtainable in each patient under control and drug conditions. Plasma concentrations of diltiazem were stable and averaged 43±4, 73±6, and 136±11 ng/ml for doses 1, 2, and 3, respectively. Sinus node recovery time, intra-atrial conduction time, atrial effective refractory period, and HV interval were unaffected by diltiazem infusion. Effects of diltiazem were limited to changes in AV nodal parameters. Stable, dose-dependent increases in Wenckebach cycle length were observed after all three doses of diltiazem (increases of 54±13, 84±18, and 174±33 msec for doses 1, 2, and 3, respectively). Small nonsignificant increases in AH interval and atrioventricular effective refractory period (AVERP) were observed after dose 1 of diltiazem. At long cycle lengths, diltiazem caused modest increases in AH interval (3±4 and 25±8 msec for doses 2 and 3, respectively) and AVERP (36±12 and 70±25 msec). Drug effects were far greater at short cycle lengths (45±17 msec, 58±12 msec for AH interval and 80±24 msec, 163±41 msec for AVERP; p<0.05 versus values at long cycle lengths). At rapid rates, effects of diltiazem on AVERP substantially exceeded those on AV conduction, a result that could account for the beneficial effects of diltiazem during paroxysmal AV reentrant tachycardia by decreasing the excitable gap.

Conclusions. Depressant effects of diltiazem on human AV nodal function are highly dependent on atrial rate; the rate-dependent actions on AV nodal refractoriness probably contribute to beneficial effects of diltiazem in patients with supraventricular arrhythmias. (Circulation 1992;86:870–877)

KEY WORDS • diltiazem • atrioventricular node • AV nodal refractoriness • AV nodal conduction • supraventricular tachycardia

Tachycardia enhances the channel-blocking effects of antiarrhythmic drugs. This property has been documented best in the case of sodium channel blockers. Frequency-dependent sodium channel blockade results in enhanced depression of the upstroke velocity of fast channel action potentials1–3 and leads to rate-dependent ventricular conduction slowing in vivo.4–6 This last observation has been well documented in humans7,8 and may account for tachycardia slowing9 or proarrhythmic effects10 in patients with ventricular tachycardia.

The electrophysiological and negative inotropic effects of calcium channel blockers are also dependent on underlying rate.11,12 All three classes of calcium channel blockers13 depress inward calcium current to a greater degree during rapid stimulation than at slower rates.14–17 Therapeutic concentrations of these agents have been shown in autonomic-blocked dogs to slow atrioventricular (AV) nodal conduction and increase AV nodal refractoriness preferentially during tachycardia, with kinetics of conduction change in vivo similar to those observed for calcium current in vitro.18

In contrast to the extensive data regarding the rate-dependent effects of sodium channel blockers in humans,7–10,19,20 relatively little is known about the frequency-dependent effects of calcium channel blockers on human AV nodal properties. Ellenbogen and coworkers21 found that verapamil caused rate-dependent increases in atrioventricular conduction time in 10 patients undergoing electrophysiological evaluation. These find-
ings were confirmed in a subsequent study in which the kinetics of rate-dependent actions of verapamil were estimated with a mean time constant for onset of block of 2.9 seconds.22

Diltiazem is effective in both the acute and chronic treatment of paroxysmal supraventricular tachycardia.23-29 We have recently shown that rate-dependent effects of diltiazem lead to highly selective depression of AV nodal function during experimental atrial fibrillation and atrioventricular reentrant tachycardia in autonomically blocked dogs.30,31 If present under clinical conditions in humans, these properties would lead to enhanced AV nodal depression during supraventricular arrhythmias, conferring a desirable selectivity of action for tachyarrhythmias compared with sinus rhythm. The possibility of a rate-dependent action of diltiazem on AV nodal function in humans has not been evaluated. Furthermore, because the likelihood of a reentrant arrhythmia is governed by both refractory period and conduction velocity, it is important to determine the relative actions of diltiazem on both variables.

The purpose of this study was to evaluate the importance of heart rate in modulating the electrophysiological effects of diltiazem in humans. Specifically, we sought to evaluate 1) the frequency-dependent effects of diltiazem on AV nodal conduction and refractoriness, 2) the kinetics of rate-dependent AV nodal conduction slowing, and 3) the relative magnitude of effects of diltiazem on AV nodal refractoriness versus AV nodal conduction at different rates.

Methods

Patient Selection

Patients undergoing clinical electrophysiological studies for known or suspected cardiac arrhythmias were screened. Patients with any of the following characteristics were excluded from the study: severe congestive heart failure (New York Heart Association class III or IV or ejection fraction <30%); first-, second-, or third-degree AV block at baseline; sinus bradycardia (<55 beats per minute); permanent pacemaker; hypotension (<90 mm Hg systolic); preexcitation on the ECG; any cardioactive medication within five half-lives before study entry; recent (<1 month) myocardial infarction.

Electrophysiological Study

All patients were studied in the fasting state. Patients were mildly sedated with intravenous midazolam (1–2 mg) before introduction of two to four catheters via the femoral veins. After completion of the clinically indicated electrophysiological study, two quadripolar catheters were positioned in the high right atrium and across the tricuspid valve to record local bipolar atrial and His bundle electrograms, respectively. Three surface ECG leads (I, aVF, V1) and intracardiac electrograms were amplified (Electronics for Medicine, Pleasantville, N.Y.) and recorded with an ink-jet recorder (Siemens-Elena Mingograf, Solera, Sweden). Surface ECG signals were filtered at 0.1–50 Hz; intracardiac electrograms were filtered at 40–200 Hz. All stimulation was performed with 2-msec rectangular impulses delivered through the distal poles of the right atrial catheter with a programmable stimulator (Bloom Associates, Narberth, Pa.).

Wenckebach cycle length was determined by decreasing atrial pacing cycle length by 10-msec decrements until second-degree AV block occurred. This was repeated before and after each experimental protocol to ensure stability of AV nodal function under control conditions and during diltiazem infusion. RR, PA, AH, and HV intervals were measured during sinus rhythm using standard criteria.32 Constant-rate atrial pacing was then carried out at a variety of cycle lengths between the sinus cycle length and the Wenckebach cycle length.

Sinus node recovery time, AH interval, atrial, and AV nodal effective refractory periods were determined at each cycle length.32 All determinations were preceded by 2 minutes of atrial pacing at the selected cycle length. The kinetics of change in AH interval during tachycardia were then assessed. After a rest period of 2 minutes without atrial stimulation, rapid atrial pacing was performed for a period of 2 minutes. A cycle length 50 msec greater than the Wenckebach cycle length was chosen in each case.

After control measurements were completed, diltiazem was administered intravenously, and the experimental protocol was repeated. Patients received one of three doses designed to produce low, intermediate, and high stable plasma concentrations of diltiazem. The dosing regimens used were based on known pharmacokinetic properties of diltiazem33 and were designed to result in a range of concentrations spanning those observed with therapeutic doses in humans.

Diltiazem was administered as an intravenous bolus over 2 minutes. A second equivalent bolus was given 15 minutes later. A constant maintenance infusion was started at the same time as the first bolus. This infusion was continued for a minimum of 45 minutes before repeat electrophysiological measurements were made. Patients allocated to dose 1 received two 6.25-mg boluses and a 2.5-mg/hr infusion, dose-2 patients received two 12.5-mg boluses and a 5.0-mg/hr infusion, and dose-3 patients received two 25.0-mg boluses and a 10.0-mg/hr infusion. Blood samples were obtained during the maintenance drug infusion before and after each experimental protocol for subsequent measurement of plasma diltiazem concentrations by reverse-phase high-performance liquid chromatography (HPLC).

The experimental protocol was reviewed and approved by the institutional review board of the Montreal Heart Institute, and written informed consent was obtained from each patient.

Data Analysis

Electrophysiological recordings were obtained at 250 mm/sec, resulting in a measurement accuracy of ±2.0 msec. Tabulated summaries of the data are presented as mean±SEM. Statistical comparisons between control and experimental group means were made using Student’s paired t test. Two-tailed tests were used for all statistical comparisons; a probability of 5% or less was taken to indicate statistical significance.

The range of cycle lengths that could be studied was limited by the Wenckebach cycle length and spontaneous automaticity, which determined the shortest and longest pacing cycle lengths, respectively, under any
experimental condition. Because the range of cycle lengths varied among patients, we analyzed results in terms of the longest and shortest cycle lengths in each patient during each drug infusion. In all cases, results in the presence of diltiazem were compared with results under control conditions at the same cycle length within each patient. The shortest cycle length maintaining 1:1 conduction under both control and drug conditions in a given patient was termed the “fast cycle length,” and the longest cycle length maintaining consistent capture under both conditions was termed the “slow cycle length.” Effects of a given infusion at the fast cycle length in each patient were then grouped for statistical analysis, as were effects at the slow cycle length.

Results

Clinical Characteristics

The clinical characteristics, indications for electrophysiological study, plasma diltiazem concentrations, and blood pressure responses of the patient population are shown in Table 1.

Sixteen of the 25 patients underwent electrophysiological evaluation to confirm the absence of an accessory pathway 2–5 days after successful catheter ablation. Diltiazem plasma concentrations were stable over the course of the protocol and were associated with small dose-dependent decreases in systolic and diastolic blood pressure (Table 1).

Most patients tolerated repeated bolus doses and the infusion of diltiazem. Treatment-related adverse experiences occurred in five patients. These included headache in two patients, hypotension, nausea, pain at injection site, and vomiting, each occurring in one patient. The patient who experienced hypotension was treated with atropine and discontinued from the study and recovered without any sequelae. Electrophysiological data from this patient are not included.

Electrophysiological Effects During Sinus Rhythm and Steady-State Pacing

Diltiazem administration caused dose-dependent increases in Wenckebach cycle length and AH interval recorded during sinus rhythm (Table 2). Small increases in sinus cycle length were observed at the highest dose. Sinus node recovery time, intra-atrial conduction time (PA interval), atrial effective refractory period, and HV interval were unaffected by diltiazem infusion. Drug effects, as reflected by changes in Wenckebach cycle

### Table 1. Clinical Characteristics of Patient Population

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Age (years)</th>
<th>Sex (Male/Female)</th>
<th>Underlying heart disease</th>
<th>Indication for electrophysiological study</th>
<th>Blood pressure (mm Hg)</th>
<th>Concentration (ng/ml)</th>
</tr>
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<td></td>
<td>Systolic C</td>
<td>D</td>
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<tr>
<td><strong>Dose 1</strong></td>
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<td></td>
<td></td>
<td></td>
<td>115±4</td>
<td>113±5</td>
</tr>
<tr>
<td>5</td>
<td>49±5</td>
<td>4/1</td>
<td>WPW (4)</td>
<td>Postablation (4)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>None (1)</td>
<td>Syncpe (1)</td>
<td></td>
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</tr>
<tr>
<td><strong>Dose 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>129±6</td>
<td>123±4</td>
</tr>
<tr>
<td>10</td>
<td>43±6</td>
<td>8/2</td>
<td>WPW (4)</td>
<td>Postablation (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CAD (2)</td>
<td>Syncpe (2)</td>
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<td></td>
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<td>CM (2)</td>
<td>Palpitations (2)</td>
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<td></td>
<td>Posttransplant (1)</td>
<td>Atrial flutter (1)</td>
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<tr>
<td><strong>Dose 3</strong></td>
<td></td>
<td></td>
<td></td>
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<td>123±3</td>
<td>113±4*</td>
</tr>
<tr>
<td>10</td>
<td>44±5</td>
<td>5/5</td>
<td>WPW (8)</td>
<td>Postablation (8)</td>
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<td></td>
<td></td>
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<td>CAD (1)</td>
<td>NSVT (1)</td>
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<td></td>
<td>None (1)</td>
<td>Syncpe (1)</td>
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</tbody>
</table>

B, A, Before and after experimental protocol, respectively; C, D, control (predrug) and values in the presence of drug, respectively; CAD, coronary artery disease; CM, cardiomyopathy; NSVT, nonsustained ventricular tachycardia; WPW, Wolff-Parkinson-White syndrome (electrophysiological study to confirm successful ablation of accessory pathway).

*p<0.01 control vs. drug.

### Table 2. Electrophysiological Effects of Diltiazem

<table>
<thead>
<tr>
<th>RR</th>
<th>CSNRT</th>
<th>PA</th>
<th>AERP</th>
<th>AH</th>
<th>HV</th>
<th>WCL</th>
</tr>
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</tr>
<tr>
<td><strong>Dose 1</strong> (n=5)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Control</td>
<td>758±66</td>
<td>330±53</td>
<td>28±7</td>
<td>245±24</td>
<td>89±6</td>
<td>46±3</td>
</tr>
<tr>
<td>Drug</td>
<td>784±71</td>
<td>320±80</td>
<td>33±7</td>
<td>258±27</td>
<td>101±10</td>
<td>45±2</td>
</tr>
<tr>
<td><strong>Dose 2</strong> (n=10)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>756±25</td>
<td>282±20</td>
<td>24±3</td>
<td>221±8</td>
<td>85±5</td>
<td>46±5</td>
</tr>
<tr>
<td>Drug</td>
<td>785±22</td>
<td>329±31</td>
<td>23±3</td>
<td>229±10</td>
<td>95±8*</td>
<td>48±4</td>
</tr>
<tr>
<td><strong>Dose 3</strong> (n=10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>794±45</td>
<td>373±58</td>
<td>20±3</td>
<td>229±23</td>
<td>82±6</td>
<td>43±2</td>
</tr>
<tr>
<td>Drug</td>
<td>897±74*</td>
<td>421±73</td>
<td>16±4</td>
<td>234±24</td>
<td>106±5†</td>
<td>44±2</td>
</tr>
</tbody>
</table>

AH, AH interval; AERP, atrial effective refractory period; CSNRT, corrected sinus node recovery time; HV, HV interval; PA, intra-atrial conduction time; RR, sinus cycle length; WCL, Wenckebach cycle length. All values are in milliseconds. PA, AH, and HV intervals were measured during sinus rhythm. AERP was measured at a cycle length of 600 msec.

*p<0.05, †p<0.01 control vs. drug.
length, were stable during each experimental protocol, with less than 10% variation during each drug infusion. Whereas rapid pacing slightly increased AH interval and AV effective refractory period (AVERP) under control conditions, rate-dependent changes were much larger in the presence of diltiazem (Table 3). Figure 1 illustrates the effects of atrial pacing on AH interval in a patient receiving dose 2 of diltiazem. Under control conditions, AH interval increased at short pacing cycle lengths. After diltiazem administration, small increases in AH interval at long cycle lengths were noted. As the cycle length decreased, changes in AH interval relative to control increased. As a result, effects of diltiazem on AV nodal conduction were amplified during rapid atrial pacing. The mean increases in AH interval induced by diltiazem administration during pacing at slow and rapid rates are displayed in Figure 2. For example, after dose 3 of diltiazem, a 2.5-fold-greater drug effect was noted at the shorter pacing cycle length compared with changes observed at the longer cycle length.

The AV nodal effective refractory period was determined under control conditions and after drug infusion in two patients receiving dose 1, seven patients receiving dose 2, and six patients receiving dose 3 of diltiazem. Atrial refractoriness exceeded AV nodal refractoriness, preventing direct measurement of the latter in the remaining patients. Effects of diltiazem in a representative patient are shown in Figure 3. In this and other patients, small increases in AV nodal refractoriness were observed under control conditions as cycle length was shortened. Diltiazem increased AVERP modestly (60 msec in this example) at a cycle length of 800 msec. As pacing cycle length was shortened in the presence of the drug, progressive increases in AVERP over control were observed. In the case shown, the maximum increase (220 msec) was observed at a cycle length of 600 msec. Mean data for the seven patients receiving dose 2 and the six patients receiving dose 3 are shown in Figure 4. An average of twofold to threefold amplification of effects of diltiazem on AV nodal refractoriness resulted from rapid pacing in these patients.

**Dynamic Changes in AV Conduction During Atrial Tachycardia**

The kinetics of change in AH interval after the onset of rapid pacing was assessed in each patient. The AH interval of a patient receiving dose 2 is plotted versus

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**Table 3. Rate-Dependent Effects of Diltiazem on Atrioventricular Nodal Properties**

<table>
<thead>
<tr>
<th>Dose 1 (n=5)</th>
<th>Cycle length</th>
<th>AH</th>
<th>AVERP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Slow 630±37</td>
<td>Fast 430±26</td>
<td>Slow CL 112±9</td>
</tr>
<tr>
<td>Drug</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose 2 (n=10)</td>
<td>Control</td>
<td>Slow 695±19</td>
<td>Fast 475±23</td>
</tr>
<tr>
<td>Drug</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose 3 (n=10)</td>
<td>Control</td>
<td>Slow 763±35</td>
<td>Fast 569±31</td>
</tr>
<tr>
<td>Drug</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Atrioventricular nodal refractoriness was determined in seven and six patients for doses 2 and 3, respectively. Atrial refractoriness prevented determination of atrioventricular effective refractory period (AVERP) in the remaining patients. Atrial refractoriness prevented determination of AVERP in three of five patients receiving dose 1. No data are given for this dose for this reason. AH, AH interval; CL, cycle length. All values are in milliseconds.

*p<0.05; †p<0.01 control vs. drug.

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**Figure 1.** Plot of AH interval vs. atrial pacing cycle length in a representative patient before and after dose 2 of diltiazem. Diltiazem increased AH interval in a rate-dependent manner, with larger increases over control observed at shorter cycle lengths.

**Figure 2.** Bar graph of diltiazem-induced increases (mean±SEM) in AH interval at slow and fast cycle lengths (CL). Values for slow and fast cycle lengths used are displayed in Table 3. Diltiazem caused dose-dependent increases in AH interval. Greater changes in AH interval were observed during pacing at fast cycle length. *p<0.05 AH interval at fast CL vs. AH interval at slow CL.
beat number after the onset of rapid atrial pacing in Figure 5. Under control conditions, initial increases in AH interval occurred over the first four to five beats after the onset of rapid pacing, with little change thereafter. After diltiazem infusion, the AH interval recorded during sinus rhythm changed little relative to control (beat 0 in Figure 5). However, progressive increases in AH interval, not observed under control, occurred as rapid pacing continued. As a result, large drug-related increases in AH interval were observed at steady state during rapid pacing. The AH interval recorded after diltiazem infusion was fitted to a monoexponential relation of beat number in this example. The resulting regression curve (solid line) had a time constant of 12.7 beats or 5.8 seconds \( (r=0.99) \).

The data shown in Figure 5 were obtained in a patient who had received a cardiac transplantation and whose cardiac parasympathetic and sympathetic innervation had therefore been interrupted. Autonomic tone was intact in the remaining patients. Dynamic changes in AH interval after the onset of rapid pacing were much more complex in these patients. Figure 5 shows a typical example. During sinus rhythm (beat 0), diltiazem did not alter AV conduction. Under control conditions, rapid pacing caused an abrupt increase in AH interval within three to four beats with stabilization thereafter. In the presence of diltiazem, the AH interval gradually increased to a maximum after approximately 18 beats and declined thereafter. This pattern, suggesting modulation of diltiazem's actions by a reflex (possibly autonomic) response was seen in all patients with intact autonomic function, precluding meaningful kinetic analysis.

Figure 6 shows a typical example. During sinus rhythm (beat 0), diltiazem did not alter AV conduction. Under control conditions, rapid pacing caused an abrupt increase in AH interval within three to four beats with stabilization thereafter. In the presence of diltiazem, the AH interval gradually increased to a maximum after approximately 18 beats and declined thereafter. This pattern, suggesting modulation of diltiazem's actions by a reflex (possibly autonomic) response was seen in all patients with intact autonomic function, precluding meaningful kinetic analysis.
Discussion

This study demonstrates that diltiazem alters human AV nodal properties in a dose- and rate-dependent manner. As previously noted in autonomically blocked dogs,18,30,31 tachycardia accentuates diltiazem-induced changes in AV nodal conduction and refractoriness. These phenomena were observed in the present study at concentrations and doses used to treat clinical supraventricular arrhythmias24-29,34 and are therefore likely to be manifest when the drug is used clinically to treat supraventricular arrhythmias.

Potential Significance of Rate-Dependent Actions of Diltiazem in Humans

Intravenous diltiazem is highly effective in terminating tachycardias caused by reentry within the AV node23,29 or involving an accessory bypass tract23,28,29 and in slowing the ventricular response to atrial fibrillation or flutter.34,35 Oral diltiazem prevents the induction of AV reentrant tachycardia36 and controls the ventricular response to atrial fibrillation during chronic therapy.36-39

These beneficial effects of diltiazem are manifest at doses that produce little change in AV conduction during sinus rhythm and at mean plasma concentrations ranging from 126 to 234 ng/ml26,37-39 in the same range as produced by the high dose in the present study. Previous work in dogs suggests that the rate-dependent actions of diltiazem on AV node refractoriness are responsible for its efficacy in experimental models of atrial fibrillation30 and AV reentrant tachycardia.31 The current study shows that the ability of diltiazem to increase AV nodal refractoriness in humans exhibits rate dependency (Figures 3 and 4) very similar to that observed in canine models.18,30,31 These findings suggest that the clinical efficacy of diltiazem in treating supraventricular tachyarrhythmias at doses that have little depressant effect on the AV node during sinus rhythm is due to rate-dependent amplification of the drug's action during tachyarrhythmia.

Diltiazem is capable of either slowing or terminating supraventricular reentrant tachyarrhythmias.23,25,27-29 The drug's tendency to slow reentry is due to its depressant effect on AV nodal conduction velocity, and its ability to terminate reentry is due to prolongation of AV nodal refractoriness. The balance between these two actions can be considered in terms of the "excitable gap," as initially conceptualized by Mines.40 The persistence of reentry within a circuit depends on the existence of excitable tissue in front of the reentrant wave front at all times during the reentrant cycle. This gap can be expressed in terms of the difference between the tachycardia cycle length (time for a single cycle of excitation in the circuit) and the refractory period at a given site. Because diltiazem terminates reentry by an action on the AV node, its effect on the likelihood of reentry involving this structure will be reflected by the difference between drug-induced increases in the AH interval (acting to increase the tachycardia cycle length and the excitatory gap by an equivalent amount) and drug-induced increases in the AVERP (acting to decrease the excitatory gap within the AV node). This index of drug-induced changes in the excitatory gap was calculated for patients in whom AVERP could be measured at both fast and slow cycle lengths (Figure 7). As indicated in this figure, diltiazem-induced increases in AVERP exceeded changes in AH interval, decreasing the potential excitable gap. Moreover, this effect was dose and rate dependent. If, for a given dose and tachycardia frequency, diltiazem succeeded in eliminating the excitable gap, the tachycardia would be terminated. On the other hand, if an excitable gap remained, the tachycardia would continue but at a slower rate as determined by the drug's AV conduction slowing action.

Verapamil also has frequency-dependent effects on AV nodal function. These actions have been noted in animal and human studies18,21,22 and are likely to be of importance in accounting for the efficacy of verapamil in patients with supraventricular tachycardia. One previous animal study evaluated the effects of both drugs on AV nodal function and found that both had comparable rate-dependent effects but that diltiazem had a shorter time constant for onset of block than verapamil.18 Unfortunately, the present study was able to characterize the kinetics of diltiazem in only one patient, thus precluding comparisons with the kinetics of verapamil's rate-dependent effects in humans.

Kinetics of Rate-Dependent Actions of Diltiazem

Accurate quantification of the kinetics of diltiazem's effects was achieved in only one patient who had received a cardiac transplant, and thus was autonomically denervated. The onset time constant of 12.7 beats measured in this patient is in the same range as previous estimates of drug-induced conduction slowing in autonomically blocked dogs18 and calcium current depression in vitro.41 Accurate estimates of the kinetics of diltiazem were not feasible in the remaining patients. This is probably because of reflex responses after the onset of rapid pacing in the presence of the drug.

Mechanism of Rate-Dependent Actions of Diltiazem

Our results are consistent with expectations of both the modulated receptor42,43 and guarded access hypoth-
Potential Limitations

No patient received drugs to block autonomic effects. Changes in autonomic tone probably occurred during different pacing protocols and probably explain the difficulty in obtaining reliable estimates of the onset kinetics of the effect of diltiazem on AV nodal function. Despite these limitations in kinetics analysis, rate-dependent effects of diltiazem on AV nodal conduction and refactoriness were demonstrated and were consistent with effects of diltiazem in autonomically blocked dogs. We have previously shown that in the anesthetized dog, intact autonomic reflexes reduce the effect of diltiazem for any given plasma concentration but do not prevent frequency-dependent drug action. Although the presence of intact autonomic tone may have limited our ability to perform kinetic analysis, it supports the clinical applicability of our results because most patients receiving intravenous diltiazem for supraventricular arrhythmias will have intact autonomic reflexes.

Our estimates of drug-induced changes in the excitability gap should not be misconstrued as an attempt to precisely calculate changes in the excitability gap during arrhythmia. The fastest cycle lengths that we studied were longer than typical cycle lengths during tachycardia. Sixteen of the 25 patients evaluated in this study had a history of AV reciprocating tachycardia caused by an accessory pathway. The mean cycle length of supraventricular tachycardia was 361 ± 25 msec in these patients. The fast cycle lengths studied were generally longer and ranged from 350 to 650 msec (see Table 3). Based on the tendency for predicted drug effects on the excitable gap to increase at shorter cycle lengths, however, we believe that we have underestimated the changes that would occur during tachycardia. Our analysis is more directly applicable to AV reentry with antegrade conduction over the AV node and retrograde conduction via a bypass tract. During AV nodal reentry, both antegrade and retrograde limbs may consist of AV nodal tissue, and the properties of the dual pathways may be in some ways atypical; therefore, our estimates are only qualitatively relevant to the actions of diltiazem on AV nodal reentrant tachycardias.

Conclusions

Depressant effects of diltiazem on human AV nodal function are highly dependent on atrial rate. Tachycardia enhances diltiazem-induced increases in AV nodal refractoriness and AV nodal conduction time, with increases in refractory period predominating over changes in conduction. These rate-dependent actions lead to selective drug effects during tachycardia and probably contribute significantly to the beneficial effects of diltiazem in the treatment of paroxysmal supraventricular tachycardia, atrial fibrillation, and atrial flutter.

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