Frequency-dependent effects of verapamil on atrioventricular nodal conduction in man

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ABSTRACT  We sought to determine if verapamil induces frequency-dependent prolongation of atrioventricular nodal conduction in 10 consecutive patients studied in the electrophysiology laboratory. We used a maintenance infusion of verapamil designed to produce plasma concentrations of verapamil in the “therapeutic” range and that did not alter heart rate or blood pressure significantly. Frequency-dependent prolongation of atrioventricular nodal conduction (AH interval) was demonstrated in all 10 patients (p < .001), and no change in HV conduction time with decreasing cycle length was noted in any patient while receiving verapamil. Two patterns of use-dependent response were seen. In four patients frequency-dependent prolongation of the Δ(AH) interval [Δ(AH) = AHverapamil − AHcontrol at a given cycle length] was seen with each decrement in pacing cycle length. In six patients frequency-dependent prolongation of the Δ(AH) interval was not manifest until the fifth to eighth pacing cycle length tested. There was no association between the pattern observed and the initial heart rate or AH interval. After an abrupt change in pacing cycle length, the kinetics of Δ(AH) interval prolongation were rapid; equilibrium was achieved by five to eight pulses in all patients. There was no correlation between the magnitude of prolongation of the AH interval noted at a particular cycle length and the concentration of verapamil during the maintenance infusion. These results indicate that verapamil causes use-dependent prolongation of atrioventricular nodal conduction in man.


A DESIRABLE GOAL of antiarrhythmic drug therapy is to terminate or suppress tachycardia without affecting impulse initiation or propagation at physiologic heart rates.1,2 Ideally, a drug used to treat reentrant tachycardia will demonstrate maximal effects on conduction and refractoriness during tachycardia, but will have minimal effects at slower heart rates after its termination. The extent of a drug’s effects on conduction velocity can be inferred from its effects on phase 0 maximum upstroke velocity (Vmax) of the action potential.3 In 1957, Johnson and McKinnon4 showed that quinidine decreased Vmax progressively as the driving rate was increased. Observations similar to this have been made with other local anesthetic types of antiarrhythmic drugs in nerve and cardiac muscle.1,2 Subsequent studies in nerve and cardiac muscle have characterized the use- or frequency-dependent action of local anesthetic agents, leading to the evolution of the modulated receptor hypothesis.5,6 Experiments in vitro have demonstrated use-dependent block for a variety of sodium channel-blocking agents, including disopyramide, flecainide, mexiletine, and lidocaine.7–10 Recently, preliminary reports have appeared describing frequency-dependent prolongation of conduction time in the human heart with procanamide, amiodarone, lidocaine, and mexiletine.11,12 Use-dependent block has also been demonstrated for calcium-channel blockers in vitro. Wit and Cranefield13 studied the effects of verapamil on isolated rabbit atrioventricular nodes and were able to demonstrate frequency-dependent prolongation of atrioventricular nodal conduction. In 1975, while studying the effect of verapamil on cat papillary muscle, Bayer et al.14,15 were also able to infer that the drug caused frequency-dependent blockade of the slow inward current. Later, Ehara and Kaufman16 and McDonald et al.17 directly demonstrated frequency-dependent block of the calcium current with verapamil and its cogener, methoxy-
verapamil. Excitation and, as a result, conduction in the atrioventricular node, are dependent on the slow inward (calcium) current.\textsuperscript{18} Extrapolation of these findings in vitro to man would predict that the effect of verapamil on atrioventricular conduction should be frequency dependent. Demonstration of this action would represent a significant advance in our understanding of the relevance of these findings in vitro to man.

Methods

The study group consisted of 10 consecutive adult patients referred for electrophysiologic evaluation of symptomatic or suspected cardiac arrhythmias. Patients were excluded from this study if they demonstrated manifest preexcitation on the electrocardiogram, atrioventricular block on Holter or electrocardiographic monitoring, an ejection fraction less than 30% as determined by radionuclide angiography, two-dimensional echocardiography, or cardiac catheterization, or if they had symptomatic congestive heart failure. Patients taking calcium antagonists (nifedipine, diltiazem, verapamil), \( \beta \)-blockers, or digoxin were also excluded from this study. All cardioactive medications were withheld for at least five half-lives before the study. Informed consent was obtained from all patients.

Electrophysiologic study protocol. The studies were performed in nonsedated, fasting patients. Three multipolar catheters were introduced percutaneously and positioned in the heart under fluoroscopic guidance in the right atrial appendage, across the tricuspid valve to record a His bundle potential, and in the right ventricular apex in each patient.

Stimulation was performed with a custom-designed, programmable stimulator with an optically isolated current source producing 2 msec pulses at twice diastolic threshold. Bipolar intracardiac electrograms were recorded with five surface electrocardiographic leads (I, II, III, V\(_1\), and V\(_6\)) and were displayed on an oscilloscope. Graphic records were obtained on-line with a multichannel ink-jet recorder (Siemens Mingograph) at 200 mm/sec. A 10 msec time code was generated with the data during all recordings.

The following routine intracardiac electrophysiologic studies were performed on all patients: (1) Incremental atrial pacing was performed beginning at rates just above the sinus rate to the point at which atrioventricular block occurred. (2) Right atrial refractory period was determined by the extrastimulus technique at a driven cycle length of 600 msec. In each of six patients, atrial pacing was performed for 2 min at a driven cycle length of 50 to 100 msec shorter than the patient’s spontaneous cycle length and was then suddenly decreased by 100 to 150 msec. Continuous recordings were obtained during pacing. Each patient then underwent incremental atrial pacing for 1 min at each cycle length, starting at cycle lengths just below the sinus cycle length and decreasing stepwise (25 msec steps) until atrioventricular block occurred. Graphic records were obtained during the last 10 sec at each pacing cycle length for data analysis.

All patients then received 10 mg of verapamil (Isoptin, Knoll Pharmaceutical, Whippany, NJ) in 4 ml of saline administered intravenously over 2 min. Blood pressure was monitored by an external continuous monitor (Infrasonde model D4000), and rhythm was monitored continuously during the verapamil infusion. Each patient then received a rapid loading infusion of verapamil, 0.375 mg/min for 30 min, followed by a maintenance infusion at 0.125 mg/min via an IVAC pump through an 18-gauge Teflon cannula inserted into a superficial arm vein.

Plasma for verapamil assay was obtained from a vein in the opposite arm after the maintenance infusion was begun. The plasma was placed in heparinized glass tubes and immediately centrifuged, separated, frozen, and stored at \(-20^\circ\text{C}\) until assay. Plasma samples were extracted in diethyl ether after addition of an internal standard solution of DS17-HCl. Peak height ratios of drug concentration vs internal standard were measured by high-pressure liquid chromatography with use of a fluorometric detection assay as previously described.\textsuperscript{19} Verapamil concentrations were based on three calibration curves, the average correlation coefficient of which was \(0.997 \pm 0.001\). Five minutes after the establishment of a maintenance infusion, the electrophysiologic protocol was repeated.

Data analysis. The AH and HV intervals were measured with use of criteria previously defined.\textsuperscript{20} The AH interval was measured between the earliest reproducible rapid atrial deflection and the onset of the earliest deflection from baseline on the His bundle catheter recording. The AH interval was measured for 3 to 5 beats, and an average value was obtained (incremental atrial pacing). If the AH interval varied more than 5 msec in sequential beats, the patient was excluded from the study. Two patients were excluded from this study because of excessive variation in AH conduction times. The HV interval was measured from the onset of the His bundle deflection to the onset of ventricular depolarization. During incremental atrial pacing the HV interval was measured for 3 to 5 beats and an average value was obtained (incremental atrial pacing). All data were recorded at 200 mm/sec. It has been reported that the accuracy of measurements made at 100 mm/sec is approximately \( \pm 5\) msec.\textsuperscript{20} \(\Delta(\text{AH})\) interval was defined as the difference between the AH interval measured during the infusion of verapamil and that during the control study at the same cycle length.

Statistical methods. Changes in heart rate and blood pressure after the bolus dose of verapamil were analyzed with the Wilcoxon signed-rank test. Trends in heart rate and blood pressure during the loading and maintenance infusions were analyzed by computing the slope of the measurement vs time separately for each patient, and then testing for whether the slopes had a mean value that was significantly different from zero with the Wilcoxon signed-rank test. Frequency dependence was analyzed with the sign test based on divergence of \(\Delta(\text{AH})\) interval with decreasing cycle length. The AH interval vs cycle length curves were assessed separately for each patient to determine if the difference in AH interval between drug and control curves was greater for the shorter cycle lengths tested. The sign test determined whether the proportion of divergent curves was significantly greater than one half. Linear regression analysis was used to correlate verapamil concentration with the magnitude of \(\Delta(\text{AH})\) intervals at a given cycle length over the entire range of cycle lengths tested.

Results

Patients studied. The clinical and electrocardiographic characteristics of the patient population are shown in table 1. Nine of the 10 patients had normal ejection fractions, and one patient (No. 2) had an ejection fraction of 32%. The baseline descriptors of atrioventricular nodal function in the patients are shown in table 2. All refractory periods were determined at a cycle length of 600 msec unless otherwise indicated. In four patients the functional refractory period of the atrium precluded determination of the effective refractory period of the atrioventricular node.
TABLE 1
Clinical and electrocardiographic descriptors of patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/sex</th>
<th>Reason for study</th>
<th>Heart disease</th>
<th>PR (sec)</th>
<th>QRS (sec)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>42/F</td>
<td>VE</td>
<td>None</td>
<td>0.10</td>
<td>0.08</td>
</tr>
<tr>
<td>2</td>
<td>46/M</td>
<td>VT</td>
<td>CM</td>
<td>0.16</td>
<td>0.08</td>
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<tr>
<td>3</td>
<td>31/F</td>
<td>Syncope</td>
<td>None</td>
<td>0.14</td>
<td>0.10</td>
</tr>
<tr>
<td>4</td>
<td>69/F</td>
<td>Syncope</td>
<td>None</td>
<td>0.18</td>
<td>0.10</td>
</tr>
<tr>
<td>5</td>
<td>57/M</td>
<td>SVT</td>
<td>None</td>
<td>0.18</td>
<td>0.08</td>
</tr>
<tr>
<td>6</td>
<td>30/M</td>
<td>SVT</td>
<td>None</td>
<td>0.16</td>
<td>0.08</td>
</tr>
<tr>
<td>7</td>
<td>54/F</td>
<td>Palpitations</td>
<td>None</td>
<td>0.10</td>
<td>0.08</td>
</tr>
<tr>
<td>8</td>
<td>29/F</td>
<td>Palpitations</td>
<td>None</td>
<td>0.16</td>
<td>0.08</td>
</tr>
<tr>
<td>9</td>
<td>49/M</td>
<td>VT</td>
<td>CAD</td>
<td>0.16</td>
<td>0.08</td>
</tr>
<tr>
<td>10</td>
<td>46/F</td>
<td>VE</td>
<td>None</td>
<td>0.16</td>
<td>0.09</td>
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</tbody>
</table>

VT = ventricular tachycardia; SVT = supraventricular tachycardia; CAD = coronary artery disease; CM = cardiomyopathy; VE = complex ventricular ectopy (on Holter monitoring).

Plasma verapamil concentration. The verapamil level was determined 2 min after the beginning of the maintenance infusion (0.125 mg/min). The levels ranged from 37 to 125 ng/ml (mean ± SD, 85 ± 35 ng/ml).

Hemodynamics. Analysis of measurements of blood pressure showed a 12% decrease in mean systolic blood pressure at 2 min during the bolus phase of drug administration, which was a significant decrease (p < .05). There was no significant change in mean diastolic blood pressure at 2 min (p > .05). Mean heart rate (82 beats/min) increased significantly at 2 min (90 beats/min, p < .05). There was no significant change in mean heart rate, systolic pressure, or diastolic pressure during the loading and maintenance phases of the verapamil infusion (p < .05). These results are presented in figure 1.

TABLE 2
Electrophysiologic descriptors of patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>AH/CL</th>
<th>AVN ERP (msec)</th>
<th>AVN FRP (msec)</th>
<th>Minimum CL with 1:1 AV conduction (msec)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Verapamil</td>
<td>Control</td>
<td>Verapamil</td>
</tr>
<tr>
<td>1</td>
<td>42/870</td>
<td>58/840</td>
<td>293</td>
<td>490</td>
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<tr>
<td>2</td>
<td>70/640</td>
<td>90/580</td>
<td>&lt;263&lt;sup&gt;a&lt;/sup&gt;</td>
<td>DNM</td>
</tr>
<tr>
<td>3</td>
<td>75/920</td>
<td>80/800</td>
<td>299</td>
<td>391</td>
</tr>
<tr>
<td>4</td>
<td>52/880</td>
<td>120/860</td>
<td>&lt;292</td>
<td>&lt;400</td>
</tr>
<tr>
<td>5</td>
<td>57/880</td>
<td>100/845</td>
<td>338</td>
<td>549</td>
</tr>
<tr>
<td>6</td>
<td>35/640</td>
<td>40/700</td>
<td>&lt;258</td>
<td>&lt;320</td>
</tr>
<tr>
<td>7</td>
<td>62/625</td>
<td>80/600</td>
<td>&lt;265&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;326&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>96/630</td>
<td>122/620</td>
<td>268</td>
<td>316</td>
</tr>
<tr>
<td>9</td>
<td>68/810</td>
<td>92/840</td>
<td>341</td>
<td>480</td>
</tr>
<tr>
<td>10</td>
<td>75/1000</td>
<td>100/1040</td>
<td>300</td>
<td>433</td>
</tr>
</tbody>
</table>

DNM = did not measure; CL = cycle length (measured in msec); AVN = atrioventricular nodal; ERP = effective refractory period; FRP = functional refractory period.

<sup>a</sup>Refractory period terminated because of nonsustained atrial flutter/atrial fibrillation.

<sup>b</sup>Refractory period determined at 500 msec.
In each patient studied, during the infusion of verapamil, evidence of use-dependent prolongation of the $\Delta(AH)$ interval was evident as the pacing cycle length was decreased ($p < .001$). Analog data from patient 9 are shown in figure 3. Two patterns of frequency-dependent prolongation of the AH interval were seen. In six patients (Nos. 1, 3, 4, 6, 9, and 10) there was no change in the $\Delta(AH)$ interval for the initial four to seven cycle lengths tested; however, at subsequent shorter cycle lengths, there was a nonlinear increase in this interval. In two patients, prolongation of the $\Delta(AH)$ interval was absent for the first four cycle lengths tested, in one patient it was absent for the initial five pacing cycle lengths, in one patient it was absent for the initial six pacing cycle lengths tested, and in two patients it was absent for the initial seven pacing cycle lengths. For these six patients the $\Delta(AH)$ interval between the first and second cycle lengths tested ranged from 0 to 2 msec (mean ± SD, 1 ± 0.5 msec).

In four patients (Nos. 2, 5, 7, and 8) there was a progressive increase in the $\Delta(AH)$ interval noted with each decrement in pacing cycle length. In these patients the $\Delta(AH)$ interval between the first and second cycle lengths tested ranged from 5 to 11 msec (mean ± SD, 7 ± 2 msec).

There was a wide spectrum of baseline heart rates and AH intervals observed in patients demonstrating each pattern of frequency dependence. These two patterns of frequency dependence are shown in figure 4 with sample data from patients 4, 6, and 7.

In six patients, atrial pacing was begun at a cycle length of 800 msec. The mean data for these six patients are shown in figure 5, A. There was a progressive increase in the mean $\Delta(AH)$ interval as the cycle length was decreased. At a cycle length of 600 msec, the mean $\Delta(AH)$ interval was 44 msec.

**Frequency dependence of HV conduction time.** Since verapamil has been shown to decrease phase 0 $V_{\text{max}}$ in polarized ventricular muscle cells, we also examined the effects of verapamil on conduction time of the HV interval. There was no change in the mean HV conduction time as the cycle length was decreased at control or during the infusion of verapamil. This is illustrated in figure 5, B, for the six patients in which atrial pacing was begun at a cycle length of 800 msec.

**Concentration-response relationship.** There was no
correlation between the verapamil level during the maintenance infusion and the Δ(AH) intervals observed at cycle lengths of 800 msec (n = 6, r = −.7, p < .05), 600 msec (n = 5, r = −.02, p > .05), 500 msec (n = 4, r = −.8, p > .05), and 400 msec (n = 4, r = −.7, p > .05).

**Discussion**

The most important finding of this study is the demonstration of verapamil's frequency-dependent prolongation of AH conduction time in man. After an abrupt change in atrial pacing cycle length, the AH interval rapidly reached a new equilibrium value within 8 beats. On the other hand, verapamil had no effect on the HV interval at any pacing cycle length tested. We could not establish any correlation between verapamil concentration and the magnitude of the Δ(AH) interval at any cycle length tested.

One of the most intriguing findings to emerge from studies of use- or frequency-dependent block of local anesthetic type antiarrhythmic drugs has been that these drugs preferentially slow conduction during tachycardia, but have relatively little effect on conduction at normal heart rates. These studies have also led to the evolution of the modulated receptor hypothesis that states that local anesthetic types of antiarrhythmic drugs diffuse to a binding site in the aqueous pore of the ionic channel through either an aqueous (hydrophilic) or membrane (hydrophobic) pathway. Since most antiarrhythmic agents have pKₐ's in the 7 to 10 range, they exist as a combination of the neutral and the charged forms of the drug. Receptor affinity or access of drugs to the binding site is believed to vary with the state of the channel. For example, with depolarization of a Purkinje fiber, the majority of the sodium channels will be transiently shifted to the open or activated state. In this state, both charged and uncharged forms of the drug can access the sodium channel through the hydrophilic pathway from the inside of the cell and the uncharged form can access the channel through the hydrophobic pathway in the membrane. During the plateau phase of repolarization, the majority of sodium channels are in the inactivated state, and now access to the sodium-channel binding site is restricted to the uncharged form of the drug via the membrane (hydrophobic) path. Association of drug with the ionic channel occurs predominantly during the upstroke and plateau phase of the action potential, while dissociation occurs predominantly during diastole. When the drug is bound to its receptor site in the channel, that channel can no longer conduct. Thus, as the driving rate of a preparation is increased, the rest (diastolic) interval becomes shortened, and there is less time for the drug to dissociate from the channels and to completely recover from block. Frequency-dependent block of sodium channels as deduced from measurement of the sodium current of phase 0 Vₘₐₓ has been demonstrated in vitro for all the commonly used antiarrhythmic agents as well as for many investigational antiarrhythmic drugs.

Less information is available about the function
A similar pattern is seen in the AH interval during verapamil infusion. Over the next nine CLs, the AH interval progressively increased in magnitude. A similar pattern was seen in patient 6 (C), despite the small baseline increment in the AH interval during the infusion of verapamil.

FIGURE 4. Two patterns of frequency (use) dependence. In patient 7 (A) use dependence was demonstrated by an increase in AH interval during verapamil infusion at every cycle length (CL) tested. A second pattern is shown in B and C. In patient 4 (B), AH interval during verapamil infusion was relatively constant over the first four CLs tested. Over the next nine CLs, the AH interval progressively increased in magnitude. A similar pattern was seen in patient 6 (C), despite the small baseline increment in the AH interval during the infusion of verapamil.

FIGURE 5. Data for the six patients in whom testing was begun at a cycle length of 800 msec. A, The mean Δ(AH) interval increased from 18 msec at a cycle length of 800 to 44 msec at a cycle length of 600 msec. B, There was no increase in HV interval (ΔHV = 0) at any of the cycle lengths tested.

of the calcium channel because of the greater variability in its molecular structure and function in different species as well as in different tissues of the same species. Although information about gating of calcium channels is still incomplete, there is evidence to suggest that there are many similarities between the sodium and calcium channels. For example, an inactivation as well as an activation process controls channel permeability. Furthermore, similarities exist between calcium- and sodium-channel blockers. For example, the calcium-channel blockers that show use dependence have a pKₐ in the 7 to 10 range. As in the case of sodium-channel blockers, permanently charged derivatives of calcium-channel antagonists do not induce frequency-dependent block when applied to the outer surface of the membrane, but do induce block when applied to the inner surface of the membrane. This implies that the pathways by which the channel binding site is accessed are similar for calcium- and sodium-channel blocking drugs.
The calcium-dependent slow inward current plays a major role in transmission of impulses through the atrioventricular node. Studies performed in the 1970s demonstrated that the calcium current is primarily responsible for the action potential upstroke in N and NH cells of the atrioventricular node.\textsuperscript{18} Verapamil is known to depress calcium current in voltage-clamped preparations of atrioventricular node obtained from mammalian myocardium.\textsuperscript{27} Since propagation velocity in the atrioventricular node is dependent on the underlying calcium current as well as passive membrane properties, a drug-induced decrease in ionic current should be reflected in a prolongation of atrioventricular nodal conduction time.

Unfortunately, there is a scarcity of clinical evidence indicating that use-dependent blockade may occur in humans. Evidence for its presence could be inferred from the observation of frequency-dependent changes in propagation velocity or conduction time. Recently, preliminary observations have suggested that type I antiarrhythmic drugs will cause cycle length–dependent prolongation of the HV interval or QRS duration.\textsuperscript{11, 12} However, there have been no studies in which the possibility of use-dependent blockade by calcium- (slow-current) blocking drugs has been examined in man.

In our study, frequency-dependent prolongation of the AH interval was demonstrated in each patient. Two patterns of prolongation of the AH interval were noted. One pattern showed a constant \(\Delta(\text{AH})\) interval for the first four to seven pacing cycle lengths tested, followed by progressively increasing \(\Delta(\text{AH})\) intervals at the remaining pacing cycle lengths. The second pattern demonstrated a nonlinear increase in \(\Delta(\text{AH})\) interval that was noted by the second cycle length tested. There was no correlation between the pattern of use dependence seen and the baseline heart rate or AH interval.

Furthermore, there was no correlation between hemodynamic response to the infusion of verapamil and the pattern of frequency dependence observed. There are several other factors that would be expected to modulate the magnitude and pattern of frequency-dependent prolongation of the AH interval. Cellular phenomena, such as changes in diastolic membrane potential, may cause different degrees of tonic block.\textsuperscript{2, 22} Catecholamines have been shown to augment the calcium-channel current, and changing catecholamine levels could modulate the degree of prolongation of the AH interval seen with rapid atrial pacing.\textsuperscript{29} Finally, atrioventricular nodal conduction reflects a wide spectrum of atrioventricular nodal physiology, and interindividual differences in baseline properties could contribute to the different responses we observed with incremental atrial pacing.\textsuperscript{29}

The kinetics of equilibration of the AH interval with abrupt changes in atrial pacing cycle length in man were studied to compare our observations on conduction time in vivo with observations on calcium current in vitro. Earlier work with different mammalian myocardial preparations has shown that after onset of a pulse train, verapamil induces steady-state block of the calcium current by 10 to 15 pulses.\textsuperscript{17, 26} A comparison such as this presumes a relatively linear relationship between propagation velocity and available calcium conductance. In all six patients studied, equilibrium values for \(\Delta(\text{AH})\) intervals were obtained by 5 to 8 beats, which is similar to the number of impulses required to attain equilibrium in vitro. From a practical viewpoint, this justifies our assumption that data obtained 45 sec after a change in pacing cycle length represented steady-state values.

Although verapamil is primarily considered to be a calcium-channel blocker, previous investigations have demonstrated that the (+) isomer of verapamil decreases \(V_{\text{max}}\) of phase 0 of the action potential in mammalian ventricular myocardium in a rate-dependent fashion, presumably by blocking the sodium channel.\textsuperscript{30, 31} Since verapamil exists as a racemic mixture, the (+) isomer might also cause rate-dependent prolongation of HV conduction time. In our study, no evidence of rate-dependent prolongation of the HV interval was seen during the infusion of verapamil. The most likely explanation for the discrepancy between our findings and observations in vitro is that the levels of verapamil produced by the infusion are approximately tenfold less than those shown to cause a rate-dependent decrease in \(V_{\text{max}}\) in vitro.

We also attempted to show a concentration-response relationship. We predicted that the concentration of verapamil would be higher in a patient with a greater \(\Delta(\text{AH})\) interval at a given cycle length. This, however, was not the case. There are several explanations for the lack of correlation between the level of verapamil and the degree of frequency dependence demonstrated. Unquantifiable influences are the wide spectrum of atrioventricular nodal function manifested by different AH intervals at rest and the different responses of the AH interval to incremental pacing in each patient. In addition, differing degrees of change in autonomic tone may have contributed to the variable degrees of frequency dependence noted in individual patients. To minimize this complication, we excluded patients with heart failure in whom verapamil might have caused hypotension and a subsequent change in autonomic
tide.\(^3^3\) For the maintenance infusion, we used an infusion protocol that Reiter et al.\(^3^3\) have shown to result in constant plasma concentrations of verapamil. This protocol did not cause a significant change in heart rate or blood pressure during the loading or maintenance phase of the infusion in our patients, implying that changes in autonomic tone were minimal.\(^3^3\)

Verapamil administered intravenously is the agent of choice for terminating acute episodes of paroxysmal supraventricular tachycardia without hemodynamic compromise.\(^3^4\) Its efficacy approaches 90% for termination of reentrant supraventricular tachycardia, regardless of the mechanism of the tachycardia. The infusion of verapamil studied produced drug levels similar to those reported in patients taking 80 mg of oral verapamil every 6 hr.\(^3^5\) The changes in effective and functional refractory periods of the atrioventricular node and in cycle length sustaining 1:1 atrioventricular conduction during the maintenance infusion of verapamil were similar to those reported in several other clinical studies.\(^3^5-3^9\) The magnitude of use dependence we observed \((\Delta(AH))\) at final cycle length tested \(-\Delta(AH))\) at initial cycle length tested) varied from 25 to 70 ms (mean \(\pm SD\), 51 \(\pm 17\) ms). This additional increase in AH interval resulting from frequency-dependent prolongation of atrioventricular nodal conduction is of the same order of magnitude as the increase in AH intervals seen just before termination of tachycardia in many patients receiving intravenous or oral verapamil.\(^3^5,3^7,4^0\) Thus, these data suggest that the frequency- or rate-dependent effects demonstrated in this study are of sufficient magnitude to be of therapeutic significance in the termination of paroxysmal supraventricular tachycardia.

In conclusion, the results of this study demonstrate use-dependent blockade of atrioventricular nodal conduction with verapamil in man. The kinetics of block are rapid and were achieved in five to eight pulses. There was no evidence of use-dependent prolongation of His-Purkinje conduction (HV interval). The degree of use dependence observed in this study did not correlate with the verapamil concentration.

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