Effects of Oral Verapamil in Patients with Atrioventricular Reentrant Tachycardia Incorporating an Accessory Pathway

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SUMMARY In 14 patients with atrioventricular reentrant tachycardia incorporating an accessory pathway, electrophysiologic studies were performed before and serially at 0.5–1-hour intervals for 6 hours after the fourth dose of 80 mg of oral verapamil given every 6 hours. Verapamil increased both the longest atrial paced cycle length producing type 1 atrioventricular block and the effective refractory period of the atrioventricular conduction system at all measurements. Before verapamil, sustained tachycardia could be induced in all 14 patients. After verapamil, six patients had induction of echo beats alone at all measurements, and in eight patients nonsustained or sustained tachycardia could be induced, particularly after the fourth hour. Follow-up study with oral verapamil at the same dosage in 13 patients for 7 ± 5 months (± SD) revealed that the six patients with induction of echo beats alone have been free of symptomatic arrhythmia, while six of the remaining eight patients had occasional attacks of sustained tachycardia. Thus, oral verapamil increases atrioventricular nodal refractoriness, with an effect lasting up to 6 hours. Electrophysiologic study performed 5–6 hours after verapamil can be used to predict clinical responses in patients with atrioventricular reentrant tachycardia.

INTRAvenous Verapamil is the drug of choice in terminating acute episodes of paroxysmal supraventricular tachycardia. The efficacy of oral verapamil in preventing the recurrence of tachycardia, nonetheless, is controversial. Wellens et al. found that the effects of i.v. verapamil were qualitatively identical to those of oral verapamil. Klein et al. found that the effects of i.v. verapamil were similar to those of oral verapamil, and that the effects of either preparation on acute episodes of tachycardia predicted subsequent clinical responses. Rinkenberger et al. found that oral verapamil as a single drug was generally ineffective in preventing recurrence of paroxysmal supraventricular tachycardia. In this study, using serial electrophysiologic testing techniques, we systematically evaluated the effects of oral verapamil on induction and sustenance of atrioventricular reentrant tachycardia incorporating a retrogradely conducting accessory pathway, and correlated the electrophysiologic effects of oral verapamil to the plasma verapamil concentrations and subsequent follow-up responses.

Materials and Methods

The study group consisted of 14 patients, 10 male and four female, ages 17–69 years (mean ± sd 39 ± 17 years). All patients had electrocardiographic documentation of paroxysmal supraventricular tachycardia requiring multiple hospital visits for termination with parenteral drug administration and electrophysiologic induction of sustained atrioventricular reentrant tachycardia incorporating a retrogradely conducting accessory pathway. Of these 14 patients, 13 had a normal resting ECG without ventricular preexcitation, and one had ventricular preexcitation with a long antegrade accessory pathway effective refractory period to allow measurements of antegrade normal pathway conduction properties. The frequency of paroxysmal supraventricular tachycardia ranged from daily attacks to one attack per month. Thirteen patients had no demonstrable organic heart disease and one had hypertensive cardiovascular disease.

Electrophysiologic Studies

Each patient gave informed, written consent. Electrophysiologic studies were performed with the patient in the postabsorptive, nonsedated state. Cardiac medications were discontinued for at least 5 plasma half-lives before the study. A #7 quadrupolar electrophatheter was percutaneously introduced into the right femoral vein, advanced to the right atrium and positioned across the tricuspid valve. The proximal two electrodes were used for His bundle recording and the distal two electrodes for right ventricular pacing. A #7 hexapolar electrophatheter was introduced into the right antecubital vein by a small incision and advanced to the right atrium and then into the coronary sinus. The distal two electrodes were used to record a left atrial electrogram from the coronary sinus, the middle two electrodes to record a right atrial electrogram, and the proximal two electrodes for right atrial stimulation. The distal two electrodes of the hexapolar electrophatheter as well as the quadrupolar electrophatheter were also positioned at different sites of coronary sinus and right atrium to map the atrial activation sequence during induced episodes of atrioventricular reentrant tachycardia. Multiple surface and intracardiac electrograms were simultaneously recorded on a multichannel oscilloscopic recorder (Electronics for Medicine VR-16) at a paper speed of 100 mm/sec. Stimuli were provided by a programmable digital stimulator (DTU PC 100, manufactured by M. Bloom) and were approximately twice diastolic threshold and 2 msec in duration.

Conduction properties were evaluated with atrial
and ventricular incremental pacing and extrastimulus testing. Antegrade and retrograde conduction intervals were measured and defined as previously described. Atrial extrastimulus testing with either single extrastimulus or double extrastimuli were coupled to sinus and driven cycle lengths. For comparison, refractory periods were measured at an identical basic driven cycle length of either 600 or 500 msec as well as an identical stimulus current strength. The antegrade effective refractory period of the atrioventricular conducting system was defined as the longest atrial coupling interval at which the premature atrial stimulus was not conducted to the ventricles, and it was measured from the high right atrial electrograms. The retrograde effective refractory period of the accessory pathway was defined as the longest ventricular coupling interval at which the premature ventricular stimulus was blocked in the accessory pathway, as suggested by ventriculoatrial block or by occurrence of a sudden increment in ventriculoatrial conduction time associated with changes of retrograde atrial activation sequence as seen during the control study. Incorporation of a retrogradely conducting accessory pathway during induced episodes of tachycardia was suggested by eccentric retrograde atrial activation sequence, lengthening of ventriculoatrial interval with development of bundle branch block ipsilateral to the accessory pathway, and ability to capture the atria with critically timed ventricular extrastimuli delivered when the His bundle is refractory. Sustained tachycardia was defined as induced episodes of tachycardia that lasted longer than 2 minutes and required termination with electrical stimulation. Nonsustained tachycardia was defined as episodes of induced atrioventricular reentrant tachycardia that were terminated spontaneously within 2 minutes. In case of nonsustained tachycardia, the site of block (weak link) was determined.

After the control studies, the quadripolar electrode catheter was removed while the hexapolar electrode catheter was withdrawn from the coronary sinus, advanced to the right ventricle and secured for subsequent serial electrophysiologic studies. The proximal two electrodes of the hexapolar catheter were kept at the junction of superior vena cava and the right atrium, as during the control study. The distal two electrodes were used for ventricular pacing during subsequent electrophysiologic studies. After the hexapolar catheter was secured, the atrial effective refractory period was again measured, and it was used as the control value for those measured after oral verapamil.

The patient was then placed on oral verapamil, 80 mg (in 40-mg tablets of racemic mixture of d, l-verapamil) every 6 hours for four doses. For 6 hours after the last dose of verapamil, serial electrophysiologic studies were repeated at 30 minutes and 1 hour and then hourly. In five patients, heart rate, blood pressure and blood samples for measurement of plasma verapamil concentration were taken immediately before the last dose of verapamil and at each subsequent electrophysiologic study. Plasma verapamil concentration was determined using high-performance liquid chromatography (measured by Bioscience Laboratory). The patients were ambulatory between each measurement, which took 10 minutes.

Data Analysis and Follow-up
The data were expressed as mean ± SD and were analyzed with the t test for paired data. All patients were discharged on oral verapamil, 80 mg every 6 hours, and were followed in clinic. When therapeutic regimens were changed or when the patient became noncompliant, the follow-up period was counted up to the date of the change or up to the last date of compliance.

Results
Induction of Atrioventricular Reentrant Tachycardia (table 1, figs. 1 and 2)
Sustained atrioventricular tachycardia was induced in all 14 patients during the control study. Thirty minutes after verapamil, sustained tachycardia was induced in two patients, nonsustained tachycardia in four, and a single atrioventricular reentrant atrial echo in eight. One hour after verapamil, sustained tachycardia was not inducible in any of the 14 patients, nonsustained tachycardia was induced in three and a single atrial echo in 11. Two hours after verapamil, sustained tachycardia was not inducible in any patient, nonsustained tachycardia was induced in two patients and a single atrial echo in 12. Three hours after verapamil, sustained tachycardia was induced in one patient, nonsustained tachycardia in three patients and a single atrial echo in 10. Four hours after verapamil, sustained tachycardia was induced in one patient, nonsustained tachycardia in six patients and a single atrial echo in seven. Five hours after verapamil, sustained tachycardia was induced in four patients, nonsustained tachycardia in four and a single atrial echo in six. Six hours after verapamil, sustained tachycardia was induced in six patients, nonsustained tachycardia in two and a single atrial echo in six.

Thus, six of the 14 patients (cases 1–6) had induction of only a single atrial echo at all measurement periods (fig. 1), one (case 7) had induction of nonsustained tachycardia during the later measurements, and 7 (cases 8–14) had induction of sustained tachycardia during the later measurements, particularly at 5 and 6 hours after verapamil (fig. 2). In all 14 patients, when a single echo or nonsustained tachycardia was induced after verapamil, the weak link was in the antegrade direction. All episodes of sustained tachycardia after verapamil were considerably slower than those before verapamil (fig. 2).

Effects on Antegrade Conduction (figs. 3 and 4)
Antegrade conduction properties of the normal pathway were evaluated by both incremental atrial pacing and extrastimulus testing. The longest atrial paced cycle length that produced type 1 atrioventricular block before and after verapamil could be compared in 13 patients. In the remaining patient, measurements after
TABLE 1. Clinical Characteristics, Electrophysiologic Effects of Verapamil and Follow-up Data

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Frequency of PSVT (/month)</th>
<th>Induction of PSVT after verapamil (hours)</th>
<th>Follow-up</th>
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<td>22</td>
<td>F</td>
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Abbreviations: PSVT = paroxysmal supraventricular tachycardia; NA = data not available.

Verapamil were limited by atrioventricular reentrant atrial echoes during sinus rhythm as well as with the initiation of atrial pacing. The longest atrial paced cycle length that produced atrioventricular block was 291 ± 39 msec before verapamil and increased to 403 ± 42 msec at 30 minutes, 463 ± 59 msec at 1 hour, 465 ± 65 msec at 2 hours, 433 ± 61 msec at 3 hours, 420 ± 63 msec at 4 hours, 409 ± 61 msec at 5 hours, and 377 ± 51 msec at 6 hours after verapamil (fig. 3). All measurements after verapamil were significantly longer than the control measurement (p < 0.001). The peak effect was seen at 1 and 2 hours after verapamil.

Measurements of antegrade effective refractory period of the atrioventricular conducting system after verapamil were frequently disturbed by induction of echoes during basic driven cycle length. Thus, the antegrade effective refractory period of the atrioventricular conducting system could not be compared at each measurement in some of the patients, and it was analyzed as changes compared with control. When

![Figure 1](http://irc.ahajournals.org/)

Effect of verapamil on induction of atrioventricular reentrant tachycardia in case 3. (top) Induction of sustained tachycardia during the control study at a basic driven cycle length (CL) of 500 msec and a coupling interval of 260 msec. I, AVF and V1 = lead I, AVF and V1 of the surface electrocardiogram; HRA = high right atrial electrogarm; CS = left atrial electrogram recorded from the coronary sinus; HBE = His bundle electrogram; CL = cycle length; S1 = basic driven stimulus; HRA, A1, and H1 = high right atrial, low septal right atrial and His bundle responses to S1; S2 = extrastimulus; HRA, A2, and H2 = high right atrial, low septal right atrial and His bundle responses to S2. HRA = atrioventricular reentrant atrial echo. (middle and bottom) Induction of a single atrioventricular reentrant atrial echo ½ hour and 6 hours after verapamil. The coupling interval was 340 msec.
atrioventricular block was induced at the basic driven cycle length after verapamil, the antegrade effective refractory period of the atrioventricular conducting system was taken and analyzed as the basic driven cycle length. The antegrade effective refractory period of the atrioventricular conducting system increased more than 87 ± 18 msec \( (p < 0.05, n = 9) \) at 30 minutes, more than 162 ± 23 msec \( (p < 0.001, n = 10) \) at 1 hour, more than 181 ± 52 msec \( (p < 0.001, n = 11) \) at 2 hours, more than 137 ± 46 msec \( (p < 0.01, n = 10) \) at 3 hours, more than 121 ± 34 msec \( (p < 0.02, n = 8) \) at 4 hours, more than 90 ± 37 msec \( (p < 0.05, n = 9) \) at 5 hours and more than 66 ± 33 msec \( (p < 0.05, n = 9) \) at 6 hours after verapamil (fig. 3). The atrial effective refractory period was measured in only five patients. It was 218 ± 23 msec before verapamil and was 270 ± 28 msec \( (p < 0.02) \) at 30 minutes, 286 ± 15 msec \( (p < 0.01) \) at 1 hour, 264 ± 17 msec \( (p < 0.05) \) at 2 hours, 276 ± 19 msec \( (p < 0.02) \) at 3 hours, 274 ± 21 msec \( (p < 0.02) \) at 4 hours, 264 ± 30 msec \( (NS) \) at 5 hours, 274 ± 27 msec \( (p < 0.05) \) at 6 hours after verapamil (fig. 3).

Effects on Retrograde Conduction (fig. 4)

The shortest ventricular paced cycle length was 280 msec; therefore, the longest ventricular paced cycle length that produced ventriculoatrial block could not be compared in all patients at every measurement. It was analyzed as change from control. There were no significant changes in the longest ventricular paced cycle length that produced ventriculoatrial block after verapamil, except at 30 minutes and at 5 hours after verapamil (fig. 4). The longest ventricular paced cycle length that produced ventriculoatrial block lengthened more than 29 ± 14 msec \( (p < 0.01, n = 8) \) at 30 minutes and more than 38 ± 23 msec \( (p < 0.05, n = 5) \) at 5 hours after verapamil. Likewise, the effective refractory period of the retrograde accessory pathway was analyzed by comparing the value to the control measurement. It increased more than 72 ± 32 msec \( (p < 0.01, n = 13) \) at 30 minutes, more than 62 ± 19 msec \( (p < 0.01, n = 12) \) at 1 hour, more than 62 ± 19 msec \( (p < 0.01, n = 13) \) at 2 hours, more than 62 ± 25 msec \( (p < 0.01, n = 12) \) at 3 hours, more than 61 ± 23 msec \( (p < 0.01, n = 11) \) at 4 hours, more than 57 ± 22 msec \( (p < 0.01, n = 11) \) at 5 hours, and more than 50 ± 13 msec \( (p < 0.05, n = 11) \) at 6 hours after the last dose of verapamil (fig. 4).

Plasma Verapamil Concentration, Blood Pressure and Heart Rate (fig. 5)

Plasma concentration of verapamil was measured in
five patients and was 36.8 ± 15 ng/ml before the last dose of verapamil, 69.2 ± 21.6 ng/ml at 30 minutes, 88.2 ± 30.5 ng/ml at 1 hour, 112.6 ± 53.9 ng/ml at 2 hours, 88.8 ± 18.8 ng/ml at 3 hours, 60.4 ± 28.5 ng/ml at 4 hours, 45.8 ± 19.4 ng/ml at 5 hours, and 36.8 ± 13.6 ng/ml at 6 hours after the last dose of verapamil. Plasma verapamil concentration reached a peak at 2 hours and then decreased. The blood pressure and the heart rate did not change significantly at each measurement after verapamil. Systolic pressure was 103 ± 7 mm Hg before verapamil, 107 ± 15 mm Hg at 30 minutes, 107 ± 12 mm Hg at 1 hour, 107 ± 13 mm Hg at 2 hours, 109 ± 13 mm Hg at 3 hours, 107 ± 9 mm Hg at 4 hours, 107 ± 10 mm Hg at 5 hours, and 110 ± 12 mm Hg at 6 hours after the last dose of verapamil. Diastolic pressure was 68 ± 7 mm Hg before verapamil, 74 ± 10 mm Hg at 30 minutes, 76 ± 8 mm Hg at 1 hour, 70 ± 13 mm Hg at 2 hours, 72 ± 12 mm Hg at 3 hours, 73 ± 9 mm Hg at 4 hours, 72 ± 8 mm Hg at 5 hours, 72 ± 7 mm Hg at 6 hours after the last dose of verapamil. Heart rate was 75 ± 6 beats/min before verapamil, 66 ± 13 beats/min at 30 minutes, 69 ± 14 beats/min at 1 hour, 73 ± 17 beats/min at 2 hours, 71 ± 13 beats/min at 3 hours, 69 ± 13 beats/min at 4 hours, 70 ± 11 beats/min at 5 hours, and 74 ± 10 beats/min at 6 hours after the last dose of verapamil.

Follow-up Data (table 1)
Excluding case 9, in whom verapamil was discontinued after a week because of urinary retention, 13 patients have been followed for 2–14 months (mean ± SD 7 ± 5 months). During the follow-up, case 3 noted mild constipation and case 6 noted mild dizziness at the beginning of therapy; these symptoms improved, and both patients were kept on verapamil. Case 8 developed mild ankle edema, which subsided after addition of diuretics.

Among the six patients (cases 1–6) with induction of only a single atrial echo during electrophysiologic studies after verapamil administration, five were free of symptomatic arrhythmia and one (case 4) experienced six episodes of transient palpitation. In the remaining seven patients with induction of either non-sustained or sustained tachycardia during electrophysiologic studies after verapamil administration, six had documented tachycardia and one (case 11) experienced four episodes of transient palpitation. Therapeutic regimens were changed in three of these seven patients due to ineffectiveness of chronic verapamil therapy. In case 8, digoxin was added and in case 13, verapamil was replaced with digoxin and propranolol. In case 14, successful surgical incision of the accessory pathway was performed. In the remaining four patients, an additional 80 mg of oral verapamil taken at the time of tachycardia usually terminates the tachycardia.

Discussion
Verapamil inhibits the slow inward current carried by calcium or sodium ions.22–25 It is particularly effective in tachyarrhythmias involving the atrioventricular node.1–11 It terminates acute episodes of paroxysmal supraventricular tachycardia and slows the ventricular
Figure 4. Changes before and after verapamil, in the antegrade effective refractory period of the atrioventricular conducting system (ΔERP-AVCS), the longest ventricular paced cycle length producing ventriculoatrial block (ΔCL-VAB) and the effective refractory period of the retrograde accessory pathway (ΔERP-RAP). See text for discussion.

Figure 5. Plasma verapamil concentration and effect of verapamil on blood pressure (BP) and heart rate (HR). See text for discussion. C = control.
rate in atrial flutter or fibrillation. The alpha-phase half-life of i.v. verapamil was 0.1–0.5 hour, while the beta-phase was 2.6–7.7 hours. 26, 27 Thus, after an i.v. bolus of verapamil, the effects are seen within the first 10 minutes and diminish within 30 minutes. There are minor discrepancies concerning the pharmacokinetics of oral verapamil. Schommerus et al. 26 found that after oral administration of 80 mg of 14C-D, L-verapamil dissolved in 100 ml of water, the plasma levels of both 14C-activity and verapamil peaked within 30–45 minutes, while the half-lives of the alpha- and beta-phase were identical to those observed during i.v. verapamil. Koike et al. 27 found that after a 120-mg tablet of verapamil, the serum verapamil level peaked at 1.25–2.28 hours and declined thereafter. The discrepancy between these two studies was most likely because of a difference in the forms of verapamil administered. Our data with administration of oral verapamil are consistent with those of Koike et al. in that the peak plasma level of verapamil was achieved at 2 hours and declined after the peak level was achieved. The plasma verapamil levels in this study correlated well with the electrophysiologic effects of verapamil on the atrioventricular node in that both the longest atrial paced cycle length producing atrioventricular block and the antegrade effective refractory period of the atrioventricular conducting system lengthened in parallel to the plasma verapamil concentration. The peak electrophysiologic effects were at 1 and 2 hours after the last dose of verapamil.

These findings differ from the observations of Schlepper et al. 28 They found that after a single oral dose of 240 mg of verapamil, the effects on the atrioventricular node were seen at 2 hours and peaked at 5 hours. The discrepancy between our study and the study of Schlepper et al. may be explained by the difference in the study design. Verapamil has a vasodilating effect as well as a negative inotropic effect and can cause hypotension with a secondary reflex increment of the sympathetic tone. 29–31 After multiple oral doses of verapamil in our study, evidence of increased sympathetic tone was not observed as the heart rate and the blood pressure were not changed after verapamil. Secondary reflex increment of sympathetic tone after a single large dose of verapamil could have occurred in the study of Schlepper et al. If so, the initial effects of verapamil on the atrioventricular node could have been attenuated. Despite a profound effect of verapamil on the atrioventricular node, nonsustained or sustained tachycardia was inducible in half of the patients 4 hours after the last dose of verapamil. At this time, concomitant slowing of atrioventricular nodal conduction time with lengthening of the cycle length of tachycardia negated the beneficial effect of an increase in the atrioventricular nodal effective refractory period, making the tachycardia sustainable. 12, 13, 32 Electrophysiologic studies performed between 5 and 6 hours after the last dose of verapamil best correlate with the subsequent responses to chronic verapamil administration.

The effect of verapamil on the longest ventricular paced cycle length producing ventriculoatrial block (a measurement of retrograde accessory pathway refractoriness) was inconclusive. Significant changes were noted only at 30 minutes and 5 hours after verapamil. The effect of verapamil on the retrograde effective refractory period of the accessory pathway, nevertheless, was significant. This finding is contradictory to the previous observations in that verapamil lacked an effect on antegrade or retrograde accessory pathway conduction. 10, 11, 30, 31, 33 Since we have also demonstrated a significant lengthening of the atrial effective refractory period after verapamil, it is tempting to assume that lengthening of retrograde effective refractory period of the accessory pathway reflects a prolonged atrial effective refractory period. Although animal and human studies have demonstrated no effect of i.v. verapamil on atrial effective or functional refractory period, 10, 11, 30, 31, 33 microelectrophysiologic studies have shown prolongation of action potential duration and effective refractory period of canine Purkinje fibers. 24 The short action of i.v. verapamil may not allow accurate measurement of atrial effective or functional refractory periods in intact animals or in man. A secondary reflex increment of sympathetic tone could also nullify the effect of verapamil on the atrium. More importantly, Bayer et al. 34 demonstrated that the d-isomer of verapamil has a specific inhibitory effect on fast inward sodium channel on mammalian Purkinje fibers. The commercially available verapamil is a racemic mixture of both d- and l-isomers. The effect of the d-isomer cannot be ignored when a large dose of verapamil is used. The increase in the atrial effective refractory period by verapamil can explain previous observations of conversion of atrial flutter to atrial fibrillation and atrial flutter or fibrillation to sinus rhythm following intravenous verapamil administration. 1–3, 8, 9 Nevertheless, one should be cautious in interpreting our data concerning the atrial effective refractory period. The catheter technique we used could have caused a systematic error in the measurement of the atrial effective refractory period as a result of poor contact of the catheter against the atrial wall.

One could then ask why changes in atrioventricular nodal refractoriness tended to parallel changes in plasma verapamil concentration while changes in the effective refractory period of the atrium and the retrograde accessory pathway conduction did not. Could there be differences in clearance or metabolism of the d- and the l-isomers? Could the plasma half-life of the d-isomer be somewhat longer than that of the l-isomer? If so, then the effective refractory period of the atrium and the retrograde accessory pathway conduction might not shorten as the plasma verapamil concentration declined. This possibility requires further pharmacokinetic investigation.

In conclusion, oral verapamil increases atrioventricular nodal refractoriness, with an effect that lasts for as long as 6 hours. It prevents recurrence of tachycardia in some patients, but is generally unsatisfactory as a single agent in most patients with troublesome atrioventricular reentrant tachycardia. Electrophysiologic study performed at fifth or sixth hour after the last dose
of verapamil can be used to predict subsequent clinical responses to chronic verapamil administration.

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