Effects of Intravenous and Chronic Oral Verapamil Administration in Patients with Supraventricular Tachyarrhythmias

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SUMMARY The efficacy of i.v. and oral verapamil was studied in 28 patients with supraventricular tachycardia (SVT). Verapamil (5–10 mg i.v.) terminated SVT in all six patients with atrioventricular nodal (AVN) reentrant tachycardia. In all patients verapamil prolonged antegrade AVN conduction time. Two patients had associated sinus nodal reentrant tachycardia that persisted after the AVN tachycardia terminated.

In six patients with SVT using an accessory pathway for retrograde conduction, i.v. verapamil terminated SVT in four and slowed SVT in two patients. Verapamil did not affect the electrophysiologic properties of the accessory pathway and the effect on the SVT, as with AVN reentry, was caused by changes in antegrade AVN function. Verapamil lengthened AVN antegrade conduction time in patients with accessory pathways less than it did in patients with AVN reentry.

Verapamil at doses that resulted in AVN Wenckebach block had no effect on the discharge rate of the three patients with automatic atrial tachycardia. In 13 of 14 patients with atrial fibrillation or flutter, i.v. verapamil promptly decreased the ventricular rate. One patient with preexcitation had an increase in ventricular rate after verapamil. The shortest RR intervals before and after verapamil were 260 and 220 msec, respectively, and after verapamil more ventricular beats were preexcited.

Oral verapamil was given to 19 of 28 patients. Ten discontinued the drug within 30 days because of side effects or ineffectiveness. Seven patients treated for a mean of 19 months have shown evidence of improvement, judged by decreased frequency and shorter duration of tachycardia when it did recur. Thus, i.v. verapamil is an effective antiarrhythmic drug for most patients with SVT, but oral verapamil is effective in only selected patients.

VERAPAMIL has been used to treat supraventricular tachycardia (SVT) for several years in Europe and recently has been approved for investigational use in the United States. In this study we assessed its efficacy and safety and evaluated its electrophysiologic mechanism of action in patients with different types of SVT.

Methods

Patient Selection

The study population consisted of 28 patients who had recurrent, symptomatic SVT that had been incompletely controlled with other antiarrhythmic agents because of lack of efficacy or drug intolerance. The salient clinical features of the patients are summarized in tables 1 and 2. The patients were divided into four groups, based on the type of SVT. Group A consisted of six patients with SVT due to atrioventricular (AV) nodal reentry. Group B was made up of six patients who had reentrant tachycardia using an accessory pathway (concealed or manifest Wolff-Parkinson-White [WPW] syndrome). Group C consisted of three patients with apparent automatic atrial tachycardia. Group D included 12 patients with atrial fibrillation and two patients with atrial flutter. Patient 11 in group B had both reentrant tachycardia and atrial fibrillation associated with the WPW syndrome, and is also considered in group D (as patient 28).

The mean age of the 15 patients in groups A, B and C was 48 ± 3 years (range 19–60 years); nine were women and six were men. Twelve patients had recurrent arrhythmia as the only cardiac problem. One patient had mitral valve prolapse, another had idiopathic hypertrophic subaortic stenosis and one patient developed SVT after pulmonary embolization.

Group D included four women and 10 men, mean age 51.3 ± 8.9 years (range 33–66 years). Three patients had recurrent atrial fibrillation with no known heart disease; one patient had WPW type A; one had congestive cardiomyopathy; one had obstructive cardiomyopathy; two patients had coronary artery disease; two had chronic obstructive lung disease; one patient had iatrogenic hyperthyroidism; two patients had mitral stenosis; and one patient had mitral stenosis with a repaired atrial septal defect.

After the nature of the medication and its possible side effects was explained, each patient gave written informed consent to receive verapamil. Patients who underwent an electrophysiologic study gave written informed consent for that procedure. Patients in all four groups received i.v. verapamil by hand infusion over 60 seconds as a bolus of 0.075 mg/kg, not exceeding a
Table 1. Clinical Features of Patients with Supraventricular Tachycardia (Groups A, B and C)

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Diagnosis</th>
<th>Previous treatment</th>
<th>Response to verapamil (dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>47</td>
<td>AVN reentry</td>
<td>Propranolol 40 mg qid, Digoxin 0.25 mg qd, Quinidine 200 mg qid</td>
<td>Converted to NSR (10 mg)</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>61</td>
<td>AVN reentry, MVP</td>
<td>Digoxin 0.25 mg qd, Quinidine NA, Propranolol 60 mg q 6 hr, Disopyramide 150 mg q 6 hr</td>
<td>Converted to NSR (5 mg)</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>46</td>
<td>AVN reentry</td>
<td>Digoxin 0.25 mg qd, Propranolol 60 mg qid, Disopyramide 200 mg qid</td>
<td>Converted to NSR (10 mg)</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>55</td>
<td>AVN reentry, sinus nodal reentry</td>
<td>Digitoxin 0.1 mg qd, Propranolol 30 mg qid</td>
<td>Converted to NSR (5 mg)</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>58</td>
<td>AVN reentry</td>
<td>Propranolol NA, Digoxin 0.25 mg qd</td>
<td>Converted to NSR (5 mg)</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>60</td>
<td>AVN reentry</td>
<td>Digoxin 0.25 mg qd, Disopyramide 100 mg qid, Propranolol 40 mg qid</td>
<td>Converted to NSR (10 mg)</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>56</td>
<td>Concealed AP</td>
<td>Digoxin 0.25 mg bid, Quinidine 500 mg q 6 hr, Procaainamide 500 mg q 3 hr</td>
<td>Slowed cycle length 40 msec (10 mg)</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>60</td>
<td>Concealed AP</td>
<td>Digoxin 0.25 mg qd, Propranolol 40 mg qid, Quinidine 400 mg qid</td>
<td>Converted to NSR (5 mg)</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>49</td>
<td>WPW</td>
<td>Digoxin 0.25 mg qd, Propranolol 80 mg qid, Quinidine NA</td>
<td>Converted to NSR (10 mg)</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>28</td>
<td>WPW</td>
<td>Propranolol 40 mg qid, Quinidine 200 mg qid</td>
<td>Converted to NSR (5 mg)</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>50</td>
<td>WPW</td>
<td>Digoxin 0.125 mg qd, Quinidine 600 mg qd, Propranolol 60 mg qid</td>
<td>Slowed cycle length 30 msec (10 mg)</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>49</td>
<td>WPW</td>
<td>Digoxin 0.25 mg qd, Quinidine 300 mg qid, Propranolol 40 mg qid</td>
<td>Converted to NSR (5 mg)</td>
</tr>
</tbody>
</table>

Group C

13  F   56          | SVT, obstructive cardiomyopathy | Digoxin 0.125 mg qd, Propranolol 10 mg qid, Disopyramide 150 mg q 4 hr | AVN Wenckebach block (10 mg) |
14  M   19          | SVT         | Digoxin 0.25 mg qd, Propranolol 40 mg qid | AVN Wenckebach block (5 mg) |
15  M   27          | SVT         | Quinidine 300 mg q 6 hr, Propranolol 80 mg qid, Digitoxin 0.1 mg qd | AVN Wenckebach block (5 mg) |

Abbreviations: AVN = atrioventricular node; AP = accessory pathway; MVP = mitral valve prolapse; NA = not available; NSR = normal sinus rhythm; SVT = supraventricular tachycardia; WPW = Wolff-Parkinson-White syndrome.

total of 5.0 mg. If the tachycardia continued 30 minutes after the first bolus, a second bolus of 0.15 mg/kg, not exceeding a total of 10 mg, was administered over 60 seconds to patients in groups A, B and C. The second bolus given to patients in group D was 0.075 mg/kg, not exceeding 5.0 mg, over 60 seconds. In four patients from group D, the initial bolus was followed by an infusion of verapamil (0.0025 mg/kg/min) for 30 minutes. Group A and B patients were given a trial of oral verapamil if they converted to normal sinus rhythm after i.v. administration. Patient 14 in group C received a trial of oral verapamil. Group D patients that responded to i.v. verapamil with restoration of normal sinus rhythm or with reduction of ventricular response to less than 85% of control during atrial fibrillation or atrial flutter were treated with oral verapamil.
Table 2. Clinical Features and Response to Verapamil in Group D

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Diagnosis</th>
<th>Previous therapy</th>
<th>Duration of arrhythmia before verapamil administration</th>
<th>Mean heart rate (beats/min)</th>
<th>Blood pressure (mm Hg)</th>
<th>Response to verapamil (dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>F</td>
<td>52</td>
<td>Paroxysmal AF, congestive cardiomyopathy</td>
<td>Propranolol NA Procainamide NA Dilantin 100 mg tid Digitoxin 0.15 mg qd</td>
<td>2 hours</td>
<td>150 100</td>
<td>112/78 100/68</td>
<td>Ventricular rate decreased 56 beats/min before conversion; converted to NSR 44 min (4.2 mg)</td>
</tr>
<tr>
<td>17</td>
<td>M</td>
<td>44</td>
<td>Paroxysmal AF</td>
<td>Digoxin 0.25 mg qd Propranolol 40 mg qid Quinidine 500 mg qid Disopyramide 150 mg qid</td>
<td>15 minutes</td>
<td>140 72</td>
<td>130/86 120/80</td>
<td>Ventricular rate decreased by 68 beats/min (5.0 mg; I 6.3 mg)</td>
</tr>
<tr>
<td>18</td>
<td>M</td>
<td>62</td>
<td>Paroxysmal AF</td>
<td>Digoxin 0.25 mg qd Propranolol 60 mg q 4 hr</td>
<td>15 minutes</td>
<td>140 84</td>
<td>120/72 120/76</td>
<td>Ventricular rate decreased by 56 beats/min (5.0 mg)</td>
</tr>
<tr>
<td>19</td>
<td>F</td>
<td>46</td>
<td>Paroxysmal AF, MS</td>
<td>Digoxin 0.25 mg qd Disopyramide 100 mg 5 x daily Propranolol 80 mg tid Quinidine NA</td>
<td>15 minutes</td>
<td>168 120</td>
<td>118/82 100/70</td>
<td>Ventricular rate decreased by 48 beats/min (5.0 mg; I 5.6 mg)</td>
</tr>
<tr>
<td>20</td>
<td>M</td>
<td>38</td>
<td>Paroxysmal AF, CAD, S/P CABG, COPD</td>
<td>Digoxin 0.375 mg qd</td>
<td>7 hours</td>
<td>184 92</td>
<td>90/70 86/66</td>
<td>Ventricular rate decreased by 92 beats/min; atrial flutter 2:1 → 4:1; conversion to atrial fibrillation</td>
</tr>
<tr>
<td>21</td>
<td>M</td>
<td>62</td>
<td>Paroxysmal AF, COPD</td>
<td>Propranolol NA</td>
<td>1 1/2 hours</td>
<td>166 132</td>
<td>150/90 112/76</td>
<td>Ventricular rate decreased by 34 beats/min (3.0 mg)</td>
</tr>
<tr>
<td>22</td>
<td>M</td>
<td>50</td>
<td>Paroxysmal AF, MS</td>
<td>Digoxin 0.25 mg qd</td>
<td>7 1/2 hours</td>
<td>168 128</td>
<td>94/62 90/80</td>
<td>Ventricular rate decreased by 40 beats/min; conversion to NSR, 39 min (5.0 mg)</td>
</tr>
<tr>
<td>23</td>
<td>M</td>
<td>33</td>
<td>Paroxysmal AF</td>
<td>Digoxin 0.25 mg qd Propranolol 40 mg q 6 hr</td>
<td>15 minutes</td>
<td>144 92</td>
<td>105/72 108/73</td>
<td>Ventricular rate decreased by 52 beats/min (5.0 mg)</td>
</tr>
<tr>
<td>24</td>
<td>F</td>
<td>51</td>
<td>Paroxysmal AF, S/P ASD repair, MS</td>
<td>Digoxin 0.1 mg qd Propranolol 40 mg qid Procainamide NA</td>
<td>15 minutes</td>
<td>140 88</td>
<td>116/80 108/60</td>
<td>Ventricular rate decreased by 52 beats/min (5.0 mg; I 5.0 mg)</td>
</tr>
<tr>
<td>25</td>
<td>M</td>
<td>51</td>
<td>Atrial flutter, CAD, S/P CABG</td>
<td>Digoxin 0.25 mg i.v. Propranolol 80 mg q 8 hr</td>
<td>12 hours</td>
<td>166 96</td>
<td>110/70 110/70</td>
<td>Ventricular rate decreased by 70 beats/min; atrial flutter 2:1 → 3:1; AF after 2 min with ventricular rate 104 beats/min (5.0 mg)</td>
</tr>
<tr>
<td>26</td>
<td>F</td>
<td>59</td>
<td>Paroxysmal AF, hyperthyroidism</td>
<td>Digoxin 0.25 mg qd Disopyramide 150 mg q 6 hr</td>
<td>26 hours</td>
<td>124 80</td>
<td>130/80 100/70</td>
<td>Ventricular rate decreased by 44 beats/min; converted to NSR 2 hr (5.0 mg)</td>
</tr>
<tr>
<td>27</td>
<td>M</td>
<td>66</td>
<td>Paroxysmal AF, obstructive cardiomyopathy</td>
<td>Propranolol 40 mg qid Quinidine NA</td>
<td>4 hours</td>
<td>200 186</td>
<td>112/72 105/70</td>
<td>Ventricular rate decreased by 14 beats/min; 5 1/2 sec asystole 31 min after 5 mg (5.0 mg)</td>
</tr>
<tr>
<td>28</td>
<td>M</td>
<td>50</td>
<td>Paroxysmal AF, WPW</td>
<td>Digoxin 0.25 mg qd Propranolol 60 mg qid</td>
<td>15 minutes</td>
<td>186 204</td>
<td>120/60 90/60</td>
<td>At 3 min, rate increased to 204 beats/min, mostly accessory pathway conduction (5.0 mg)</td>
</tr>
<tr>
<td>29</td>
<td>M</td>
<td>54</td>
<td>Paroxysmal AF</td>
<td>Digoxin 0.25 mg qd Propranolol 60 mg qid Quinidine NA Disopyramide 100 mg qid</td>
<td>15 minutes</td>
<td>125 70</td>
<td>134/82 130/80</td>
<td>Ventricular rate decreased by 55 beats/min (5.0 mg)</td>
</tr>
</tbody>
</table>

Abbreviations: AF = atrial fibrillation; ASD = atrial septal defect; C = control; CABG = coronary artery bypass graft; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; I = infusion; MS = mitral stenosis; NA = not available; NSR = normal sinus rhythm; V = verapamil; WPW = Wolf-Parkinson-White syndrome.
Continuous electrocardiographic monitoring and recordings were performed during verapamil administration and continued for 24 hours after the last i.v. dose. Vital signs were obtained immediately before injection of verapamil and at 1, 3, 5, 10, 15, 30 and 60 minutes afterward. Thereafter, vital signs were obtained every hour for 2 hours, every 2 hours for 4 hours and every 4 hours until time of discharge from the hospital, a minimum of 72 hours after i.v. administration of the drug.

Electrophysiologic Study

Electrophysiologic studies were performed in 20 patients in the nonsedated, postabsorptive state 24–72 hours after discontinuation of all antiarrhythmic therapy. Three or four tripolar or quadripolar catheters were inserted transvenously and positioned in the high right atrium, the coronary sinus or left atrium through a patent foramen ovale, across the septal leaflet of the tricuspid valve for His bundle recording, and in the right ventricular apex. Tracings were recorded on a multichannel oscilloscopic recorder (Electronics for Medicine VR 12) at a paper speed of 100 mm/sec using filter settings of 30 and 500 Hz for the intracardiac electrograms, and 0.1 to 20 Hz for the surface ECGs. The right and/or left atrium and apex of the right ventricle were stimulated using a programmable stimulator (Medtronic model 5325) that delivered square-wave stimuli at 1½–2 times the late diastolic threshold.

Pacing was performed at two or more cycle lengths (400–700 msec) shorter than the spontaneous cycle length to determine refractory periods and initiate tachycardia by the extrastimulus technique. The method of initiation of supraventricular tachycardia and the echo zone interval were documented. The shortest pacing cycle length was obtained at which 1:1 antegrade and retrograde AV nodal or accessory pathway conduction occurred. Rapid atrial pacing was used to induce atrial fibrillation in patients in whom the arrhythmia occurred spontaneously and did not have it at the time of study, or in evaluation of antegrade conduction in patients with WPW syndrome.

After determination of baseline electrophysiologic measurements, tachycardia was induced and maintained for 15 minutes before administration of verapamil. Thirteen patients in groups A, B and C and six patients in group D received verapamil during the electrophysiologic study.

Oral Verapamil

Twenty-one patients received oral verapamil, initially administered at a dosage of 60 mg every 8 hours and increased to a maximum of 120 mg every 6 hours, depending on response. The medication was discontinued if an adverse reaction occurred or if the medication was judged ineffective because it failed to prevent recurrent episodes of tachyarrhythmia.

Definitions

Standard definitions for refractoriness and conduction were used for the atrium, ventricle and normal conduction system as well as for accessory pathways.

The echo zone was considered as the A1A2 or V1V2 interval that initiated SVT.

Ventricular rate during atrial fibrillation and atrial flutter was determined by averaging the rate over 60 seconds.

AV nodal reentrant tachycardia was diagnosed by the following criteria: (1) induction of tachycardia related to AV nodal (AH) conduction delay, (2) retrograde atrial activation before or simultaneously with the onset of ventricular activation during SVT, (3) demonstration of "discontinuous" A1A2 curves, (4) normal retrograde atrial activation sequence during tachycardia and ventricular stimulation with low right atrium activated before other atrial sites, (5) inability to preexcite the atrium by premature ventricular stimulation during SVT at a time when the His bundle was refractory.

Reentrant SVT using an accessory pathway retrogradely during SVT was diagnosed by the following criteria: (1) eccentric retrograde atrial activation sequence during tachycardia, (2) development of bundle branch block ipsilateral to the accessory pathway with resultant increased cycle length and/or ventriculoatrial (VA) conduction interval during SVT, (3) preexcitation of the atria with a ventricular extrastimulus during tachycardia when the His bundle was refractory. The term SVT is applied to this tachycardia, although the term reciprocating tachycardia may be more appropriate.

Automatic atrial tachycardia was diagnosed by the following criteria: (1) SVT initiated by premature atrial complexes showing no increase in initial AH conduction, (2) AH prolongation during SVT to the same interval that occurred during right atrial stimulation at the same cycle length, (3) premature atrial complexes introduced during SVT resulted in resetting of the SVT and not termination, (4) overdrive atrial stimulation failed to terminate SVT, (5) periods of 3:2, 2:1 AV nodal block occurred during SVT, demonstrating that the AV node distal to the site of block and the ventricles were not required as part of a reentry circuit, (6) atrial activation sequence of the first P wave initiating SVT was the same as the remaining P waves during the SVT.

Results

Group A — SVT Due To AV Nodal Reentry

Before Verapamil Administration

The sequence of stimulation that induced SVT, echo zones and other electrophysiologic characteristics for patients 1–4 are summarized in table 3. Patients 5 and 6 are not included because patient 5 had no electrophysiologic study and patient 6 received an ineffective 5-mg initial i.v. dose at the time of electrophysiologic study. She refused further trial with
TABLE 3. Electrophysiologic Variables Before and After Verapamil in Group A

<table>
<thead>
<tr>
<th>Pt.</th>
<th>PCL</th>
<th>ERPRA</th>
<th>AH interval</th>
<th>HV interval</th>
<th>ERPAVN</th>
<th>ERPRV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>V</td>
<td>C</td>
<td>V</td>
<td>C</td>
</tr>
<tr>
<td>1</td>
<td>600</td>
<td>220</td>
<td>240</td>
<td>130</td>
<td>220</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>600</td>
<td>260</td>
<td>250</td>
<td>70</td>
<td>100</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>500</td>
<td>230</td>
<td>230</td>
<td>70</td>
<td>90</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>550</td>
<td>250</td>
<td>270</td>
<td>115</td>
<td>160</td>
<td>45</td>
</tr>
</tbody>
</table>

Measurements are in milliseconds.

*Sinus nodal reentry.

Abbreviations: AVN = atrioventricular node; C = control; CS = coronary sinus; ERPAVN = effective refractory period of the AV node; ERPRA = effective refractory period of the right atrium; ERPRV = effective refractory period of the right ventricle; FRPAVN = functional refractory period of the AV node; HA' = interval from the His bundle deflection to the retrograde low atrial deflection recorded on the His bundle lead; PCL = pacing cycle length; RA = right atrium; SVT = supraventricular tachycardia; V = verapamil.

Verapamil and the SVT was terminated electrically. A single premature atrial stimulus initiated SVT in patients 1, 3 and 4, while patient 2 required two premature atrial stimuli. Patients 1 and 3 demonstrated AV nodal responses consistent with dual AV nodal pathways (fig. 1). For patients 1-4, during SVT, the AH interval was 313 ± 7 msec (mean ± SEM), the HA' interval was 36 ± 2 msec and the SVT cycle length was 350 ± 6 msec. Patient 4 also had a different SVT, originating in the high right atrium, that was consistent with sinus nodal reentry13-15 (fig. 2).

**FIGURE 1.** Patient 3. Initiation of supraventricular tachycardia in a patient with dual atrioventricular (AV) nodal pathways. Panels A and B show the last two paced beats (S1) of a train delivered to the coronary sinus at a pacing cycle length of 500 msec. The results of premature atrial stimulation at an S1S2 interval of 250 msec on two occasions are shown. (A) S2 was conducted to the ventricle with an AH interval of 170 msec. (B) S2 was conducted with an AH interval of 300 msec, followed by AV nodal reentry. In panel C, coronary sinus pacing at a constant cycle length (340 msec) resulted in a sudden increase in the AH interval from 155 to 305 msec, indicating antegrade block in the fast pathway. RA = right atrial electrogram; HBE = His bundle electrogram; CS = coronary sinus electrogram; I, II, III, V1 = scalar electrocardiographic leads.
After Verapamil Administration

Verapamil, 5 mg, terminated SVT in patients 2, 4 and 5, but only slowed the SVT (by 58 msec, mean) in patients 1, 3 and 6. Ten milligrams of verapamil terminated SVT in the latter three patients. The mean time from administration of effective verapamil dose to termination of SVT was 97 ± 12 seconds (for all six patients). The AH interval prolonged to 393 ± 16 msec just before termination and accounted for lengthening of SVT cycle length to 425 ± 20 msec, since the HV and the HA' intervals were unchanged. Patients 1, 3 and 4 had cycle length alternans before termination of SVT, caused by alternation in AH in-
tervals (fig. 3). SVT in each patient terminated during antegrade propagation, with block of the atrial depolarization proximal to the His bundle recording site in the AV node (fig. 3).

In patient 4, before verapamil administration, a second tachycardia that showed a sequence of atrial activation consistent with sinus nodal reentry was induced (fig. 2). In patients 2 and 4 after verapamil administration, sinus nodal reentry occurred after termination of the AV nodal reentrant SVT. This second type of tachycardia had cycle lengths of 320–380 msec before and 495 msec after verapamil administration in patient 4, and 360–380 msec after verapamil administration in patient 2. The sinus nodal reentrant SVT terminated abruptly and was replaced by sinus rhythm 5–10 minutes after the AV nodal reentrant SVT terminated.

Five to 10 minutes after verapamil administration, single premature atrial stimulation reinitiated SVT only in patients 3 and 4, and in patient 3 the echo zone was shifted rightward (table 3). Patient 2 still needed two premature atrial stimuli to induce SVT, although the required premature intervals were longer. Single premature ventricular stimulation started SVT in patient 1 after, but not before verapamil administration (fig. 4). The cycle length of the SVT was longer than control in all four patients (mean 410 ± 23 msec) after verapamil administration due to AH prolongation (369 ± 25 msec). HV and HA' intervals were unchanged.

Verapamil prolonged AV nodal conduction time determined during sinus rhythm or atrial pacing, increased the antegrade effective and functional AV nodal refractory periods and lengthened the shortest cycle length at which 1:1 AV propagation occurred. Retrograde VA intervals and effective refractory period of the AV node determined in two patients were unchanged, as was the shortest cycle length at which 1:1 VA propagation occurred (one patient) (table 3).

Group B — SVT Associated with Wolff-Parkinson-White Syndrome

Before Verapamil Administration

Four patients had left lateral accessory pathways that conducted bidirectionally and two patients had concealed left lateral accessory pathways. Patient 12 did not receive verapamil during the electrophysiologic study because she could not tolerate the SVT for the required 15-minute control period. She received verapamil later during a spontaneous episode.

The sequence of stimulation that induced SVT, echo zones and other electrophysiologic characteristics are summarized in table 4. A single premature right or left atrial stimulus induced SVT in patients 7, 8, 10 and 11, while two premature right atrial stimuli or premature ventricular stimulation were required in patient 9. During SVT, the AH interval was 153 ± 23 msec, the HA interval was 163 ± 15 msec, and the cycle length of the tachycardia was
316 ± 12 msec. In all patients, conduction during SVT proceeded antegradely in the normal pathway and retrogradely in the accessory pathway.

After Verapamil Administration

In the presence of verapamil (5 mg) the reentrant SVT terminated in three, slowed in two and was not altered in one patient. A dose of 10 mg terminated SVT in patient 9 but not in patients 7 and 11. Patient 11 developed atrial fibrillation during the study, refused electrical cardioversion and the effect of verapamil on his reentrant SVT was assessed during a subsequent spontaneous episode.

Patient 11 also received verapamil after he developed atrial fibrillation. The shortest RR interval before and after verapamil (5 mg) was 260 and 220 msec, respectively. Further, in the presence of verapamil, more ventricular beats were activated over the accessory pathway (fig. 5).

Time from administration of effective verapamil dose to termination of SVT in four patients was 108.8 ± 38 seconds. SVT in each of these patients terminated in the antegrade limb of the normal pathway, with block of the atrial impulse proximal to the His bundle recording site. The AH interval prolonged from 149 ± 29 msec before verapamil, to 193 ± 33 msec just before termination, and accounted for lengthening of the SVT because the HV and HA' intervals did not change.

Similar patterns of premature stimulation reinitiated SVT in patients 7, 9 and 10, 5-10 minutes after verapamil administration. Single premature ventricular stimulation initiated SVT in patient 8. The cycle length of SVT induced after verapamil administration was only 44 msec longer than the cycle length of the SVT preceding verapamil administration.

During sinus rhythm or atrial pacing after termination of SVT, the AH interval increased slightly in two patients, did not change in one patient and decreased slightly in one. Other measurements of AV nodal conduction showed minimal changes (table 4). Verapamil did not alter antegrade or retrograde conduction or refractoriness in the accessory pathway.

**Figure 4.** Patient 1. (A) Atrioventricular (AV) nodal reentry before and after verapamil administration. During induced supraventricular tachycardia (SVT) before verapamil administration, the AH interval was 330 msec and the HA' interval was 40 msec. (B) One and one-half minutes after verapamil administration the SVT cycle length increased 70 msec because of an increase in the AH interval; the SVT subsequently terminated. (C) The last paced beat (S1) of a train during ventricular pacing at a cycle length of 600 msec is displayed. Premature ventricular stimulation at an S1S2 interval of 310 msec reinitiated AV nodal reentrant tachycardia 5 minutes after verapamil administration. The HA' interval after premature ventricular stimulation and during tachycardia was still 40 msec, while the SVT cycle length increased to 90 msec because of AH prolongation. Abbreviations: see figure 1.
Table 4. Electrophysiologic Characteristics in Group B

<table>
<thead>
<tr>
<th>Pt.</th>
<th>PCL C</th>
<th>ERPR A C</th>
<th>ERPR V C</th>
<th>AH interval C</th>
<th>VA interval C</th>
<th>ERP A V N antegrade C</th>
<th>Shortest PCL with 1:1 AVN conduction C</th>
<th>ERP A P antegrade C</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>600</td>
<td>280</td>
<td>260</td>
<td>240</td>
<td>80</td>
<td>120</td>
<td>&lt;300</td>
<td>300</td>
</tr>
<tr>
<td>8</td>
<td>600</td>
<td>250</td>
<td>240</td>
<td>210</td>
<td>90</td>
<td>145</td>
<td>&lt;260</td>
<td>290</td>
</tr>
<tr>
<td>9</td>
<td>500</td>
<td>240</td>
<td>240</td>
<td>270</td>
<td>---</td>
<td>90</td>
<td>135</td>
<td>NM</td>
</tr>
<tr>
<td>10</td>
<td>600</td>
<td>200</td>
<td>190</td>
<td>230</td>
<td>80</td>
<td>125</td>
<td>250</td>
<td>320</td>
</tr>
<tr>
<td>11</td>
<td>500</td>
<td>170</td>
<td>*</td>
<td>*</td>
<td>90</td>
<td>*</td>
<td>180</td>
<td>&lt;220</td>
</tr>
</tbody>
</table>

Measurements are in milliseconds.
* Atrial fibrillation.
Abbreviations: AVN, C, ERP A V N, ERP R A, ERP V R, PCL, RA, SVT and V; see table 3; AP = accessory pathway; ERP A P = effective refractory period of the accessory pathway; HA' = interval from the His bundle deflection to the retrograde atrial deflection recorded on the His bundle lead; RV = right ventricle; WPW = Wolff-Parkinson-White syndrome; VA = interval from ventricular activation to earliest retrograde atrial activation; NM = not measurable.

Group C — Automatic Atrial Tachycardia

Before Verapamil Administration

Patient 14 had atrial tachycardia that was almost continuous, originating in the area of the lower right atrial septum, at a mean cycle length of 417 msec (fig. 6A). Patients 13 and 15 had recurrent intermittent atrial tachycardia originating in the high right atrium, but with a sequence of activation different from sinus rhythm. Cycle length for patient 13 varied from 545–375 msec, while patient 15 had a mean cycle length of 403 ± 14 msec. All patients had complete VA block during ventricular pacing.

After Verapamil Administration

All patients developed AV nodal Wenckebach block 1 minute after verapamil administration (fig. 6B–D), with no change in the cycle length of the atrial tachycardia.

![Figure 5](http://cirt.ahajournals.org/). Patient 11. Effect of verapamil on ventricular activation during atrial fibrillation. Tracings were recorded before and 3 and 10 minutes after verapamil administration. An increase in ventricular rate and an increased number of preexcited ventricular complexes occurred 3 minutes after verapamil administration; the effect diminished at 10 minutes.
Table 4. (Continued)

<table>
<thead>
<tr>
<th>ERPAP retrograde</th>
<th>Shortest PCL with 1:1 retrograde conduction (AP)</th>
<th>Echo zone SVT induced</th>
<th>Cycle length of SVT</th>
<th>AH during SVT</th>
<th>HV during SVT</th>
<th>HA' during SVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>V</td>
<td>C</td>
<td>V</td>
<td>C</td>
<td>V</td>
<td>C</td>
</tr>
<tr>
<td>250</td>
<td>255</td>
<td>300</td>
<td>—</td>
<td>RA 290–360</td>
<td>RA 270–310</td>
<td>RV 250</td>
</tr>
<tr>
<td>250</td>
<td>&lt;250</td>
<td>300</td>
<td>300</td>
<td>RA 260–270</td>
<td>RV 300</td>
<td>340</td>
</tr>
<tr>
<td>&lt;280</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>RA S250</td>
<td>RV 400</td>
<td>300</td>
</tr>
<tr>
<td>280</td>
<td>280</td>
<td>&lt;250</td>
<td>&lt;250</td>
<td>RA 270–305</td>
<td>RA 280–390</td>
<td>280</td>
</tr>
<tr>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>RA 180–220</td>
<td>*</td>
<td>340</td>
</tr>
</tbody>
</table>

Group D — Atrial Fibrillation And Atrial Flutter

Before Verapamil Administration

The ventricular rate in 12 patients with atrial fibrillation was 154.8 ± 6.5 beats/min and in two patients with atrial flutter was 175 ± 6.4 beats/min.

After Verapamil Administration

Verapamil reduced the mean ventricular rate in the patients with atrial fibrillation to 81.6% of the mean control rate (fig. 7) within 3 minutes of administration. In four patients, the ventricular rate continued to decrease until it was 77.4% of control 15 minutes after administration of verapamil. Over the next 15 minutes, the ventricular rate for the entire group began to increase slightly. One patient, who did not show significant slowing initially, developed a 5.5-second period of asystole 31 minutes after taking 5 mg of verapamil (fig. 8). In two patients sinus rhythm returned 2 and 5 hours, respectively, after drug administration.

Both patients with atrial flutter developed atrial fibrillation after i.v. verapamil. One patient initially increased the degree of AV block from 2:1 to 4:1 within 1 minute and converted to atrial fibrillation at 2
minutes. Sinus rhythm occurred transiently in this patient. However, premature atrial complexes reinitiated atrial flutter with 4:1 AV block. The second patient initially increased AV block from 2:1 to 3:1 then converted to atrial fibrillation.

Hemodynamic Changes

The hemodynamic effects after i.v. verapamil in 28 patients are summarized in table 5. The hemodynamic changes were transient in all patients and produced no symptoms.

Oral Verapamil (table 6)

Six patients in group A, four patients in group B, one patient in group C and eight patients in group D received verapamil orally. Two other patients with recurrent automatic atrial tachycardias that could not be initiated in the electrophysiology laboratory were administered oral verapamil but not i.v. verapamil. Ten patients discontinued the drug within the first 30 days of treatment (mean 10.4 days), four because of side effects and six because of ineffectiveness, defined as recurrence of tachycardia and/or incomplete control of the ventricular rate during atrial flutter/fibrillation. The most common early side effects were nausea, vomiting and light-headedness (four patients). Later side effects included constipation (three patients), ankle edema not associated with congestive heart failure (five patients) and postural hypotension (one patient). Constipation and ankle edema were generally mild and tolerated with the addition of a laxative or diuretic. Seven patients have been treated with verapamil for a mean of 19 ± 1.2 months with evidence of improvement, judged by decreased frequency and shorter duration of tachycardia when it

![Figure 7](image_url)

**Figure 7.** Response of atrial fibrillation after i.v. verapamil. The heart rate response in beats per minute (ordinate) is plotted against time in minutes (abscissa). Unbroken lines indicate response after bolus injection and dashed lines indicate i.v. infusion. The mean ventricular response was reduced to 81.6% of control rate at 3 minutes (p < 0.01). After maximal response the ventricular rate tends to increase slightly at 30 minutes.

![Figure 8](image_url)

**Figure 8.** Patient 27. Transient atioventricular block during atrial fibrillation after verapamil. The patient failed to demonstrate initial significant slowing of ventricular rate after 5 mg of verapamil; however, 31 minutes later he developed 5.5 seconds of asystole. The ventricular response before and after the pause is the same.
TABLE 5. Hemodynamic Effects of Intravenous Verapamil (Groups A, B, C and D)

<table>
<thead>
<tr>
<th></th>
<th>Lowest value within 10 minutes of administration</th>
<th>Significances of difference from control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure</td>
<td>92.2 ± 2.4</td>
<td>83.7 ± 1.7</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic pressure</td>
<td>120.3 ± 2.4</td>
<td>107.3 ± 2.2</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic pressure</td>
<td>77.7 ± 2.2</td>
<td>71.3 ± 1.5</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

TABLE 6. Long-term Treatment with Oral Verapamil

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Dose</th>
<th>Duration of therapy</th>
<th>Other medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>120 mg q 8 hr</td>
<td>20 mo</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>120 mg q 8 hr</td>
<td>23 mo</td>
<td>Digitoxin 0.1 mg qd</td>
</tr>
<tr>
<td>8</td>
<td>80 mg q 6 hr</td>
<td>14 mo</td>
<td>Digoxin 0.25 mg qd</td>
</tr>
<tr>
<td>9</td>
<td>120 mg q 8 hr</td>
<td>22 mo</td>
<td>Aprindine 60 mg q 8 hr</td>
</tr>
<tr>
<td>10</td>
<td>80 mg q 8 hr</td>
<td>16 mo</td>
<td>None</td>
</tr>
<tr>
<td>12</td>
<td>80 mg q 6 hr</td>
<td>21 mo</td>
<td>Quinidine 300 mg q 6 hr</td>
</tr>
<tr>
<td>24</td>
<td>80 mg 5 x daily</td>
<td>20 mo</td>
<td>Digoxin 0.25 mg qd</td>
</tr>
</tbody>
</table>

did recur. The mean daily dosage has been 330 ± 15 mg. Only two patients continue to receive verapamil as a single agent (table 6).

Discussion

Significance Of This Study

In this study, we have confirmed that verapamil slows the ventricular response during a variety of SVTs by lengthening AV nodal conduction time and antegrade AV nodal effective and functional refractory periods. By a similar mechanism, verapamil terminated reentrant SVTs that used the AV node as the antegrade limb of the tachycardia circuit. All SVTs that terminated did so with block of the antegrade impulse in the AV node. We have also found, as previously reported, that verapamil affected conduction and refractoriness only in the antegrade pathway used in patients with AV nodal reentrant SVTs, and that it exerted no significant effect on conduction and refractoriness of accessory pathways.

Finally, we showed that an occasional patient with atrial fibrillation developed sinus rhythm after verapamil administration, while both patients with atrial flutter developed transient atrial fibrillation.

New observations from this study include: (1) Verapamil appeared to terminate AV nodal reentry more successfully than sinoatrial nodal reentry; (2) verapamil lengthened antegrade conduction time in the AV node of patients with concealed or manifest WPW syndrome less than it did in patients with AV nodal reentry; (3) verapamil had no effect on the discharge rate of automatic atrial tachycardias; (4) verapamil increased the ventricular response during atrial fibrillation in a patient with WPW syndrome; and (5) verapamil was relatively ineffective when given orally as a single agent in either preventing recurrences or slowing the ventricular rate in patients with SVT.

Effects On AV Nodal Conduction

Existing experimental data suggest that cells in the AV node are slow-channel-dependent, and that AV nodal conduction can be slowed or blocked and refractoriness prolonged by agents that interfere with the slow inward current. Verapamil exerts such an action and is very effective, particularly when given intravenously, in terminating SVT or slowing the ventricular rate during atrial flutter or atrial fibrillation.

In this investigation, patients with a spectrum of SVTs were studied. In groups A and B, 10 of the 12 patients (83%) converted to normal sinus rhythm less than 2 minutes after 5 or 10 mg of i.v. verapamil. The remaining two patients demonstrated a prompt reduction in ventricular rate due to lengthening of antegrade AV nodal conduction time. The mechanism of termination of SVT in each patient was related to prolongation and eventual block of antegrade AV nodal conduction, without significant effect on retrograde conduction, either within the AV node (presumably) in group A patients, or in extranodal accessory pathways (group B patients). The AH prolongation in patients who had manifest or concealed WPW was less than that which occurred in patients with AV nodal reentry, though termination in group B patients resulted from antegrade conduction block in the AV node. AV nodal conduction in patients with manifest WPW may be more rapid, with shorter effective and functional refractory periods than in patients without WPW, and perhaps is more resistant to the effects of verapamil.

Several studies suggest that the retrograde limb of the reentrant pathway in some patients with AV nodal reentry has functional properties different from the antegrade pathway. The differential effect of verapamil on the antegrade vs the retrograde pathway confirms these observations and suggests that cells in the retrograde pathway in these patients either are less sensitive than cells in the antegrade pathway to slow-channel blockers or are not composed of fibers dependent on the slow inward current. A very short retrograde pathway composed of AV nodal tissue cannot be excluded. However, an “insulated cable” of AV nodal fibers does not seem likely because it would still be affected by i.v. verapamil. The location, morphologic and electrophysiologic definition of the pathway, possibly only functioning retrogradely, awaits further investigation.

A recent study evaluating the effects of verapamil in
dogs suggested that the drug exerted a greater effect on the AV node than it did on the sinoatrial node. Further, the effect of verapamil appears greatest in the upper segment of the AV junction. In man, verapamil administered intravenously (0.10 mg/kg) did not significantly change heart rate or sinoatrial node recovery time, suggesting no measurable effect on sinus node automaticity. At this dose, however, AV nodal conduction time increased as evidenced by PR prolongation. A dose (0.15 mg/kg) slightly but significantly slowed sinus node discharge rate. However, effects on AV nodal conduction were more pronounced. A dose of 0.20 mg/kg had a more pronounced effect on sinus nodal discharge rate and recovery time and produced advanced AV block. Thus, verapamil exerts a dose-related depressant effect on sinoatrial nodal discharge. The effect on the AV node occurred at lower doses.

The difference in sensitivity to verapamil between the sinoatrial and AV nodes may be more apparent than real. The hemodynamic changes during verapamil infusion would be expected to result in a withdrawal of vagal and increase in adrenergic tone. At rest, the influences of the autonomic nervous system are predominantly vagal on sinoatrial nodal automaticity but are more balanced regarding AV nodal conduction (unpublished observation). Thus, vagal withdrawal may mask the direct effects of verapamil on the sinoatrial node, as demonstrated by Breithardt et al.

One of our patients before verapamil administration and that patient plus another after verapamil administration, had a SVT probably caused by sinus nodal reentry. In both instances, this tachycardia persisted 5–10 minutes after verapamil had terminated the AV nodal reentrant tachycardia. It would appear that the sinoatrial nodal reentrant tachycardia resisted the suppressing effects of verapamil more than did the AV nodal reentrant tachycardia (see above). In fact, in patient 2, verapamil might have even caused the SVT by producing only partial conduction delay in the sinoatrial node. The lack of effect on SVT caused by sinoatrial nodal reentry could be related to the lower dose used.

Cycle length alternans during SVT must be due to alternation in the rate of discharge of an automatic focus, to alternation in the pathways or to alternation in conduction time in the pathway. Patients 1 and 3, who had a discontinuous AV nodal curve, and patient 4, who did not have a demonstrable dual AV nodal curve, developed cycle length alternans before termination of SVT caused by alternation in AH intervals. Such alternation is not uncommon after verapamil administration. Since the SVT was presumably due to AV nodal reentry, alternation can be explained by postulating the presence of three pathways — antegrade conduction alternating between a slow and a fast pathway, with constant retrograde conduction over a third pathway. However, unless many patients with AV nodal reentrant SVT have three or more pathways, the relatively frequent occurrence of cycle length alternans after verapamil administration suggests that the third explanation, that is, alternation in conduction time over only one pathway antegrade, is more likely. Why this occurs is unclear. It is important to note that VA conduction time remained fixed. Thus, the cycle with the shorter AH interval might allow the succeeding cycle insufficient time for complete recovery of AV nodal refractoriness, thereby prolonging the AH interval in the next cycle. The subsequent long AH interval might provide more time for complete recovery of AV nodal refractoriness and permit a shorter AH interval in the next cycle. Action potential duration and refractoriness of AV nodal cells lengthen with slow conduction, so this explanation may be too simplistic.

Effects On Automaticity

Recent animal experimental observations suggest that triggered sustained rhythmic activity (1) may be induced in a variety of atrial preparations; (2) may exhibit overdrive acceleration; (3) may be suppressed by verapamil; and (4) in some instances, may be slow-channel-dependent. However, verapamil did not affect the discharge rate or site of origin of the (presumed) automatic atrial tachycardia in the three patients we studied. The reduction in ventricular rate in these patients was due to an increase in AV nodal conduction time and refractoriness, resulting in a decreased ventricular response. It is possible that larger doses of verapamil might have suppressed the tachycardia. We found similar results (based on the scalar ECG) in two additional patients who were treated only with oral verapamil but did not have an electrophysiology study while on therapy. The atrial tachycardia in all three patients who were studied showed overdrive suppression, not acceleration, and did not appear to originate from the left atrium or coronary sinus. Earliest atrial activation during tachycardia was recorded in the lower right atrial septum in one patient and in the high right atrium in two patients. Thus, this study provides no evidence to suggest that these rhythms showed triggered activity or were caused by the slow inward current.

Effect In Atrial Flutter and Atrial Fibrillation

The consistent effect of verapamil in patients with atrial fibrillation was a prompt decrease in the ventricular response, usually lasting for at least 30 minutes. One patient who had a minimal decrease in ventricular response immediately after verapamil administration developed 5.5 seconds of ventricular asystole 31 minutes after a 10-mg bolus. We are not certain that this response can be attributed to verapamil. The patients with atrial flutter demonstrated an increase in AV block, followed by transient periods of atrial fibrillation. The development of atrial fibrillation in this fashion has been noted, though the mechanism is not clear. Verapamil reportedly converts to sinus rhythm approximately 30% of episodes of atrial flutter and 10% of episodes of
atrial fibrillation. In our series, three patients converted to sinus rhythm long after peak drug effect, raising questions regarding causality. However, it is not unreasonable to postulate that in some patients with atrial flutter or atrial fibrillation the slow response may play a role in the maintenance of the arrhythmia, and that verapamil could suppress the slow response and thus affect the tachyarrhythmia.

The increase in the ventricular rate during atrial fibrillation after verapamil administration in the patient with WPW syndrome may have several explanations. First, the rate increase was small and may have been spurious, as the recording time was relatively short. Assuming the change was real, it may have been secondary to sympathetic discharge in response to a blood pressure drop after i.v. verapamil, although the effects of sympathetic tone on accessory pathways are not well understood. Presumably, increased sympathetic tone would facilitate conduction over the AV node. Finally, verapamil, by blocking AV nodal conduction, may have prevented atrial fibrillation impulses traveling through the AV node from concealing retrogradely through the accessory pathway and keeping it partially refractory. This last mechanism could contribute to the increase in ventricular rate produced in some patients by digitalis.

Effect Of Oral Verapamil

Orally administered verapamil as a single drug was generally not effective in preventing recurrent episodes of SVT, atrial fibrillation or atrial flutter. Only one patient with SVT associated with type A WPW and one patient with AV nodal reentry use verapamil alone. Although verapamil alone may prevent recurrence of SVT in some patients with manifest or concealed WPW, oral effectiveness cannot be predicted from the response to i.v. administration.

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