Acceleration of the Ventricular Response During Atrial Fibrillation in the Wolff-Parkinson-White Syndrome After Verapamil

SAJAD GULAMHUSEIN, M.D., PATRICK KO, M.D., S. GEORGE CARRUTHERS, M.D., AND GEORGE J. KLEIN, M.D.

SUMMARY We examined the electrophysiologic effects of verapamil in eight patients with the Wolff-Parkinson-White syndrome. Verapamil shortened the antegrade effective refractory period of the accessory pathway in three patients and abbreviated the shortest cycle length with 1:1 conduction over the accessory pathway in two patients. More significantly, verapamil decreased the shortest RR interval between preexcited ventricular complexes during atrial fibrillation (279 ± 20 msec vs 236 ± 18 msec, mean ± SEM; p < 0.01). After verapamil, two patients required cardioversion for hemodynamic deterioration after acceleration of the ventricular response during atrial fibrillation. In the four patients with predominantly preexcited ventricular complexes during atrial fibrillation the ventricular rate accelerated after verapamil, whereas in patients with predominantly normal ventricular complexes, the average ventricular rate decreased or did not change after verapamil. Verapamil may result in significant acceleration of ventricular response during atrial fibrillation in the Wolff-Parkinson-White syndrome. The safety of verapamil in individual patients with the Wolff-Parkinson-White syndrome should be established by electrophysiologic testing before its use.

VERAPAMIL, a synthetic papaverine derivative, was initially introduced as a potent peripheral and coronary vasodilator. It was later found to have significant antiarrhythmic activity, the mechanism of which was related to selective inhibition of transmembrane fluxes of calcium. The main electrophysiologic effects of verapamil include slowing of conduction and prolongation of refractoriness in the atrioventricular node without significantly affecting intraatrial or intraventricular conduction. Thus, verapamil has been effective in the acute termination of reentrant tachycardia involving the atrioventricular node and slowing the ventricular response during atrial fibrillation or flutter in patients without preexcitation.

The effects of verapamil on accessory atrioventricular pathways in the Wolff-Parkinson-White syndrome are not well established. Although Spurrell et al. reported that verapamil has minimal effects, other investigators have suggested that verapamil may shorten refractoriness of the accessory pathway. We determined the effects of verapamil on the electrophysiologic properties of the accessory pathway in a series of patients with the Wolff-Parkinson-White syndrome.

Methods

Patient Population

The study population consisted of eight patients referred to University Hospital for the assessment of recurrent tachycardia (table 1). All had characteristic electrocardiographic features of the Wolff-Parkinson-White syndrome: PR interval of 0.12 msec or less, Δ wave and QRS duration of 0.10 msec or more. Seven patients had ECG-documented supraventricular tachycardia. One of these patients also had documented episodes of intermittent atrial fibrillation. One patient gave a history of recurrent short episodes of palpitation without electrocardiographic documentation.

### Electrophysiologic Studies

All patients underwent an electrophysiologic study in the nonsedated, postabsorptive state after they gave written, informed consent. Antiarrhythmic agents were discontinued at least 48 hours before the study. Four electrode catheters, three quadripolar and one tripolar, were introduced transvenously and positioned in each of the high right atrium, coronary sinus, right ventricular apex and across the septal leaflet of the tricuspid valve for His bundle recording. Intracardiac recordings were made simultaneously with leads I, II, III, V1, and V6 of the surface ECG on a 16-channel Elema Mingograph at a paper speed of 100 mm/sec. Programmed stimulation was carried out using a stimulator that delivered square-wave stimuli at one and one-half to two times diastolic threshold.

Standard methods for determination of atrioventricular conduction and refractoriness were used. If atrial fibrillation did not occur during the study, it was induced by rapid atrial pacing (cycle length 200–50 msec; pulse duration 2–4 msec; stimulus intensity two or three times threshold) and recorded for at least 2 minutes.

After determining baseline electrophysiologic measurements, verapamil, 0.15 mg/kg, was given as an i.v. bolus over 2 minutes, followed by a continuous infusion of verapamil at a rate of 0.005 mg/kg/min. The electrophysiologic study was then repeated.
TABLE 1. Clinical Summary

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Tachycardia diagnosis</th>
<th>Location of AP</th>
<th>Associated diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31</td>
<td>F</td>
<td>RT</td>
<td>Left lateral</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>44</td>
<td>M</td>
<td>RT</td>
<td>Left posterolateral</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
<td>M</td>
<td>RT</td>
<td>Right posterolateral</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>37</td>
<td>M</td>
<td>RT</td>
<td>Posteroseptal and left lateral</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>34</td>
<td>M</td>
<td>RT</td>
<td>Right posterolateral</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>21</td>
<td>M</td>
<td>Palpitations</td>
<td>Right posterolateral</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>27</td>
<td>F</td>
<td>RT</td>
<td>Right posterolateral</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>70</td>
<td>M</td>
<td>RT, AF</td>
<td>Left posterolateral</td>
<td>CAD</td>
</tr>
</tbody>
</table>

Abbreviations: AF = atrial fibrillation; AP = accessory pathway; CAD = coronary artery disease; RT = reciprocating tachycardia.

Definitions and Diagnostic Criteria

The antegrade effective refractory period of the accessory pathway was defined as the longest A1A2 interval that failed to conduct to the ventricle over the accessory pathway (A1 and A2 represent the atrial electromograms of the last drive beat and premature beat, respectively, measured at the atrial site closest to the accessory pathway).21-25

The retrograde effective refractory period of the accessory pathway was defined as the longest V1V2 interval that failed to conduct to the atrium over the accessory pathway, (V1V2 represents the ventricular electrogram of the last drive beat and premature beat, measured at the ventricular site closest to the accessory pathway).

Mean ventricular rate during atrial fibrillation was determined by averaging over 120 seconds. Percent preexcitation was the ratio of preexcited beats to the number of ventricular complexes during atrial fibrillation.

Participation of the accessory pathway in observed reciprocating tachycardia was determined by criteria described previously.24

Statistical Analysis

Intervals in atrial fibrillation and functional properties of the accessory pathway before and after verapamil were compared using the t test for paired data.

Results

Mechanism of Induced Arrhythmias

All patients had accessory atrioventricular pathways of the Kent type.26 One patient had two accessory pathways (table 1). Sustained reciprocating tachycardia could be reproducibly initiated by programmed stimulation in seven patients. In all instances, the atrioventricular node participated as the antegrade limb and the accessory pathway as the retrograde limb of the reentrant circuit.24

Atrial fibrillation was induced in all patients. In one patient atrial fibrillation was induced during atrial catheter manipulation. In the other seven, rapid atrial pacing was required. Spontaneous degeneration of reciprocating tachycardia to atrial fibrillation was observed in one patient. Atrial fibrillation terminated spontaneously in all patients before verapamil.

Effect of Verapamil on the Accessory Pathway

Functional properties of the accessory pathway could be determined in five of eight patients after verapamil infusion (table 2). The antegrade effective refractory period of the accessory pathway decreased in three patients and was unchanged in two (fig. 1A). The retrograde effective refractory period of the accessory pathway decreased in two patients, was unchanged in one patient and could not be determined in the rest (fig. 1B). Antegrade conduction over the accessory pathway was enhanced in two patients and was unchanged in three patients (fig. 1C). Retrograde conduction over the accessory pathway was enhanced in two patients and unchanged in three (fig. 1D).

The changes in these measurements for the group were not statistically significant.

Effect of Verapamil on Induced Arrhythmias

Verapamil terminated reciprocating tachycardia within 10 minutes in all patients with this arrhythmia. Tachycardia was terminated in all instances by development of block in the atrioventricular node.

After verapamil, atrial fibrillation was induced in two patients by a single atrial extrastimulus during antegrade refractory period determination. Rapid atrial pacing was required in the others. In contrast to the control study, atrial fibrillation remained sustained in four patients, requiring interventions for symptomatic or hemodynamic deterioration. Two patients required cardioversion and two were given additional antiarrhythmic drugs (disopyramide and procainamide).

The average ventricular response during atrial fibrillation increased in four patients after verapamil (table 3, fig. 2A). In these patients, the QRS morphology became predominantly preexcited and there was a 50 msec or greater decrease in the shortest RR interval between preexcited complexes.

Of the remaining four patients, verapamil slowed the average ventricular response in three and did not affect it in one patient (table 3). Slowing of the ven-
Table 2. Properties of the Accessory Pathway

<table>
<thead>
<tr>
<th>Pt</th>
<th>ERP of accessory pathway</th>
<th>Shortest PCL with 1:1 AP conduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antegrade</td>
<td>Retrograde</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>Verapamil</td>
</tr>
<tr>
<td>1</td>
<td>360</td>
<td>310</td>
</tr>
<tr>
<td>2</td>
<td>295</td>
<td>280</td>
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<tr>
<td>3†</td>
<td>276</td>
<td>—</td>
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<tr>
<td>4</td>
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<td>320</td>
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<tr>
<td>5</td>
<td>250</td>
<td>—</td>
</tr>
<tr>
<td>6†</td>
<td>&lt;270</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>260</td>
<td>260</td>
</tr>
<tr>
<td>8</td>
<td>280</td>
<td>223</td>
</tr>
</tbody>
</table>

Measurements are in milliseconds.
* Did not have any evidence of retrograde ventriculoatrial conduction.
† Developed rapid sustained atrial fibrillation.

Abbreviations: AP = accessory pathway; CNM = cannot measure; ERP = effective refractory period; PCL = pacing cycle length.

Table 3. Intervals During Atrial Fibrillation

<table>
<thead>
<tr>
<th>Shortest RR</th>
<th>Normal QRS</th>
<th>Preexcited QRS</th>
<th>Mean RR</th>
<th>% preexcited</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt</td>
<td>Control</td>
<td>Verapamil</td>
<td>Control</td>
<td>Verapamil</td>
</tr>
<tr>
<td>1</td>
<td>345</td>
<td>560</td>
<td>368</td>
<td>320</td>
</tr>
<tr>
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</tr>
<tr>
<td>7</td>
<td>—</td>
<td>—</td>
<td>215</td>
<td>168</td>
</tr>
<tr>
<td>8</td>
<td>335</td>
<td>—</td>
<td>270</td>
<td>210</td>
</tr>
</tbody>
</table>

All measurements are in milliseconds.
Figure 1. Functional properties of the accessory pathway. (A) Comparison of the antegrade effective refractory period (ERP) of the accessory pathway before and after verapamil. (B) Comparison of the retrograde ERP of the accessory pathway before and after verapamil. (C) Comparison of the shortest pacing sinus cycle length (SCL) sustaining 1:1 antegrade conduction over the accessory pathway before and after verapamil. (D) Comparison of the shortest SCL sustaining 1:1 retrograde conduction over the accessory pathway before and after verapamil.

Error bars indicate the SEM. The solid circles indicate that the data point was an exact determination and the open circles indicate that the determination was an estimate. Open squares indicate that the determination was an estimate. The corresponding data points between open circles and squares are not connected, as they do not represent exact determination.

who demonstrated slowing of the mean ventricular response and prolongation of the shortest RR interval between normally conducted beats after verapamil. However, it is unlikely that slowing of atrioventricular conduction is an important factor in patients who have a rapid ventricular response during atrial fibrillation with most complexes conducted over the accessory pathway.
Second, verapamil may shorten the refractory period of the accessory pathway directly. This hypothesis is less likely, as accessory pathways are generally composed histologically of myocardial cells and behave electrophysiologically like myocardium. Verapamil has not been shown to have any direct effect on the electrophysiologic properties of myocardial tissue.

Finally, verapamil may shorten the refractory period of the accessory pathway as a result of a reflex

**Figure 2.** Intervals in atrial fibrillation before and after verapamil infusion. (A) Comparison of the mean RR interval in atrial fibrillation. (B) Comparison of the shortest (S) RR interval between normally conducted beats in atrial fibrillation. After verapamil, the corresponding data point was not plotted in three patients as all beats became preexcited and two consecutive normally conducted beats were not observed. (C) Comparison of the shortest RR interval between preexcited beats in atrial fibrillation. Before verapamil, the corresponding data point in one patient was not plotted as most beats were normal and two consecutive preexcited beats were not observed. (D) Comparison of the percentage of preexcited (PRX) beats during atrial fibrillation before and after verapamil. Error bars represent 1 SEM.
increase in adrenergic tone brought about by its peripheral vasodilating effect. This hypothesis is supported by the uniform observation of a decrease in systolic blood pressure (5–10 mm Hg) after verapamil in our patients. Indeed, the change in the occurrence of nonsustained to sustained atrial fibrillation after verapamil in four of our patients could be a result of increased sympathetic tone.

Clinical Implications

Verapamil can cause hemodynamic deterioration because of an increase in ventricular response over the accessory pathway during atrial fibrillation in the Wolff-Parkinson-White syndrome. It should not be administered to slow ventricular response during atrial fibrillation when most QRS complexes are preexcited. Although verapamil is useful for terminating reciprocating tachycardia complicating the Wolff-Parkinson-White syndrome, close observation in a controlled environment is advisable because of the possible deterioration of reciprocating tachycardia to atrial fibrillation. Although these data cannot be extrapolated to chronic oral therapy with verapamil, patients with Wolff-Parkinson-White syndrome, given verapamil should have electrophysiologic assessment to establish the safety of this medication in case of atrial fibrillation.

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