Comparative Effects of Three Calcium Antagonists, Diltiazem, Verapamil and Nifedipine, on the Sinoatrial and Atrioventricular Nodes

Experimental and Clinical Studies

CHUICHI KAWAI, M.D., TOMOTSUGU KONISHI, M.D., EIICHI MATSUYAMA, M.D., AND HITOSHI OKAZAKI, M.D.

SUMMARY  Diltiazem, verapamil and nifedipine suppress sinoatrial (SA) nodal function in the excised rabbit heart. Clinically, however, their suppressive effect on the SA node is modified considerably by the reflex increase in sympathetic tone as a result of the fall in blood pressure caused by the vasodilating action of the calcium antagonists. Diltiazem, verapamil and nifedipine suppress atrioventricular (AV) nodal conduction and prolong refractory periods in the excised rabbit AV node. Clinically, diltiazem and verapamil exert a similar suppressive effect on the AV node and are useful for treating and preventing AV nodal reentrant tachycardia. Nifedipine, in clinically practical doses, has no antiarrhythmic properties, probably because of reflex activation of the sympathetic system secondary to its hypotensive effect, which is greater than that of the other two calcium antagonists. Diltiazem and verapamil may sometimes worsen AV conduction, especially in patients with conduction disturbances. Nifedipine, on the other hand, can be used as a coronary vasodilator with the least untoward effect on AV conduction.

THE CELLS of the sinoatrial (SA) and atrioventricular (AV) nodes show no evidence of a fast component. The entire action potential appears to result from a slow inward current. Recent investigations have suggested that the calcium-antagonistic properties of some coronary therapeutic agents might also contribute to their antiarrhythmic effects by inhibiting slow inward currents. The antiarrhythmic effects of verapamil have been reported, but nifedipine appears to have no antiarrhythmic effect despite its high activity in antagonizing the effect of calcium ions. Diltiazem, also a potent coronary vasodilator, suppresses epinephrine- and ouabain-induced arrhythmias in guinea pigs. However, very few systematic comparative studies have reported the effect of these three calcium antagonists on the SA and AV nodes. In this report we present experimental and clinical studies of the effects of diltiazem, verapamil and nifedipine on the SA and AV nodes.

Methods

Experimental Setup

Under pentobarbital anesthesia (30 mg/kg) and artificial respiration, the rabbit right atrium was excised and cut into two portions: preparation 1, with the SA node and the crista terminalis, and preparation 2, with the crista terminalis, the interatrial septum, the AV node and the His bundle (fig. 1). Forty-seven rabbits were used for preparation 1 and 12 for preparation 2. The experimental setup has been partly described. The tissues were superfused in Tyrode solution equilibrated with 95% O₂ and 5% CO₂. The
1. Experimental preparations in excised rabbit right atrium. (1) Sinoatrial node (dotted area) and crista terminalis (CT). (2) Atrioventricular node (designated as 1.) and His bundle (designated as 2.) App = appendage; SVC = superior vena cava; IVC = inferior vena cava; IAS = interatrial septum; CS = coronary sinus; AO = aorta; PA = pulmonary artery; TV = tricuspid valve. Reprinted with permission of Excerpta Medica from New Drug Therapy with a Calcium Antagonist.

Temperature was maintained at 34.0 ± 1.0°C. Transmembrane resting and action potentials were recorded with glass microelectrodes with resistances of 10–20 MΩ from the cells in preparation 1 and from those in preparation 2 (fig. 1).

The recording equipment consisted of a preamplifier (WPI model 750), a cathode-ray oscilloscope (Nihonkohden VC-9) and a photographic recorder (San-ei Co.). The recordings were taken at a paper speed of 25 mm/sec for preparation 1 and 200 mm/sec for preparation 2. For the intracellular recording from the crista terminalis, a close bipolar surface lead was sometimes used in place of intracellular recordings using two silver wire electrodes with a 1-mm interelectrode distance and a differential preamplifier (WPI DAM-5A). The preparations were driven with rectangular pulses of twice-diastolic-threshold voltage and 1-msec duration, generated by an electronic stimulator (Nihonkohden MSE-40) and applied with an isolation transformer and platinum wire electrodes. The modes of stimulation were: 30-second overdrive from the crista terminalis at a rate of 120–240 beats/min for determining sinus recovery time (SRT), and one premature stimulus (Sₙ) with varied coupling intervals in every eighth basic stimulus (Sₙ) from the atrial site to determine refractory periods of the AV node.

SRT was the time interval between upstrokes of the last stimulated and the first recovering spontaneous action potentials. SRT was the maximum time interval among three trials of overdrive at each rate, ranging from 120–240 beats/min, with increments of 30 beats/min and expressed in percentage of spontaneous cycle length (table 1).

In the measurements of effective and functional refractory periods (ERP and FRP), the basic cycle length (Sₙ–Sₙ) was set as 400 or 500 msec, long enough to dominate over the automaticity of the preparation.

### Table 1. Effects of Diltiazem, Verapamil and Nifedipine in Different Concentrations on the Sinoatrial Node in the Rabbit

<table>
<thead>
<tr>
<th>Concentration (g/ml)</th>
<th>No. of experiments</th>
<th>Average sinus slowing (%) (mean ± sd)</th>
<th>No. of experiments</th>
<th>Control (mean ± sd)</th>
<th>After (mean ± sd)</th>
<th>%SRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diltiazem</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 × 10⁻⁷</td>
<td>6</td>
<td>12.0 ± 4.9</td>
<td>3</td>
<td>114.0 ± 7.0</td>
<td>187.8 ± 48.6</td>
<td>†</td>
</tr>
<tr>
<td>5 × 10⁻⁷</td>
<td>3</td>
<td>37.0 ± 5.3</td>
<td>*</td>
<td>125.0 ± 6.0</td>
<td>284.4 ± 25.7</td>
<td></td>
</tr>
<tr>
<td>1 × 10⁻⁶</td>
<td>6</td>
<td>46.8 ± 13.9</td>
<td></td>
<td>116.0 ± 2.8</td>
<td>&gt; 500§</td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 × 10⁻⁷</td>
<td>4</td>
<td>13.0 ± 8.7</td>
<td>3</td>
<td>124.4 ± 0.6</td>
<td>229.6 ± 70.0</td>
<td>†</td>
</tr>
<tr>
<td>5 × 10⁻⁷</td>
<td>9</td>
<td>20.3 ± 10.5</td>
<td>*</td>
<td>126.6 ± 4.8</td>
<td>325.0 ± 35.5</td>
<td></td>
</tr>
<tr>
<td>2 × 10⁻⁶</td>
<td>9</td>
<td>57.5 ± 24.8</td>
<td></td>
<td>118.3 ± 4.8</td>
<td>&gt; 500§</td>
<td></td>
</tr>
<tr>
<td>Nifedipine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 × 10⁻⁷</td>
<td>3</td>
<td>8.0 ± 2.0</td>
<td>3</td>
<td>117.3 ± 9.5</td>
<td>173.7 ± 27.1</td>
<td>†</td>
</tr>
<tr>
<td>5 × 10⁻⁷</td>
<td>3</td>
<td>25.7 ± 7.1</td>
<td>*</td>
<td>118.3 ± 8.4</td>
<td>269.1 ± 30.0</td>
<td></td>
</tr>
<tr>
<td>1 × 10⁻⁶</td>
<td>4</td>
<td>55.0 ± 6.6</td>
<td></td>
<td>117.0 ± 1.4</td>
<td>&gt; 500**</td>
<td></td>
</tr>
</tbody>
</table>

Analysis of variance:

* *p < 0.01.
† †p < 0.001.

Complete arrest in:

† seven experiments.
§ one experiment.
‖ two experiments.
** one experiment.

Abbreviations: %SRT = sinus node recovery time expressed in percentage of spontaneous cycle length.
The coupling interval \((S_1-S_2)\) was decreased by 10-msec steps from the basic cycle length until AV conduction block occurred. Then the ERP was sought from the last conducted \(S_1\), decreasing the coupling interval by 1 msec. All measurements were repeated 15 minutes after the addition of diltiazem, verapamil or nifedipine.

Patients

Each patient gave written consent to the study. During diagnostic cardiac catheterization and/or His bundle study in 31 patients (16 with secundum atrial septal defect, 12 with preexcitation syndrome, two with paroxysmal supraventricular tachycardia and one with accelerated idioventricular rhythm), the SRT was measured after 30-second overdrive at a rate that induced the longest SRT, ranging from 100-150 per minute, and ERP and FRP were measured by the extrastimulus method. The modes of stimulation were the same as for the isolated rabbit heart experiments except for the use of quadripolar electrode catheters (Elecath, #6F) and an electronic stimulator (ME 537V, Metro Electric Co.). High right atrial and His bundle electrograms, together with standard electrocardiographic leads (I, aVF, V1) were displayed and recorded at a paper speed of 100 mm/sec (Electronics for Medicine, VR-12). The measurements were repeated after i.v. administration of 10-20 mg of diltiazem in 10 patients, 10 mg of verapamil in 13, and 1 mg of nifedipine in eight. Each dose was injected over 3 minutes. The AH and the HV intervals and the minimal right atrial pacing rate to produce AH Wenckebach block were also measured before and after administration of the calcium antagonists. The serum concentration of diltiazem was determined in venous blood obtained from the antecubital vein opposite that of the injection site in seven patients. It was also determined in two patients who were taking oral medication who were not studied electrophysiologically.

The \(t\) test was used to assess the statistical significance in both experimental and clinical studies. The statistical significance of changes was tested by analysis of variance according to Newman-Keuls’ multiple comparison.

Results

Effect on the SA Node

After 3 minutes a solution of \(2 \times 10^{-6}\) g/ml, diltiazem suppressed the frequency of spontaneous firing, the amplitude and the rate of rise of the action potential and the slope of diastolic depolarization in the excised rabbit SA node preparation. After 4 minutes, intermittent sinus arrest or intra-SA nodal block developed (fig. 2). There was no essential change in the resting potentials. Verapamil and nifedipine had similar effects on the SA nodal action potential. The number of experiments, average sinus rate slowing and rate of prolongation of SRT (expressed as percent of basic cycle length) before and after diltiazem, verapamil and nifedipine in different concentrations are shown in table 1. The effects of these agents are dose-dependent. Changes of the average sinus rate slowing \((p < 0.01)\) and rate of prolongation (%SRT) \((p < 0.001)\) with different concentrations of each drug are statistically significant. At the same concentration there was no significant difference among the three agents. A representative example of prolongation of the SRT after nifedipine is shown in figure 3.

In clinical cases, however, diltiazem, verapamil and nifedipine tended to increase the sinus rate and shorten the SRT (table 2). Among these variables, the increase in the sinus rate \((p < 0.05)\) and the shortening of the SRT \((p < 0.01)\) by nifedipine were statistically significant. The following differences were statistically significant: changes in the sinus rate, diltiazem vs nifedipine \((p < 0.005)\), verapamil vs nifedipine \((p < 0.05)\); in the SRT, diltiazem vs nifedipine \((p < 0.05)\), verapamil vs nifedipine \((p < 0.05)\); and in the systolic blood pressure, diltiazem vs nifedipine \((p < 0.01)\), verapamil vs nifedipine \((p < 0.05)\).

Effect on the AV Node

In the excised rabbit AV nodal preparation, electrically stimulated at a basic cycle length of 400 msec,
nifedipine 10^{-7} g/ml 15min.

FIGURE 3. Effect of nifedipine on sinus recovery time (SRT) in an excised rabbit sinoatrial (SA) nodal preparation. Overdrive stimulation at a rate of 180 beats/min was given to the crista terminalis (CT) for 30 seconds. The SRT of 110% basic cycle length in controls was prolonged to 180% after addition of nifedipine in a concentration of 10^{-7} g/ml. The overdrive tests were repeated by moving the position of the exploring (SA) electrode in an area of 2 × 5 mm. No full-sized action potentials are recorded between the last driven beat and the first recovery beat that precedes the CT firing. Thus, the presence of intra-SA block during the prolonged recovery period was almost ruled out. Voltage calibration on the right end is 50 mV.

Table 2. Effects of Diltiazem, Verapamil and Nifedipine on the Sinus Rate, Sinus Node Recovery Time and Blood Pressure in Clinical Cases

<table>
<thead>
<tr>
<th></th>
<th>Age (years)</th>
<th>Sex (M/F)</th>
<th>Sinus rate (beats/min)</th>
<th>SRT (msec)</th>
<th>Syst blood pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>C</td>
<td>A</td>
<td>C</td>
</tr>
<tr>
<td>Diltiazem (n = 10)</td>
<td>21.6</td>
<td>8/2</td>
<td>83.0</td>
<td>84.5</td>
<td>1067</td>
</tr>
<tr>
<td>± SD</td>
<td>±14.4</td>
<td>±12.1</td>
<td>±283</td>
<td>±248</td>
<td>±12</td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Verapamil (n = 13)</td>
<td>33.1</td>
<td>8/5</td>
<td>81.2</td>
<td>88.4</td>
<td>1113</td>
</tr>
<tr>
<td>± SD</td>
<td>±14.8</td>
<td>±15.9</td>
<td>±165</td>
<td>±291</td>
<td>±16</td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Nifedipine (n = 8)</td>
<td>30.5</td>
<td>3/5</td>
<td>78.0</td>
<td>98.4</td>
<td>1331</td>
</tr>
<tr>
<td>± SD</td>
<td>±17.4</td>
<td>±23.5</td>
<td>±393</td>
<td>±379</td>
<td>±16</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Significance of change (analysis of variance):
*p < 0.05.
†p < 0.01.
‡p < 0.005.
Abbreviations: SRT = sinus node recovery time; C = control; A = after drug administration.
(table 5, fig. 6). The HV interval was unchanged after the administration of calcium antagonists.

Diltiazem or verapamil prolonged the ERP and FRP of the AV node; nifedipine shortened the ERP and FRP (table 5, fig. 7).

**Discussion**

Since Kohlhordt et al. demonstrated that slow ionic currents are blocked by verapamil and compound D600, the suppressive effects of verapamil on the electrical activity in the SA and AV nodes have been reported by Zipes and Fischer, Wit and Cranefield, and Okada and Konishi. The present study demonstrates that diltiazem, verapamil and nifedipine exert similar suppressive effects on the SA nodal action potentials in the excised rabbit atrium.

The finding that the effects were dose-related is consistent with previous reports. These calcium antagonists, in identical concentrations, equally prolonged the SRT of the SA node cells.

The effects of diltiazem, verapamil and nifedipine on the sinus rate and the SRT in clinical cases are different from those in excised rabbit SA node preparations. The tendency toward an increase in the sinus rate and a shortening of the SRT is most prominent with nifedipine, which has the greatest hypotensive effect among the three calcium antagonists. Only one-tenth as much nifedipine can be tolerated clinically because of this hypotensive action. It is assumed that the effects of diltiazem, verapamil and nifedipine on the human SA node in situ are modified by reflex activation of the sympathetic tone secondary to their different degrees of hypotensive effect. This hypothesis is supported by Breithardt et al. demonstrating prolongation of sinus node spontaneous cycle

**Table 3. Effects of Diltiazem, Verapamil and Nifedipine on Effective and Functional Refractory Periods of the Atrioventricular Node in the Rabbit**

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of experiments</th>
<th>Control ERP (msec)</th>
<th>After ERP (msec)</th>
<th>Control FRP (msec)</th>
<th>After FRP (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diltiazem</td>
<td>4</td>
<td>106</td>
<td>161</td>
<td>209</td>
<td>243</td>
</tr>
<tr>
<td></td>
<td>± 8</td>
<td>±15</td>
<td>±37</td>
<td>±28</td>
<td>±28</td>
</tr>
<tr>
<td></td>
<td><em>p</em></td>
<td>&lt; 0.05</td>
<td>&lt; 0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td>4</td>
<td>125</td>
<td>224</td>
<td>232</td>
<td>313</td>
</tr>
<tr>
<td></td>
<td>± 8</td>
<td>±47</td>
<td>±76</td>
<td>±12</td>
<td>±46</td>
</tr>
<tr>
<td></td>
<td><em>p</em></td>
<td>&lt; 0.01</td>
<td>&lt; 0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nifedipine</td>
<td>4</td>
<td>99</td>
<td>152</td>
<td>198</td>
<td>244</td>
</tr>
<tr>
<td></td>
<td>± 8</td>
<td>±19</td>
<td>±17</td>
<td>±10</td>
<td>±14</td>
</tr>
<tr>
<td></td>
<td><em>p</em></td>
<td>&lt; 0.01</td>
<td>&lt; 0.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ERP = effective refractory period; FRP = functional refractory period; AVN = atrioventricular node.

**Table 4. Plasma Concentration of Diltiazem in Clinical Cases**

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Dose (mg)</th>
<th>Plasma level (g/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KO</td>
<td>15</td>
<td>M</td>
<td>20 l.v.</td>
<td>1.13 × 10⁻⁵</td>
</tr>
<tr>
<td>YS</td>
<td>19</td>
<td>F</td>
<td>19</td>
<td>2.03 × 10⁻⁴</td>
</tr>
<tr>
<td>MI</td>
<td>36</td>
<td>M</td>
<td>20</td>
<td>1.25 × 10⁻⁴</td>
</tr>
<tr>
<td>TO</td>
<td>41</td>
<td>M</td>
<td>10</td>
<td>3.30 × 10⁻⁷</td>
</tr>
<tr>
<td>MN</td>
<td>15</td>
<td>M</td>
<td>10</td>
<td>1.68 × 10⁻⁷</td>
</tr>
<tr>
<td>HI</td>
<td>16</td>
<td>M</td>
<td>10</td>
<td>8.20 × 10⁻⁸</td>
</tr>
<tr>
<td>HN</td>
<td>17</td>
<td>M</td>
<td>10</td>
<td>5.10 × 10⁻⁸</td>
</tr>
<tr>
<td>SM</td>
<td>63</td>
<td>M</td>
<td>60 p.o.</td>
<td>1.10 × 10⁻⁸</td>
</tr>
<tr>
<td>TU</td>
<td>70</td>
<td>M</td>
<td>30</td>
<td>6.20 × 10⁻⁸</td>
</tr>
</tbody>
</table>
length and recovery time when autonomic blockers are given before verapamil. As a result, the calcium antagonists may not suppress the SA node clinically as much as they do in the excised rabbit SA node preparation. However, in patients with sick sinus syndrome, calcium antagonists may cause prolonged sinus arrest or SA block due to the original suppressive effects on the SA node in the absence of proper response of the sick sinus node to the hypotension induced by these agents.\(^\text{14}\)

Verapamil in a concentration of \(5 \times 10^{-7}\) g/ml suppressed the spontaneous firing rate of the AV nodal action potential, and in a concentration of \(2 \times 10^{-4}\) g/ml it reduced the overshoot markedly without significantly reducing the maximum diastolic potential.\(^\text{12}\) Raschack demonstrated that both verapamil and nifedipine cause a dose-dependent prolongation of FRP in the isolated left atrium of the guinea pig and of ERP of the AV node in the rabbit.\(^\text{11}\) Verapamil also depressed AV nodal conduction in the dog.\(^\text{8}\) The present study provides direct evidence that diltiazem, verapamil and nifedipine in identical concentrations prolonged ERP and FRP of the AV node equally in the isolated right atrium.

Diltiazem and verapamil suppress AV nodal conduction in the human as well as in the excised rabbit AV nodal preparation.

The action of nifedipine on AV conduction in clinical cases is different from that of diltiazem and verapamil. Nifedipine appears to facilitate rather than

---

**Table 5. Effects of Diltiazem, Verapamil and Nifedipine on Atrioventricular Conduction, and Effective and Functional Refractory Periods of the Atrioventricular Node in Clinical Cases**

<table>
<thead>
<tr>
<th></th>
<th>Diltiazem (n = 10)</th>
<th>Verapamil (n = 13)</th>
<th>Nifedipine (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(C) - (A)</td>
<td>(C) - (A)</td>
<td>(C) - (A)</td>
<td>(C) - (A)</td>
</tr>
<tr>
<td>AH (msec)</td>
<td>80 - 97</td>
<td>90 - 114</td>
<td>92 - 88</td>
</tr>
<tr>
<td>(\pm SD)</td>
<td>(\pm 26)</td>
<td>(\pm 27)</td>
<td>(\pm 12)</td>
</tr>
<tr>
<td>(p)</td>
<td>(&lt; 0.01)</td>
<td>(&lt; 0.01)</td>
<td>(&lt; 0.05)</td>
</tr>
<tr>
<td>AH block (beats/min)</td>
<td>154.4 - 137.3</td>
<td>142.8 - 121.9</td>
<td>129.2 - 139.5</td>
</tr>
<tr>
<td>(\pm SD)</td>
<td>(\pm 19.5)</td>
<td>(\pm 7.6)</td>
<td>(\pm 25.6)</td>
</tr>
<tr>
<td>(p)</td>
<td>(&lt; 0.01)</td>
<td>(&lt; 0.05)</td>
<td>(&lt; 0.05)</td>
</tr>
<tr>
<td>IV (msec)</td>
<td>47 - 47</td>
<td>42 - 42</td>
<td>44 - 44</td>
</tr>
<tr>
<td>(\pm SD)</td>
<td>(\pm 5)</td>
<td>(\pm 6)</td>
<td>(\pm 5)</td>
</tr>
<tr>
<td>(p)</td>
<td>(\text{NS})</td>
<td>(\text{NS})</td>
<td>(&lt; 0.05)</td>
</tr>
<tr>
<td>ERP(_{AVN}) (msec)</td>
<td>297 - 361</td>
<td>287 - 388</td>
<td>409 - 449</td>
</tr>
<tr>
<td>(\pm SD)</td>
<td>(\pm 45)</td>
<td>(\pm 36)</td>
<td>(\pm 41)</td>
</tr>
<tr>
<td>(p)</td>
<td>(&lt; 0.05)</td>
<td>(&lt; 0.05)</td>
<td>(&lt; 0.05)</td>
</tr>
<tr>
<td>FRP(_{AVN}) (msec)</td>
<td>409 - 449</td>
<td>417 - 466</td>
<td>480 - 417</td>
</tr>
<tr>
<td>(\pm SD)</td>
<td>(\pm 41)</td>
<td>(\pm 52)</td>
<td>(\pm 50)</td>
</tr>
<tr>
<td>(p)</td>
<td>(&lt; 0.05)</td>
<td>(&lt; 0.05)</td>
<td>(&lt; 0.05)</td>
</tr>
</tbody>
</table>

**Abbreviations:** RAP = right atrial pacing; ERP = effective refractory period; FRP = functional refractory period; AVN = atrioventricular node; \(C\) = control; \(A\) = after drug administration.
suppress AV conduction. The direct suppressive effect of nifedipine on AV nodal conduction seems weak because of low dose (one-tenth that of diltiazem or verapamil) and is overcome by a reflex increase in sympathetic tone as the result of a fall in blood pressure. Nifedipine seems to be a more potent hypotensive agent than diltiazem or verapamil, so should also induce a more pronounced reflex activation in the sympathetic system. The increase in sympathetic tone after nifedipine was confirmed by the increase in plasma norepinephrine concentration determined by the method of high-performance liquid chromatography in our laboratory. The results were partly reported in a preliminary paper (The Fourth International Adalat symposium in Paris, October 1979). These clinical findings are consistent with those of experiments in open-chest dogs by Taira et al.\textsuperscript{17}

Nifedipine, therefore, can be used as a coronary vasodilator with the least untoward effects on AV conduction.

The difference of response between the SA and AV nodes to the hypotensive effect of these calcium antagonists is probably because the nodes have a different sensitivity to reflex release of sympathetic transmitters.

Verapamil has been reported to be highly effective in the treatment of paroxysmal supraventricular tachycardia,\textsuperscript{18} and more recently of hypertrophic cardiomyopathy.\textsuperscript{19, 20} Beneficial effects of diltiazem on reentrant tachycardia involving AV conduction have also been reported.\textsuperscript{21} Our experience supports these results. However, besides their antiarrhythmic effects, diltiazem and verapamil suppress AV conduction and therefore aggravate AV block; thus, caution should be
used when these agents are considered for patients
with ischemic heart disease associated with latent or
manifest AV block of any degree.
Nifedipine does not have the antiarrhythmic
properties of diltiazem and verapamil. The beneficial
effect on arrhythmia secondary to improved
coronary perfusion, however, is beyond the scope of the present
study.

Acknowledgment

We thank Eisai Pharmaceutical Company, Tanabe Seiyaku
Company and Bayer Yakuhin Company for supplying us with
verapamil, diltiazem and nifedipine, respectively. The authors are
also indebted to Dr. Alice S. Cary for pertinent advice on the
manuscript and Dr. T. Sukurai for statistical analysis.

References

1. Cranefield PF: The conduction of the cardiac impulse. The slow
response and cardiac arrhythmias. Mt Kisco, NY, Futura
Publishing, 1975, p 97
2. Cranefield PF, Aronson RS, Wit AL: Effect of verapamil on the
normal action potential and on a calcium-dependent slow
response of canine cardiac Purkinje fibers. Circ Res 34: 204,
1974
3. Zipes DP, Fischer JC: Effect of agents which inhibit the slow
channel on sinus node automaticity and atrioventricular con-
duction in the dog. Circ Res 34: 184, 1974
4. Raschack M: Differences in the cardiac actions of the calcium
antagonists. Verapamil and nifedipine. Arzneim Forsch 26:
1330, 1976
5. Kawai C, Konishi T, Matsuyama E, Okazaki H: Effect of
nifedipine on atrioventricular (A-V) conduction. Clinical and
experimental studies. In International Adalat Panel Discussion,
edited by Lichtlen PR, Kimura E, Taira N. Amsterdam, Ex-
cepta Medica, 1979, p 7
6. Fleckenstein A, Trithart H, Doring HJ, Byron KY: Bay a 1040
— ein hochaktiver Ca**-antagonistischer Inhibitor der elektro-
mechanischen Koppelungsprozesse im Warmbluter-Myokard.
Arzneim Forsch 22: 22, 1972
7. Yamada K, Shimamura T, Nakajima H: Studies on a new 1,5-
benzothiazepine derivative (CRD-401) V. Antiarrhythmic ac-
8. Kawai C, Konishi T, Matsuyama E, Okazaki H: Effects of
diltiazem on sinoatrial and atrioventricular nodes in com-
parison with other calcium-antagonists. In New Drug Therapy
with a Calcium Antagonist. Diltiazem Hakone Symposium ’78,
edited by Bing RJ. Amsterdam, Excerpta Medica, 1979, p 141
9. Matsuyama E, Konishi T, Okazaki H, Matsuda H, Kawai C:
Effects of verapamil on accessory pathway properties and in-
duction of circus movement tachycardia in patients with the
Wolff-Parkinson-White syndrome. J Cardiovasc Pharmacol 3:
11, 1981
of the transmembrane Na and Ca channels in mammalian
cardiac fibers by the use of specific inhibitors. Pfluegers Arch
335: 309, 1972
11. Wit AL, Cranefield PF: Effect of verapamil on the sinoatrial
and atrioventricular nodes of the rabbit and the mechanism by
which it arrests reentrant atrioventricular nodal tachycardia.
Circ Res 35: 413, 1974
12. Okada T, Konishi T: Effects of verapamil on SA and AV nodal
action potentials in the isolated rabbit heart. Jpn Circ J 39: 913,
1975
13. Breithardt G, Seipel L, Wiebringhaus E: Dual effect of
verapamil on sinus node function in man. In The Sinus Node.
Structure, Function and Clinical Relevance, edited by Bonke
FIM. The Hague, Martinus Nijhoff Medical Division, 1978, p
129
verapamil on sinus node in patients with normal and abnormal
sinus node function. Circulation 54 (suppl III): II-19, 1976
for the determination of picogram amounts of norepinephrine
and epinephrine by high-performance liquid chromatography.
J Chromatogr 177: 376, 1979
16. Yui Y, Fujita T, Yamamoto T, Itokawa Y, Kawai C: Deter-
mination of norepinephrine and epinephrine in human plasma
by high-performance liquid chromatography. Clin Chem 26:
194, 1980
pharmacological investigations of effects of nifedipine on atrio-
ventricular conduction in comparison with those of other cor-
ory vasodilators. In 2nd International Adalat Symposium,
edited by Lochner W, Braasch W, Kroneberg G. Berlin,
Springer-Verlag, 1975, p 40
18. Schamroth L, Kriikler DM, Garrett C: Immediate effects of in-
travenous verapamil in cardiac arrhythmias. Br Med J 1: 660,
1972
19. Rosing DR, Kent KM, Jeffrey JS, Seides SF, Maron BJ, Ep-
stein SE: Verapamil therapy: a new approach to the pharma-
dynamic treatment of hypertrophic cardiomyopathy. 1. Hemo-
dynamic effects. Circulation 60: 1201, 1979
20. Rosing DR, Kent KM, Maron BJ, Epstein SE: Verapamil
therapy: a new approach to the pharmacologic treatment of
hypertrophic cardiomyopathy. II. Effects on exercise capacity
and symptomatic status. Circulation 60: 1208, 1979
21. Wakasa Y, Ikeda T, Oshiro Y, Numa T, Sugimoto T: Bene-
ficial effects of diltiazem on re-entrant tachycardia involv-
ing A-V conduction. Proceedings VIth World Symposium Car-
diac Pacing, Montreal, 1979
Comparative effects of three calcium antagonists, diltiazem, verapamil and nifedipine, on the sinoatrial and atrioventricular nodes. Experimental and clinical studies.
C Kawai, T Konishi, E Matsuyama and H Okazaki

Circulation. 1981;63:1035-1042
doi: 10.1161/01.CIR.63.5.1035

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/63/5/1035

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/