Electrophysiologic and Hemodynamic Effects of Verapamil

Correlation with Plasma Drug Concentrations

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SUMMARY Verapamil was administered intravenously to 30 open-chest dogs and the electrophysiologic and hemodynamic effects of the drug were correlated with the corresponding plasma concentrations. At concentrations below 152 ng/ml, verapamil prolonged the A-H interval, abolished ventriculoatrial conduction, but did not significantly change sinus rate, cardiac output, left ventricular dp/dt, or systemic vascular resistance. Concentrations above 200 ng/ml were associated with slowing of the sinus rate, high degree atrioventricular block during atrial pacing, 24% decrease in mean aortic pressure, and decreased cardiac output and left ventricular dp/dt. Sinus arrest, high degree atrioventricular block during sinus rhythm, decreased systemic vascular resistance and increased left ventricular end-diastolic pressure occurred when plasma verapamil concentrations exceeded 400 ng/ml. These results show that plasma verapamil concentrations reliably reflect the electrophysiologic and hemodynamic actions of the drug, and that "therapeutic" drug effects can be achieved at plasma concentrations at which myocardial depressant effects are unlikely.

VERAPAMIL has been widely used to convert supraventricular tachycardia to sinus rhythm and to slow the ventricular rate in atrial flutter or atrial fibrillation.6-8 Electrophysiologic studies have shown that verapamil inhibits the ionic current carried through the slow channel by Ca++ and/or Na+ ions.6,9 This slow inward current plays a major role in the formation and propagation of impulses within the sinoatrial (SA) and atrioventricular (A-V) nodes. The therapeutic efficacy of verapamil in supraventricular tachycardia, atrial flutter, and atrial fibrillation is attributed to its effects on conduction and refractoriness within the A-V node.9-12 Clinical studies have established that the drug prolongs the A-H and P-R intervals, and occasionally causes higher degree A-V block, sinus bradycardia and asystole.10,13-17 Other actions of verapamil related to inhibition to Ca++ influx into the cell may interfere with excitation-contraction coupling in myocardium18 and vascular smooth muscle.19 This may explain depressed contractility and decreased peripheral vascular resistance.

Verapamil administration to both healthy subjects and patients with heart disease usually decreases systemic blood pressure without significant changes in pulmonary arterial pressure and cardiac output.14,21,22 In some patients verapamil lowered cardiac output, decreased left ventricular dp/dt, and increased left ventricular end-diastolic pressure.14,22 The significance of these observations is difficult to evaluate because the salutary and toxic effects of verapamil have not been correlated with plasma concentrations of the drug.

This study was designed to evaluate the potential usefulness of plasma verapamil concentration measurements in the treatment of arrhythmias. We have studied the correlation of a wide range of plasma verapamil concentrations with hemodynamic and electrophysiologic effects of the drug in dogs. Our study shows that changes in the A-V nodal conduction and refractoriness can be obtained at plasma drug concentrations below those concentrations associated with depression of cardiac output, decreased left ventricular dp/dt, and development of sinus bradycardia or high degree A-V block.

Materials and Methods

We studied 30 mongrel dogs (16-18 kg) anesthetized with intravenous sodium pentothal (30 mg/kg), mechanically ventilated through endotracheal tubes with an air-oxygen mixture. The adequacy of ventilation was monitored by determinations of arterial pH, pCO2, and pO2 at 30 min intervals. A right thoracotomy was performed through the fourth intercostal space and the heart was suspended in a pericardial cradle.

A micromanometer-tipped catheter (Millar Instruments, Inc.) was introduced into the left ventricle through a stab wound at its apex, and secured with a purse-string suture. A collar-type flow probe (Zepeda) was fitted around the ascending aorta and connected to an electromagnetic flowmeter (Benton Instrument Co.). The pulsatile flow signal was calibrated against cardiac output measured by the Fick or by the dilution method. A 7 French end-hole catheter was placed into the descending aorta via a femoral artery, and a balloon-tipped catheter was introduced into the pulmonary artery through a jugular vein.

Lead II of the electrocardiogram (ECG) was recorded with needle electrodes. A 5 French His bundle bipolar electrode (USCI), introduced via the right carotid artery, was positioned within the posterior sinus of Valsalva. Hemodynamic and electrophysiologic data were displayed and recorded on photographic paper moving at 100 mm/sec on a multichannel light beam recorder (Electronics for Medicine, Inc., Model DR8). Filter settings between 40-500 Hz were employed for the recording of His bundle electrograms.
Verapamil, supplied as pure powder (Knoll Pharmaceutical Co.), was diluted in sterile saline to a final concentration of 3 mg base/ml, and the solution prepared for intravenous use by passage through a 0.45 μ filter. Using the previously established elimination kinetics of verapamil in dogs,23 we designed regimens consisting of a loading dose followed by an infusion at a constant rate to produce a range of effective but nonlethal plasma drug concentrations.24

Verapamil was given according to one of the following four schedules: 1) 1.5 mg bolus followed by infusion at 0.03 mg/min; 2) 3.0-4.2 mg bolus followed by infusion at 0.06 mg/min; 3) 7.0-8.5 mg bolus followed by infusion at 0.15 mg/min; and 4) 14.0-21.5 mg bolus followed by infusion at 0.33 mg/min. Each bolus was administered at a rate of 3 mg/min, since faster rates of administration may produce second or third degree A-V block,23 and each infusion was continued for at least 20 minutes. Six animals received the drug beginning with schedule 1, followed by schedule 2, and subsequently by schedule 3; 16 received the drug beginning with schedule 2, followed by schedule 3, six the same sequence followed by schedule 4; and two received the drug only according to schedule 3.

Experimental Protocol

The measurements of aortic blood flow velocity, left ventricular dp/dt, left ventricular end-diastolic pressure, mean aortic pressure, pulmonary artery pressure, and A-H interval were expressed as an average value from 5 beats recorded during atrial pacing at a constant rate. Systemic and pulmonary vascular resistances were expressed in arbitrary units. Driving stimuli were delivered by a stimulator (Grass Instrument Co., Model S4GR), as rectangular pulses of 1.5-2.0 msec duration and 1.5 times diastolic-threshold strength, through bipolar plunge wire electrodes, inserted into one or more of the following sites: the superior vena cava-right atrial junction, His bundle, and right ventricular wall. His bundle pacing was used when second or third degree A-V block appeared. His bundle pacing was considered successful when both the configuration and the duration of the QRS complexes in the paced complexes were the same as in those recorded during sinus rhythm, or right atrial pacing.25 In all experiments in which the heart was paced, the rate was kept constant, and the driving rate was the slowest required to suppress the spontaneous rhythm, usually about 2.5 Hz.

Intra-atrial conduction time was measured as the interval between the atrial stimulus artifact (S) and the end of the A wave on the His bundle electrogram record. Sinoatrial node recovery time was defined as the longest interval from the last pacing artifact to the first spontaneous P wave after atrial pacing for periods of one minute, at rates increasing by 10 beats/minute up to 30 to 50 beats/minute above the pre-pacing rate.24 Corrected sinus recovery time was defined as SA node recovery time minus the P-P interval before pacing.

Atrial and A-V nodal refractory periods were measured using premature atrial beats (A₁) induced at progressively earlier intervals, following every eighth driven atrial beat (A₉). The effective atrial refractory period was defined as the longest S₁S₂ interval at which S₂ failed to elicit a P wave. The effective refractory period of the A-V node was defined as the longest A₁A₂ interval at which A₂ failed to elicit an H spike. The functional refractory period of the A-V node was defined as the shortest H₁H₂ that resulted from any A₁A₂ interval. Atrioventricular nodal anterograde and retrograde conductions were evaluated by pacing the atrium, His bundle, or ventricle at incrementally faster rates until second degree A-V block occurred.

Blood samples for measurement of plasma verapamil concentrations were drawn before and at the end of each verapamil schedule, while simultaneous hemodynamic and electrophysiologic data were recorded. Plasma verapamil concentrations were measured by a method previously reported.27 In three experiments verapamil doses were higher than those in schedule 4 in order to produce plasma concentrations within the 1000-2000 ng/ml range. The data

Table 1. Electrophysiologic and Hemodynamic Effects of Verapamil

<table>
<thead>
<tr>
<th>Study Variable</th>
<th>Control (N = 30)</th>
<th>Low (N = 15)</th>
<th>Intermediate (N = 14)</th>
<th>High (N = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous P-P interval (msec)</td>
<td>397.5 ± 13.2</td>
<td>441.7 ± 17.3</td>
<td>554.3 ± 23.0**</td>
<td>655.7 ± 63.2**</td>
</tr>
<tr>
<td>Sinus arrest (%) experiments</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>33.3</td>
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<tr>
<td>A-H interval (msec)</td>
<td>64.8 ± 2.1</td>
<td>94.4 ± 5.4*</td>
<td>135.8 ± 12.1*</td>
<td>—</td>
</tr>
<tr>
<td>2° or 3° A-V block during sinus rhythm (%) experiments</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>50.0</td>
</tr>
<tr>
<td>2° or 3° A-V block during atrial pacing (%) experiments</td>
<td>0</td>
<td>0</td>
<td>57.1</td>
<td>100.0</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>2.86 ± 0.14</td>
<td>2.78 ± 0.12</td>
<td>2.49 ± 0.12****</td>
<td>2.15 ± 0.22***</td>
</tr>
<tr>
<td>Left ventricular dp/dt (mm Hg/sec)</td>
<td>1967.1 ± 64.7</td>
<td>1874.7 ± 59.2</td>
<td>1616.8 ± 61.9**</td>
<td>1167.5 ± 119.0**</td>
</tr>
<tr>
<td>Left ventricular end-diastolic pressure (mm Hg)</td>
<td>7.4 ± 0.6</td>
<td>6.8 ± 0.7</td>
<td>7.6 ± 0.7</td>
<td>12.9 ± 1.7****</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>99.1 ± 2.8</td>
<td>87.2 ± 2.3***</td>
<td>85.8 ± 4.9***</td>
<td>51.2 ± 5.5**</td>
</tr>
<tr>
<td>Systemic vascular resistance (Units)</td>
<td>38.9 ± 2.2</td>
<td>34.7 ± 2.8</td>
<td>34.7 ± 2.0</td>
<td>24.1 ± 1.4****</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure (mm Hg)</td>
<td>14.7 ± 0.7</td>
<td>13.3 ± 0.5</td>
<td>14.6 ± 0.8</td>
<td>13.2 ± 1.0</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (units)</td>
<td>5.2 ± 0.4</td>
<td>4.9 ± 0.3</td>
<td>5.9 ± 0.4</td>
<td>6.3 ± 0.4</td>
</tr>
</tbody>
</table>

*p < 0.001.

**p < 0.005.

***p < 0.01.

****p < 0.001.

1Low = 92.2 ± 9.0 (range, 25-152); Intermediate = 262.0 ± 14.7 (200-377); High = 843.0 ± 208.8 (400-2040). N = number of experiments.
were analyzed using Student's paired t-test and linear regression by the least squares method.

**Results**

**Plasma Verapamil Concentrations**

Plasma drug concentrations measured correlated with dosage of the drug ($r = 0.967$).

This report analyzes the data from 35 experiments in which hemodynamic and electrophysiologic measurements were made simultaneously and correlated with plasma verapamil concentrations (table 1). The results of experiments in which only part of the data was obtained corroborated the results of complete studies, but were not included in the statistical analysis. To facilitate the analysis of the results, plasma verapamil concentrations were divided arbitrarily into three groups: low (25-152 ng/ml), intermediate (200-377 ng/ml) and high (400-2040 ng/ml). Low concentrations resulted from the administration of schedules one and two, intermediate from schedules two and three, and high concentrations from schedules three and four.

**Electrophysiologic Effects**

*Spontaneous Sinus Rate, Corrected SA Node Recovery Time, Effective Atrial Refractory Period, and Intra-Atrial Conduction Time*

The heart rate decreased progressively with increasing plasma verapamil concentration. The average spontaneous P-P interval increased 11.4% at low, 29.6% at intermediate, and 71.6% at high plasma verapamil concentrations. Table 1 shows that the decrease in spontaneous rate was significant only at intermediate and high plasma verapamil concentrations. Sinus arrest did not occur at low and intermediate plasma concentrations but occurred in two of six experiments at high concentrations.

At intermediate and high concentrations, SA node recovery time lengthened progressively with increasing plasma verapamil concentration but this was due to prolongation of P-P interval, because the corrected sinus recovery time (42.9 ± 21.7 msec) did not change significantly at any plasma verapamil concentration. Verapamil caused no significant changes in atrial effective refractory period and intra-atrial conduction time at any plasma concentration.

**A-H Interval, A-V Nodal Functional and Effective Refractory Periods, Anterograde and Retrograde A-V Nodal Conductions**

During atrial pacing, the A-H interval increased significantly at both low and intermediate plasma verapamil concentrations. The average increase at low concentrations was 46.8% and at intermediate concentrations 93.8%. The A-H interval increased progressively with increasing plasma verapamil concentrations ($r = 0.775$) (fig. 1).

During sinus rhythm, second or third degree A-V block occurred in 50% of experiments at high plasma verapamil concentrations, but not at low or intermediate concentrations. During atrial pacing, second or third degree A-V block occurred in 57.1% of experiments at intermediate concentrations, and in all experiments at high concentrations (table 1).

Verapamil increased the functional and the effective refractory periods of the A-V node in all experiments at all drug concentrations. Both increased with increasing drug concentration (fig. 2).

Anterograde and retrograde A-V nodal conduction were compared in seven experiments in which the atria and the ventricles were paced at increasing rates until the onset of conduction block. Before verapamil administration, Wenckebach type V-A block occurred at slower pacing rates...
than Wenckebach type A-V block in all experiments (table 2). At low plasma verapamil concentrations, retrograde A-V nodal conduction was abolished, while 1:1 antegrade conduction was maintained (table 2). Figure 3 shows an example of this phenomenon at plasma verapamil concentration 142 ng/ml during ventricular pacing. Verapamil increased the A-H interval from 65 to 105 msec (A, C) and suppressed retrograde conduction (B, D). His bundle pacing in six dogs failed to restore retrograde conduction to the atria; this suggests that the site of verapamil-induced V-A block was the A-V node.

A-V Nodal Re-entry

Before verapamil administration, premature atrial and ventricular stimuli during atrial and ventricular pacing at various rates induced A-V nodal re-entrant complexes in seven dogs. This phenomenon could not be reproduced in these animals at low plasma verapamil concentrations (fig. 4). Figure 4a shows retrograde VA conduction before verapamil administration, and an A-V nodal re-entrant complex following a ventricular stimulus V₂ delivered 170 msec after V₁; figure 4b shows that retrograde conduction and re-entrant complexes did not occur at a plasma verapamil concentration of 49 ng/ml.

QRS Duration, Q-T and H-V Intervals

QRS duration, Q-T and H-V intervals did not change significantly at any plasma verapamil concentration.

Hemodynamic Effects

Cardiac Output

The average cardiac output did not change significantly in 15 dogs at low plasma verapamil concentrations (table 1). In two of these dogs cardiac output increased by less than 10%, and in the remaining dogs decreased by less than 10%, or did not change. However, the average cardiac output decreased significantly by 10.4% at intermediate, and by 19.8% at high plasma concentrations (table 1).

Left Ventricular dp/dt

The average left ventricular peak dp/dt did not change significantly at low plasma verapamil concentrations, but decreased significantly by 17.2% at intermediate and by 36.3% at high concentrations (table 1). Decreased left ventricular peak dp/dt correlated with plasma verapamil concentrations (r = 0.884) (fig. 5).

Left Ventricular End-Diastolic Pressure

Left ventricular end-diastolic pressure increased significantly by an average of 61.1% at high plasma verapamil concentrations, but did not change significantly at low and intermediate concentrations (table 1).

Systemic and Pulmonary Artery Pressures and Vascular Resistances

The decrease in mean aortic pressure averaged 11.6% at low, 19.8% at intermediate, and 43.7% at high plasma verapamil concentrations. Systemic vascular resistance

| Table 2. Effect of Low Verapamil Concentration on Onsets of Atrioventricular and Ventriculoatrial Block |
|---|---|---|
| Dog | Control* | After Verapamil* | Plasma Verapamil Concentration (ng/ml) |
| 1 | AV < 300 VA = 340 | AV = 400 No VA | 152 |
| 2 | AV = 180 VA = 275 | AV = 300 No VA | 49 |
| 3 | AV = 165 VA = 240 | AV = 290 No VA | 64 |
| 4 | AV = 180 VA = 275 | AV = 270 No VA | 70 |
| 5 | AV = 190 VA = 250 | AV = 280 No VA | 26 |
| 6 | AV < 200 VA = 260 | AV = 250 No VA | 25 |
| 7 | AV = 180 VA = 260 | AV = 380 No VA | 142 |

AV = Atrioventricular. VA = Ventriculoatrial. * = Longest S-S interval at which 2° block occurred.

FIGURE 3. Retrograde A-V nodal block induced by low concentrations of verapamil. Electrocardiogram (ECG) and His bundle electrogram (HE) were recorded during atrial (A, C) and ventricular (B, D) pacing. In A, control: A-H interval was 65 msec during atrial pacing (cycle length = 460 msec). In B, ventricular pacing (cycle length = 460 msec) resulted in 1:1 retrograde conduction and the stimulus-low atrium interval (S-Ar) was 115 msec. In C and D, at plasma verapamil concentration (V) of 142 ng/ml, A-H interval increased to 105 msec, while retrograde V-A conduction was abolished.
from the low level of verapamil binding to plasma proteins, which makes the majority of the drug in plasma available for interaction with active receptor sites.

The assay for measurement of plasma verapamil concentrations used in this study was the previously reported fluorometric technique. Although this method may measure both parent drug and one or more major metabolites, the close correlation between drug effects and plasma concentrations suggests that the "fluorescent verapamil" includes the pharmacologically active compounds. Previous studies have raised the possibility that metabolites could contribute to the action of the drug. None of the previous studies reported correlations between the concentrations and the effects of the drug.

Electrophysiologic Effects of Verapamil

In agreement with previous studies, verapamil slowed the rate of the SA pacemaker, prolonged A-V nodal conduction, increased the durations of the effective and functional refractory periods of the A-V node, but did not change intra-atrial conduction time, and the durations of the QRS, H-V, and Q-T intervals. Although Angus et al. have shown that the prolongation of P-R interval by verapamil in anesthetized dogs was due in part to cholinergic stimulation, and in part to a direct depression of atrioventricular conduction. Our study was not designed to measure the possible contribution of the cholinergic stimulation to the observed effects on the function of S-A and A-V nodes.

We have shown that in dogs sinus rate did not change significantly at plasma concentrations less than 152 ng/ml, and sinus arrest occurred only when plasma verapamil concentrations exceeded 400 ng/ml. In man, severe bradycardia and asystole have been reported following intravenous administration of verapamil. But in these reports verapamil was given as a relatively rapid intravenous injection, and some patients were receiving other drugs that might have contributed to sinus bradycardia, e.g., digitalis or beta-blocking agents.

In our study, no significant prolongation of corrected...
sinus recovery time occurred at any plasma verapamil concentrations. A recent clinical study reported that verapamil prolonged sinus recovery time in patients with “sick sinus syndrome” but not in persons with normal SA node function.22

The therapeutic efficacy of verapamil in terminating supraventricular re-entrant tachycardia has been well documented.4, 5, 13 The mechanism of verapamil action on A-V nodal re-entry was studied in tissues isolated from rabbit hearts.15 In this preparation, the prevention of A-V nodal re-entry by verapamil was attributed to complete anterograde block of premature impulses within the A-V node due to critical prolongation of refractory period.11 In our study, suppression of re-entry after verapamil administration occurred at the time when premature atrial impulses were still conducted through the A-V node, and the duration of the A-H intervals of these premature impulses was within the range of A-H intervals in premature complexes which had initiated re-entrant complexes before verapamil administration. This suggests that the absence of re-entry after atrial premature impulses in verapamil-treated dogs was caused by suppression of retrograde V-A conduction rather than anterograde A-V block.

In our experiments, verapamil consistently suppressed retrograde conduction through the A-V node while anterograde conduction was maintained. This phenomenon may represent a specific verapamil effect or a nonspecific manifestation of relative weakness of the retrograde V-A conduction. Our results before administration of verapamil confirm those of Damato et al.16 that in dogs V-A conduction time exceeds A-V conduction time, and that the site of retrograde delay and block is the A-V node.14

Our results suggest that the A-V node is more sensitive to verapamil than the SA node because at plasma verapamil concentrations below 152 ng/ml A-V nodal conduction was prolonged, but the sinus rate was unchanged. At concentrations within the 200–377 ng/ml range, the A-H interval was prolonged by an average of 93.8% while sinus rate slowed by an average of 29.6%.

Hemodynamic Effects

In vitro, verapamil depresses myocardial contractility.27, 30, 36 However, clinical studies have shown variable hemodynamic effects depending on the type of patient, the drug dose, and the rapidity of drug administration.14, 15, 21 The direct action of verapamil on arterial smooth muscle19, 21 may reduce “afterload.” This effect, combined with tachycardia induced by sympathetic stimulation,29 may prevent depression of cardiac output in patients given verapamil. We maintained heart rate constant but the cardiac output did not decrease when plasma verapamil concentrations were below 152 ng/ml. At these concentrations left ventricular peak dp/dt, a more sensitive and less afterload-dependent indicator of left ventricular function,48 also remained unchanged.

Our results are in partial agreement with the results of Angus et al.20 who studied the hemodynamic effects of rapid bolus injections of verapamil, and evaluated the role of the sympathetic nervous system in modifying these effects in anesthetized dogs. They found that low doses of verapamil decreased peripheral vascular resistance, lowered blood pressure, increased heart rate, contractility and cardiac output due to a sympathetic reflex. In our study, low doses of verapamil caused a slight decrease in systemic blood pressure but no significant change in the peripheral vascular resistance, or cardiac output. The difference between our results and those of Angus et al. may be due to different experimental conditions (spontaneous rate vs constant rate maintained by pacing), or differences in the administered verapamil doses. At the higher verapamil doses, Angus et al. reported direct myocardial depressant effect of verapamil.29

Clinical Implications

Our study has confirmed and extended the results of McAllister et al.28 who found a linear correlation between plasma verapamil concentrations and the duration of P-R interval in the surface ECG. In the present study, plasma verapamil concentrations reflected other electrophysiologic effects such as A-H intervals at constant heart rates, severity of A-V block, and sinus rate, and also hemodynamic effects of the drug. The efficacy of verapamil in treatment of supraventricular arrhythmias is attributed to the prolongation of A-V nodal conduction and increase in A-V nodal refractory period.4, 12 Therefore, the effect of verapamil on the A-H interval may be of greatest clinical significance. Although in our study both A-H prolongation and decrease in left ventricular dp/dt were linearly related to plasma verapamil concentrations, the two correlations differed in their slopes and intercepts (figs. 1 and 5), i.e., marked lengthening of A-H interval could be achieved at plasma drug concentrations which produced negligible effects on left ventricular peak dp/dt.

We have found no overlap between potentially therapeutic and potentially toxic plasma verapamil concentrations in the anesthetized dogs. However, additional controlled studies in man will be needed to confirm the clinical applicability of our animal model.

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