Near-total Reduction in Verapamil Bioavailability by Rifampin*

**Electrocardiographic Correlates**


We evaluated the significance of the interaction between rifampin and verapamil in six volunteers who received single doses of verapamil, 10 mg intravenously (IV), then 120 mg orally two days later. Subjects were then given rifampin, 600 mg orally every day for 15 days. After 13 and 15 days of rifampin therapy, the IV and oral doses of verapamil were repeated. Electrocardiograms (ECG) were done and serum verapamil and norverapamil concentrations measured before and for 12 h after each dose. For IV verapamil, there was a small decrease in area under the serum concentration-time curve and an increase in clearance after rifampin therapy (p<0.05). There were no changes in elimination half-life, volume of distribution, or AUC for percentage of change in P–R interval-time curve.

Rifampin is one of the drugs of choice for combination chemotherapy for pulmonary tuberculosis and is considered a first-line agent in the treatment of a variety of mycobacterial diseases. Verapamil is commonly prescribed for the treatment and prophylaxis of supraventricular tachyarrhythmias, chronic stable angina, coronary artery spasm, and hypertension. In addition, it is useful for migraine headaches, Raynaud's phenomenon, esophageal spasm, hypertrophic cardiomyopathy, and asthma. Therefore, it is likely that some patients with pulmonary tuberculosis will require treatment with verapamil for a concurrent illness.

Recently we observed a patient with supraventricular tachycardia receiving rifampin for pulmonary tuberculosis who responded to intravenous (IV) bolus and continuous infusion verapamil but experienced recurrent SVT when given oral verapamil despite doses of 1,920 mg/day. Serum verapamil concentrations during the oral regimen were surprisingly low, considering the doses administered. Discontinuation of rifampin therapy resulted in a significant rise in verapamil concentrations and subsequent control of SVT. This observation has been supported by other reports.

Rifampin is a potent inducer of hepatic microsomal enzymes and enhances the metabolism of many drugs. Not all drugs that are oxidized in the liver are predictably affected, however, as the enzyme induction is apparently selective. Further, the effect of rifampin on a high extraction drug such as verapamil has not been fully characterized. To determine whether rifampin consistently alters verapamil pharmacokinetics and to characterize the extent of the interaction, we examined the effect of rifampin on the serum concentrations of verapamil and its cardiovascular effect, employing evaluation of the P–R interval of the surface ECG.

**MATERIAL AND METHODS**

**Subjects**

Six healthy volunteers (four men, two women), 24 to 37 years old, were studied. All were in excellent health with normal cardiac, renal, and hepatic function judging from results of physical examination, 12-lead ECG, and routine laboratory tests. All subjects were nonsmokers, drank alcohol only occasionally, and did not receive medications for at least two weeks before the study. They were asked to abstain totally from alcohol and drugs other than verapamil and rifampin during the investigation. The study was approved by the Institutional Review Board of the University of Illinois at Chicago. All subjects gave written informed consent.

**Procedures**

Following an overnight fast, each volunteer received a single IV dose of verapamil, 10 mg infused over ten minutes through an antecubital vein. Venous blood samples were taken through an indwelling cannula in the contralateral forearm before the infusion.
and at 10, 20, 30, 45, 60, and 90 minutes and 2, 3, 4, 6, 8, 10, and 12 h after the infusion was started. Blood samples were centrifuged and the serum separated and stored at −20°C until assayed. Rhythm strips from lead 2 of the ECG were recorded at the time each blood sample was taken.

Two days later, a single oral dose of verapamil, 120 mg, was given to each subject. Blood samples were obtained and ECG rhythm strips recorded as in the IV study. After the 12-h blood sample was obtained, the subjects started receiving rifampin, 600 mg by mouth every night for 15 days. After 13 and 15 days of rifampin therapy, the IV and oral studies of verapamil were repeated. The serum concentrations of verapamil and its major active metabolite, norverapamil, were determined by a modification of the high performance liquid chromatographic method of Harapat and Kates. The sensitivity of this assay was 1.5 ng/ml, with an intraassay variation of 5 percent for verapamil and 8 percent for norverapamil and an interday variation of 7 percent for verapamil and 8 percent for norverapamil. As minimal amounts of norverapamil were observed following IV verapamil administration, serum norverapamil concentrations were quantified only following oral verapamil administration.

**Data Analysis**

Initial estimates of the IV pharmacokinetic parameters were obtained with BSTRIP (Micromath Inc). These initial estimates were then used to generate a best fit of the data using a two- and three-compartment open infusion model by nonlinear iterative least squares regression. Visual inspection of the fitted curves, analysis of the residual plots, and a model-discriminating F ratio test were used to select the appropriate pharmacokinetic model. A weighting factor of 1/y² was used in fitting the data. Area under the serum concentration-time curve (AUC), systemic clearance, volume of distribution at steady state, and elimination half-life (T½) were calculated following IV verapamil before and after rifampin treatment using standard compartmental pharmacokinetic equations.

The AUCs following the single oral verapamil doses before and after rifampin treatment were determined using the trapezoidal method with extrapolation to infinity. The elimination rate constant (ke) was calculated by nonlinear least squares regression of the terminal data points. The T½ was then calculated by 0.693/ke. The maximum verapamil serum concentration (Cmax) and time to maximum serum concentration (Tmax) following oral administration were obtained from visual inspection of the individual AUCs. Oral bioavailability was calculated from the ratio of oral to IV AUC adjusted for the dose difference. The AUCs and T½ for norverapamil were calculated as above.

The cardiovascular effects of verapamil were evaluated by assessing changes in P–R interval over time. To determine the mean P–R interval at each time point, a minimum of ten consecutive cardiac cycles were measured from the ECG rhythm strips. The area under the percentage of change in P–R interval-time curve (AUCn) was calculated using the trapezoidal method.

Statistical differences in the various pharmacokinetic and pharmacodynamic parameters between the two study periods (before and after rifampin treatment) were evaluated by Student's two-tailed t test for paired data. A p value < 0.05 was considered significant.

**RESULTS**

**Pharmacokinetic Effects**

For IV verapamil, the serum drug concentration vs time curves were similar before and after treatment with rifampin (Fig 1). The verapamil serum concentrations after the IV dose were best described by a two-compartment model. A small (18 percent) but statistically significant decrease in mean AUC (p<0.05) and a corresponding increase in mean C1 (p<0.05) were observed after rifampin therapy (Table 1). There were

![Graph](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21585/)
Table 1—Effects of Rifampin on the Disposition of Intravenous Verapamil in Six Healthy Volunteers*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before Rifampin</th>
<th>After Rifampin</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elimination T1/2, h</td>
<td>5.0 ± 1.6</td>
<td>4.1 ± 0.85</td>
<td>NS</td>
</tr>
<tr>
<td>Cl, ml/min</td>
<td>991.0 ± 185.4</td>
<td>1228.2 ± 267.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Vss, L</td>
<td>315.4 ± 79.7</td>
<td>290.3 ± 44.8</td>
<td>NS</td>
</tr>
<tr>
<td>AUC-verapamil, ng - h/ml</td>
<td>173.7 ± 29.5</td>
<td>142.2 ± 30.4</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

*Values expressed as mean ± SD. T1/2, half-life; Cl, clearance; Vss, distribution volume at steady state; AUC, serum concentration-time curve.
†NS = not significant.

no significant changes in the Vss or T1/2.

For oral verapamil, a 93 percent reduction in mean verapamil AUC (p<0.005), 85 percent reduction in mean norverapamil AUC (p<0.005), 92 percent reduction in mean bioavailability (p<0.005), and a 96 percent reduction in mean Cmax (p<0.005) were observed after rifampin treatment (Table 2 and Fig 2). The norverapamil to verapamil AUC ratio increased (p<0.01) by 62 percent after rifampin administration. No significant changes in verapamil T1/2 or Tmax were found between the two study periods.

Cardiovascular Effects

The baseline mean (± SD) P-R intervals recorded before each verapamil dose were similar: 166±13 ms and 176±13 ms before IV dosing and 169±12 ms and 170±14 ms on oral dosing, before and after rifampin, respectively. Figure 3 illustrates baseline and maximum P-R interval prolongation after verapamil for all study periods. After IV verapamil therapy, there was significant P-R interval prolongation compared with baseline; the mean maximum percentage of change in P-R interval was 26.6±10.7 before and 25.7±8.4 after rifampin therapy (NS). There was no significant difference in the AUCPRF before rifampin therapy, 28.6±11.6 h; after rifampin therapy, 26.5±8.4 h).

When verapamil was given orally, significant P-R interval prolongation occurred only during the control period, ie, before treatment with rifampin. The mean maximum change in the P-R interval was 23.3±9.3 percent before and 3.9±2.3 percent after rifampin therapy (p<0.001). There was a significant decrease in the AUCPRF from 64.5±34.0 h for oral verapamil alone vs 2.7±3.1 h after treatment with rifampin (p<0.001).

DISCUSSION

The present study demonstrates that treatment with rifampin greatly decreases the bioavailability of orally administered verapamil in healthy volunteers. As expected, reduced verapamil bioavailability was accompanied by a significant decrease in the cardiovascular effect of the drug. In the presence of rifampin, oral verapamil therapy caused virtually no change in the P-R interval. While rifampin produced a small increase in verapamil clearance following IV dosing, no significant attenuation of the ECG effects occurred. Thus, the effect of rifampin on IV disposition appears to be of little if any clinical significance.

The pharmacokinetic profile of verapamil observed in this study before treatment with rifampin is in close agreement with earlier findings for both IV and oral dosing.17 The most likely basis for the observed drug interaction is enhancement of the first-pass metabolism of verapamil owing to enzyme induction by rifampin. The pharmacokinetic sequelae of increasing hepatic drug metabolism by enzyme induction (increasing intrinsic clearance) for different types of drugs have been reviewed.18 For drugs with high hepatic extraction like verapamil—ie, where elimination is limited by hepatic blood flow—increasing the intrinsic clearance by enzyme induction should result in a minimal change in AUC, elimination half-life, or systemic clearance during IV administration. After oral administration, the AUC will be reduced, reflecting increased presystemic metabolism, and bioavailability decreased. Our findings closely follow this pattern.

In addition to enzyme induction, other possible mechanisms for the decrease in oral bioavailability would include a decrease in hepatic blood flow or verapamil protein binding during rifampin treatment. A previous report showed no effect on liver blood flow by rifampin.19 Also, the change in systemic clearance would be larger and inverse to that observed if altered blood flow were the primary mechanism for the reduced bioavailability.18,19 A preliminary investigation evaluating the effect of rifampin on the protein binding

Table 2—Effects of Rifampin on the Disposition of Oral Verapamil in Six Healthy Volunteers*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before Rifampin</th>
<th>After Rifampin</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elimination T1/2, h</td>
<td>4.8 ± 1.7</td>
<td>5.2 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>Cmax-verapamil, ng/ml</td>
<td>194.8 ± 107.8</td>
<td>7.2 ± 4.2</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Tmax, h</td>
<td>1.02 ± 0.38</td>
<td>1.21 ± 0.24</td>
<td>NS</td>
</tr>
<tr>
<td>AUC-verapamil, ng - h/ml</td>
<td>536.8 ± 173.8</td>
<td>34.3 ± 16.2</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>0.26 ± 0.10</td>
<td>0.02 ± 0.02</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>AUC-norverapamil, ng - h/ml</td>
<td>743.8 ± 182.5</td>
<td>109.2 ± 66.4</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>AUC-ratio (norverapamil/verapamil)</td>
<td>1.5 ± 0.3</td>
<td>3.8 ± 2.0</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*Values expressed as mean ± SD.
†NS = not significant.

Near-total Reduction in Verapamil Bioavailability by Rifampin (Barbara et al)
of verapamil in our subjects disclosed a small but statistically significant decrease in verapamil protein binding, from 89.5 percent to 86.3 percent after rifampin administration. However, this small decrease in protein binding would account for less than 20 percent of the observed change in systemic clearance or bioavailability following rifampin treatment. Therefore, an increase in intrinsic clearance as a result of the enzyme induction properties of rifampin appears to be primarily responsible for the large decrease in verapamil bioavailability that occurred after rifampin treatment. While an increase in the norverapamil to verapamil AUC ratio was observed, the significant decrease in both norverapamil serum concentrations and AUC following rifampin suggests that N-demethylation was induced to a lesser extent than other metabolic pathways.

Previous studies have established that there is a significant relationship between serum verapamil concentration and prolongation of the P–R interval. In the present study, the time course of changes in the P–R interval paralleled changes in serum verapamil concentration. The similarity of baseline P–R intervals demonstrates that rifampin has no obvious effect on atrioventricular conduction in man. Rifampin pretreatment did not alter the effect of IV verapamil on the P–R interval. However, rifampin virtually eliminated the ECG response to oral verapamil. Indeed, we are unaware of a reported drug-drug interaction of this magnitude. The interaction described could have important clinical implications. Administration of rifampin, and perhaps of other enzyme-inducing drugs, to patients receiving oral verapamil (in usual doses) may lead to low verapamil concentrations and therapeutic failure. Conversely, discontinuation of rifampin in a patient concurrently receiving oral verapamil might be expected to lead to an increase in verapamil concentrations and possible toxicity.

We did not examine this interaction at steady-state
conditions after long-term oral therapy. Because oral verapamil accumulates with continual dosing, therapeutic concentrations might be achieved by administering larger than normal doses in these situations. In a previous case, we were able to achieve trough serum verapamil concentrations ranging from 123 to 184 ng/ml in a patient with SVT receiving rifampin by administering very large doses of verapamil (480 mg every six hours; 1,920 mg/day). Although these concentrations are similar to those reported by others to be useful in the prevention of SVT, arrhythmias continued to occur. One potential explanation for this discrepancy may be stereospecific first-pass metabolism. The current preparations of verapamil are composed of a racemic mixture of the dextrorotatory (d) and levorotatory (l)-isomers. The l-isomer is approximately six to ten times more potent than the d-isomer in prolonging the P-R interval and is largely responsible for the negative dromotropic effects of racemic verapamil given orally. Further, after oral administration, the l-isomer is metabolized to a much greater extent than the d-isomer during the first pass through the liver. It is possible that enzyme induction by rifampin and other agents is stereoselective. Thus, despite "therapeutic" concentrations of verapamil, there may be a relative deficiency of the more potent l-isomer. Although the effect of enzyme induction on the metabolism of verapamil enantiomers has yet to be determined, other drug-drug interactions with a stereoselective basis have been reported.

Several approaches exist for caring for patients who are receiving rifampin and require treatment with verapamil. Patients can receive short-term IV verapamil administered as intermittent boluses or by constant infusion, since the interaction is not clinically significant with IV verapamil administration. However, institution of long-term oral verapamil therapy is more problematic. For patients in whom verapamil is essential, consideration should be given to discontinuation of rifampin and substitution of other suitable agents without enzyme-inducing properties. Alternative drugs may also be sought, but careful consideration should be given to the possibility that the alternative agent may interact with rifampin as well. The specific therapeutic course of action should be made based on the clinical circumstances of the individual patient.

Treatment with rifampin notably enhances the first-pass metabolism of oral verapamil, significantly reducing its bioavailability and abolishing its cardiovascular effects. Enhanced first-pass metabolism of verapamil appears to be primarily due to enzyme induction by rifampin and must be appreciated if effective therapy is to be administered. Although the interaction with IV verapamil is of limited clinical significance, oral verapamil in usual doses administered to a patient receiving rifampin can be expected to result in therapeutic failure.

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REFERENCES


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12th Annual Ain Shams Medical Congress

This 12th annual medical congress, jointly sponsored by the ACCP Chapter in Egypt, will be held in Cairo, March 4-9. The main theme is "The lung in health and disease." For information, contact Prof. Hassan Hosny Youssef, Chairman, Chest Medical Department, Faculty of Medicine, Abbasaya, Cairo, Egypt.