VERAPAMIL, a calcium antagonist, is an effective antiarrhythmic agent.\(^1\)\(^-\)\(^7\) It also appears to be useful in other clinical settings.\(^3\)\(^-\)\(^8\)\(^-\)\(^13\) Many of the patients who receive verapamil are also treated with digitalis. Since various drugs affect the serum digoxin concentration and clearance,\(^16\)\(^-\)\(^21\) we tested the effect of verapamil on the pharmacokinetics of digoxin in a consecutive series of 49 patients who were taking digoxin as treatment of chronic atrial fibrillation.\(^22\)

**Methods**

**Subjects**

The study included 49 patients (20 men and 29 women), ages 30-78 years (mean ± sd 61 ± 9.6 years), who were taking a daily maintenance dose of 0.25 mg of digoxin (manufactured by Teva Group, Inc.; bioavailability of this brand equals that of Lanoxin\(^23\)) for chronic atrial fibrillation. The dose of digoxin had remained unchanged for at least 2 months before the study. The diagnosis of the patients and their functional capacity are listed in tables 1 and 2.

**Main Protocol**

The main protocol of the study is illustrated in figure 1. The patient took the daily digoxin dose between 8 p.m. and 9 p.m. The blood samples for serum digoxin concentration were always drawn during the next morning, 12-14 hours after ingestion of digoxin. When the patients were receiving verapamil, the morning dose of verapamil was taken between 6 a.m. and 7 a.m. All other medications, such as diuretics, vasodilators and potassium chloride, were continued without alteration of the dose during the study. No patient was taking quinidine or other antiarrhythmic agents. After the first blood sample, drawn at the end of phase I, treatment was begun with 240 mg/day of verapamil in three divided doses, while digoxin treatment was unchanged (phase II). A second blood sample for serum digoxin concentration was obtained 2 weeks later. In 26 patients, verapamil was stopped and the daily maintenance dose of digoxin was doubled (phase III). Two weeks later, serum digoxin concentration was again determined (fig. 1). Verapamil was then started again in five patients and serum digoxin concentration was determined a second time 2 weeks later. These five patients thus received 0.25 mg/day during weeks 1-4 and 0.5 mg/day during weeks 5-8. Thus, we obtained 54 paired comparisons of serum digoxin concentrations with and without verapamil (49 obtained with 0.25 mg of digoxin and five with 0.5 mg of digoxin) during the main protocol of our study. A complete history and a 12-lead ECG were obtained from every patient and a physical examination was performed at the end of each study period (weeks 2, 4, 6 and 8). The patients were specifically evaluated for symptoms and signs of digitalis toxicity.

**Time and Dose Response**

The time-response curve of digoxin concentrations to verapamil treatment was tested in seven subjects by
TABLE 1. Cardiac Diagnosis of 49 Patients with Chronic Atrial Fibrillation

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherosclerotic heart disease</td>
<td>3</td>
</tr>
<tr>
<td>Hypertensive heart disease</td>
<td>6</td>
</tr>
<tr>
<td>Hyperthyroidism (controlled)</td>
<td>3</td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
<td>23</td>
</tr>
<tr>
<td>Idiopathic atrial fibrillation</td>
<td>13</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>49</td>
</tr>
</tbody>
</table>

determining serum digoxin at 2-day intervals after the inception of verapamil. The effect of two different daily doses of verapamil on serum digoxin concentration was determined in seven patients who were taking a maintenance dose of 0.25 mg/day. They received, first, 160 mg/day of verapamil for 2 weeks, and then 240 mg/day for another 2 weeks. Blood samples were obtained at the end of each treatment period.

The 24-hour renal digoxin and creatinine clearances were determined in seven patients and three normal subjects during therapy with digoxin alone and during the combination of digoxin and verapamil.

Digoxin concentrations in the serum and in the urine (after 1:10 and 1:50 dilutions) were determined by a commercially available standard radioimmunoassay technique, using a digoxin (125I) radioimmunoassay kit (Rianen digoxin RIA kit, New England Nuclear). To verify that verapamil does not interfere in vitro with the radioimmunoassay method, verapamil was added in increasing concentrations, starting from 25 µg/ml to seven samples of serum containing known concentrations of digoxin. To evaluate the possibility that the presence of verapamil or its metabolites might in some way give a false-positive test for digoxin in vivo, the sera of 20 patients who were taking verapamil only, on a chronic basis, were tested for digoxin.

All results were analyzed for statistical significance by a paired t test and analysis of variance.

Results

Figure 2 presents the 49 paired comparisons of serum digoxin concentration, with and without verapamil, obtained during treatment with 0.25 mg of digoxin in the 49 patients with chronic atrial fibrillation. Mean serum digoxin concentration rose from

TABLE 2 Functional Capacity of the 49 Patients According to the New York Heart Association Classification

<table>
<thead>
<tr>
<th>Class</th>
<th>No. of pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>8</td>
</tr>
<tr>
<td>II</td>
<td>35</td>
</tr>
<tr>
<td>III</td>
<td>6</td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
</tr>
</tbody>
</table>

Figure 1. Protocol used to determine the influence of verapamil on serum digoxin concentrations (SDC) in paired comparisons in 49 patients. In phases I and II, the dosage of digoxin was 0.25 mg/day. The dosage was increased to 0.5 mg/day in phases III and IV, as illustrated by the height of the digoxin bar.

0.76 ± 0.35 ng/ml (mean ± sd) with digoxin alone to 1.31 ± 0.54 ng/ml after the addition of verapamil (p < 0.0005). This increase in serum digoxin concentration occurred at all levels of initial concentration of digoxin before the addition of verapamil. The serum digoxin concentration during treatment with 0.5 mg of

Figure 2. Effect of verapamil on serum digoxin concentration (SDC) in 49 patients. The solid circles represent individual comparisons made while the patients took digoxin 0.25 mg/day; the solid triangles represent paired comparisons in five patients when their dose of digoxin was 0.5 mg/day. Means for each dosage of digoxin are represented by open circles and triangles; lines indicate standard deviation. The diagonal line represents the line of unity. All values except three are situated above the line of unity, indicating an increase in the serum digoxin concentration during addition of verapamil.
digoxin also rose in five patients, from $1.39 \pm 0.46$ to $2.51 \pm 0.80$ ng/ml ($p < 0.05$).

In the 26 patients who participated in phases I, II and III of the main protocol, the serum digoxin concentration increased from $0.81 \pm 0.38$ ng/ml during treatment with 0.25 mg of digoxin only to $1.36 \pm 0.49$ ng/ml after the addition of verapamil ($p < 0.01$). The serum digoxin concentration increased further, to $1.67 \pm 0.75$ ng/ml ($p < 0.01$) when the double dose of 0.5 mg of digoxin was the only treatment given.

In nine patients, serum digoxin concentration was tested at several hourly intervals after administration of verapamil to determine if the influence of verapamil on the serum digoxin concentration was a transient or a long-lasting effect. The increased serum digoxin concentration lasted for as long as the 10 hours during which it was tested after the dose of verapamil (table 3). When the serum digoxin concentration was retested 2 weeks after stopping verapamil, it had again decreased significantly from the values during verapamil therapy.

The dose-response and time-response curves of digoxin to addition of verapamil are illustrated in figures 3 and 4. The serum digoxin concentration in seven subjects ($0.60 \pm 0.11$ ng/ml before verapamil) was higher during therapy with 240 mg of verapamil than with 160 mg ($1.24 \pm 0.40$ ng/ml vs $0.84 \pm 0.18$ ng/ml, $p < 0.01$). The serum digoxin concentration in seven subjects rose linearly, from $0.72 \pm 0.71$ ng/ml during the first few days of therapy with 240 mg of verapamil, reaching at the end of 1 week 90% of the levels observed at the end of 2 weeks of combined therapy ($1.20 \pm 0.43$ vs $1.34 \pm 0.44$ ng/ml, $p < 0.005$).

The in vitro addition of verapamil to seven sera with known concentrations of digoxin did not alter the original concentration ($0.96 \pm 0.70$ vs $1.00 \pm 0.72$ ng/ml, $p > 0.45$), indicating that verapamil does not induce artificial error in the determination of digoxin concentrations by the technique that we used. Furthermore, the determination for digoxin in the sera of 20 patients who were receiving only verapamil on a chronic basis was always negative, indicating that

---

**TABLE 3. The Mean (± sd) Serum Digoxin Concentration After the Last Dose of Verapamil**

<table>
<thead>
<tr>
<th>Time after verapamil</th>
<th>Hours</th>
<th>Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10*</td>
<td>2</td>
</tr>
<tr>
<td>SDC (ng/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.06 ± 0.34</td>
<td>1.08 ± 0.30</td>
<td>1.02 ± 0.35</td>
</tr>
</tbody>
</table>

*SDC measured 10 hours after the night dose and just before the morning dose of verapamil. Abbreviation: SDC = serum digoxin concentration.

---

**FIGURE 3. Dose response of serum digoxin concentration (SDC) to different doses of verapamil (V) in seven patients taking 0.25 mg/day of digoxin. SDC increases significantly during 160 mg of verapamil and even more so during treatment with 240 mg. D = digoxin.**

**FIGURE 4. Time response of serum digoxin concentration (SDC) to a uniform dose of verapamil (240 mg/day) in seven subjects. A progressive, linear increase in the mean SDC was observed. Statistical significance was achieved already 3 days after the inception of verapamil treatment.**
FIGURE 5. Mean and individual renal digoxin clearances in patients with chronic atrial fibrillation (A) and in normal volunteers (B). (A) The connected solid circles represent six patients in whom serum digoxin concentration increased during verapamil treatment. The mean digoxin clearance before and after addition of verapamil was calculated with the data of these six patients only. The connected open circles represent one patient in whom serum digoxin concentration remained at 0.7 ng/ml before and after addition of verapamil. The number next to each subject represents the serum digoxin concentration (in ng/ml) before and after addition of verapamil in both A and B. In six of seven patients and in the three volunteers, there was a significant decrease in renal digoxin clearance. In the seventh patient with unchanged digoxin clearance, there was no rise in digoxin serum concentration. D = digoxin alone; D + V = digoxin and verapamil.

Verapamil or its metabolites do not produce a falsely elevated serum digoxin concentration in any way.

Twenty-four-hour renal digoxin clearance decreased during combined digoxin and verapamil therapy (26.1 ± 9.7 vs 55.1 ± 12.3 ml/min, p < 0.005) in all six patients tested in whom serum digoxin concentration increased (fig. 5A). Creatinine clearance did not change significantly (48.5 ± 7.2 vs 53.5 ± 9.8 ml/min, p > 0.2). The control creatinine clearance was low, presumably because of the age of these six patients (63.3 ± 3 years). In three normal volunteers (mean age 33 years), in whom mean creatinine clearance was 93 ± 1 ml/min, the mean digoxin clearance also decreased, from 129 ± 32.7 to 79.0 ± 34.9 ml/min (p < 0.005), while the simultaneous serum digoxin level increased from 0.76 ± 0.23 ng/ml to 1.30 ± 0.21 ng/ml (p < 0.005; fig. 5B).

Our method of calculating renal digoxin clearance by using the 8-a.m. serum digoxin concentration as the denominator of the equation UV/P may result in overestimation of the true renal digoxin clearance. Since this overestimation applies equally well to both phases of the study, (i.e., before and during verapamil), the difference in digoxin clearances between the two phases is valid.

Renal digoxin clearance did not change significantly in one patient in whom serum digoxin concentration was unaffected by verapamil (53 vs 54 ml/min, fig. 5A).

Seven patients exhibited signs or symptoms suggestive of mild-to-moderate digoxin toxicity during combined digoxin and verapamil treatment (table 4). Serum digoxin concentration was in the toxic range (greater than 2.0 ng/ml) in five of these seven patients. The rhythm disturbances and symptoms disappeared when the dose of digoxin or verapamil was decreased.

Discussion

Our results indicate that verapamil significantly increases serum digoxin concentration in almost all patients who take a steady daily maintenance dose of digoxin. This effect lasts for at least 10 hours after intake of verapamil (table 3), and thus represents a true increase in the steady-state concentration of digoxin.
and is not a transient phenomenon. While this is not harmful in underdigitized patients, it may be hazardous in those who were previously well digitized, as illustrated by seven patients in this study (table 4). The extent of elevation of digoxin concentrations after verapamil seems to be an individual response and, while serum digoxin concentration may increase only slightly in some patients, it may reach the toxic range in others. The increase in serum digoxin is gradual and is relatively rapid — most of it is attained within 1 week of the inception of verapamil treatment (fig. 4). The magnitude of the rise in serum digoxin concentration is directly related to the dosage of verapamil (fig. 3). Serum digoxin concentration during treatment with 0.25 mg/day of digoxin and 240 mg/day of verapamil can be expected to have a value intermediate to those obtained during treatment with 0.25 mg and 0.5 mg of digoxin.

Our results initially appear to conflict with those of Doering,17 who reported no significant increase in serum digoxin concentrations during verapamil treatment. The conflict may, however, be more apparent than real; Doering reported results on six patients only and may have been using lower doses of verapamil, and lower doses of verapamil lead to relatively small increases in digoxin concentrations. The trends of Doering’s results (1.25 ± 0.5 ng/ml during verapamil vs 1.08 ± 0.38 ng/ml) are definitely compatible with ours.

How verapamil increases the serum digoxin concentration is not clear. Artificial laboratory error was ruled out by the absence of effect on serum digoxin concentrations when verapamil was added in vitro and also by the gradual rise of digoxin concentrations in vivo over several days. Metabolites of verapamil do not influence the digoxin assay in blood or in the urine, since testing for digoxin in the sera of patients who were taking only verapamil over a long period (more than 1 month) was always unproductive. Furthermore, the radioimmunoassay technique is specific for digoxin and is not influenced by unrelated chemical compounds circulating in the blood.

Four mechanisms could theoretically explain the interaction between the two drugs: decreased renal digoxin clearance, decreased nonrenal digoxin clearance, decreased volume of distribution of digoxin and increased absorption from the gastrointestinal tract.

Our findings show that verapamil significantly decreases renal digoxin clearance in patients in whom serum digoxin concentration increases (fig. 5). This occurs without a significant change in creatinine clearance. Digoxin is eliminated in the kidneys both by glomerular filtration and tubular secretion.25, 29 The fact that verapamil decreases renal digoxin clearance without significantly altering glomerular filtration (as suggested by the unchanged creatinine clearance) indicates that verapamil decreases tubular secretion of digoxin. This would be similar to the effect of quinidine on renal digoxin clearance.17, 19, 27

Although it is tempting to attribute the increase in serum digoxin concentration to this decrease in renal digoxin clearance, nonrenal digoxin clearance could also be decreased by verapamil, as has been suggested for quinidine.17, 28, 29

Finally, like spironolactone,29 verapamil could decrease the apparent volume of distribution of digoxin by nonspecific binding to the digoxin receptors in tissues.81 Our data do not completely exclude this possibility. However, we found that the serum digoxin concentrations, when measured 2 hours after a dose of verapamil, were not different from those measured 4 hours, 6 hours and 10 hours after the last dose (table 3). This argues against a significant change in the volume of distribution and against any significant role this might play in the increase of serum digoxin concentration.

The clinical implications of the interaction between verapamil and digoxin remain to be delineated. Digoxin intoxication may not be a major problem; only seven of 49 patients (14%) had symptoms and ECG findings compatible with mild-to-moderate intoxication. Also, these signs disappeared quickly after the regimen was altered, and in no patient was it necessary to discontinue verapamil, which has become a routine adjunct to the management of chronic atrial fibrillation in our patients.22 However, serum digoxin concentrations and possible signs and symptoms of digoxin toxicity must be examined in any patient simultaneously receiving verapamil and digoxin.

### Table 4. Signs and Symptoms Suggestive of Digoxin Toxicity

<table>
<thead>
<tr>
<th>Pt</th>
<th>Treatment</th>
<th>Symptoms</th>
<th>ECG findings</th>
<th>SDC (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>D&lt;sub&gt;1&lt;/sub&gt; + V</td>
<td>—</td>
<td>VPCs</td>
<td>2.00</td>
</tr>
<tr>
<td>2</td>
<td>D&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Anorexia</td>
<td>VPCs</td>
<td>1.94</td>
</tr>
<tr>
<td>2</td>
<td>D&lt;sub&gt;1&lt;/sub&gt; + V</td>
<td>—</td>
<td>Bigeminy (VPCs)</td>
<td>2.23</td>
</tr>
<tr>
<td>3</td>
<td>D&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Nausea and vomiting</td>
<td>Bigeminy (VPCs)</td>
<td>3.70</td>
</tr>
<tr>
<td>3</td>
<td>D&lt;sub&gt;1&lt;/sub&gt; + V</td>
<td>Malaise, feeling of swelling</td>
<td>AV junctional rhythm</td>
<td>0.88</td>
</tr>
<tr>
<td>4</td>
<td>D&lt;sub&gt;1&lt;/sub&gt; + V</td>
<td>—</td>
<td>VPCs</td>
<td>2.42</td>
</tr>
<tr>
<td>5</td>
<td>D&lt;sub&gt;1&lt;/sub&gt; + V</td>
<td>—</td>
<td>VPCs</td>
<td>2.09</td>
</tr>
<tr>
<td>6</td>
<td>D&lt;sub&gt;1&lt;/sub&gt; + V</td>
<td>Anorexia, nausea</td>
<td>—</td>
<td>2.10</td>
</tr>
<tr>
<td>7</td>
<td>D&lt;sub&gt;1&lt;/sub&gt; + V</td>
<td>Nausea, vomiting</td>
<td>HR = 50</td>
<td>1.40*</td>
</tr>
</tbody>
</table>

Patients 1 and 2 had ECG signs of toxicity during digoxin 0.5 mg also. The symptoms and ECG findings disappeared after changing the therapeutic regimen.

*Blood level obtained 60 hours after last dose of digoxin.

Abbreviations: D<sub>1</sub> + V = digoxin, 0.25 mg, and verapamil combination; D<sub>2</sub> = digoxin, 0.5 mg; HR = heart rate (beats/min); VPCs = ventricular premature complexes; SDC = serum digoxin concentration.

**Addendum**

Since the present article was accepted, another article has appeared (Pedersen KE, Dorph-Pedersen A, Hvidt S, Klitgaard NA, Nielsen-Kudsk F: Digoxin-verapamil interaction. Clin Pharmacol Ther 30: 311, 1981) that confirms our findings of increased serum digoxin concentration and decreased renal clearance after verapamil therapy.
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H O Klein, R Lang, E Weiss, E Di Segni, C Libhaber, J Guerrero and E Kaplinsky

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