Acute and Chronic Pharmacodynamic Interaction of Verapamil and Digoxin in Atrial Fibrillation

Janice B. Schwartz, M.D., Deborah Keele, M.D., Robert E. Kates, Ph.D., Edward Kirsten, Ph.D., and Donald C. Harrison, M.D.

SUMMARY The safety, efficacy, and pharmacologic effect of combined verapamil and digoxin were studied in 10 patients with chronic atrial fibrillation. Heart rate recordings, treadmill exercise tests, physical examinations and serum digoxin concentrations during chronic digoxin therapy were compared with those after the acute administration of verapamil and 1, 2, 4, 6 and 10 weeks after the addition of oral verapamil to digoxin therapy. After both i.v. and chronic oral verapamil administration, resting and exercise heart rates were significantly lower. Increasing serum concentrations of verapamil correlated with increasing suppression of heart rate at rest and during exercise. The mean resting heart rate by 24-hour ambulatory ECG decreased from 87 ± 9 beats/min to 72 ± 6 beats/min. The mean treadmill exercise heart rate decreased more markedly, from a mean of 151 ± 26 beats/min to 106 ± 22 beats/min (both p < 0.001). During chronic therapy, heart rate reductions were seen 1 week after the addition of verapamil and were maintained without change for the duration of the trial. Blood pressures at rest and during exercise were unchanged. Cardiomegaly was present on the entry chest x-ray in six patients; after verapamil, heart size decreased in three and was unchanged in one; two patients had transient congestive heart failure that responded to diuretics. Serum digoxin levels increased from a mean of 1.6 ± 0.4 ng/ml to 2.7 ± 0.9 ng/ml (p < 0.001) during verapamil. The increase was observed in nine of 10 patients but was not related to clinical signs of digitalis excess and no episodes of asystole were seen on the serial 24-hour ECGs. Chronic oral administration of verapamil, 320 mg/day, resulted in mean verapamil concentrations of 130–280 ng/ml (mean interdose concentration 140 ± 41 ng/ml) with great intersubject and intrasubject variability. We conclude that verapamil is effective in further suppressing the ventricular response rate in atrial fibrillation when given in combination with digitalis and can serve as an adjunct to digitalis therapy in the chronic management of patients with atrial fibrillation.

VERAPAMIL is being studied extensively in the United States. Its major electrophysiologic action in conscious humans is to depress the slow response in the specialized conduction tissue in the sinoatrial node and the atrioventricular junction and impede atrioventricular conduction.1,2 This blocking effect of i.v. verapamil on atrioventricular conduction has been used to slow the ventricular response in atrial fibrillation and flutter and to abolish supraventricular tachycardias due to nodal or atrioventricular reentry.3,4

Experience with administration of verapamil for the long-term management of atrial arrhythmias has been extremely limited.5 This may be because caution is advised when verapamil is used in combination with digitalis,6 which also inhibits the atrioventricular node. This study was designed to evaluate the efficacy and safety of combined verapamil and digitalis administration in patients with chronic atrial fibrillation and to define the relationship between the serum verapamil concentration and heart rate suppression during i.v. and long-term oral administration.

Methods

Patients

Ten patients (seven males and three females), mean age 60 ± 4 years, were studied. Each patient had a history of chronic atrial fibrillation documented by 24-hour ambulatory ECG recordings. Each had been treated with digitalis and had an exercise heart rate greater than 100 beats/min during exercise ≤ 3 mets. At entry into the study, all subjects had normal BUN, creatinine and liver enzyme tests.

Atrial fibrillation was associated with rheumatic valvular disease in four patients, chronic obstructive pulmonary disease in two patients and coronary artery disease in one patient. No cause for atrial fibrillation was found in three patients. At entry into the study, two patients were in New York Heart Association functional class I, four were in class II and four were in class III. Five patients had a history of congestive heart failure. The patient characteristics are listed in table I.

All patients gave informed consent and the protocol was approved by the Stanford Medical Committee on the Use of Human Subjects in Research.

Study Design

Baseline Digoxin Period

Digoxin was dispensed to each patient in tablet strengths of 0.125, 0.25 and 0.5 mg in doses previously prescribed. Each patient underwent practice treadmill testing and a 24-hour ambulatory ECG was recorded. The digoxin dosage was increased until serum levels were greater than 1 ng/ml on two occasions no less than 1 week apart; thereafter, the digoxin dose and concomitant medications remained unchanged (table I). A baseline chest x-ray, an ambulatory ECG, and a treadmill exercise test were then performed, and blood was obtained to determine the baseline serum digoxin concentrations.
Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Weight (kg)</th>
<th>NYHA</th>
<th>Concomitant disease</th>
<th>Concomitant medications</th>
<th>History of CHF</th>
<th>C/T ratio</th>
<th>Digoxin (mg/day)</th>
<th>Verapamil dose (mg/day)</th>
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<td>63</td>
<td>M</td>
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<td>0.25</td>
<td>320</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>M</td>
<td>79.2</td>
<td>II</td>
<td>Rheumatic valvular disease (s/p, MVR, AVR)</td>
<td>Triamterene, hydrochlorothiazide, warfarin</td>
<td>+</td>
<td>0.55</td>
<td>0.25</td>
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</tr>
<tr>
<td>4</td>
<td>69</td>
<td>F</td>
<td>76</td>
<td>II</td>
<td>COPD, nontropical sprue, osteoarthritis, kyphoscoliosis</td>
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<td>0.375</td>
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<td>0.5</td>
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</tbody>
</table>

Abbreviations: NYHA = New York Heart Association; CHF = congestive heart failure; C/T = cardiothoracic; MVR = mitral valve replacement; AVR = aortic valve replacement; CVA = cerebrovascular accident; COPD = chronic obstructive pulmonary disease; s/p = status post; + = present; - = absent.

Acute Verapamil Combined with Digoxin

Within 1 week after completion of the baseline period, the patients entered Stanford University Hospital. Each patient received a 15-mg i.v. bolus of verapamil infused at 1 mg/min. Heart rate was monitored by continuous ECG recording, blood pressure measured by a cuff sphygmomanometer, and venous blood drawn to determine serial verapamil concentrations.

Intravenous Infusion Studies

Two days later, verapamil infusions were given to approximate steady-state levels of 15 ng/ml (in five patients only), 30, 60 and 120 ng/ml. Before and after the infusion, heart rate and blood pressure were determined at rest, after dumbbell exercise (7 lb × 30 arm bends), and after sublingual nitroglycerin, 0.3 mg. Serum for verapamil concentration determination was obtained before and twice (10 minutes apart) after the infusion.

Chronic Oral Verapamil Combined with Digoxin

Two days after completion of the i.v. protocol, oral verapamil, 320 mg/day (80 mg every 6 hours), was begun. The digoxin dose and other medications were not altered. Each patient was examined 1 week later and the verapamil dose titrated, if necessary, to produce a 15% or greater decrease in treadmill exercise heart rate from maximal baseline heart rate at the same work load. The verapamil dose remained unchanged for the next 2 months. Physical examination, 24-hour ambulatory ECG recording, treadmill exercise test, serum digoxin concentration, serum verapamil and norverapamil concentration, serum antinuclear antibodies and routine chemistry evaluation were performed after 2, 4, 6 and 10 weeks of combined digoxin and verapamil.

Testing

Ambulatory Monitoring

Patients were encouraged to engage in their normal daily activities and recordings were made on the same day of the week for each test. Avionics and Oxford recording systems were used and all tapes were processed by the Stanford computer system to quantitatively display heart rate responses over 24 hours.11 Heart rate trends were examined and premature ventricular complexes (PVCs) were quantitated for each 24-hour period.

Exercise Testing

Each subject performed an exercise test 1 hour after
a dose of verapamil on the same day of the week and at the same time of day. The patients were instructed to avoid food, caffeine and nitroglycerin for 2 hours before the test. With continuous ECG monitoring, patients exercised on a motor-driven treadmill for 3 minutes. The work load was based on individual exercise tolerance during a practice treadmill test. A 0% grade and a speed of 3 mph were used for all tests in eight patients and a 0% grade and a speed of 1 mph were used for all tests in two patients. A 12-lead ECG was recorded at the onset and termination of exercise, and leads I, II and V1 were sampled after each minute of exercise. Heart rates were averaged over 60 seconds. Auscultatory sphygmomanometer blood pressure measurements were recorded at rest, after 3 minutes of exercise, and during the recovery period.

Serum Drug Levels
Five milliliters of heparinized blood were drawn to determine serum digoxin concentrations at the same time of day at each visit. Determinations were made by radioimmunoassay. Verapamil has been found not to interfere in vitro with the radioimmunoassay in several laboratories (Kirsten E: personal communication). Five milliliters of heparinized blood were drawn at the end of the dosing interval (trough) and 1 hour after verapamil ingestion (concomitant with treadmill exercise testing and during ambulatory monitoring). Serum verapamil and norverapamil concentrations were determined by high-performance liquid chromatography.

Chest Roentgenograms
Anteroposterior and lateral chest x-rays were performed at entry into the study and after 10–12 weeks of digoxin and verapamil administration. Interpretations were performed by radiologists unaware of the patient’s drug therapy.

Statistical Analysis
Changes in all measurements over time were analyzed using the Friedman nonparametric analysis of variance with multiple comparisons and one-tailed probability. Observations made on only two occasions were compared by paired t test. Values are given as mean ± SD.

Results
Intravenous Bolus Studies
The mean serum digoxin concentration for the group immediately before the verapamil infusion was 1.6 ± 0.4 ng/ml (± SD) (range 1.0–2.1 ng/ml). Resting heart rates markedly decreased in all patients after the 15-minute verapamil infusion (fig. 1). Heart rates decreased from a mean of 97 ± 15 beats/min to 74 ± 13 beats/min (p < 0.001). The maximal heart rate reduction occurred when the verapamil concentration was highest (250 ± 57 ng/ml). The time required for the resting heart rate to return to baseline values varied considerably (range 1–12 hours; mean 5.4 ± 4.3 hours), but occurred when verapamil con-

Serial digoxin concentrations were still measurable (15 ± 2 ng/ml). Norverapamil was not detected after an i.v. bolus of verapamil. Serial digoxin concentrations were determined during the infusion on two occasions and there was no significant change during or for 2 hours after the infusions. Systolic blood pressure decreased from 125 ± 10 mm Hg to 119 ± 13 mm Hg (p < 0.03).

Intravenous Infusion Studies
The mean serum digoxin concentration for the group immediately before the verapamil infusions was 1.4 ± 0.5 ng/ml (range 1.0–2.4 ng/ml). No significant change was present during the 6–8-hour infusions in two patients in whom serial determinations were made.

With increasing concentrations of verapamil, the heart rate decreased in all patients at rest (fig. 2). Heart rate reductions at 15 and 30 ng/ml were significantly different from those at 60 and 120 ng/ml (p < 0.03), but differences between 15 and 30 ng/ml and between 60 and 120 ng/ml were not significant. In five patients, dumbbell exercise was performed to assess the suppression of exercise-induces tachycardia and nitroglycerin was given to assess the heart rate suppression during baroreceptor activation. Increasing concentrations of verapamil again produced increasing reductions in heart rate responses (fig. 2). These reductions in exercise heart rate were similar in magnitude to those in patients at rest. The mean resting supine blood pressure for the group before the administration of verapamil was 124 ± 11 mm Hg. This decreased to 113 ± 13 mm Hg when the serum

FIGURE 1. The ventricular response rate during atrial fibrillation for each subject before and immediately after i.v. administration of 15 mg of verapamil over 15 minutes. The decrease in ventricular response rate was statistically significant (p < 0.001).
The mean percent reduction in ventricular response (heart rate) for five patients at rest and after sublingual nitroglycerin (NTG) and dumbbell exercise. The mean percent reduction in heart rate was significantly greater (p < 0.03) at 60 and 120 ng/ml than at 15 and 30 ng/ml.

**Chronic Verapamil and Digoxin**

**Verapamil Dosage**

Eight patients were maintained on the initial dose of verapamil (320 mg/day). One patient required 480 mg/day to produce adequate heart rate suppression and in one patient an initial dose of 160 mg/day was chosen. Drug compliance was ascertained by tablet count at each visit and measurement of serum drug concentrations.

**Twenty-four-hour Ambulatory ECGs**

Mean hourly heart rates for the entire group were significantly lower (p < 0.001) during combined verapamil and digoxin administration than during chronic digoxin therapy alone (fig. 3). This lowering was observed after 1 week of verapamil therapy and did not change significantly during the 2 months of study.

The mean maximal heart rate for a 24-hour period during baseline digoxin administration was 146 ± 24 beats/min, compared with 118 ± 19 beats/min (p < 0.001) after the addition of verapamil. Corresponding minimal heart rates during a 24-hour period were 66 ± 13 beats/min (range 50–80 beats/min) during digoxin and 51 ± 7 beats/min (range 43–64 beats/min, p < 0.01) during combined treatment. The minimal heart rates were recorded during sleep in all patients. Figure 4 shows the changes in the RR interval histogram with the addition of verapamil to digoxin therapy.

After verapamil administration, the frequency of longer RR intervals and lower heart rates increased. The median, minimal and maximal cycle lengths were prolonged. Episodes of marked narrowing or "regularization" of the range of RR intervals were observed on one or more ambulatory ECGs during the outpatient period in three patients. In one of these patients, this was also observed on the baseline ambulatory ECG.

In seven patients, the PVC frequency did not change (fig. 5). Patient 3 had a marked and sustained increase in PVC frequency during a 24-hour ambulatory ECG after the addition of verapamil. In patient 5, the PVC frequency decreased markedly and in patient 7, the PVC frequency increased transiently during an episode of congestive heart failure. Complete atrio-ventricular block or asystole was not observed on any recording.

**Exercise Data**

The mean heart rate during treadmill exercise decreased significantly, from 151 ± 26 beats/min to...
Figure 5. The frequency of premature ventricular complexes (PVCs) over a 24-hour period is plotted on a logarithmic scale for all 10 patients on digoxin alone and after 1, 4 and 8 weeks of verapamil and digoxin. The three lines connecting the squares represent the three patients in whom marked changes were seen. The frequency of PVCs increased in one, decreased in another and increased transiently in the third.

106 ± 22 beats/min (p < 0.001), with the addition of verapamil to digoxin therapy. This degree of reduction in exercise heart rate was maintained without significant change throughout the study (fig. 6). Systolic and diastolic blood pressures were not significantly changed at rest or during exercise with the addition of verapamil in our patients. In one patient, multif orm PVCs and short runs of ventricular tachycardia occurred during recovery from exercise after the addition of verapamil to digoxin.

Verapamil Levels

The mean steady-state verapamil concentration 1 hour after an oral dose (peak) was 232 ± 43 ng/ml during the 10 weeks on a stable dose (table 2). The corresponding mean serum verapamil concentration immediately before a dose (trough) was 175 ± 38 ng/ml and averaged 74% of the peak concentration when all data pairs were examined. The trend for decreasing serum concentrations with time was statistically significant for the trough serum concentrations (p < 0.03), but not for the peak serum concentrations.

There was significant intersubject variability in both trough and peak serum verapamil concentrations. The average intersubject coefficient of variation was 52% for all trough samples and 50% for all peak samples.

Figure 6. Mean resting and exercise heart rates for the 10 patients during digoxin therapy (week 0) and after 1, 2, 4, 6 and 10 weeks of combined verapamil and digoxin therapy. Resting and exercise heart rates were significantly reduced (p < 0.001). This reduction was maintained without significant change over the next 9 weeks.

In addition, there was considerable intrasubject variability with time; the average coefficient of variation was 38% for trough concentrations and 34% for the approximate peak concentrations.

The serum concentration of norverapamil, the major metabolite of verapamil, was also measured. During the 10 weeks of verapamil administration, the mean norverapamil serum concentration was 192 ± 38 ng/ml before a verapamil dose and 195 ± 32 ng/ml 1 hour after a verapamil dose. Marked variation was seen both between patients and within patients. The trend for a decrease with time was significant (p < 0.05).

Although calculations based on the number of pills returned at each visit showed that at least 80% of the prescribed tablets had been removed from the bottles, six of 10 patients stated they had missed verapamil doses on occasions.

Digoxin Levels

After initial titrations, the mean daily digoxin dose for the group was 0.46 ± 0.18 mg/day (range 0.25–1.0 mg/day); the mean serum digoxin concentration was 1.6 ± 0.35 ng/ml (range 1.0–2.1 ng/ml). After the addition of verapamil, digoxin levels increased to 2.2 ± 0.6 ng/ml after 1 week of verapamil and to 2.7 ± 0.9 ng/ml after 4 weeks of verapamil, and remained significantly elevated (p < 0.001) over control levels throughout verapamil administration (fig. 7). No accompanying change in serum creatinine or urine pH was observed. Only one patient did not have an increase in digoxin level. She also had the lowest serum concentrations of verapamil, a history of nontropical
sprue (on a gluten-free diet), and took five concomitant medications (patient 4, table 1).

Chest Roentgenograms
Cardiomegaly was present on the baseline chest x-ray in six patients. After the chronic administration of digoxin and verapamil, decreases in cardiothoracic ratio and pulmonary vascular markings were noted in three of these six patients. One had no change between the baseline and final chest x-ray and two had transient signs of congestive heart failure.

Side Effects
After i.v. verapamil, a seven-beat run of ventricular tachycardia at a rate of approximately 100 beats/min and a short run of a tachycardia with a rate of 150 beats/min and a bundle branch block configuration were seen in one patient. During the first week of chronic oral verapamil, one patient reported fatigue and another sleepiness. Both of these complaints resolved by week 2 of therapy. In patients 4 and 7, fluid retention and mild congestive heart failure were present after 2–3 weeks of verapamil therapy.

Verapamil (320 mg/day) markedly suppressed heart rate in both patients (mean hourly heart rate 60 beats/min, range 49–65 beats/min in one and 43–70 beats/min in the other). We considered this the major factor in the precipitation of congestive heart failure. Both patients were female, had a history of congestive heart failure and were taking furosemide. An increase in the furosemide dosage promptly resolved the congestive heart failure, even though the verapamil dose was not altered. Complete blood count, serum calcium, phosphate, glucose, BUN, creatinine, urinalysis, fluorescent antinuclear antibodies and eye examinations did not change.

**Discussion**
In some patients with chronic atrial fibrillation, routine digitalization often does not protect against exercise-induced increases in heart rate. Verapamil has been widely used in Europe as an antiarrhythmic and antianginal agent since 1962 and decreases the ventricular response in atrial fibrillation. Most studies have focused on the i.v. administration of verapamil in patients with recent onset atrial fibrillation. However, one study showed that verapamil alone or in combination with digoxin increases exercise tolerance in patients with chronic atrial fibrillation. In addition, pharmacologic information has been limited due to the previous lack of a sensitive and specific drug assay. Although verapamil suppresses toxic digitalis arrhythmias in laboratory animals, drug interactions during chronic combined digitalis and verapamil administration have not been reported.

We selected patients with chronic atrial fibrillation who were taking digitalis and had heart rates greater than 100 beats/min at low levels of exercise and were thus considered to have inadequate heart rate control with digoxin alone. We included patients with evidence of compromised left ventricular function who would be representative of the actual population for whom the drug might be of benefit. After stable digoxin dosages and steady-state serum digoxin concentrations were documented, we examined the heart rate responses at rest and during exercise and the heart size on chest x-ray of our patients during chronic digoxin therapy. We then administered i.v. verapamil and observed a further decrease in resting heart rates, with no deleterious circulatory effects. The dose of 15 mg over 15 minutes resulted in a mean serum verapamil concentration of 250 ± 57 ng/ml and produced a

<table>
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<th>Before</th>
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<td>128 ± 69</td>
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<td>155 ± 34</td>
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Values are ng/ml (mean ± sd).

![Figure 7](http://circ.ahajournals.org/)

**Figure 7.** Mean serum digoxin concentrations for the 10 patients before the verapamil (week 0) and after 1, 2, 4, 6 and 10 weeks of combined digoxin and verapamil. The increase in serum digoxin concentration was significant (p < 0.001) after only 1 week of verapamil administration. This elevation was maintained during combined verapamil and digoxin administration.
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decrease of 23 ± 9% in resting heart rate despite a slight decrease in systolic blood pressure. The peak effect was seen after the infusions, but heart rates did not return to basal levels for 5.4 ± 4.3 hours. This alteration in the heart rate lasted longer than the rate decrease in other patients with atrial fibrillation.4, 6 These differences in the duration of action of verapamil on heart rate suppression are probably related to the lower dose and serum concentrations of verapamil in previous studies.6 This would be consistent with our observations of the increasing suppression of both resting, exercise and nitroglycerin-stimulated heart rates with i.v. infusion of verapamil to increasing steady-state levels. These findings document a correlation between the serum concentration of verapamil and the reduction of ventricular response rates to atrial fibrillation.

Oral verapamil, 320 mg/day, significantly reduced both resting and exercise heart rates in all but one patient, who required 480 mg/day. The mean maximal ambulatory heart rates during the 24-hour ECG recordings were decreased after 1 week of verapamil (p < 0.001) and remained suppressed without appreciable change for the duration of the trial. The treadmill exercise heart rates were similarly decreased (approximately 30%), and blood pressure responses did not change significantly. The lowest daily heart rates were also decreased, but rates lower than 43 beats/min were not observed and diurnal variation was preserved.

We observed an increase in mean, minimal and maximal RR intervals in all patients. The range of RR intervals narrowed markedly in three patients. Similar observations have been reported, but the underlying mechanism is not known.17, 18, 27 No episodes of asystole were noted on the multiple 24-hour ambulatory ECG recordings.

Verapamil concentrations were 80–500 ng/ml, with group mean levels of 130–280 ng/ml before and 1 hour after a dose. Great intersubject and intrasubject variability was seen despite identical dosages. This is consistent with the expected observations after administration of a drug that undergoes extensive hepatic first-pass elimination.21 Serum concentrations of norverapamil, the major metabolite, were present in amounts approximately equal to serum verapamil concentrations, but did not accumulate after 1 week of verapamil administration. Accumulation was seen in serum digoxin concentrations.

Serum digoxin concentrations increased in nine of 10 patients after the addition of verapamil to digoxin. Though the increase was statistically significant after only 1 week of verapamil administration, the increase continued for the first 4 weeks of combined drug administration. The increase in serum digoxin concentration after 1 week was not accompanied by any further increment in suppression of heart rates at rest or during exercise; nor did any patient complain of nausea, vomiting, anorexia, headaches, fatigue, yellow-green vision or other symptoms commonly attributed to digitalis excess. An asymptomatic but statistically significant increase in PVC frequency was observed in one patient. The regularized ventricular rates we observed in three patients occurred when the serum digoxin levels were 1.4–2.2 ng/ml in patient 3, 1.1–1.8 ng/ml in patient 4, and 2.5–4.4 ng/ml in patient 7.

Lang and co-workers28 found a dose-dependent verapamil-induced elevation in digoxin concentration in patients with chronic atrial fibrillation. This increase developed over 7–14 days, and only seven of 49 patients showed signs of digoxin toxicity.

Although objective signs of improvement were present on the chest x-ray in three patients (New York Heart Association functional class III at entry), mild congestive heart failure developed in two patients after 2 weeks of verapamil (patients 4 and 7). Although both patients received diuretics throughout the study, fluid retention and weight gain preceded symptoms of shortness of breath, dyspnea, and the appearance of pulmonary rales by 1 week. Both patients had a history of congestive heart failure and had cardiomegaly on the baseline chest x-ray. In retrospect, the initial dose of verapamil (320 mg/day) was probably too large, as the onset of congestive heart failure was preceded by marked suppression of heart rate in both patients and serum verapamil concentrations were consistently greater than 300 ng/ml in one. Although verapamil has a negative inotropic effect in experimental animal preparations,29–32 this effect has not been documented in humans.33 In recent studies, left ventricular performance objectively improved after verapamil administration.34, 35 We cannot, however, rule out the possibility of a negative inotropic effect contributing to the precipitation of congestive heart failure in two of our patients. Nonetheless, congestive heart failure cleared in both patients with diuretic therapy even though the verapamil dosage was not changed.

Verapamil provided increased control of ventricular response rates in digitalized patients with chronic atrial fibrillation. The responses were dose-dependent and titratable. Verapamil was safe and well-tolerated in the absence of left ventricular dysfunction for 2 months in our 10 patients. There is evidence that if hepatic dysfunction of congestive cardiomyopathy exists, a lower initial dosage should be chosen. Although an increase in serum digoxin concentrations can be expected in most patients, it may not be associated with toxicity or necessitate dosage adjustments. We conclude that verapamil can serve as an adjunct to digitalis in the treatment of chronic atrial fibrillation.

References


4. Heng MK, Singh BN, Roche AHG, Norris RM, Mercer CJ:
Effects of intravenous verapamil on cardiac arrhythmias and on the electrocardiogram. Am Heart J 90: 487, 1975
Acute and chronic pharmacodynamic interaction of verapamil and digoxin in atrial fibrillation.
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