Pharmacokinetic Interactions Between Digoxin and Other Drugs

FRANK I. MARCUS, MD, FACC

Tucson, Arizona

Drug interactions with digoxin are important because of this agent's narrow therapeutic index. Among the drugs that can decrease digoxin bioavailability are cholestyramine, antacid gels, kaolin-pectate, certain antimicrobial drugs and cancer chemotherapeutic agents. In selected patients, antibiotics may enhance digoxin bioavailability by eliminating intestinal flora that metabolize digoxin.

Antiarrhythmic drugs, such as quinidine and amiodarone, can markedly increase steady state serum digoxin levels. Certain calcium channel blocking drugs, particularly verapamil, have a similar effect. Potassium-sparing diuretic drugs, such as spironolactone, can alter digoxin pharmacokinetics.

Indomethacin may decrease renal excretion of digoxin in preterm infants. Finally, rifampin, an antibiotic used in the treatment of tuberculosis, may lower steady state serum digoxin levels in patients with severe renal disease. Physicians must maintain constant vigilance whenever medications are added to or withdrawn from a therapeutic regimen that includes digoxin.

(J Am Coll Cardiol 1985;5:82A–90A)

There is a high incidence of toxicity during the therapeutic use of this class of drugs. Interactions of cardiac glycosides with other drugs contribute significantly to the high prevalence of digitalis toxicity. This review will focus on the pharmacokinetic interactions of digoxin. The drugs that have been investigated for interactions are listed in Table 1 and their mechanisms and magnitude are summarized in Table 2.

**Historical Perspective**

Drug interactions with digoxin could only have been suspected but not verified before the availability of assays sufficiently sensitive to measure digoxin in biological fluids (1–4). In 1971, Caldwell and Greenberger (5) investigated the possibility that cholestyramine, an anion exchange resin known to bind neutral sterols, might be effective in decreasing the duration of digitalis toxicity. Subsequently, Smith (6) documented that cholestyramine coadministered with digoxin could decrease digoxin absorption. Binnion (7) also reported extremely low levels of serum digoxin in a patient who was taking kaolin-pectate with digoxin and identified that kaolin-pectate decreased the bioavailability of digoxin. This led to an intensive investigation of drugs that might decrease digoxin bioavailability. The startling observation by Ejvinsson (8) that quinidine coadministered with digoxin caused a marked elevation in plasma concentrations of digoxin led to exploration of other antiarrhythmic drug interactions with digoxin. Subsequently, the pace of investigation of drug interactions with digoxin has escalated and numerous interactions with digoxin have been unveiled (9–11).

The focus on drug interactions with digoxin is appropriate for this agent since it not only is one of the most commonly prescribed drugs, but also has a narrow therapeutic index.

---

**Drugs That Affect Bioavailability of Digoxin**

**Cholestyramine.** When 4 to 8 g of cholestyramine are given at the same time as digoxin, there is a 25% decrease in steady state serum digoxin levels (12). The mechanism of this interference appears to be related to physical binding of digoxin to the resin (5). Administration of digoxin 8 hours before cholestyramine prevents the interference with absorption of the glycoside (12). This interaction can also be minimized by prescribing digoxin in a solution contained in a gelatin capsule (Lanoxicap). The Lanoxicap preparation also produces less variability in digoxin absorption when cholestyramine is given with the capsules as compared with the tablets.

**Antacids.** Antacid gels (13), but not the tablets (14), appear to decrease the absorption of a single dose of digoxin by approximately 25%. The mechanism of this reduction of digoxin absorption by antacids is unclear. Since only magnesium trisilicate has been found to adsorb digoxin in vitro (15) while other antacids also lowered plasma levels in human beings, the decreased absorption of digoxin may be due to factors other than adsorption. The effect of con-
comitant administration of antacids and digoxin on steady state plasma levels of digoxin remains to be established. Until this information is available, it is advisable not to administer digoxin at the same time as antacids.

**Kaolin-pectate and bran.** The decreased bioavailability of digoxin as a result of the coadministration of an antidiarrheal suspension containing 18% kaolin and 0.4% pectin (Kaopectate) was first reported by Binnion (7) after observing ineffective blood levels of digoxin in a patient who had taken the antidiarrheal at the same time as digoxin. Brown and Juhl (13) subsequently verified Binnion’s findings in a cross-over study employing 10 normal volunteers. The magnitude of this drug interaction is still not clear since there have been no studies to determine the effect of this combination on steady state plasma levels of digoxin. The decrease in digoxin absorption can be abolished by giving digoxin 2 hours before administration of the antidiarrheal agent (16) or may be minimized by administration of the capsule formulation of digoxin (17).

When digoxin was given at the beginning of a meal containing a high content of fiber, there was a 20% decrease in cumulative 6 day urinary digoxin excretion (12). Others (18) were not able to document a decrease in digoxin absorption when digoxin was given 15 to 30 minutes before a meal containing high fiber content. The mechanism of this possible interaction appears to be an adsorption of digoxin to bran (19).

**Antimicrobial drugs.** Certain antimicrobial drugs such as neomycin, sulfasalazine and paraaminosalicylic acid (PAS), often used for their effect on intestinal function and flora, appear to depress digoxin absorption (12,20,21). This interaction results in an 18 to 28% decrease in the bioavailability of digoxin and is not minimized by temporal separation of the time of administration of digoxin and the concurrently administered antimicrobial agent.

Antibiotic treatment may increase serum digoxin levels by an entirely different mechanism. Digoxin undergoes bio-transformation to dihydrodigoxin and its corresponding aglycone, dihydrodigoxigenin. These two metabolites, which are relatively inactive, are referred to as digoxin reduction products. Digoxin reduction products appear to be made exclusively by bacteria in the gastrointestinal tract, probably in the colon (22). The reduced metabolites virtually disappear from the stool and urine after therapy with certain antibiotics, and this can lead to an increase in bioavailability of digoxin (23). In a recent study (23), a 5 day course of erythromycin or tetracycline was found to raise the serum digoxin concentrations by 43 to 116% in three volunteers who produced large amounts of digoxin reduction products (>35 to 40% of total urinary digoxin and its metabolites). Since only 10% of subjects produce large amounts of these reduced derivatives, this increase in digoxin levels due to antibiotics should occur in only a minority of patients (22,24).

Administration of digoxin in capsule form decreases the percent of digoxin reduction products formed, presumably by more complete absorption of digoxin in the small intestine (25). Thus, the increase in bioavailability during administration of these antibiotics should be minimized with the use of the capsule forms of digoxin.

**Drugs that alter gut motility.** Digoxin absorption is not affected by medications that alter gut motility, such as propantheline (Probanthine) or metoclopramide (26).

**Cancer chemotherapeutic agents.** Digoxin absorption and steady state levels may be markedly decreased by cancer chemotherapy (27). This inhibition of digoxin absorption is reversible after 1 week. The mechanism of this interaction appears to be temporary damage of the intestinal mucosa by the cytostatic drugs.

### Table 1. Generic and Trade Names of Drugs Investigated for Interaction With Digoxin

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestyramine</td>
<td>Questran</td>
</tr>
<tr>
<td>Kaolin-pectate</td>
<td>Kaopectate</td>
</tr>
<tr>
<td>Neomycin</td>
<td>Neomycin</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Azulfidine</td>
</tr>
<tr>
<td>Para-amino salicylic acid</td>
<td>PAS, Teebacin</td>
</tr>
<tr>
<td>Propantheline</td>
<td>Probanthine</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Quinidine</td>
</tr>
<tr>
<td>Hydroxychlooroquine</td>
<td>Plaquinil</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Cordarone</td>
</tr>
<tr>
<td>Procaainamide</td>
<td>Pronestyl</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>Norpace</td>
</tr>
<tr>
<td>Mexiletine</td>
<td>Mexil</td>
</tr>
<tr>
<td>Flecainide</td>
<td>Flecainide</td>
</tr>
<tr>
<td>Morticine</td>
<td>Ethmozine</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Calan, Iopin</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Cardizem</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Procardia</td>
</tr>
<tr>
<td>Tiapamil*</td>
<td></td>
</tr>
<tr>
<td>Nicardipine*</td>
<td></td>
</tr>
<tr>
<td>Gallopamil*</td>
<td></td>
</tr>
<tr>
<td>Lidoflazin*</td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Aldactone</td>
</tr>
<tr>
<td>Triamterene</td>
<td>Dyrenium; also in Dyazide</td>
</tr>
<tr>
<td>Amiloride</td>
<td>Midamor; also in Moduretic</td>
</tr>
</tbody>
</table>

*U.S. trade names not now available.

**Interaction of Digoxin With Antiarrhythmic Drugs**

**Quinidine.** In 1978, Eijvinson (8) reported that the concurrent administration of quinidine to 12 patients increased average serum digoxin concentrations from 0.9 to 1.6 ng/ml. One of the six patients whose plasma concentrations rose above therapeutic range developed symptoms of digitalis intoxication. This observation has since been amply confirmed (28–30). The mechanism of this interaction is complex. Quinidine may enhance digoxin bioavailability (31), although this is disputed (32). There is a decrease in the
volume of distribution of digoxin, suggestive of a displacement of digoxin binding by quinidine (33,34).

**Renal and nonrenal clearance of digoxin.** The most important mechanisms responsible for the digoxin-quinidine interaction are a quinidine-induced reduction of both renal and nonrenal clearances of digoxin (33–35). Since glomer-

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Interaction: Effect on Digoxin</th>
<th>Mean Magnitude of Interaction*</th>
<th>Type of Study</th>
<th>Suggested Intervention</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestyramine</td>
<td>Adsorption of digoxin</td>
<td>↓ 25%</td>
<td>Single Dose</td>
<td>X</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Steady State</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1) Give digoxin 8 hours before cholestyramine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2) Use solution or capsule form of digoxin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Temporal separation of time of administration</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Antacids</td>
<td>Unclear</td>
<td>↓ 25%</td>
<td>X</td>
<td>Temporal separation of time of administration</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1) Give digoxin 2 hours before kaolin-pectate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2) Use solution or capsule form of digoxin</td>
<td>13,16,17</td>
<td></td>
</tr>
<tr>
<td>Kaolin-pectate</td>
<td>Adsorption of digoxin</td>
<td>?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bran</td>
<td>Adsorption of digoxin</td>
<td>↓ 20%</td>
<td>X</td>
<td>Temporal separation of time of administration</td>
<td>12,18</td>
</tr>
<tr>
<td>Neomycin</td>
<td>Unknown</td>
<td>↓ 28%</td>
<td>X</td>
<td>Increase dose of digoxin</td>
<td>21</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td></td>
<td>↓ 18%</td>
<td>X</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>PAS</td>
<td></td>
<td>↓ 22%</td>
<td>X</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>↑ Bioavailability by ↑ intestinal metabolism of digoxin by certain gut flora</td>
<td>↑ 43 to 116%</td>
<td>X</td>
<td>1) Measure serum digoxin concentration</td>
<td>23,25</td>
</tr>
<tr>
<td>Tetracycline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(in &lt;10% of subjects)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinidine</td>
<td>? ↓ Bioavailability</td>
<td>↑ 100%</td>
<td>X</td>
<td>1) Decrease dose by 50%</td>
<td>28–30</td>
</tr>
<tr>
<td></td>
<td>↓ volume of distribution, ↓ renal and nonrenal clearance</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>↓ Renal and nonrenal clearance</td>
<td>↑ 70 to 100%</td>
<td>X</td>
<td>Same as for quinidine</td>
<td>53,54,57</td>
</tr>
<tr>
<td>Verapamil</td>
<td>↓ Renal and nonrenal clearance</td>
<td>↑ 70 to 100%</td>
<td>X</td>
<td>Same as for quinidine</td>
<td>66,67</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>? ↓ Renal clearance</td>
<td>↑ 22%</td>
<td>X</td>
<td>None</td>
<td>71,72</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>Unknown</td>
<td>↑ 15%</td>
<td>X</td>
<td>None</td>
<td>76</td>
</tr>
<tr>
<td>Tiapamil</td>
<td>Unknown</td>
<td>↑ 60%</td>
<td>X</td>
<td>Same as for quinidine</td>
<td>76</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>↓ Renal and nonrenal clearance</td>
<td>↑ 30%</td>
<td>X</td>
<td>Measure serum digoxin concentration</td>
<td>86,90</td>
</tr>
<tr>
<td>Triameterene</td>
<td>↓ Nonrenal clearance</td>
<td>↑ 20%</td>
<td>X</td>
<td>Measure serum digoxin concentration</td>
<td>86</td>
</tr>
<tr>
<td>Indomethacin (preterm infants)</td>
<td></td>
<td></td>
<td>X</td>
<td>Decrease dose by 25%</td>
<td>97</td>
</tr>
</tbody>
</table>

*Alteration in bioavailability or serum concentration. For single dose studies, the magnitude of the anticipated change in serum digoxin concentration was estimated from pharmacokinetic data, particularly the change in total body clearance. ↑ = increased; ↓ = decreased; ? = questionable.
ular filtration rate is unchanged during concurrent digoxin-quinidine administration, it is clear that the decreased renal elimination of digoxin in human beings results from a quinidine-induced decrease in tubular secretion of digoxin (36). Decisive evidence for a decrease in the nonrenal excretion of digoxin under the influence of quinidine was established by comparing the kinetics of digoxin in anuric patients on chronic hemodialysis when given digoxin alone and concomitantly with quinidine (37–39). The combination therapy resulted in a rise in serum digoxin concentration in these anuric patients.

The increase in digoxin serum concentration is directly, but not linearly, related to the dose of quinidine (41,40). The rate at which a new digoxin steady state is achieved is dependent on the digoxin elimination half-life. If the half-life of digoxin is 36 hours, approximately 7 days (1.5 days × 5 half-lives) are required to achieve a new steady state digoxin level. However, in patients with a glomerular filtration rate of less than 50 ml/min, the time required for digoxin to reach a new steady state with the addition of quinidine may be considerably longer.

Electrophysiologic and inotropic effects. It is clear that the elevation of digoxin levels by concurrent quinidine administration results in enhanced electrophysiologic effects demonstrated on the surface electrocardiogram as a prolongation of the PR interval, by central nervous system manifestations of toxicity such as anorexia, nausea, vomiting and scotomata and also by enhanced ventricular ectopic activity (41–45).

The elevated serum digoxin levels induced by concurrent administration of digoxin and quinidine have been reported not to show an enhanced inotropic effect as measured by systolic time intervals (46–48). Schenck-Gustafsson et al. (49), however, measured inotropic effects of digoxin at steady state during digoxin administration alone and during digoxin and quinidine administration. They then gave sufficient digoxin to achieve a serum digoxin concentration similar to that obtained when digoxin and quinidine were given concomitantly. They concluded that digoxin elevation due to quinidine was accompanied by an increased cardiac effect.

Digitalis toxicity. Clinical evidence indicates that there are increased electrophysiologic and inotropic effects associated with the elevation of serum digoxin as a result of concurrent quinidine administration. This combination of drugs can cause signs and symptoms of digitalis toxicity. Therefore, the dose of digoxin should be decreased by approximately 50% and the serum digoxin levels should be measured approximately 1 week after the two drugs are given together. If the dose of quinidine is increased, one can anticipate a further increase in serum digoxin levels.

Quinine, the 1-isomer of quinidine, also reduces total body clearance and increases the half-life of digoxin (50). It is likely that hydroxychloroquine, a quinine derivative, has similar interactions with digoxin (51).

Amiodarone. In 1981, Moysey et al. (52) observed a mean increase in plasma digoxin concentration of 70% in seven patients when amiodarone, 600 mg/day, was administered concurrently with digoxin. The mean concentration of digoxin after amiodarone was 2 ng/ml. Four patients developed symptoms compatible with digoxin toxicity. The plasma digoxin level increased by 25% within 24 hours after the initiation of amiodarone treatment. These observations have subsequently been confirmed (53,54). There is suggestive evidence that the increase in digoxin levels may in part be directly related to the dose of amiodarone since a linear correlation was observed between plasma amiodarone levels and digoxin serum levels (55). However, a daily amiodarone dose of 400 mg is sufficient to reduce clearance of a digoxin concentration by 26% (56).

Mechanism. The digoxin-amiodarone interaction is due in part to a decrease in the renal clearance of digoxin, a decrease in nonrenal clearance and an increase in digoxin half-life. No significant decrease in the volume of distribution of digoxin was observed after amiodarone therapy (56,57).

Digitalis toxicity. When serum digoxin levels are raised as a result of the amiodarone-digoxin interaction, digitalis toxicity may result. Generally, the toxic manifestations consist of bradycardia or various degrees of atrioventricular (AV) block rather than digitalis-toxic tachyarrhythmias (57,58). Recommendations for digoxin dose adjustment during concomitant amiodarone therapy are similar to those when quinidine is given with digoxin.

Other antiarrhythmic drugs. There are several antiarrhythmic drugs that do not appear to have any clinically relevant pharmacokinetic interactions with digoxin. These include procainamide (59), disopyramide (59–61), mexiletine (59,62), flecainide (63) and ethmozine (64).

Interaction of Digoxin With Calcium Channel Blocking Drugs

The pharmacokinetic interaction between digoxin and calcium channel blocking drugs varies from none with nifedipine to an increased serum digoxin level of more than 70% when verapamil and digoxin are given concomitantly.

Verapamil. In 1980, Klein et al. (65) reported that serum digoxin levels increased 70% during concurrent treatment with verapamil. They found (66) that the effect of verapamil on serum digoxin concentration developed gradually within the first few days after verapamil was coadministered with digoxin and approached the new steady state value within 7 days after the start of verapamil therapy. The interaction is dose-dependent. The mechanism of the digoxin-verapamil interaction consists of decreases in both renal and extrarenal clearance of digoxin by verapamil (67). Since the creatinine clearance does not change under the influence of verapamil, the decreased renal clearance of digoxin appears to be due to an inhibition of tubular secretion.
The elevated plasma digoxin concentration induced by verapamil is associated with an inotropic effect as assessed by a measurement of systolic time intervals (68). When the serum digoxin levels are markedly elevated as a result of coadministration of verapamil, lethal cardiac toxicity may occur (69). This is more likely to take the form of severe bradycardia or asystole, rather than initiation of the tachyarrhythmias that are observed when quinidine induces elevated serum digoxin levels (67,70). It seems prudent to decrease the dose of digoxin by 50% when verapamil and digoxin are given concurrently.

**Diltiazem.** There is minimal pharmacokinetic interaction between diltiazem and digoxin (71). An average increase in steady state plasma digoxin concentration of 22% was observed when diltiazem, 180 mg/day, was given to 24 normal subjects who were receiving β-acetyldigoxin, 0.2 mg daily (72). This interaction may be due to a diltiazem-induced decrease in renal clearance of digoxin (71). The magnitude of the diltiazem interaction is small; therefore, digoxin dose adjustment is probably unnecessary.

**Nifedipine.** There is no pharmacokinetic interaction between nifedipine and digoxin, either in patients (73) or in normal subjects (74,75).

**Other calcium channel blocking drugs.** Tiapamil, a congener of verapamil, causes an increase in serum digoxin levels of 60%, similar to that of verapamil (76). Nicardipine is related to nifedipine and increases plasma digoxin minimally, in the order of 15%. A similar minimal increase in digoxin levels is induced by gallopamil (77). There is no pharmacokinetic interaction between digoxin and lidoflazine (78).

**Interaction With Diuretic Drugs**

**Furosemide and sodium-induced diuresis.** Diuresis induced by furosemide does not significantly affect the excretion of digoxin (79,80). However, Naafs et al. (81) reported that diuresis caused a 70% increase in digoxin clearance and a 20% decrease in serum digoxin levels in 10 patients who were taking digoxin for atrial fibrillation and who did not have congestive heart failure. These subjects were initially sodium-depleted, both by dietary restriction of sodium as well as by diuretic drugs. When the sodium diet was liberalized to a moderately high sodium diet, the digoxin clearance increased by 70% and the serum digoxin levels decreased by 20%. Mechanisms that have been identified for renal excretion of digoxin include glomerular filtration, tubular secretion and proximal tubular reabsorption of digoxin. Naafs et al. (81) postulated that one of the mechanisms responsible for the increase in digoxin clearance due to sodium loading was diminished passive proximal back diffusion of filtered and secreted digoxin. Sodium loading has been shown to diminish proximal fractional reabsorption of glomerular ultrafiltrate. Thus, it is possible that patients who are on a strict low sodium diet and whose dietary sodium is increased may show some moderate decrease in steady state serum digoxin levels (81).

**Diuresis-induced hypokalemia.** Although thiazides and loop diuretics themselves do not alter the kinetics of digoxin excretion, they induce a dose-dependent loss of potassium from the body, resulting in a decreased serum potassium concentration. It is well known that hypokalemia is associated with sensitivity to digitalis and, thus, increases its toxicity (82,83), but it is not well appreciated that when the serum potassium is as low as 2 to 3 mEq/liter, the tubular secretion of digoxin is nearly blocked. This reduced tubular secretion of digoxin results in a diminished plasma clearance of digoxin and thereby a prolonged elimination half-life of digoxin (84,85). Thus, hypokalemia itself can result in an increase in serum digoxin level as well as enhancing toxicity (85).

**Potassium-sparing diuretic drugs.** The potassium-sparing diuretic drugs, spironolactone, triamterene and amiloride, have been reported to induce changes in digoxin kinetics (86–89). Spironolactone increases the plasma concentration of digoxin by inhibiting tubular secretion of digoxin. This results in a decrease in the renal clearance of digoxin. The extrarenal clearance of digoxin also decreases (88,90). In contrast, amiloride alters digoxin pharmacokinetics by different mechanisms. This drug causes an increase in renal clearance, but a marked decrease in extrarenal clearance. The net result is a tendency to decrease digoxin total body clearance (87). Possible mechanisms for these observations include an increased tubular secretion of digoxin to account for the increased renal clearance and a decrease in the hepatic elimination rate of digoxin to account for the decrease in extrarenal clearance. Triamterene does not alter renal elimination of digoxin, but reduces the extrarenal clearance of digoxin. When triamterene is given with digoxin, the total digoxin elimination is reduced by 20% (86).

The effects of the potassium-sparing diuretic drugs on steady state serum digoxin levels have not been adequately evaluated. Potassium-sparing diuretic drugs have different mechanisms and sites of action, which may account for their differing effects on digoxin pharmacokinetics. Spironolactone exerts its effects from the capillary side of the renal tubular cell, whereas triamterene and amiloride act on the luminal side (91). Spironolactone does not increase intracellular potassium concentration, whereas triamterene and amiloride do.

**Combined digitalis, quinidine and diuretic drug therapy.** Patients with cardiac disease are frequently treated with multiple medications and the combination of a potassium-sparing diuretic drug, digoxin and quinidine is not unusual. This combination of quinidine and spironolactone caused significant reductions in total body clearance of digoxin, nonrenal digoxin clearance and digoxin renal clearance beyond the reductions induced by either drug alone (90). Therefore, the effects of these two drugs on steady state serum digoxin concentrations should be additive.
Clinical significance. The clinical significance of an anticipated elevation of steady state serum digoxin levels induced by the potassium-sparing diuretic drugs is not clear. Waldorff et al. (86,87) found that both spironolactone and amiloride attenuated the positive inotropic effect of digitalis evaluated by systolic time intervals and echocardiography, whereas triamterene induced no changes in digoxin-elicited inotropy. Since the magnitude of this interaction of potassium-sparing diuretic drugs has not been established, measurement of the steady state serum digoxin levels may be warranted.

Miscellaneous Drug Interactions With Digoxin

Anti-inflammatory drugs. No pharmacokinetic interaction has been observed with aspirin (92), benoxaprofen (93) or tiaprofenic acid (94). Elevated serum levels of digoxin were observed after 1 week of concomitant therapy with ibuprofen, but this increase in digoxin level did not persist after 28 days (95).

Indomethacin therapy did not alter digoxin pharmacokinetics in healthy adult volunteers with normal renal function (96), but was found to cause an increase of 45% in serum digoxin levels in preterm infants when coadministered with digoxin for the treatment of patent ductus arteriosus (97). Administration of indomethacin to the infants was associated with a significant decrease in urinary output, suggesting that the increase in serum digoxin level was due to a decreased glomerular filtration rate and a decrease in the renal clearance of digoxin. These authors (97) suggested that when indomethacin is added to digoxin therapy in preterm infants, the digoxin dose should be reduced by 50%. The increase in serum digoxin level associated with indomethacin may also apply to adult patients since a lowering of effective renal plasma flow has been observed in patients after indomethacin administration (96). Therefore, the potential for digoxin-indomethacin interaction may be greater in patients with abnormalities in renal function.

Rifampin. Rifampin, an antibiotic used for the treatment of tuberculosis, has been shown to remarkably lower the steady state serum digoxin level in several patients dependent on dialysis (98,99). There is limited evidence (98) to suggest that this interaction is due to an increased bio-transformation of digoxin in these patients with minimal to no renal function. Rifampin accelerates the metabolism of numerous drugs, including digoxin (100). Other possible explanations for the digoxin-rifampin interaction include decreased absorption of digoxin or increased biliary excretion.

A complex drug interaction involving rifampin, digoxin and quinidine has been reported (101). Therapy with rifampin produced a decline in both the serum quinidine concentration and serum digoxin concentration. It was postulated that rifampin increased the metabolism of quinidine; in turn, the interaction between quinidine and digoxin was diminished, thereby lowering serum digoxin levels. It is possible that digoxin metabolism was directly accelerated by rifampin. This case report (101) illustrates the complex interaction that may occur with multiple drug therapy.

Cimetidine. Fraley et al. (102) reported a 25% decrease in steady state serum digoxin concentrations when digoxin was given together with cimetidine. These results are in contrast to those of Jordens et al. (103) who studied the pharmacokinetics of oral digoxin in eight healthy volunteers, both with and without concurrent cimetidine. They concluded that cimetidine had no effect on the area under the plasma concentration versus time curve of digoxin.

Vasodilator drugs. Total renal clearance of digoxin was increased by 50% in 8 patients during administration of nitroprusside or hydralazine (104). Because the glomerular filtration rate was unchanged and the estimated renal blood flow was increased, the mechanism of this alteration in digoxin renal clearance was thought to be an increase in tubular secretion of digoxin. It is not yet known whether long-term vasodilator therapy increases the dosage requirements for digoxin in patients with congestive heart failure.

Summary

An intensifying myriad of interactions with digoxin is now being revealed. It is no wonder that digoxin intoxication has been so difficult to avoid. Patients with heart disease may be treated concomitantly with anticholesterolemic drugs, diuretic drugs, calcium channel blocking agents, vasodilators and antimicrobials, some of which have been shown to interact with digoxin. The accumulated information regarding drug interactions with digoxin should contribute to greater safety in the use of the drug, provided that the physician maintains constant vigilance whenever any medication is added to or withdrawn from a therapeutic regimen that includes digoxin.

Although there has been a tremendous increase in our knowledge of the drug interactions, more investigation is needed to define the full scope and magnitude of these interactions with digitalis, particularly during steady state. We are also greatly in need of accurate and sensitive methods to reliably measure the inotropic and vagotonic effects of digitalis to assess the effects of these drug interactions.

I am indebted to Paul Fenster, MD and Paul Nolan, MD for critical review of this manuscript. I gratefully acknowledge the secretarial assistance of Debbie Hunter.

References
2. Oliver GC Jr, Parker BM, Brasfield DL, Parker CW. The measurement...


