Decreased Bioavailability of Digoxin Due to Hypocholesterolemic Interventions

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SUMMARY This study tested the hypothesis that hypocholesterolemic interventions interfere with the bioavailability of orally administered digoxin. Using single dose studies of bioavailability, cumulative six-day urinary digoxin excretion (expressed as a percentage of each individual's control value) was 103% with a normal fiber diet, 82% with a high fiber diet, 83% with 4 g of cholestyramine, 69% with 8 g of cholestyramine, 80% with 8 g cholestyramine administered eight hours before digoxin, 92% with 8 g of cholestyramine administered eight hours after digoxin and 80% after completion of two weeks of treatment with para-aminosalicylic acid.

Analysis of the urinary excretion data and associated serum levels revealed significant interference with the absorption of digoxin in all instances except for administration of digoxin either with a normal fiber diet or administration eight hours before cholestyramine. The cholestyramine-digoxin interaction was further studied using steady-state investigation of bioavailability. Serum levels and daily urinary digoxin excretions (expressed as a percentage of each individual's control value) were: 75% and 80% for digoxin administered simultaneously with 4 g of cholestyramine daily; 69% and 86% for digoxin administered simultaneously with the first daily dose of cholestyramine given as 4 g, four times a day, and 96% and 93% with cholestyramine 8 g twice a day, eight hours before and eight hours after digoxin ingestion. Serum levels and urinary excretions for all three cholestyramine interventions were significantly less than control.

The results of the single dose and steady-state experiments demonstrate that cholestyramine's reduction of digoxin oral bioavailability is related to the dose of cholestyramine and the proximity of the time of administration of the two drugs.

CLINICALLY SIGNIFICANT INTERFERENCE with absorption of oral digoxin due to concomitant administration of such drugs as antacids,1 kaolin-pectin1 and sulfasalazine (salicylazosulfapyridine)2 has been demonstrated. Hypocholesterolemic interventions which alter intestinal function are also likely to cause significant interference. Cholestyramine is an effective oral hypocholesterolemic agent which has been well documented to bind both digoxin and digitoxin in vitro.3 However, Hall and co-workers did not demonstrate any dramatic effect of cholestyramine upon digoxin absorption.4 Para-aminosalicylic acid (PAS-C) also effectively lowers cholesterol.5, 6 While it may not correlate directly with its hypocholesterolemic effect, induction of malabsorption is a proven effect of this drug.7

Based on epidemiologic data, an association between atherosclerosis and a low intake of dietary fiber has been suggested.8 Like cholestyramine, these non-nutritive fibers have been shown to be adsorbent agents capable of binding such materials as bile salts.9

Based on these considerations, the present investigation studied systematically the effects of these hypocholesterolemic interventions upon the absorption of digoxin. Single dose studies of digoxin bioavailability were used to study the interactions with cholestyramine, dietary fiber and para-aminosalicylic acid. The interaction of cholestyramine and digoxin was further investigated using steady-state studies of bioavailability.

Methods

Single Dose Study Involving Dietary Fiber and Cholestyramine

The study used single dose estimates of bioavailability10 with 12 normal adult volunteer subjects without evidence of any cardiac, renal, gastrointestinal or other abnormalities. Each volunteer was evaluated before the actual protocol by determining creatinine renal clearance, serum electrolytes, calcium, glutamic oxalacetic transaminase and pyruvic transaminase, alkaline phosphatase, bilirubin and D-xylene absorption, as well as with chest x-ray examination, electrocardiography, clinical history and physical examination.

The volunteers were given 0.75 mg of digoxin (Lanoxin tablets, 0.25 mg, Burroughs Wellcome Company, Lot #660-1, in vitro dissolution rate 78% in one hour) in the fasting state, with a meal containing 0.75 g of crude fiber representing a regular fiber diet typical of the average American meal, with a meal containing 5 g of crude fiber representing a high fiber diet, and simultaneously with 4 g of cholestyramine. The two diets consisted of breakfast meals containing 600 calories distributed as 40% fat, 15% protein and 45% carbohydrate. They included 280 mg of cholesterol. The only difference was in the dietary fiber content, which, when expressed as neutral detergent fiber, was estimated to be 3.5 g in the regular fiber diet and 18.9
g in the high fiber diet. Digoxin was administered at the beginning of the meal. The order of administration was randomized according to a Latin square design. At least 14 days elapsed between each administration of digoxin. Volunteers did not eat for eight hours before and for four hours after each dose of digoxin.

Blood samples were obtained from a forearm vein at 0, 10, 20, 30, 45, 60, 90 and 120 minutes and three, four, six and eight hours after each digoxin administration. Separate urine collections were made from zero to two hours, two to four hours, four to six hours, six to eight hours, eight to 24 hours, and then daily for the next five days after each digoxin administration. Assessment of bioavailability was based on the area under the eight-hour serum concentration curve and on the six-day cumulative urinary excretion of digoxin.

**Single Dose Study Involving Cholestyramine and Para-aminosalicylic Acid**

In this single dose study, 10 adult volunteers were given 0.75 mg of digoxin (Lanoxin, Burroughs Wellcome Company, Lot #373-V, in vitro dissolution rate 77.8% in one hour) in the fasting state, simultaneously with 8 g of cholestyramine, eight hours after 8 g of cholestyramine and eight hours before 8 g of cholestyramine. These doses were simultaneous with the last 2 g dose of PAS-C (tablets, 500 mg, Hellwig Pharmaceuticals), given as 2 g four times a day for two weeks. Urine and blood samples and assessment of bioavailability were determined as above.

**Steady-state Study of Cholestyramine-digoxin Interaction**

Four of the 12 individuals included in the dietary fiber-cholestyramine single dose study participated in four randomized treatment periods, each separated by two weeks. During each treatment phase, each received 0.5 mg of digoxin (Lot #660-1) orally every day for 14 days. Digoxin serum levels were measured 24 hours after each dose. Twenty-four-hour urinary digoxin levels were determined for the 14 days of digoxin administration and also, in order to determine a urinary excretion half-life, for six days after discontinuation of the glycoside. The four randomized treatment phases consisted of: 1) the administration of digoxin by itself as control, 2) the administration of digoxin simultaneously with cholestyramine given 4 g daily, 3) the administration of digoxin simultaneously with one of the 4 g doses of cholestyramine given four times a day for a total daily dose of 16 g, and 4) the administration of digoxin with 8 g of cholestyramine twice daily. In the latter treatment phase, the doses of cholestyramine were administered eight hours before and eight hours after each dose of digoxin, and none was administered simultaneously with digoxin.

**General Methods**

Urinary excretion half-life for digoxin was derived from the urinary elimination rate constant (k) by the standard formula \( T_{1/2} = 0.693/k \). This rate constant was derived from the slope of a semilogarithmic plot of the percentage of drug remaining to be excreted vs time during the six days following the last dose of digoxin for any treatment phase.

Serum and urinary digoxin concentrations were determined by radioimmunoassay\textsuperscript{11} using digoxin-specific antibodies produced in rabbits\textsuperscript{12}. Data was analyzed by analysis of variance (\( P < 0.01 \)) and Tukey's multiple comparison test (level of significance \( \alpha = 0.05 \)).

**Studies of Digoxin-PAS in vitro Physical Adsorption**

In vitro studies were carried out to quantify any physical adsorption between PAS and digoxin. H\textsuperscript{3}digoxin (50 \( \mu \)Ci) was added to 60 ml of digoxin elixir (Lanoxin Pediatric Elixir, Lot # 598L). One milliliter of the resulting solution was added to a 50 ml screw cap culture tube along with 19 ml of buffer solution (pH 2, 4 or 7). Duplicate control samples of 100 \( \mu l \) were taken and the \( ^3 \)H activity measured in a Beckman 100 LS scintillation counter. PAS (as PAS-C tablets ground to a fine powder) in an amount equivalent to 50, 100, 200 or 400 mg of PAS was added to the culture tube. The mixture was allowed to incubate for 30 minutes at room temperature while being agitated at a moderate speed on an Eberbach shaker. After incubation, the mixture was centrifuged, duplicate 100 \( \mu l \) samples were taken and the \( ^3 \)H activity remaining in solution was compared with the control value. For comparison, a comparable study was performed using digoxin and magnesium trisilicate, a known adsorber of the glycoside\textsuperscript{13}.

**Results**

**Single Dose Study Involving Dietary Fiber and Cholestyramine**

Figure 1 shows the mean eight-hour serum concentration curve for control and for administration with regular fiber diet, high fiber diet and 4 g of cholestyramine. The levels demonstrate that the time to peak concentration is essentially identical for control and fiber diets but is delayed with cholestyramine. The area under the eight-hour serum concentration curve is plotted in figure 2 for each subject along with the mean and standard error. The values associated with administration of digoxin with either diet or with 4 g of cholestyramine were significantly less than control but with no difference among the three interventions themselves.

The six-day urinary excretions are plotted in figure 3 for each subject, along with the mean and standard error during control and with each intervention. For control, the mean value was 41% of the oral dose given. The urinary digoxin excretions associated with the high fiber diet and with 4 g of cholestyramine were both significantly less than control and less than that found with the regular fiber diet.

The urinary excretion half-life for digoxin during the control period was 27.8 ± 0.9 (SEM) hours,
Figure 1. Time course of serum digoxin concentration after administration of 0.75 mg of digoxin by mouth to 12 healthy adult subjects. Each point represents mean ± SEM for all subjects.

Figure 2. Area under digoxin concentration curve (in [ng/ml] × min) after administration of 0.75 mg of digoxin by mouth, showing values for control (mean ± SEM = 633 ± 40), regular fiber diet (453 ± 40), high fiber diet (431 ± 40) and 4 g of cholestyramine (472 ± 37). Each subject is identified by a separate symbol (\(\triangledown\), \(\triangle\), \(\circ\), etc.).
28.4 ± 0.3 with regular fiber diet, 28.0 ± 0.4 with the high fiber diet and 28.0 ± 0.4 with cholestyramine. There were no statistically significant differences among the urinary excretion half-lives.

**Single Dose Study Involving Cholestyramine and Para-aminosalicylic Acid**

Figures 4 and 5 show the mean eight-hour serum digoxin concentration curve for control and for administration with 8 g of cholestyramine and with PAS. Serum levels demonstrate that the rate of rise and time to peak are essentially identical for control and for administration eight hours before cholestyramine (fig. 4). In contrast, administration of digoxin simultaneously with or eight hours after cholestyramine (fig. 4), as well as administration with PAS (fig. 5), was associated with strikingly reduced peak serum levels. The area under the eight-hour serum concentration curve is plotted in figure 6. The mean value for intervention with 8 g of cholestyramine, simultaneously with digoxin, was significantly less than control and less than digoxin administration eight hours before cholestyramine. In addition, the control value was also significantly greater than that for intervention with PAS and greater than that for digoxin administration eight hours after cholestyramine.

The six-day urinary excretions are plotted in figure 7. The values for control and for administration of digoxin eight hours before cholestyramine were both significantly greater than that for administration simultaneously with 8 g of cholestyramine. The value associated with simultaneous administration with 8 g of cholestyramine represents a 31% reduction compared to control, almost twice the 17% reduction found with 4 g of cholestyramine in the cholestyramine-dietary fiber experiment.

The urine excretion half-life for digoxin during control was 27.7 ± 0.6 hours, while that for administration simultaneously with 8 g of cholestyramine was 28.0 ± 0.5, with administration eight hours after cholestyramine it was 27.9 ± 0.8, with administration eight hours before cholestyramine it was 27.6 ± 0.8 and with administration of PAS it was 28.2 ± 0.7. There were no statistically significant differences among the urinary excretion half-lives for control of any of the interventions.

D-xylose absorption tests were performed in nine individuals both before and at the end of the second week of treatment with PAS. Before treatment, the six-hour D-xylose urinary excretion was 7.0 ± 0.46 (SEM) g/25 g oral dose, while that following two weeks of PAS treatment was 3.9 ± 0.54. Serum cholesterol before PAS treatment was 169 ± 9.2 mg%, while that following two weeks of
PAS treatment was 135 ± 7.0. The values for the D-xylose test and serum cholesterol during PAS treatment were significantly less than control. No correlation could be found between the individual control values for D-xylose excretion and those for digoxin excretion, nor between the change in D-xylose excretion induced by PAS compared to the change seen in digoxin excretion associated with PAS treatment. There were no changes in the complete blood counts, protime, partial thromboplastin time or blood levels of total protein, albumin, calcium, phosphate, glucose, uric acid, alkaline phosphatase, lactic dehydrogenase, total bilirubin, glutamic oxalacetic transaminase, urea, creatinine or electrolytes.

Steady-state Study of Cholestyramine-digoxin Interaction

Digoxin serum levels and urinary excretions reached a steady-state by the end of the first week of each treatment phase. The steady-state 24-hour urinary digoxin excrections and serum levels found during the second week of each treatment phase are shown in table 1. The daily urinary excretion value during control (expressed as percent of administered dose) was identical to that recovered in the six-day cumulative urinary excretions for the same four individuals during the control phase of the cholestyramine-dietary fiber-single dose experiment. The value for intervention with 4 g of cholestyramine a day was 34% of the administered dose, which correlates quite closely with the 36% recovered in the six-day cumulative urinary excretion for the same four individuals during the analogous treatment phase of the single dose experiment. The serum level and the 24-hour urinary excretion values for all three interventions with cholestyramine were significantly less than control.

Urinary excretion half-life for digoxin during the control period was 30.8 ± 0.9 (SEM) hours; with intervention of 4 g cholestyramine daily it was 29.9 ± 1.1, with 4 g four times a day it was 33.0 ± 3.0 and with 8 g twice a day it was 32.2 ± 1.0. There were no statistically significant differences among these values.

**Figure 4.** Time course of serum digoxin concentration after administration of 0.75 mg of digoxin by mouth to ten healthy adult subjects. Each point represents mean ± SEM for all subjects.
Figure 5. Time course of serum digoxin concentration after administration of 0.75 mg of digoxin by mouth to ten healthy adult subjects. Each point represents mean ± SEM for all subjects.
Studies of Digoxin-PAS in vitro Physical Adsorption

The in vitro adsorption studies failed to reveal appreciable physical interaction between digoxin and PAS (table 2). The amount of 3H-digoxin remaining in solution after incubation with PAS was within 10% of the control value in all cases except for 400 mg of PAS at pH 4. This 400 mg amount of PAS far exceeds the PAS to digoxin ratio used in our in vivo single dose study of bioavailability, which was 2000 mg–0.75 mg or 2667. Using the same system, substitution of equivalent amounts of magnesium trisilicate (a known adsorber of digoxin) for the PAS resulted in removal of greater than 90% of the 3H-digoxin from solution in all cases.

Discussion

Our studies demonstrate that cholestyramine, meals high in dietary fiber content and para-aminosalicylic acid produce significant interference with the absorption of oral digoxin. Similar instances of interference with digoxin absorption have been reported with other medications such as antacids,1 kaolin-pectin,1 sulfa salazine,2 neomycin14 and diphenylhydantoin.15

In a steady-state experiment, Smith previously reported reduction in digoxin serum levels associated with the administration of cholestyramine, 16 g a day in two individuals.16 Similarly, in a single dose experiment, Binion reported that the area under the eight-hour serum concentration curve in three individuals appeared to be decreased by simultaneous administration of digoxin and 4 g of cholestyramine.17 However, in neither of these reports was statistical analysis given nor was urinary excretion of digoxin measured. In contrast, Hall and co-workers, using a solution of 3H-digoxin adsorbed on a sugar lump, were unable to demonstrate any effect on urinary excretion of digoxin by cholestyramine in either cumulative urinary or fecal excretion following single doses of the glycoside.4

The mechanism of the interference due to cholestyramine is presumably related to physical binding of digoxin to the resin. Previous studies have demonstrated in vitro binding of digoxin to cholestyramine.3, 16 In the extensive studies by Caldwell and Greenberger,3 the binding was directly proportional to the amount of cholestyramine and inversely proportional to the amount of digoxin, with the former effect of more importance than the latter. The binding appeared to be independent of pH. While it is difficult to compare their in vitro data with our in vivo data, the 20 and 27% binding of the glycoside at digoxin concentrations of 1 µg/ml found with the digoxin-cholestyramine ratios similar to those employed in our studies are reasonably close to the 17
and 31% reductions in digoxin urinary excretion seen with 4 and 8 g of cholestyramine, respectively. As would be expected if the mechanism were physical binding, our studies demonstrate that temporal separation of the time of administration of digoxin from that of cholestyramine significantly minimizes the interference with absorption of the glycoside while maintaining a comparable dose of the resin. This can be readily accomplished by using cholestyramine in a twice-daily dosage schedule, which has been demonstrated to be equally as effective as a four-times-a-day dose regimen in terms of cholesterol reduction.18

The reduction of the area under serum curve associated with digoxin, administered with a meal of regular fiber content, is discordant with the results of the cumulative urinary excretion found with the same intervention. The reason for this discrepancy is not clear. However, the lack of interference with digoxin bioavailability by the usual American meal is supported by Greenblatt et al., who previously reported that meals per se do not reduce oral digoxin absorption.20 In contrast, the cumulative urinary excretion and serum levels of digoxin definitely support the conclusion that meals of high fiber content do decrease digoxin oral bioavailability. Dietary fiber has been demonstrated to bind bile salts in vitro.8 Given this similarity to cholestyramine, it seems reasonable to postulate that the mechanism for the reduction of digoxin absorption associated with meals of high fiber content may also be related to physical binding.

The profound reduction in D-xylose absorption associated with PAS therapy in our volunteers suggests changes in the function of the intestinal wall as a possible mechanism for the interference with digoxin absorption by PAS. Levine previously documented the production of steatorrhea by PAS in doses of 12 g per day but not by doses of 6 g per day.7 In that study, jejunal and mucosal biopsies did not demonstrate any abnormalities or alterations under light microscopy. Such alterations in intestinal absorptive function are reminiscent of those previously found with neomycin, which has also been found to alter the absorption of digoxin.14 Our in vitro studies document no significant adsorption of digoxin to PAS to explain the interference with digoxin's bioavailability.

Table 1. Steady-State Digoxin Levels Associated with 0.5 mg Daily Maintenance Administration

<table>
<thead>
<tr>
<th>Volunteer</th>
<th>LO (ng/ml)</th>
<th>MU (ng/ml)</th>
<th>HA (ng/ml)</th>
<th>KE (ng/ml)</th>
<th>Group Mean ± SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.61 ± 0.06*</td>
<td>0.73 ± 0.05</td>
<td>1.09 ± 0.07</td>
<td>0.69 ± 0.05</td>
<td>0.78 ± 0.05†</td>
</tr>
<tr>
<td>With cholestyramine 4 g qd</td>
<td>0.59 ± 0.04</td>
<td>0.41 ± 0.03</td>
<td>0.94 ± 0.04</td>
<td>0.43 ± 0.03</td>
<td>0.59 ± 0.04</td>
</tr>
<tr>
<td>With cholestyramine 8 g bid</td>
<td>0.67 ± 0.04</td>
<td>0.46 ± 0.01</td>
<td>0.57 ± 0.02</td>
<td>0.36 ± 0.02</td>
<td>0.52 ± 0.03</td>
</tr>
</tbody>
</table>

*Figures represent the mean and standard error for the seven measurements during the steady-state week for each individual.
†Figures represent the mean and standard error for the 28 measurements during the steady-state week for the entire group of four volunteers.

Table 2. In Vitro Adsorption—PAS: Digoxin

<table>
<thead>
<tr>
<th>Digoxin</th>
<th>Magnesium Trisilicate</th>
<th>PAS-C: Digoxin Ratio</th>
<th>pH2</th>
<th>pH4</th>
<th>pH7</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05 mg</td>
<td>50 mg</td>
<td>1000</td>
<td>100.2%</td>
<td>101%</td>
<td>97.6%</td>
</tr>
<tr>
<td>0.05 mg</td>
<td>100 mg</td>
<td>2000</td>
<td>98.5</td>
<td>99.4</td>
<td>94.6</td>
</tr>
<tr>
<td>0.05 mg</td>
<td>200 mg</td>
<td>4000</td>
<td>92.2</td>
<td>90.6</td>
<td>95.5</td>
</tr>
<tr>
<td>0.05 mg</td>
<td>400 mg</td>
<td>8000</td>
<td>92.8</td>
<td>80.4</td>
<td>94.2</td>
</tr>
</tbody>
</table>

pH4
In summary, cholestyramine, dietary fiber and PAS all interfere with digoxin's oral absorption. Cholestyramine's interference is dose-related and can be minimized by temporal separation of the time of cholestyramine administration from glycoside's administration.

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