# Atorvastatin Coadministration May Increase Digoxin Concentrations by Inhibition of Intestinal P-Glycoprotein-Mediated Secretion

*Rebecca A. Boyd, PhD, Ralph H. Stern, PhD, MD, Barbra H. Stewart, PhD, Xiaochun Wu, PhD, Eric L. Reyner, BS, Elizabeth A. Zegarac, MS, Edward J. Randinitis, PhD, and Lloyd Whitfield, PhD*

*The effect of atorvastatin on digoxin pharmacokinetics was assessed in 24 healthy volunteers in two studies. Subjects received 0.25 mg digoxin daily for 20 days, administered alone for the first 10 days and concomitantly with 10 mg or 80 mg atorvastatin for the last 10 days. Mean steady-state plasma digoxin concentrations were unchanged by administration of 10 mg atorvastatin. Mean steady-state plasma digoxin concentrations following administration of digoxin with 80 mg atorvastatin were slightly higher than concentrations following administration of digoxin alone, resulting in 20% and 15% higher $C_{max}$ and $AUC_{(0-24)}$ values, respectively. Since $t_{max}$ and renal clearance were not significantly affected, the results are consistent with an increase in the extent of digoxin absorption in the presence of atorvastatin. Digoxin is known to undergo intestinal secretion mediated by P-glycoprotein. Since atorvastatin is a CYP3A4 substrate and many CYP3A4 substrates are also substrates for P-glycoprotein transport, the influence of atorvastatin and its metabolites on P-glycoprotein-mediated digoxin transport in monolayers of the human colon carcinoma (Caco-2) cell line was investigated. In this model system, atorvastatin exhibited efflux or secretion kinetics with a $K_m$ of 110 μM. Atorvastatin (100 μM) inhibited digoxin secretion (transport from the basolateral to apical aspect of the monolayer) by 58%, equivalent to the extent of inhibition observed with verapamil, a known inhibitor of P-glycoprotein transport. Thus, the increase in steady-state digoxin concentrations produced by 80 mg atorvastatin coadministration may result from inhibition of digoxin secretion into the intestinal lumen.*

***Journal of Clinical Pharmacology, 2000;40:91-98***


Atorvastatin is a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor that produces low-density lipoprotein (LDL) cholesterol reductions of 40% to 60% at single daily doses of 10 to 80 mg.[1] Digoxin, a drug with a low therapeutic index, may be administered to patients who receive atorvastatin. Previous studies have demonstrated that serum or plasma digoxin concentrations were slightly elevated when digoxin was coadministered with the HMG-CoA reductase inhibitors simvastatin[2] and fluvastatin.[3] Thus, the effect of multiple-dose atorvastatin administration on the steady-state pharmacokinetics of digoxin was studied. Based on the results, the effect of atorvastatin on the transport of digoxin across intestinal cells was evaluated in vitro to gain mechanistic insight.

From the Departments of Pharmacokinetics, Dynamics, and Metabolism and Clinical Pharmacology, Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company, Ann Arbor, Michigan. Submitted for publication July 5, 1999; revised version accepted September 13, 1999. Address for reprints: Ralph Stern, Clinical Pharmacology Department, Parke-Davis, Ann Arbor, MI 48105.

## METHODS

### Clinical Studies

Two clinical studies of identical design were performed, one with a 10 mg dose of atorvastatin and one with an 80 mg dose of atorvastatin.

#### *Subjects*

Twelve healthy subjects ages 18 to 55 years, weighing at least 45 kg and having an estimated creatinine

clearance value[4] greater than or equal to 60 mL/min, were recruited for each study. Subjects were in good health as determined by medical history, physical examination, electrocardiogram, and clinical laboratory measurements. Ten subjects completed the study with 10 mg atorvastatin. One subject withdrew on the 19th day because of adverse events that were not considered drug related, and another subject (who was not included in the pharmacokinetic analysis) was withdrawn on the 10th day for asymptomatic sinus bradycardia that was present at screening. The 11 subjects (6 males, 5 females) used for pharmacokinetic analysis had a mean (range) age of 47 (32-53) years, weight of 87.1 (56.7-111.1) kg, and height of 173 (161-187) cm. Eleven subjects completed the study with 80 mg atorvastatin. One subject withdrew on the 7th day for personal reasons. The 11 subjects (11 males) used for pharmacokinetic analysis had a mean (range) age of 35 (27-53) years, weight of 83.2 (73.8-110) kg, and height of 179 (166-190) cm.

### *Study Design*

Each study was a nonblind, multiple-dose, drug-drug interaction study conducted at the Community Research Clinic, Parke-Davis Pharmaceutical Research, Ann Arbor, Michigan. Both protocols were approved by the Community Research Clinic Institutional Review Board, and the studies were conducted in accordance with the ethical principles stated in the Declaration of Helsinki. All subjects provided written informed consent before entering the studies.

Each subject received a single digoxin (Lanoxin®) 0.25 mg tablet once daily in the morning for 20 days, administered alone on days 1 through 10 and simultaneously with 10 or 80 mg atorvastatin on days 11 through 20. Tablets were administered with 8 oz water at least 1 hour before or after meals, except on days 10 and 20, when subjects were required to fast for 8 hours prior to dosing and for 4 hours after dosing. On these 2 days, identical lunches and identical dinners were served at 4 and 10 hours postdose, respectively. Subjects were not confined to the clinic during the study.

### *Pharmacokinetic Sampling and Drug Assays*

Blood samples (5 mL) for the assay of plasma digoxin concentration were collected in heparinized glass tubes immediately before and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours after the digoxin dose on days 10 (digoxin alone) and 20 (digoxin with atorvastatin). Blood samples were centrifuged, and plasma was separated and stored frozen at –20°C until assayed. In addition, all urine voided for 24 hours after the digoxin dose on days 10 and 20 was collected, the volume recorded, and a 20 mL sample stored frozen at –20°C until assayed for digoxin concentration. In the study with 80 mg atorvastatin, blood samples (5 mL) for the assay of atorvastatin concentrations were collected in heparinized glass tubes before the digoxin dose on day 1 and immediately before the atorvastatin dose on days 13, 17, and 20. Plasma was collected and stored as described above.

For the study with 10 mg atorvastatin, plasma samples were analyzed for digoxin by Phoenix International Life Sciences, Inc., Saint-Laurent, Quebec, Canada, using reagents from the Amerlux Digoxin RIA kit manufactured by Johnson & Johnson Clinical Diagnostics, Markham, Ontario, Canada. The lower limit of quantitation of the assay was 0.1 ng/mL. Precision of plasma digoxin determinations in quality control samples, expressed as percent relative standard deviation (%RSD), was 6.2% or less. Digoxin concentrations in quality control samples ranged from 117% to 99% over the concentration range of 0.3 ng/mL to 3.4 ng/mL. For the study with 80 mg atorvastatin, plasma samples were analyzed for digoxin by M-Labs, Drug Analysis and Toxicology Laboratory, University of Michigan Medical Center, Department of Pathology, Ann Arbor, Michigan, using an automated fluorescence polarization immunoassay (FPIA) kit manufactured by Abbott Laboratories. Plasma was assayed following protein precipitation. The lower limit of quantitation of the assay was 0.3 ng/mL. Precision of plasma digoxin determinations in quality control samples, expressed as percent relative standard deviation (%RSD), ranged from 2.0% to 10.3%. Digoxin concentrations in quality control samples ranged from 104% to 106% of nominal values. All urine samples were analyzed for digoxin at Phoenix International Life Sciences, Inc. by a radioimmunoassay method using reagents from the Amerlux Digoxin RIA kit. Urine was assayed after a 10-fold dilution with digoxin-free human serum. The lower limit of quantitation of the assay was 1.0 ng/mL. Precision of urine digoxin determinations in quality control samples, expressed as percent relative standard deviation (%RSD), was 9% or less. Digoxin concentrations in quality control samples ranged from 90% to 107% of nominal values. Atorvastatin was shown not to cross-react in either the plasma or urine digoxin assay. Plasma and urine digoxin concentrations were measured by immunoassay methods, which also quantitate active metabolites. Thus, all reported concentrations represent apparent digoxin concentrations.

In the study with 80 mg atorvastatin, plasma samples were analyzed for atorvastatin at Parke-Davis Pharmaceutical Research, Ann Arbor, Michigan,

according to a validated enzyme inhibition assay (EIA)[5] that quantitates inhibition of HMG-CoA reductase. The lower limit of quantitation was 0.36 ng/mL. Precision of atorvastatin determinations in calibration standards and quality control samples ranged from 0.7% to 28.8%, and concentrations in quality control samples ranged from 101% to 115% of nominal values. This assay is not specific for atorvastatin as atorvastatin metabolites with inhibitory activity are also measured, so sample concentrations are expressed as atorvastatin-equivalent concentrations. For simplicity, these values are referred to as atorvastatin concentrations in the text.

### *Pharmacokinetic and Statistical Methods*

Digoxin pharmacokinetic parameters were calculated by established noncompartmental methods. Maximum plasma digoxin concentration ($C_{max}$), the time it occurred ($t_{max}$), and the concentration at 24 hours ($C_{min}$) were recorded as observed. Area under the plasma concentration-time curve from 0 to 24 hours ($AUC_{(0-24)}$) was estimated using the linear trapezoidal method. Total urinary digoxin excretion from 0 to 24 hours ($Ae_{(0-24)}$) was calculated by multiplying the urinary digoxin concentration by the total volume of urine voided during the interval. Digoxin renal clearance ($CL_r$) was calculated as $Ae_{(0-24)}/AUC_{(0-24)}$.

Mean digoxin pharmacokinetic parameters following administration of digoxin with atorvastatin were compared qualitatively to those following administration of digoxin alone. Pharmacokinetic parameters and descriptive statistics (difference between least squares treatment mean values and associated 95% confidence intervals) were inspected for trends likely to be of clinical relevance. Results of analysis of variance (ANOVA) of digoxin pharmacokinetic parameters were used for calculating confidence intervals. For $C_{max}$ and $AUC_{(0-24)}$, natural log-transformed data were used in the ANOVA. The ANOVA model incorporated subject and treatment effects and was evaluated using the general linear model (GLM) procedure of SAS (Version 6.07, SAS Institute, Inc., Cary, NC).

## In Vitro Studies

### *Caco-2 Cell Cultures*

Human colon adenocarcinoma (Caco-2) cells from continuous culture (passages 63 to 68) were seeded at high density ($10^5$ cells/filter) onto Snapwell polycarbonate filters with a surface area of 1.13 $cm^2$. Cells were maintained with Dulbecco's minimal essential medium (DMEM) supplemented with 10% fetal calf serum, 0.1 mM nonessential amino acids, and 2 mM L-glutamine at 37°C in a humidified atmosphere of 5% $CO_2$/95% air. Medium was changed every other day until the day of the experiment. Experiments were conducted during days 23 to 28 after seeding. Transepithelial electrical resistance (TEER) was measured using Millicell-ERS (Bedford, MA), and then Snapwell inserts were removed, washed in 0.9% normal saline, and placed in the side-by-side diffusion apparatus (Precision Instruments, Corning-Costar, Cambridge, MA).

### *Transport Experiments*

A transport experiment was initiated by adding 5 mL of solution containing radiolabeled compound to one chamber (apical or basolateral) of the side-by-side diffusion apparatus and 5 mL of an appropriate solution to the opposite chamber. All diffusion chambers (minus cells) were pretreated in their respective solutions for 15 minutes at 37°C. Pretreatment solution was removed, the Snapwell inserts with cells were mounted, and new solution was added to start the experiment. The chambers were maintained at 37°C, and constant mixing of the solutions in both chambers was achieved by an air-lift system with carbogen (5% $CO_2$/95%$O_2$). Fifty microliter aliquots were removed from both apical and basolateral chambers at each time point in the experiments described below, and the radioactivity associated with samples was determined by liquid scintillation counting in a Packard Tri-Carb scintillation counter.

### *Kinetics of Atorvastatin Transport*

Transepithelial flux of atorvastatin was determined in the basolateral-to-apical ($J_{b\text{-}a}$) (secretory) direction. Kinetic studies were performed over 2 hours with $^{14}$C-atorvastatin concentrations ranging from 2 to 250 μM. Donor solutions were prepared by adding $^{14}$C-atorvastatin in Hank's balanced salt solution (HBSS) containing 136.7 mM NaCl, 5.36 mM KCl, 1.80 mM $CaCl_2$, 0.81 mM $MgSO_4$, 0.44 mM $KH_2PO_4$, 3.38 mM $Na_2HPO_4$, 4.17 mM $NaHCO_3$, 5.55 mM glucose, pH 7.4 (Gibco/BRL, Grand Island, NY). $^3$H-Mannitol was included in the donor solutions as a cell integrity marker. TEER values measured in HBSS ranged from 400 to 700 Ω-$cm^2$. Data were fit to the following Michaelis-Menten equation:

$$J_{b\text{-}a} = \frac{J_{max} \cdot C}{K_m + C}, \quad (1)$$

where C is the concentration of atorvastatin in the donor chamber (μM), $J_{max}$ is the maximal efflux

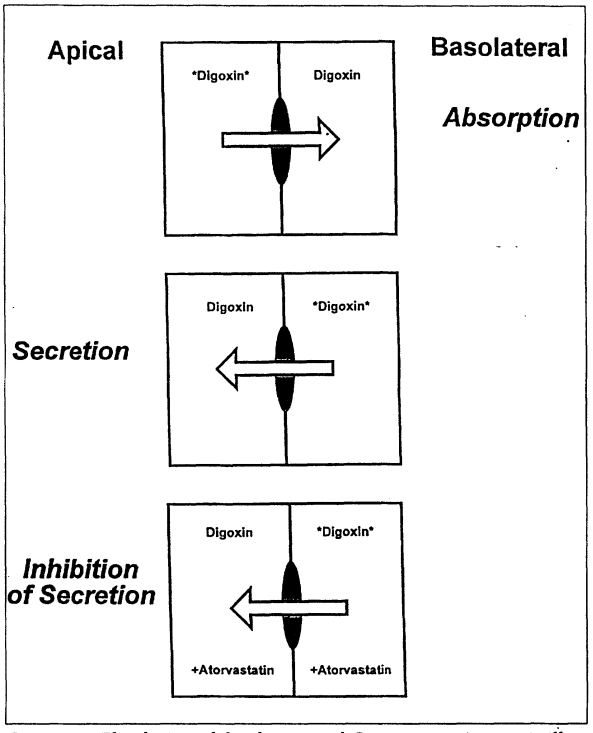


*Figure 1. The design of the directional Caco-2 experiments is illustrated. The arrows indicate the direction of transport that was measured by sampling $^{14}$C-atorvastatin (kinetic experiments) or $^{3}$H-digoxin (inhibition experiments). Transfer of compound from apical to basolateral signifies the direction of absorption, while transfer from basolateral to apical is the direction of secretion.*

(pmol/cm$^2$/mm), and $K_m$ is the affinity constant or concentration of atorvastatin at one-half of the maximal efflux (μM).

### *Inhibition of Digoxin Transport by Atorvastatin*

Digoxin (10 nM) was used at equal concentrations in both the apical and basolateral chambers with $^{3}$H-digoxin present only in one chamber, depending on which transport direction was being studied (Figure 1). Samples from both chambers were taken over a 2-hour time course. Apical solutions were prepared in MES (2-[N-Morpholino]ethanesulfonic acid) buffer (120 mM NaCl, 5 mM KCl, 25 mM glucose, 1.8 mM $CaCl_2$, 10 mM MES, pH 6.5), and basolateral solutions were prepared in MOPS (3-[N-Morpholino]propanesulfonic acid) buffer (120 mM NaCl, 5 mM KCl, 25 mM glucose, 1.8 mM $CaCl_2$, 10 mM MOPS, pH 7.4). $^{14}$C-PEG 4000 (total concentration = 0.01%) was used as a cell integrity marker. The Caco-2 cell monolayers used in the inhibition experiments had TEER values ranging from 800 to 1600 Ω-cm$^2$ (measured in the culture medium).

The effect of atorvastatin on the transport of $^{3}$H-digoxin across Caco-2 cells in both the absorptive direction (apical to basolateral) and the secretory direction (basolateral to apical) was examined. Verapamil, a well-documented P-glycoprotein inhibitor, was also tested as a positive control.[6] Inhibition of $^{3}$H-digoxin transport by the ortho- and para-hydroxy metabolites of atorvastatin (PD 152873 and PD 142542, respectively) was examined only in the basolateral-to-apical direction. In each experiment ($N$ = 3), atorvastatin or its metabolites was included in both the apical and basolateral chambers at the same concentrations. Inhibitor concentrations of 5 μM and 100 μM were evaluated. Atorvastatin is a calcium salt containing two pyrrole heptanoic acid components; atorvastatin concentrations in this article are expressed in terms of the pyrrole heptanoic acid component. Verapamil was tested only at a concentration of 100 μM. The permeability of digoxin from the basolateral-to-apical direction in the presence of atorvastatin or its metabolites was compared with the permeability value obtained for the control experiment (no inhibitor) to determine the percent inhibition by the various compounds.

The apparent permeability, $P_{app}$, of $^{3}$H-digoxin was determined using the following equation:

$$P_{app} = \frac{V_D}{A \cdot M_D(0)} \cdot \frac{dM_R}{dt}, \quad (2)$$

where $V_D$ is the volume of donor solution (5 mL), A is the area of the cell monolayer (1.13 cm$^2$), $M_D(0)$ is the initial amount of drug in the donor solution (dpm), and $dM_R/dt$ is the linear appearance rate of mass in the receiver solution (dpm/s).[7]

## RESULTS

### Clinical Studies

Mean digoxin concentrations predose and 24 hours after the dose were virtually identical on days 10 and 20 (Figure 2), indicating that digoxin concentrations had reached steady state. Mean predose atorvastatin concentrations on days 13, 17, and 20 (8.3, 9.8, and 8.1 ng/mL, respectively) in the study with 80 mg were similar, indicating that plasma atorvastatin concentrations had reached steady state by the third day of dosing. Mean steady-state plasma digoxin concentrations were unchanged by administration of digoxin with 10 mg atorvastatin (Figure 2, Table I) but were slightly

**Table I** Mean Steady-State Digoxin Pharmacokinetic Parameters with and without Concomitant Atorvastatin Administration

| | | Treatment Least Squares Mean | | | |
|---|---|---|---|---|---|
| | Parameter | Digoxin Alone | Digoxin with Atorvastatin | Difference (%) | 95% Confidence Interval |
| Atorvastatin 10 mg ($n$ = 11) | $C_{max}$ (ng/mL)[a] | 1.52 | 1.67 | 9.9 | −4.9 to 26.2 |
| | $t_{max}$ (h) | 1.23 | 1.08 | −12.2 | −39.8 to 15.4 |
| | $AUC_{(0-24)}$ (ng•h/mL)[a] | 16.6 | 17.2 | 3.6 | −4.9 to 13.5 |
| | $C_{min}$ (ng/mL) | 0.54 | 0.54 | 0.0 | −14.4 to 14.4 |
| | $Ae_{(0-24)}$ (μg) | 125 | 133 | 6.4 | −10.1 to 22.9 |
| | $CL_r$ (mL/min) | 129 | 128 | −0.8 | −13.6 to 12.0 |
| Atorvastatin 80 mg ($n$ = 11) | $C_{max}$ (ng/mL)[a] | 1.30 | 1.56 | 20.0 | 3.5 to 39.6 |
| | $t_{max}$ (h) | 1.36 | 1.18 | −13.2 | −57.9 to 31.2 |
| | $AUC_{(0-24)}$ (ng•h/mL)[a] | 14.9 | 17.1 | 14.8 | 3.4 to 27.1 |
| | $C_{min}$ (ng/mL) | 0.45 | 0.55 | 22.0 | 4.5 to 39.5 |
| | $Ae_{(0-24)}$ (μg) | 144 | 152 | 5.56 | −13.2 to 24.0 |
| | $CL_r$ (mL/min) | 160 | 149 | −6.88 | −21.0 to 6.2 |

a. Geometric means; parameters calculated using natural log-transformed data.

higher when digoxin was administered with 80 mg atorvastatin (Figure 2, Table I), resulting in 20%, 22%, and 15% higher ($p < 0.05$) $C_{max}$, $C_{min}$, and $AUC_{(0-24)}$ values, respectively (Table I). Negligible changes in mean $t_{max}$, $Ae_{(0-24)}$, and $CL_r$ values of digoxin were observed when either 10 or 80 mg atorvastatin was administered concomitantly.

### In Vitro Studies

The secretion of atorvastatin was a saturable process with an apparent $K_m$ and $J_{max}$ of 110 ± 20.3 μM and 261 ± 21.6 pmol/min/cm$^2$, respectively (Figure 3). In the absence of inhibitors, the basolateral-to-apical and apical-to-basolateral permeabilities of digoxin were 16.2 ± 2.5 × $10^{-6}$ cm/s and 3.23 ± 0.25 × $10^{-6}$ cm/s, respectively, consistent with net secretion of digoxin. The effect of inhibitors on the permeability of $^3$H-digoxin determined in the basolateral-to-apical direction across Caco-2 cell monolayers is shown in Table II. Verapamil, a known P-glycoprotein inhibitor, reduced the basolateral-to-apical permeability of digoxin by almost 60%. Atorvastatin, at the same concentration (100 μM), inhibited basolateral-to-apical digoxin permeability equally well. The ortho- and para-hydroxy metabolites of atorvastatin reduced digoxin permeability by 70.5% and 36.3%, respectively. At a lower concentration (5 μM), neither atorvastatin nor its metabolites significantly reduced digoxin permeability. Apical-to-basolateral permeability of digoxin was unaltered by verapamil or atorvastatin (data not shown).

## DISCUSSION

Higher steady-state plasma digoxin concentrations with concomitant 80 mg atorvastatin administration appear to be explained by an increase in the extent of digoxin absorption. There was a negligible change in the mean $t_{max}$ value, indicating no increase in the rate of digoxin absorption. Mean $CL_r$ values following coadministration of digoxin and atorvastatin were similar to corresponding values following administration of digoxin alone, suggesting no change in digoxin elimination. The amount of digoxin excreted in the urine did not increase to the same extent as the AUC, as would be expected with an increase in bioavailability, but urinary data are generally less reliable than plasma data due to the possibility of incomplete urine collections. Since the increase in plasma digoxin concentrations in the presence of 80 mg atorvastatin was modest and this was not a randomized crossover study, the results could be attributed to a period effect unrelated to any effect of atorvastatin. Although this cannot be ruled out, a similar interaction had been reported for other HMG-CoA reductase inhibitors (see below) and that there was a theoretical basis for a dose-related interaction involving P-glycoprotein. Thus, we explored this interaction further.

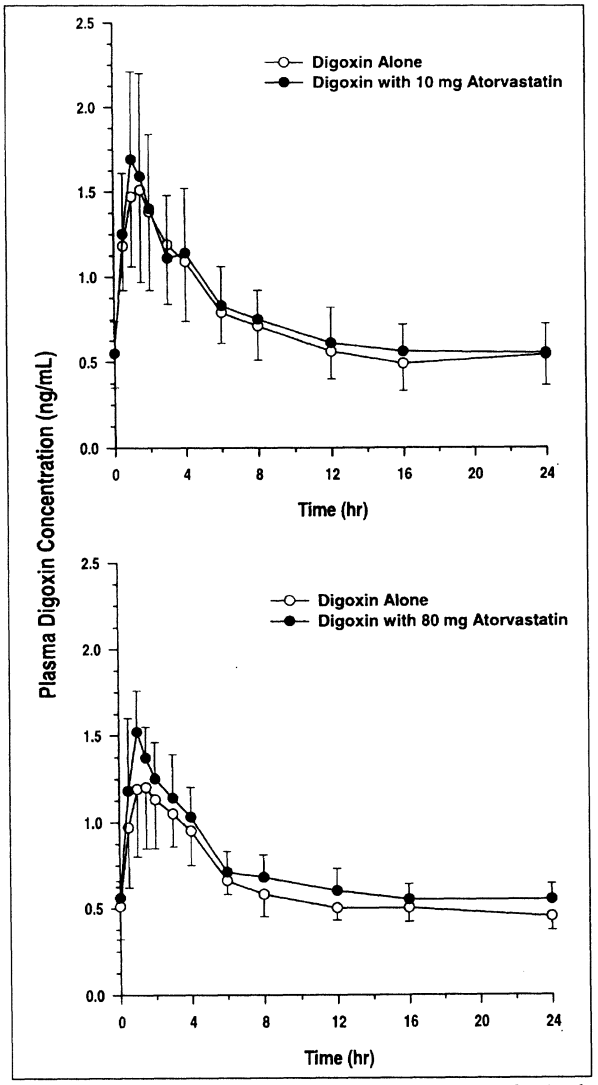


*Figure 2. Mean plasma digoxin concentration-time profiles for digoxin alone and with 10 mg atorvastatin (upper panel, N = 11) and 80 mg atorvastatin (lower panel, N = 11). Error bars represent standard deviations.*

P-glycoprotein is an efflux pump found in many tissues, and digoxin is known to undergo intestinal secretion mediated by P-glycoprotein. Secretion of digoxin from blood to the intestinal lumen has been demonstrated in vivo in animals[8,9] and in isolated mucosa of human intestine.[8] P-glycoprotein has been found in high quantities in human jejunal villus enterocytes,[10] and digoxin has been shown to be a substrate for human P-glycoprotein in vitro.[11] Thus, secretion of digoxin out of intestinal cells may occur during the absorption process, and inhibition of this process would increase the extent of absorption. Since atorvastatin is a CYP3A4 substrate[12] and many CYP3A4 substrates or their metabolites are also substrates for P-glycoprotein transport,[13] this provided a plausible explanation for an atorvastatin-digoxin drug interaction.

**Table II** Inhibition of $^3$H-Digoxin Permeability (basolateral-to-apical) across Caco-2 Cell Monolayers ($n$ = 3)

| | Percent Inhibition of $^3$H-Digoxin Basolateral-to-Apical Permeability | |
|---|---|---|
| **Inhibitor** | **5 μM Inhibitor** | **100 μM Inhibitor** |
| Verapamil | ND | 58.4 |
| Atorvastatin | 7.1 | 57.6 |
| Para-hydroxy metabolite of atorvastatin | 9.9 | 36.3 |
| Ortho-hydroxy metabolite of atorvastatin | 6.4 | 70.5 |

ND, not determined.

The influence of atorvastatin on digoxin transport in monolayers of the Caco-2 cell line was evaluated. Caco-2 cells are derived from a human colon adenocarcinoma and are widely used as a model for intestinal

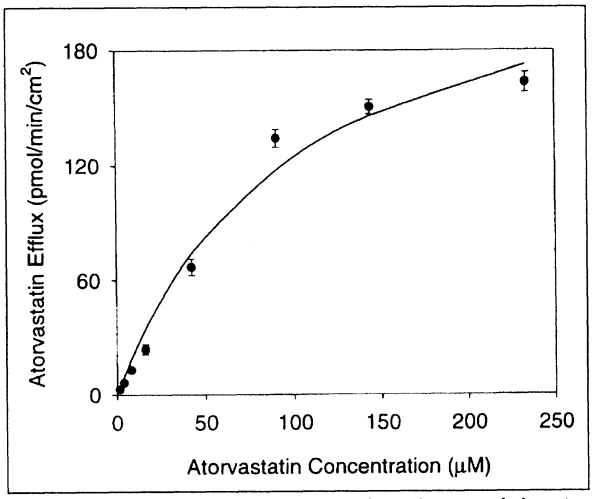


*Figure 3. Atorvastatin flux in the basolateral-to-apical direction across Caco-2 cell monolayers versus atorvastatin concentration. Each point represents a mean of three or more experiments. Error bars represent standard deviations. The solid line shows the fit of the mean data to equation (1) to obtain the Michaelis-Menten parameters reported in the Results section.*

absorption.[7] In culture, these cells form monolayers that spontaneously differentiate to resemble enterocytes of the small intestine. The cell monolayers are replete with polarized apical and basolateral membrane domains, tight junctions between cells, and membrane-bound transporters.[14] The multidrug resistance efflux pump, P-glycoprotein, is among the transporters located at the apical membrane of Caco-2 cells. At a high concentration (100 μM) close to its apparent $K_m$ (110 μM), atorvastatin inhibited digoxin secretion to the same extent as verapamil, a known inhibitor of P-glycoprotein-mediated transport. When the atorvastatin concentration (5 μM) was 22-fold lower than its apparent $K_m$, atorvastatin did not affect digoxin secretion. Ortho- and para-hydroxyatorvastatin also inhibited digoxin secretion at high concentrations (100 μM). Given that these metabolites are formed by the action of CYP3A4, which is present in the intestinal mucosa, the metabolites may also inhibit P-glycoprotein in vivo. Concentrations of atorvastatin (in intestinal cells) as high as 100 μM are possible during absorption, given that the dissolution of 80 mg atorvastatin in the 8 oz of water with which it was administered would produce an intestinal luminal concentration of 560 μM, and the nonpolar atorvastatin should diffuse rapidly into intestinal epithelial cells. In contrast, a 10 mg dose would result in intestinal luminal concentrations of only approximately 70 μM, which is below the apparent $K_m$ for atorvastatin.

Given that P-glycoprotein is found in the kidney and digoxin has been shown to be secreted via this mechanism,[11] it is possible that higher concentrations could be attributed, in part, to the inhibition of urinary secretion of digoxin. However, given that no change in renal clearance of digoxin was observed with the coadministration of atorvastatin, this seems unlikely. Other possible explanations for the increased bioavailability of digoxin include increased dissolution of digoxin tablets, decreased gastrointestinal motility, or decreased intestinal bacterial metabolism of digoxin.[15,16] Although none of these possibilities was tested, such effects attributable to atorvastatin appear unlikely.

An interaction with digoxin has been reported for two of the five other marketed HMG-CoA reductase inhibitors. In patients chronically receiving digoxin (0.125 to 0.5 mg daily), administration of a single 40 mg dose of fluvastatin resulted in an 11% increase in digoxin $C_{max}$, a 12% increase in $Ae_{(0\text{-}24)}$, and a 15% increase in $CL_r$.[3] $AUC_{(0\text{-}24)}$, $C_{min}$, and $t_{max}$ values were not altered. Simvastatin, at an unspecified dose, produced slight elevations (less than 0.3 ng/mL) in digoxin concentrations following administration of single doses (amount unspecified) of digoxin to healthy volunteers.[2] The 20% increase in $C_{max}$ observed with 80 mg atorvastatin also represented an increase in digoxin concentration less than 0.3 ng/mL. Pravastatin,[2] lovastatin,[2] and cerivastatin[2] did not alter digoxin pharmacokinetics. No explanations have been offered for the observed interactions. It is not known if these HMG-CoA reductase inhibitors are substrates for P-glycoprotein.

Since this work was completed, Greiner et al[17] have convincingly shown the importance of alterations of intestinal P-glycoprotein as a mechanism for drug interactions with digoxin. Rifampin, which increased intestinal P-glycoprotein content 3.5-fold, decreased digoxin bioavailability 30%, without altering systemic or renal clearance of digoxin.

In conclusion, concomitant administration of 10 mg atorvastatin does not alter digoxin pharmacokinetics, while concomitant administration of 80 mg atorvastatin results in an increase in steady-state digoxin concentrations of approximately 20%, apparently due to an increase in the extent of digoxin absorption. Inhibition of P-glycoprotein-mediated secretion of digoxin in the intestine by atorvastatin as an explanation for this interaction is supported by observations in the Caco-2 cell model system. In this model system, atorvastatin exhibited efflux kinetics with a $K_m$ of 110 μM. Alterations in P-glycoprotein transport of digoxin may underlie many unexplained digoxin drug interactions, as well as some interactions for which an alternate explanation has been proposed.

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