Inhibition of P-Glycoprotein–Mediated Drug Transport
A Unifying Mechanism to Explain the Interaction Between Digoxin and Quinidine

Martin F. Fromm, MD; Richard B. Kim, MD; C. Michael Stein, MB, ChB, MRCP; Grant R. Wilkinson, PhD; Dan M. Roden, MD

Background—Although quinidine is known to elevate plasma digoxin concentrations, the mechanism underlying this interaction is not fully understood. Digoxin is not extensively metabolized, but it is known to be transported by the drug efflux pump P-glycoprotein, which is expressed in excretory tissues (kidney, liver, intestine) and at the blood-brain barrier. Accordingly, we tested the hypothesis that inhibition of P-glycoprotein–mediated digoxin transport by quinidine contributes to the digoxin-quinidine interaction.

Methods and Results—First, we demonstrated active transcellular transport of both digoxin and quinidine in cultured cell lines that express P-glycoprotein in a polarized fashion. In addition, 5 \( \mu \)mol/L quinidine inhibited P-glycoprotein–mediated digoxin transport by 57%. Second, the effect of quinidine on digoxin disposition was studied in wild-type and in \( mdr1a(/-/) \) mice, in which the gene expressing the major digoxin-transporting P-glycoprotein has been disrupted. Because the in vitro data showed that quinidine itself is a P-glycoprotein substrate, quinidine doses were reduced in \( mdr1a(/-/) \) mice to produce plasma concentrations similar to those in wild-type control animals. Quinidine increased plasma digoxin concentrations by 73.0% \((P=0.05)\) in wild-type animals, compared with 19.5% \((P=NS)\) in \( mdr1a(/-/) \) mice. Moreover, quinidine increased digoxin brain concentrations by 73.2% \((P=0.05)\) in wild-type animals; by contrast, quinidine did not increase digoxin brain concentrations in \( mdr1a(/-/) \) mice but rather decreased them \((-30.7%, P<0.01)\).

Conclusions—Quinidine and digoxin are both substrates for P-glycoprotein, and quinidine is a potent inhibitor of digoxin transport in vitro. The in vivo data strongly support the hypothesis that inhibition of P-glycoprotein–mediated digoxin elimination plays an important role in the increase of plasma digoxin concentration occurring with quinidine coadministration in wild-type mice and thus support a similar mechanism in humans. (Circulation. 1999;99:552-557.)

Key Words: antiarrhythmia agents | brain | drugs | pharmacology | P-glycoprotein

One of the most common and most serious drug interactions in clinical practice is that between digoxin and the antiarrhythmic agent quinidine.\(^1,2\) Administration of quinidine to patients receiving digoxin causes a 2- to 3-fold increase in serum digoxin concentrations and frequently results in symptoms of digoxin toxicity. Clinical pharmacokinetic studies have described a number of changes in digoxin disposition when quinidine is administered concomitantly; these include enhanced digoxin absorption and reduced renal secretion and biliary excretion.\(^3-6\) However, no common mechanism underlying these changes in digoxin disposition during therapy with quinidine, or indeed with several other drugs that can elevate digoxin concentrations and cause digoxin toxicity,\(^7-11\) has been defined.

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Multiple mechanisms have been described to explain elevation of plasma drug concentrations by a second drug. One of the most common is inhibition of drug metabolism. However, digoxin is not extensively metabolized\(^12\) but is now recognized to be transported by the ATP-dependent efflux pump P-glycoprotein.\(^13-16\) The affinity of digoxin for P-glycoprotein appears to be lower than that of other substrates of P-glycoprotein (eg, vinblastine),\(^16\) suggesting a potential for drug interactions. In humans, P-glycoprotein was first described in tumor cells, where it contributes to the multidrug-resistance (MDR) phenomenon by promoting efflux of multiple, structurally unrelated anticancer drugs. In addition, a more widespread role for P-glycoprotein in drug disposition has been inferred from its expression in the apical domain of cells in normal tissues with excretory function, such as small intestine (brush border membrane of enterocytes), kidney (brush border membrane of proximal tubule cells), liver (canalicular membrane of the hepatocytes), and at the blood-brain barrier (capillary endothelial cells). Indeed, we have

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recently shown that normal P-glycoprotein function is an important determinant of the low oral absorption and low brain entry of HIV-1 protease inhibitors (indinavir, nelfinavir, saquinavir), possibly with important consequences for effective pharmacotherapy.17

In mice, 2 genes (mdr1a and mdr1b) encode drug-transporting P-glycoproteins, and mdr1a is the predominant isoform for digoxin transport.15,18,19 In mdr1a(−/−) mice, the elevation in brain digoxin concentrations is much larger (35- to 66-fold) than that in gut, liver, or kidney (0.7- to 4.8-fold).15,19 This finding suggests that other transporters may contribute to digoxin efflux in the latter tissues but that P-glycoprotein is a dominant efflux mechanism at the blood-brain barrier. The finding of altered disposition of digoxin in mdr1a(−/−) mice is also consistent with in vitro studies showing active, quinidine-sensitive transport of digoxin in P-glycoprotein–expressing cell lines.13–16

The aim of the present study was to test the hypothesis that inhibition of P-glycoprotein–mediated transport is a major mechanism underlying the digoxin-quinidine interaction. Studies were performed both in the polarized human colon carcinoma cell line (Caco-2)20,21 that expresses P-glycoprotein and in wild-type and mdr1a(−/−) mice. If P-glycoprotein is an important factor in the digoxin-quinidine interaction in vivo, quinidine should alter digoxin disposition in mdr1a(+/+) mice, elevating digoxin concentrations in plasma (and perhaps other sites), but little or no such elevation should be observed in mdr1a(−/−) mice.

Methods

Materials

Quinidine and [3H]quinidine (14.5 Ci/mmol) were obtained from Sigma Chemical Co and ARC Inc, respectively. Digoxin and [3H]digoxin (16 Ci/mmol) were purchased from Sigma and from Du Pont NEN.

Transport Studies

Caco-2 cells were used for the digoxin transport studies.20,21 When grown as a monolayer on a semipermeable filter, these cells become polarized and P-glycoprotein is expressed on their apical surface, allowing study of vectorial transcellular transport, ie, basal-to-apical and apical-to-basal transport.21 Transport of radiolabeled digoxin (5 μmol/L) was investigated after addition of drug on the basal side of the Caco-2 cells and measurement of its time-dependent appearance on the apical side (basal-to-apical transport) relative to the amount of radioactivity added at the beginning of the study. Transport in the opposite direction was determined after administration of the radiolabeled drug on the apical side of the cells (apical-to-basal transport). Inhibition of transepithelial transport was studied after addition of quinidine to both sides of the monolayer (5 and 100 μmol/L).

Caco-2 cells were grown in Transwell plates, as previously described.17 Experiments were conducted only with wells that had a measured transepithelial resistance of ≥200 Ω after correction for the resistance obtained in control blank wells. Studies were initiated by addition of 700-μL aliquots of serum-free media (Optimem, Gibco BRL) with and without radiolabeled drug to either the basal or apical compartment. After 1, 2, 3, and 4 hours, the percentage of administered radioactivity appearing in the opposite compartment was determined. The data reported represent the mean of ≥3 experiments.

Because there is some evidence that quinidine itself is a substrate of P-glycoprotein,22,23 we tested this hypothesis as described above, using [3H]quinidine (5 μmol/L). Transport was studied in LLC-PK1 porcine kidney epithelial cells and L-MDR1 cells (LLC-PK1 cells transfected with human MDR1 cDNA and stably expressing human MDR1 P-glycoprotein, kindly provided by Drs. E. Schuetz and A.H. Schinkel). Comparison of transport in the 2 cell lines can be used to identify substrates of P-glycoprotein.13 Cells were grown as previously described,15 and experiments were conducted as described above.

Drug Distribution in mdr1a(+/+) and (−/−) Mice

In vivo studies were conducted in 6- to 16-week-old, male mdr1a(−/−) mice and in matched male wild-type mice (Taconic Germantown, NY) as previously described.15,19 Drug distribution experiments consisted of 3 phases. In the first phase, radiolabeled quinidine was administered intravenously, and plasma and tissue quinidine concentrations were determined. In the second phase, radiolabeled digoxin was administered intravenously, and plasma and tissue digoxin concentrations were determined; in this phase, half the animals were pretreated with unlabeled quinidine 100 mg/kg IP 30 minutes before administration of digoxin. In the third phase, an additional group of mdr1a(−/−) mice were pretreated with a smaller dose of quinidine (40 mg/kg) to match plasma quinidine concentrations in mdr1a(+/+) animals, as described in Results.

Each group of mice consisted of 3 animals in the first phase and of 5 to 6 animals in the second and third phases. For intravenous injection, unlabeled quinidine was dissolved in 5% glucose and ethanol (4:1 vol/vol) at a concentration of 20 mg/mL. [3H]quinidine was added to this solution (4 μCi/30 g body wt), and 2.5 μL/g body wt (50 mg/kg) was injected intravenously over 10 minutes into the tail vein. Unlabeled digoxin stock solution (0.8 mg/mL in 40% vol/vol ethanol) was diluted in 5% (wt/wt) glucose to 0.2 mg/mL. [3H]digoxin was added to this solution (1 μCi/30 g body wt), and 2.5 μL/g body wt (0.5 mg/kg) was injected intravenously into the tail vein. After 4 hours, plasma and tissue samples were collected and analyzed as previously described.17 The experiments were approved by the Animal Care Committee of Vanderbilt University.

Determination of Quinidine Plasma Concentration

Unlabeled quinidine was determined in plasma with an Emit 2000 immunoassay (Behring Diagnostics Inc). This assay has a limit of quantification of 0.3 μg/mL and does not cross-react with 3-hydroxyquinidine, the main metabolite of quinidine in human plasma.

Statistical Analysis

All data are presented as mean±SD. Paired comparisons were analyzed by Student’s 2-tailed t tests. Multiple comparisons were analyzed by ANOVA with subsequent Student-Newman-Keuls tests. A value of P≤0.05 was required for statistical significance.

Results

Transport of Quinidine in LLC-PK1 and L-MDR1 Cells

In the L-MDR1 monolayer, transcellular transport was markedly greater when radiolabeled quinidine was placed in the basal side and measured in the apical side of the monolayer (ie, basal-to-apical transport) than with apical-to-basal transport (Figure 1). No such difference was observed in the parental LLC-PK1 cells, which lack P-glycoprotein. Moreover, basal-to-apical transport was greater and apical-to-basal transport was smaller in L-MDR1 cells than in LLC-PK1 cells. These data demonstrate that quinidine is transported by P-glycoprotein in this in vitro system.

Inhibition of Digoxin Transport by Quinidine in Caco-2 Cells

Figure 2 shows markedly greater basal-to-apical transport of digoxin (8.9% of radioactivity/h) than in the opposite direc-
tion (1.2%/h), indicating polarized transport of digoxin in P-glycoprotein–expressing Caco-2 cells. Addition of 100 μmol/L quinidine essentially abolished the polarized transepithelial transport of digoxin, with decreased translocation of digoxin from the basal to the apical side (3.0%/h) and increased translocation from the apical to the basal side (2.7%/h), suggesting complete inhibition of P-glycoprotein–mediated digoxin transport. The lower quinidine concentration, 5 μmol/L, still reduced digoxin basal-to-apical transport to 3.7%/h and increased apical-to-basal transport to 2.4%/h, compared with addition of digoxin alone. Thus, even the low quinidine concentration inhibited basal-to-apical transport of digoxin by 57%.

Disposition of Quinidine in mdr1a(+/+) and (−/−) Mice (First Phase)

Plasma and tissue radioactivities were determined after intravenous administration of identical doses of [3H]quinidine to mdr1a(+/+) and (−/−) mice (Table 1, Figure 3). Plasma concentrations were 4-fold higher in mdr1a(+/+) than in (−/−) mice (P<0.01). In the wild-type animals, radioactivity was detectable in the brain but was considerably lower than in the other tissues. By contrast, brain concentrations were elevated compared with those of other tissues in the mdr1a(−/−) mice, and brain concentrations were 29-fold higher than in mdr1a(+/+) mice (P<0.01).

Digoxin-Quinidine Interaction in mdr1a(+/+) and (−/−) Mice (Second and Third Phases)

As previously reported, after administration of digoxin alone, tissue concentrations were elevated in mdr1a(+/+) mice compared with mdr1a(−/−) mice, with the most pronounced increase occurring in the brain (Table 2, Figure 4).15,19 In wild-type mice, coadministration of quinidine resulted in elevated digoxin tissue concentrations compared with those in animals treated only with digoxin. For example, digoxin plasma concentrations were 1.7-fold elevated after quinidine coadministration (P<0.05). Digoxin brain concentrations were the lowest of all tissues investigated in the wild-type animals and, as in plasma, they increased 1.7-fold in the presence of quinidine (P=0.05).

### Table 1. Tissue Concentrations of Quinidine

<table>
<thead>
<tr>
<th>Tissue</th>
<th>mdr1a(+/+)</th>
<th>mdr1a(−/−)</th>
<th>Ratio (−/−)/(+/+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>1.0±0.03</td>
<td>3.5±0.2†</td>
<td>3.7</td>
</tr>
<tr>
<td>Brain</td>
<td>0.4±0.1</td>
<td>11.6±1.0†</td>
<td>29.2</td>
</tr>
<tr>
<td>Liver</td>
<td>9.7±0.3</td>
<td>42.2±6.6*</td>
<td>4.3</td>
</tr>
<tr>
<td>Kidney</td>
<td>25.6±3.9</td>
<td>62.7±6.1*</td>
<td>2.5</td>
</tr>
<tr>
<td>Heart</td>
<td>1.4±0.2</td>
<td>5.3±1.5</td>
<td>3.9</td>
</tr>
<tr>
<td>Lung</td>
<td>5.6±2.3</td>
<td>14.9±3.9*</td>
<td>2.7</td>
</tr>
<tr>
<td>Spleen</td>
<td>2.4±0.6</td>
<td>9.9±3.3*</td>
<td>4.2</td>
</tr>
<tr>
<td>Small intestine</td>
<td>3.9±0.5</td>
<td>28.9±8.7*</td>
<td>7.4</td>
</tr>
<tr>
<td>Fat</td>
<td>0.8±0.6</td>
<td>1.7±0.3</td>
<td>2.2</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.8±0.2</td>
<td>2.6±0.2</td>
<td>3.2</td>
</tr>
</tbody>
</table>

Values are μg/mL plasma, μg/g tissue.

*P<0.05, †P<0.01; mdr1a(+/+) vs mdr1a(−/−) mice.
Plasma and brain concentrations of digoxin 4 hours after administration of [14C]digoxin 0.5 mg/kg IV to mdr1a(+/-) and (-/-) mice with (D+Q) and without (D) intraperitoneal coadministration of quinidine. \( *P<0.05, **P<0.01, ***P<0.001.\)

In mdr1a(-/-) mice (second phase), coadministration of quinidine at the dose used in the wild-type mice (100 mg/kg) caused increases in digoxin concentrations in plasma, liver, and kidney (\( P<0.01, \) Table 2) similar to those observed in the wild-type animals. However, quinidine plasma concentrations at this dose were >7-fold higher in the mdr1a(-/-) mice than in the mdr1a(+/-) mice (4.3±1.7 versus 0.6±0.3 \( \mu g/mL, \) \( P<0.05, \) Table 2), in agreement with the results (above) that quinidine itself is a substrate of P-glycoprotein. Interestingly, despite these very high quinidine levels, digoxin brain concentrations did not increase but rather actually decreased in quinidine-treated mdr1a(-/-) mice (Table 2, Figure 4).

In mdr1a(-/-) mice treated with a reduced dose of quinidine (third phase), quinidine plasma concentrations were equal to those in mdr1a(+/+) mice (0.6±0.3 versus 0.6±0.4 \( \mu g/mL. \) In contrast to the findings in wild-type mice, quinidine at these matched plasma concentrations did not cause any significant increase in plasma and tissue concentrations in mdr1a(-/-) mice (Table 2, Figure 4). Even at the low quinidine concentration, digoxin brain concentrations were actually lower than in the animals treated with digoxin alone (\( P<0.01; \) the implications of this finding are discussed below.

### Discussion

Previous clinical pharmacokinetic studies have described a range of seemingly unrelated effects of quinidine on digoxin disposition. These include increased intestinal absorption, decreased renal secretion, and decreased biliary excretion.\(^3-6,24\) Each of these sites, however, is now recognized to express P-glycoprotein in a polarized fashion. Inhibition of P-glycoprotein function would result in decreased enterocyte efflux into the gut (thereby accounting for reported increased digoxin absorption) as well as decreased excretory efflux by the kidney and biliary tract. Thus, inhibition by quinidine of P-glycoprotein–mediated digoxin transport would provide a parsimonious explanation for these available descriptive pharmacokinetic data.

Several pieces of evidence from the present investigation now provide direct support for the hypothesis that inhibition of P-glycoprotein–mediated digoxin transport by quinidine plays an important role in the digoxin–quinidine interaction. First, we showed that basal-to-apical P-glycoprotein–mediated transport of digoxin in intestinal Caco-2 cells was inhibited by low concentrations of quinidine (5 \( \mu mol/L. \) Further recent studies from our group have indicated that the

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**TABLE 2. Quinidine-Digoxin Interaction in mdr1a(+/+) and mdr1a(-/-) Mice**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>mdr1a(+/+)</th>
<th>Ratio (D+Q)/D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>Digoxin 100 mg/kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Digoxin + Quinidine 40 mg/kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100 mg/kg</td>
<td>40 mg/kg</td>
</tr>
<tr>
<td>Brain</td>
<td>122±39</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>223±79</td>
<td>1.7</td>
</tr>
<tr>
<td>Liver</td>
<td>275±98</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>542±236</td>
<td>2.0</td>
</tr>
<tr>
<td>Kidney</td>
<td>99±19</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>143±20*</td>
<td>1.4</td>
</tr>
<tr>
<td>Heart</td>
<td>130±55</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>178±46</td>
<td>1.4</td>
</tr>
<tr>
<td>Lung</td>
<td>154±60</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>182±59</td>
<td>1.2</td>
</tr>
<tr>
<td>Spleen</td>
<td>63±33</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>105±26</td>
<td>1.7</td>
</tr>
<tr>
<td>Small intestine</td>
<td>304±137</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>595±236*</td>
<td>2.0</td>
</tr>
<tr>
<td>Fat</td>
<td>54±40</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>61±35</td>
<td>1.1</td>
</tr>
<tr>
<td>Muscle</td>
<td>82±28</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>128±32*</td>
<td>1.6</td>
</tr>
</tbody>
</table>

**Values for digoxin (D) are ng/g tissue, ng/mL plasma; for quinidine (Q), \( \mu g/mL. \)**

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**Figure 4.** Plasma and brain concentrations of digoxin 4 hours after administration of [14C]digoxin 0.5 mg/kg IV to mdr1a(+/+) and (-/-) mice with (D+Q) and without (D) intraperitoneal coadministration of quinidine. \( *P<0.05, **P<0.01, ***P<0.001.\)
IC₅₀ for inhibition of digoxin transport by quinidine in Caco-2 cells is 2.2 μmol/L. Second, quinidine increased plasma and tissue concentrations (e.g., in brain) of digoxin in P-glycoprotein–expressing mice [mdr1a(+/+)], whereas equivalent concentrations produced no significant increase in digoxin concentrations in plasma, brain, and other tissues in mdr1a(−/−) mice. These data, as well as reports from others,15,19 point to a more important role for the mdr1a gene product to promote drug efflux from brain than from other tissues in mice. Thus, the finding that quinidine elevated digoxin brain concentrations in mdr1a(+/+) animals but was without effect in mdr1a(−/−) animals (in which quinidine actually accumulated, Figure 3) argues further that P-glycoprotein is a major site of the digoxin-quinidine interaction.

In previous studies with mdr1a(−/−) mice, increased digoxin plasma concentrations, accumulation of digoxin in the brain, and impaired intestinal secretion of digoxin from the enterocytes into the gut lumen were observed. The inhibition of transcellular, P-glycoprotein–mediated digoxin transport by quinidine found in our experiments with Caco-2 cells, which have many characteristics of intestinal epithelial cells, provides a likely underlying explanation of the previously observed reduction of digoxin secretion into the gut lumen of rats by quinidine26 and, at least in part, of the observed increased intestinal absorption of digoxin in humans.4 Similarly, Cavet et al16 showed considerable inhibition of P-glycoprotein–mediated digoxin transport in Caco-2 cells with verapamil, nifedipine, and vinblastine. Inhibition of digoxin uptake by quinidine at the basal side of the Caco-2 cells is another theoretical explanation of our experimental findings in the Caco-2 cells. Several lines of evidence, however, argue against a major role for this process. First, no uptake transporter of digoxin has been described at the basal side of Caco-2 cells. Second, if inhibition of cellular uptake of digoxin by quinidine in tissues with excretory function (kidney, liver, intestine) were to play a major role in vivo, we would expect that the interaction would be similar in wild-type and mdr1a(−/−) mice, which is clearly not the case. Finally, direct evidence for a link between P-glycoprotein and basal-to-apical drug transport can be derived from the finding of increased plasma digoxin concentrations and complete inhibition of digoxin transport in the intestine by PSC-833, which was developed as a specific P-glycoprotein inhibitor,27 and the significant inhibition of P-glycoprotein–mediated drug transport in Caco-2 cells by monoclonal MRK16 P-glycoprotein antibodies, which bind to an external epitope of the transporter.20

Our finding of a significant increase in plasma and tissue digoxin concentrations by higher quinidine plasma concentrations (4.3 μg/mL) in mdr1a(−/−) mice in comparison to mdr1a(−/−) mice treated with digoxin alone suggests that quinidine may also inhibit other excretory mechanisms of digoxin when P-glycoprotein is absent. This additional effect of quinidine on digoxin elimination will require further study. The fact, however, that low quinidine plasma concentrations (0.6 μg/mL) resulted in a near doubling of serum digoxin in wild-type mice but exerted no significant effect in the knockout mice strongly supports the concept that at these low concentrations, the major effect of quinidine is mediated by inhibition of P-glycoprotein function.

The present findings, along with studies by others22 in nonpolarized cells, identify P-glycoprotein as a quinidine transporter. Our observation of a 29-fold accumulation of quinidine in mdr1a(−/−) mice compared with wild-type mice strongly suggests that the recently observed poor penetration of quinidine through the blood-brain barrier in humans28 can be explained by active transport of quinidine out of the brain capillary endothelial cells mediated by P-glycoprotein. This finding also provides an explanation for our observation that although quinidine increased digoxin brain concentrations in wild-type mice 1.7-fold, digoxin concentrations remained very low (21±11 ng/g) compared with those in mdr1a(−/−) mice (462±63 ng/g without quinidine coadministration). Our data suggest that low concentrations of quinidine in cells of the blood-brain barrier due to P-glycoprotein–mediated efflux may explain the observed incomplete inhibition of digoxin transport out of the brain in our experiments.

One unexpected finding in our study was that in the brains of mdr1a(−/−) mice, in contrast to the other tissues, digoxin concentrations actually decreased when quinidine was administered, compared with mdr1a(−/−) mice treated with digoxin alone. A likely explanation is that quinidine also inhibits an uptake mechanism for digoxin into the brain, and this is unmasked in the absence of P-glycoprotein–mediated efflux; the newly identified digoxin transporter oatp229 is one possibility. A recent report described effects of another P-glycoprotein inhibitor (PSC-833) on digoxin plasma and brain concentrations in wild-type and P-glycoprotein–knockout mice similar to those we observe with quinidine.27 These latter data further reinforce the idea that inhibition of P-glycoprotein elevates plasma digoxin. However, it cannot be ruled out that displacement of digoxin from skeletal muscle or other tissues by quinidine also contributes to this drug interaction.24,30

Elevated digoxin plasma concentrations have been observed not only after administration of quinidine in humans but also during concomitant therapy with multiple other drugs, including verapamil, nifedipine, propafenone, nitrendipine, cyclosporine, itraconazole, and amiodarone.7–11 Digoxin is not extensively metabolized, and many of these agents are now recognized as P-glycoprotein inhibitors.31,32 Thus, inhibition of P-glycoprotein–mediated digoxin elimination may be a common mechanism leading to elevated digoxin concentrations. More generally, our data identify inhibition of drug transport as a mechanism underlying one well-recognized drug interaction, which cannot be explained by inhibition of drug metabolism. We suggest that this is a common mechanism underlying clinically important drug interactions.

Acknowledgments

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References
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