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Impact of P-Glycoprotein-Mediated Intestinal Efflux Kinetics on Oral Bioavailability of P-Glycoprotein Substrates†

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Abstract: Studies of many P-glycoprotein (Pgp) substrates have demonstrated a significant effect of Pgp-mediated efflux on intestinal drug transport. However, most of these studies were designed to detect whether a particular drug is a Pgp substrate and thus were conducted at very low concentrations. We performed two simulations to evaluate the effect of Pgp-mediated efflux on oral drug absorption at various concentrations. In the first simulation, a steady-state model allowed us to predict whether the contribution of Pgp to oral drug absorption would be significant at clinically relevant concentrations. Our second simulation investigated the role of Pgp-mediated efflux in oral absorption with a dynamic compartmental absorption and transit model linked to a pharmacokinetic model. For high-solubility drugs, Pgp-mediated efflux altered the bioavailability only at drug concentrations corresponding to doses much lower than the usual clinical dose. The ratio of transporter-mediated transport to passive transport determined whether intestinal Pgp transporters would reduce the bioavailability of high-solubility drugs.

Keywords: Transporter; P-glycoprotein; absorption model; bioavailability

1. Introduction

P-glycoprotein (Pgp) is a transporter protein responsible for the efflux of drug compounds across the cell membrane. Pgp is expressed in the kidney tubules, adrenal glands, blood−brain barrier, muscle, lung, pancreas, intestine, placenta, testis, stomach, and liver.[1−3] Pgp expressed in the enterocyte cells lining the intestine effluxes its substrates across the apical membrane back into the intestine; therefore Pgp-mediated efflux has the potential to decrease intestinal drug absorption and increase drug metabolism in the enterocyte cells.[4−9] A number of studies have attempted to measure the effect of Pgp-mediated efflux on the oral bioavailability of certain drugs, such as digoxin, etoposide,

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methylprednisolone, cyclosporine A, paclitaxel, acebutolol, and vinblastine.[10−17]

As an example, Adachi et al. measured the effective clearance (CL_{eff}) of drugs across a mouse intestinal membrane in the presence and absence of Pgp expression. The CL_{eff} in the presence of Pgp (CL_{eff}^{Pgp}) was reduced (by as much as 87% for quinidine) relative to the CL_{eff} without Pgp in mice.[18] However, in this study, the concentrations used for the drug compounds were fairly low when compared to those that would be present in actual clinical practice. Lin et al. mentioned the possibility of exaggeration of the role of Pgp in first-pass metabolism in humans, based on the low concentrations in the animal studies.[19] Although numerous studies have been carried out to investigate Pgp-mediated efflux, most were designed to detect whether a particular drug was a Pgp substrate, and thus were not concerned with whether the applied concentration range was realistic for clinical interpretation in humans. In this study, we carried out two simulations to evaluate the effect of drug concentration on Pgp-mediated efflux. In the first simulation, a steady-state model for Pgp-mediated efflux kinetics leads to a relationship between CL_{eff}^{Pgp} and drug concentrations in the small intestine and allows us to predict if the contribution of Pgp to the oral absorption of Pgp substrates would be significant in the clinically relevant concentration range. This first simulation is relevant to in vivo perfusion studies and to in vitro studies using cell cultures in which a constant drug concentration is exposed to the apical side of the membrane. However, when a drug is delivered orally, the concentration of drug in the intestine rises and falls over time. To account for this, in our second simulation we investigated the role of Pgp-mediated efflux on oral absorption with a dynamic compartmental absorption and transit model linked to a pharmacokinetic model.

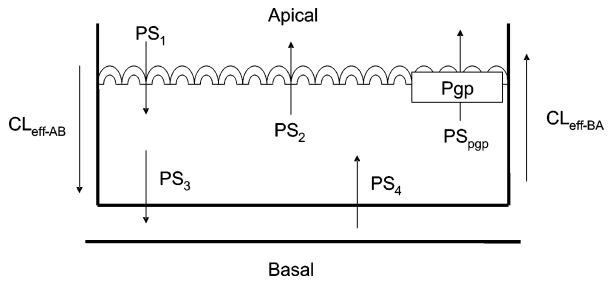

Figure 1. Schematic diagram of transcellular transporters of a drug compound in the enterocyte cells that line the membrane of the intestine.[20]

2. Experimental Section

2.1. Simulation I. The CL_{eff} across the intestinal membrane is the combination of several transport mechanisms including Pgp-mediated efflux and passive transport. CL_{eff} is the product of the apparent membrane permeability coefficient (P) and the surface area (S), so we will represent each contribution to the overall clearance by its PS product.[18] The overall clearance in the apical to basal direction (CL_{eff}^{AB}) is

$$CL_{eff}^{AB} = \frac{PS_1 PS_3}{PS_2 + PS_{Pgp} + PS_3} \quad (1)$$

CL_{eff}^{AB} is the overall PS product of the membrane, PS_1, PS_2, and PS_{Pgp} represent the PS products for the influx, non-Pgp-mediated efflux, and Pgp-mediated efflux across the apical membrane, respectively, and PS_3 is the PS product for the efflux across the basal membrane (see Figure 1).[20] This

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equation is the steady-state solution of the mass balance equation describing the accumulation of drug in the enterocytes

$$\frac{\partial M}{\partial t} = PS_1C_A - PS_2C_{ent} - PS_{Pgp}C_{ent} + PS_4C_B - PS_3C_{ent} \quad (2)$$

C_A and C_B are the drug concentration on the apical and basal sides of the membrane, respectively, M and C_{ent} are the amount and concentration of drug in the enterocytes, and PS_4 is the PS product for influx across the basal membrane.

In eq 2, $\partial M/\partial t = 0$ at steady state (constant velocity of transcellular transport). If we assume $C_B = 0$, corresponding to sink conditions on the basal side, then C_{ent}^{ss} (C_{ent} at steady state) is

$$C_{ent}^{ss} = \frac{PS_1C_A}{PS_2 + PS_{Pgp} + PS_3} \quad (3)$$

The CL_{eff}^{AB} determines the steady-state flux across the apical membrane via

$$CL_{eff}^{AB}C_A = PS_1C_A - (PS_2 + PS_{Pgp})C_{ent}^{ss} \quad (4)$$

which simplifies to eq 1.

In an in vitro cell culture study it is possible to expose the drug to the basal side of the membrane and measure the clearance in the reverse direction. The overall steady-state clearance in the basal to apical direction (CL_{eff}^{BA}) is derived by assuming sink conditions on the apical side of the membrane, $C_A = 0$. The steady-state solution of eq 2 under this assumption is

$$C_{ent}^{ss} = \frac{PS_4C_B}{PS_2 + PS_{Pgp} + PS_3} \quad (5)$$

The flux across either the apical or basal membrane must be equal to $CL_{eff}^{BA}C_B$, and so using the apical flux we find

$$CL_{eff}^{BA}C_B = PS_2C_{ent}^{ss} + PS_{Pgp}C_{ent}^{ss} \quad (6)$$

which simplifies to

$$CL_{eff}^{BA} = \frac{(PS_2 + PS_{Pgp})PS_4}{PS_2 + PS_{Pgp} + PS_3} \quad (7)$$

The equations derived above are valid even when the PS products for each transport mechanism depend on the drug concentration. In the rest of the simulation we will assume that all the PS products except PS_{Pgp} are independent of concentration. PS_{Pgp} is modeled using the following equation:

$$PS_{Pgp} = \frac{V_{max}^{eff}S}{K_m^{eff} + C_{ent}} \quad (8)$$

PS_{Pgp} is the membrane permeability clearance by Pgp-mediated efflux (cm^3/min), V_{max} is maximum Pgp-mediated efflux rate per effective area (nmol/cm^2/min), K_m^{eff} is the concentration at which half-maximal flux is achieved (μM), and C_{ent} is drug concentration in the enterocyte (μM). P_{pass} is the apparent permeability for transport by all other mechanisms, and we estimated its value by assuming that $PS_1 = PS_2 = PS_3 = PS_4 = P_{pass}S$ in eq 9. Table 1 shows the values of the parameters used in this simulation.

Table 1. The Values of J_{max}, K_m^{Pgp}, and P_{pass} Used in Simulation I[a]

drug	V_{max} (nmol/cm^2/min)	K_m^{Pgp} (μM)	P_{pass} (cm/min)	ref
verapamil	0.0163	30.82	3.4×10^{-4}	1
quinidine	0.234	868	5.0×10^{-5}	21
vinblastine	0.0233	328.89	7.4×10^{-5}	1
digoxin	0.07833	81	1.9×10^{-4}	22

[a] All of the data comes from in vivo measurements on rat jejunum.

Even though these Pgp substrates are known to be substrates of other efflux pumps like MRP1 and MRP2, there is little quantitative experimental or numerical data available to be used in this simulation. For example, the values of P_{pass}, V_{max}, and K_m^{Pgp} used in these simulations came from fits to experimental measurements of total transport; thus these values include the effects of other transporters that were not explicitly specified in the model. The main interest of this simulation study was to evaluate transporter related efflux relative to passive transport mechanisms in the absorption process. Pgp-mediated transport is believed to be the most significant active transport process for these drugs.

There are several study designs that are used to determine whether a drug is a Pgp substrate. The ratio of clearance in the BA to AB direction is one possible method:

$$\frac{CL_{eff}^{BA}}{CL_{eff}^{AB}} = \frac{(PS_2 + PS_{Pgp})PS_4}{PS_1PS_3} \quad (9)$$

A second design is to compare the AB clearance measured with and without Pgp efflux. Pgp efflux can be suppressed in in vivo studies by using knockout mice and in in vitro studies through the coadministration of Pgp inhibitors. To compare normal mice and knockout mice (mdr1a/1b(−/−)), which lack Pgp (mdr1a and mdr1b),[23] we compare the ratio of the CL_{eff}^{AB} for the two phenotypes.

$$CL_{eff}^{AB}\ \text{ratio} = \frac{CL_{eff}^{AB}(\text{mdr1a/1b}(-/-))}{CL_{eff}^{AB}(\text{normal})} = 1 + \frac{PS_{Pgp}}{PS_1 + PS_2} \quad (10)$$

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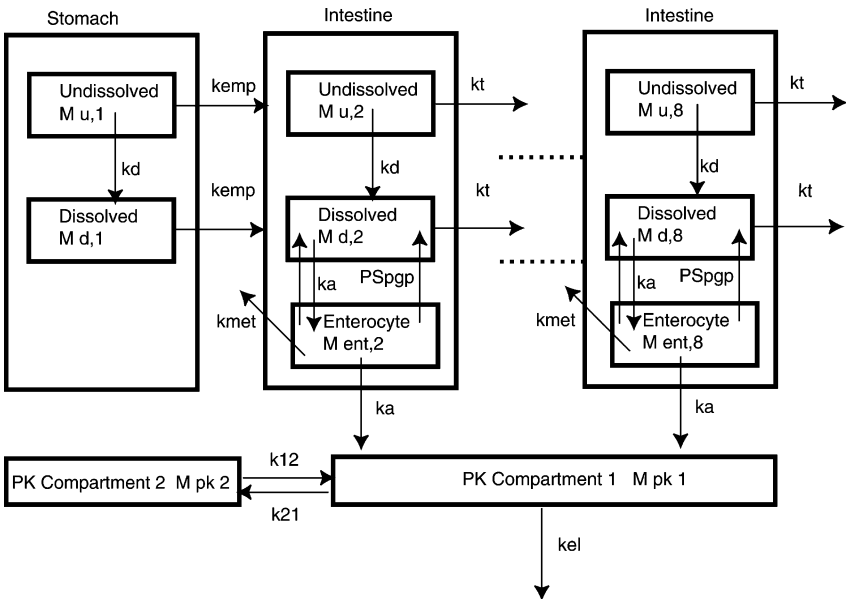

Figure 2. The compartmental absorption and transit model linked to a 2-compartment pharmacokinetic model.

Using Pgp substrates verapamil, quinidine, vinblastine, and digoxin as example drugs, PS_{Pgp} and the CL_{eff}^{AB} ratio were calculated for a wide range of the drug concentrations, from the concentration used in rat study[18] to the estimated clinical concentration in the human small intestine (calculated by dividing the dose by the volume of the small intestine, 500 mL[24,25]).

2.2. Simulation II. In order to determine the effect of Pgp-mediated efflux on the intestinal absorption process, efflux-mediated drug transport (PS_{Pgp}) and passive drug transport were incorporated into a compartmental absorption and transit model (CAT)[26] and pharmacokinetic (PK) model. In this study, imatinib mesylate, a well-known Pgp substrate,[27] was chosen to be the model drug. The CAT model is linked to a 2-compartment PK model with the first-order absorption and elimination process as shown in Figure 2.

The CAT model consists of 7 absorption compartments and a stomach compartment. The stomach is indexed as compartment 1. Each compartment has both dissolved and undissolved drug. We write the equations for the model in terms of the mass of drug in each compartment. D is the drug dose (mg) while $M_{u,i}$, $M_{d,i}$, and $M_{ent,i}$ ($i = 1, ..., 8$) are the amount of drug as solid, liquid, and absorbed in each compartment of the small intestine, respectively. M_1, $M_{PK,1}$, and $M_{PK,2}$ are the drug amount in the stomach and the two pharmacokinetic compartments.

In each compartment, there are input and output according to the gastric emptying or intestinal transit rate constants (k_{emp} and k_t), undissolved drug becomes dissolved drug according to the dissolution rate constant (k_d), and dissolved drug is absorbed according to the absorption rate constant (k_a). The pharmacokinetic model is described by the elimination rate constant k_{el} from the main compartment and the rate constants k_{12} and k_{21} that govern transport between the two compartments.

$$\frac{dM_{u,i}}{dt} = k_{t,i-1}M_{u,i-1} - k_{t,i}M_{u,i} - k_{d,i}M_{u,i} \quad (11)$$

$$\frac{dM_{d,i}}{dt} = k_{t,i-1}M_{d,i-1} - k_{t,i}M_{d,i} + k_{d,i}M_{u,i} - k_{a,i}M_{d,i} \quad (12)$$

For dissolution, the rate constant depends on the concentration in the compartment as

$$k_d = k_d^*(C_{sat,i} - C_{d,i}) \quad (13)$$

Under sink conditions, where $C_{d,i}$ is always much less than $C_{sat,i}$, there is a well-defined dissolution rate constant,

$$k_{d,sink} = \frac{3DC_{sat}}{\rho rh} \quad (14)$$

with units of time^{-1}. In this equation, D is the drug diffusion coefficient, ρ is the drug density, r is a mean particle size, and h is the diffusion layer thickness. We parametrize dissolution based in the intrinsic dissolution constant, $K_d^* = 3D/(\rho rh)$, which has units of mg/mL/h. The problems with $k_{d,sink}$ are 2-fold. First, although it is easy to do in vitro dissolution testing under sink conditions, the in vivo situation may not be at sink conditions. Second, $k_{d,sink}$ contains

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Table 2. The Parameters Applied in Simulation II for Imatinib Mesylate

dose	0−400 mg	K_m^{met}	25.6 μM
V_{max}^{met}	3×10^{-6} mg/cm^2/s	K_m^{eff}	5.35 μM
V_{max}^{eff}	6×10^{-6} mg/cm^2/s	k_{emp}	4 h^{-1}
k_t	2.11 h^{-1}	k_{el}	0.051 h^{-1}
k_d^*	40 mg/mL/h	P_{pass}	1.2×10^{-3} cm/s
C_{sat}	1.6 mg/mL	MW	589.7 g/mol
k_{12}	0.028 h^{-1}	k_{21}	0.005 h^{-1}
V_{dist}	236 L		

dependence on the solubility at which it was measured, while the in vivo solubility may change from the stomach to the intestine.

For passive transport, the rate constant k_a in each compartment is determined by the passive permeability and the compartment volume, V_i,

$$k_{a,i} = \frac{PS_1}{V_i} \tag{15}$$

To include the effect of efflux transporters and metabolic enzymes in the intestinal membrane, we devise a model of the intestinal enterocyte cells that includes passive transport in and out of the cell, efflux back into the intestine, and metabolism,

$$\frac{dM_{ent}}{dt} = PS_1C_{int} - (PS_2 + PS_3 + PS_{Pgp} + k_{met}V_{ent})C_{ent} \tag{16}$$

In the model, k_{met} is a rate constant for metabolism and V_{ent} is the volume of the enterocyte cells. We have assumed that the concentration on the basal side of the membrane is essentially zero (this is justified because the blood volume is much larger than the membrane volume and there is rapid blood flow away from the membrane).

As in simulation I, we assume that metabolism and efflux occur by saturable mechanisms, described by eq 8 and

$$k_{met}V_{ent} = \frac{V_{max}^{met}S}{K_m^{met} + C_{ent}} \tag{17}$$

but in this model, C_{ent} changes with time and is not at steady state as it is in simulation I. The V_{max} are the maximum mass flux per unit area while the K_m are the concentrations at which one-half the maximum flux occurs. We quantify both metabolic and transport activity on a per surface area basis to facilitate comparison of the two processes. Table 2 lists the values of the parameters used in the simulation. The pharmacokinetic parameters (k_{el}, k_{12}, k_{21}, V_d) were fit to pharmacokinetic data, while the rest of the model parameters were chosen beforehand on the basis of literature data for the absorption process.

Although our model allows us to include regional variation in Pgp expression, we used a single value in our model of imatinib mesylate. Regional differences in Pgp expression are especially important for drugs that are absorbed at more than one site or mainly absorbed in the colon. However, the main interest of this study is to investigate the theoretical relationship between drug transport mechanism and bioavailability, and therefore we concluded that a single value for Pgp expression is the most appropriate choice for this simulation study.

3. Results

3.1. Simulation I Results. The simulation was carried out for four well-known Pgp substrates: verapamil, quinidine, vinblastine, and digoxin. Figure 3 shows changes in P_{Pgp}, and Figure 4 presents the ratio of CL_{eff}^{AB}, calculated from eq 10, along a wide concentration range for each drug. P_{Pgp} and the ratio of CL_{eff}^{AB} are high at very low concentrations, indicating a significant contribution of Pgp to drug transport. Both decrease as the drug concentration in contact with the membrane increases. If the concentration could increase without limit, then passive transport would eventually dominate the transport of all drugs. However, there are two factors that provide an upper limit for the concentration: solubility and clinical dose.

Figures 3 and 4 indicate the solubility and usual clinical dose of each drug. The lower value of the two determines the appropriate upper concentration limit on each curve. The dose provides the limit for vinblastine, digoxin, and verapamil, while the solubility provides the limit for quinidine. For three of these drugs, Pgp transport remains significant over the clinically relevant concentration range, either because of the drug's low solubility (quinidine,vinblastine) or low dose (digoxin). For high-solubility drugs (such as verapamil) there is the potential of drawing the wrong conclusion about Pgp effects from the low-concentration experiments.

The results of simulation I suggest a simple way to evaluate the potential contribution of intestinal transporters to drug absorption. First, calculate the mean concentration as the lower of the dose divided by a characteristic intestinal volume (500 mL) or the solubility at the intestinal pH,

$$C_{mean} = \frac{D}{V_{int}} \quad \text{or} \quad C_{mean} = C_{sat} \tag{18}$$

and then evaluate the ratio of Pgp to passive transport, R_{Pgp}, as

$$R_{Pgp} = \frac{V_{max}^{eff}}{P_{pass}C_{mean}} \quad \text{if} \quad C_{mean}/K_m^{eff} \gg 1 \tag{19}$$

$$R_{Pgp} = \frac{V_{max}^{eff}}{P_{pass}K_m^{eff}} \quad \text{if} \quad C_{mean}/K_m^{eff} \ll 1 \tag{20}$$

When R_{Pgp} is equal to 1, then Pgp transport and passive transport are equally effective. For the drugs in simulation I, Table 3 shows that only verapamil has an R_{Pgp} significantly less than 1. However, to precisely determine the critical value of R_{Pgp} that will indicate a significant impact on bioavailability requires a model of the entire absorption process.

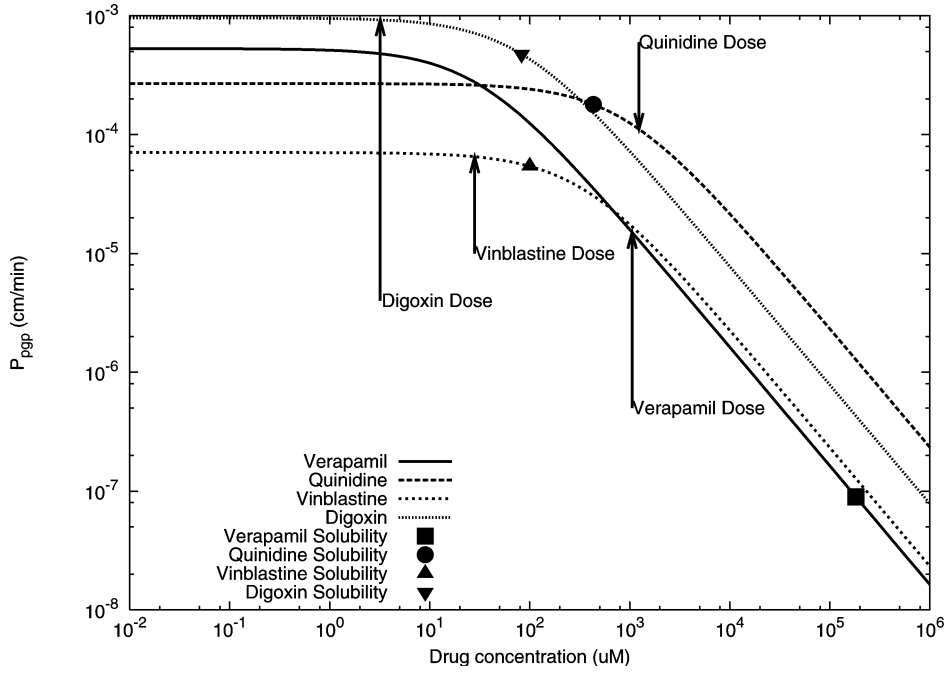

Figure 3. P_{Pgp} vs concentration for a series of drugs.

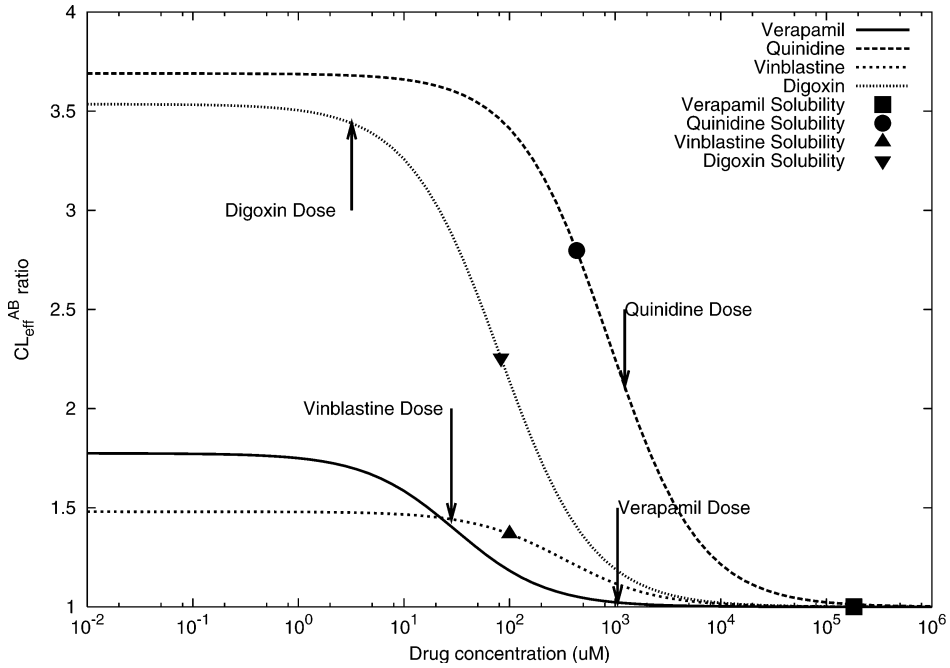

Figure 4. Ratio between CL_{eff}^{AB} in the presence and absence of Pgp expression in knockout mice vs concentration for a series of drugs.

Table 3. R_{Pgp} for the Drugs Studied in Simulation I

drug	C_{mean} (μM)	C_{mean}/K_m^{eff}	R_{Pgp}
verapamil	1055	34	0.04
quinidine	431	0.497	5.3
vinblastine	28	0.085	0.96
digoxin	3	0.039	5.07

3.2. Simulation II Results. Simulation I results suggest that, for high-solubility drugs, Pgp-mediated efflux is significant only at concentrations far below those that would occur in vivo. In this simulation, we use an integrated absorption model to determine when Pgp-mediated efflux will have a significant effect on the fraction of drug absorbed. In cell culture studies, imatinib mesylate has been clearly demonstrated to be a Pgp substrate. At a concentration of 5 μM, the ratio of $CL_{eff}^{BA}/CL_{eff}^{AB}$ was 4 and the ratio of CL_{eff}^{AB}(Suppress Pgp)/CL_{eff}^{AB}(PgP) was 2.[27] However, the usual dose of imatinib mesylate is 400 mg ($C_{mean} = 850$ μM), and at this dose Figure 5 shows that the CAT model predicts the concentration profile even when transporters are sup-

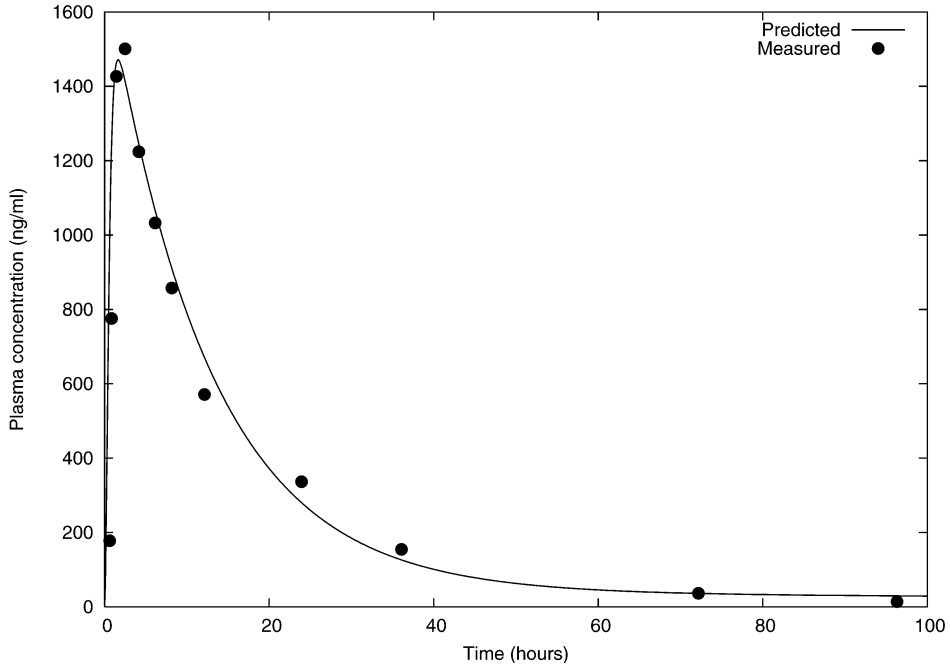

Figure 5. Comparison of plasma concentrations predicted from our model with measured data for a 400 mg dose of imatinib mesylate. The fraction error between predicted and measured pharmacokinetic parameters was 0.030 for AUC and 0.016 for C_{max}, which demonstrates that the model is acceptable for this simulation study.

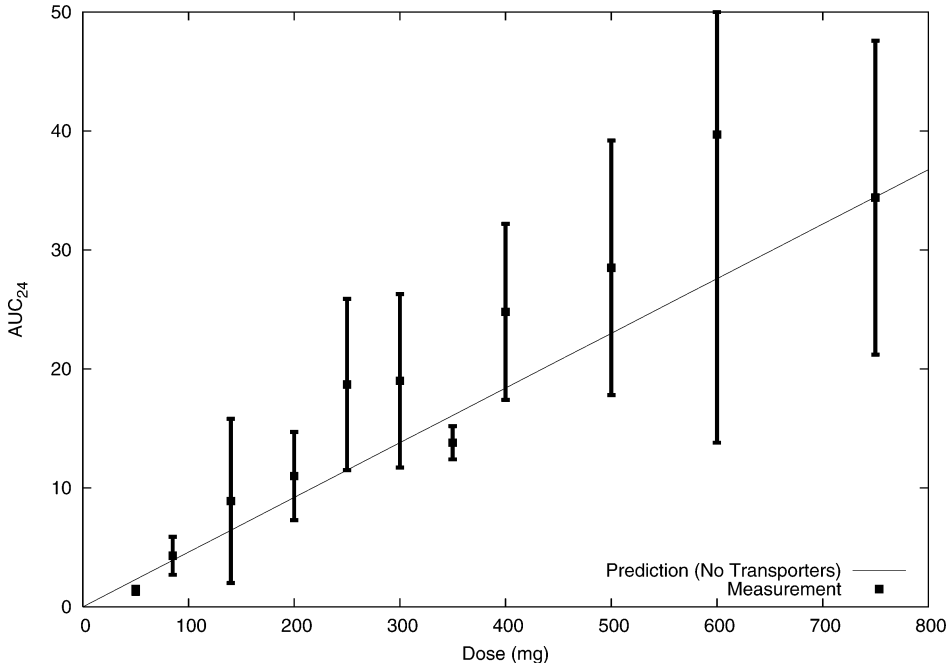

Figure 6. Predicted data and measured data[28] for imatinib mesylate AUC_{24} as a function of dose.

pressed in the model. Figure 6 shows that the model also predicts the observed dose proportionality from 25 mg up to 1000 mg, within the variability in AUC.

Thus, we have an example in which Pgp-mediated efflux does not affect absorption of imatinib mesylate, but we know that imatinib mesylate is a Pgp-substrate and is also a CYP3A4 substrate. We use the simulation to evaluate the contribution of intestinal efflux and metabolism on imatinib mesylate to determine at what dose these factors would affect bioavailability. We start with V_{max} and K_m values estimated from in vitro measurements, but we recognize that translation to human in vivo simulation is problematic and so we vary the V_{max} values over several orders of magnitude.

Because imatinib mesylate is a highly soluble and highly permeable drug, its bioavailability is predicted to be nearly unity if there were no Pgp-mediated efflux or metabolism in the intestine.[29] Either metabolism or efflux can reduce the bioavailability of imatinib mesylate. Figure 7 shows how

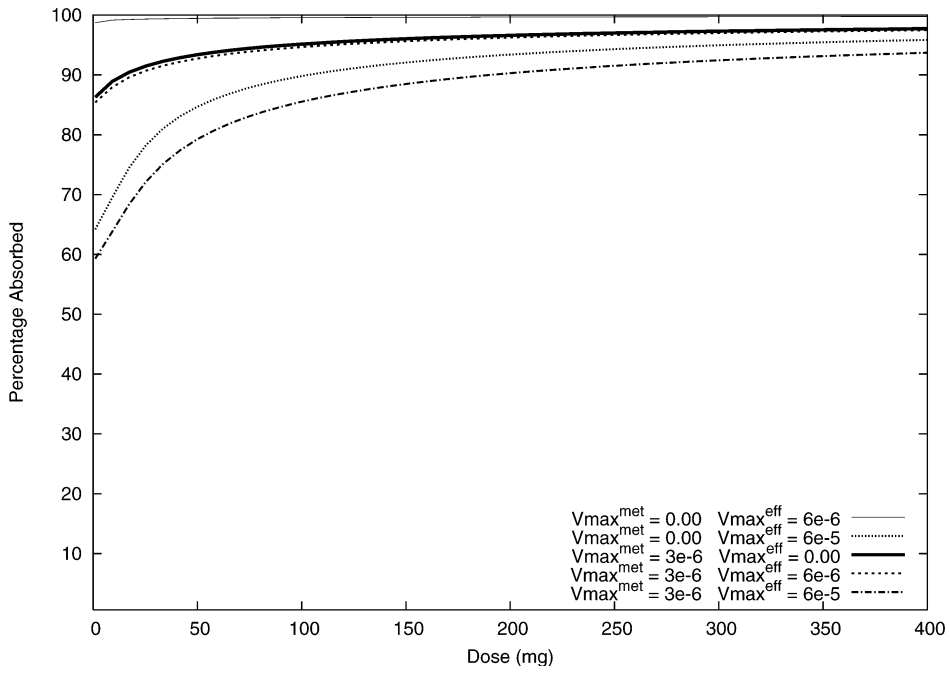

Figure 7. Percentage of drug absorbed relative to the absorption in the absence of transporters vs dose of imatinib mesylate. Both V_{max} are in units of mg/cm^2/s, and $P_{pass} = 1.2 \times 10^{-3}$ (cm/s).

the percentage of imatinib mesylate absorbed is reduced by increases in V_{max}^{eff} or V_{max}^{met}.

V_{max}^{met} of 3×10^{-6} (mg/cm^2/s) and V_{max}^{eff} of 6×10^{-6} (mg/cm^2/s) best represents the clinical observation that imatinib mesylate is dose proportional for doses between 25 and 1000 mg and is consistent with the in vitro observation that imatinib mesylate is a Pgp and CYP3A substrate. For these V_{max} choices and a P_{pass} of 1.2×10^{-3} (cm/s), the bioavailability of imatinib mesylate remained approximately the same (0.94−0.98) for doses higher than 25 mg. This is in accordance with the data presented in Figure 6.

Pgp inhibition or induction by drug interactions (higher V_{max} or lower V_{max}) can be evaluated relative to these values. Even complete inhibition of Pgp efflux or a 10-fold increase in Pgp expression would not significantly change bioavailability at the usual dose of this drug. The contribution of Pgp-mediated efflux to oral absorption of imatinib mesylate is not substantial because passive transport dominates the bioavailability of this high-permeability drug. However, if the dose were less than 25 mg, then the role of efflux transporters in drug absorption would be much more important.

Even though the effect of Pgp-mediated efflux on bioavailability is small, Figure 8 shows that the fraction of the dose that passes through the efflux transporters can be substantial. The fraction of drug effluxed by Pgp was between 0.45 and 1.25 in the doses lower than 25 mg and remained above 0.1 for doses up to 400 mg. The fraction effluxed can be greater than 1 because the reabsorption of the effluxed drug along the intestine allows the drug to be effluxed more than once. This process of recycling is why the 40% efflux of a 50 mg dose only results in a 5% decrease in bioavailability.

It has been suggested that the recycling of drug through the enterocytes can increase the fraction of drug metabolized in the intestine because a drug that is effluxed and then reabsorbed has additional opportunities to be metabolized in the intestine.[30] Figure 9 tests this hypothesis by plotting the fraction metabolized versus the fraction effluxed. When V_{max}^{eff} is smaller than V_{max}^{met}, there is a strong increase in the fraction metabolized with the fraction effluxed. However, when V_{max}^{eff} is greater than V_{max}^{met}, there is a much smaller increase. When efflux is more effective than metabolism, there will only be a small increase in the fraction metabolized because the efflux will compete efficiently with metabolism. Both efflux and metabolism act to reduce bioavailability. In the case where metabolism is more efficient, efflux transporters act synergistically to keep the enterocyte concentration from saturating the metabolic enzymes. In the case where efflux transporters are the primary barrier, metabolism is not required as rejected drug passes into the colon and is not absorbed.

Imatinib mesylate is a high-solubility, high-permeability drug. Using the simulation we can investigate what would happen for a new drug that had a different permeability. Figure 10 demonstrates that if imatinib mesylate's P_{pass} were

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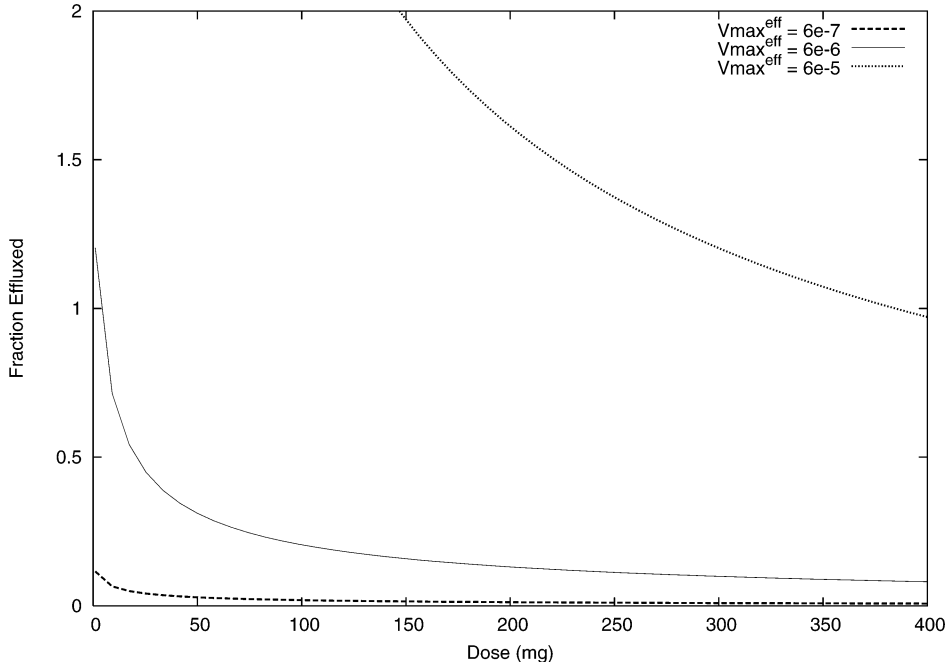

Figure 8. Fraction of drug effluxed by P-glycoprotein in the intestine vs dose of imatinib mesylate. V_{max}^{met} is fixed at 3×10^{-6} mg/cm^2/s, and $P_{pass} = 1.2 \times 10^{-3}$ (cm/s).

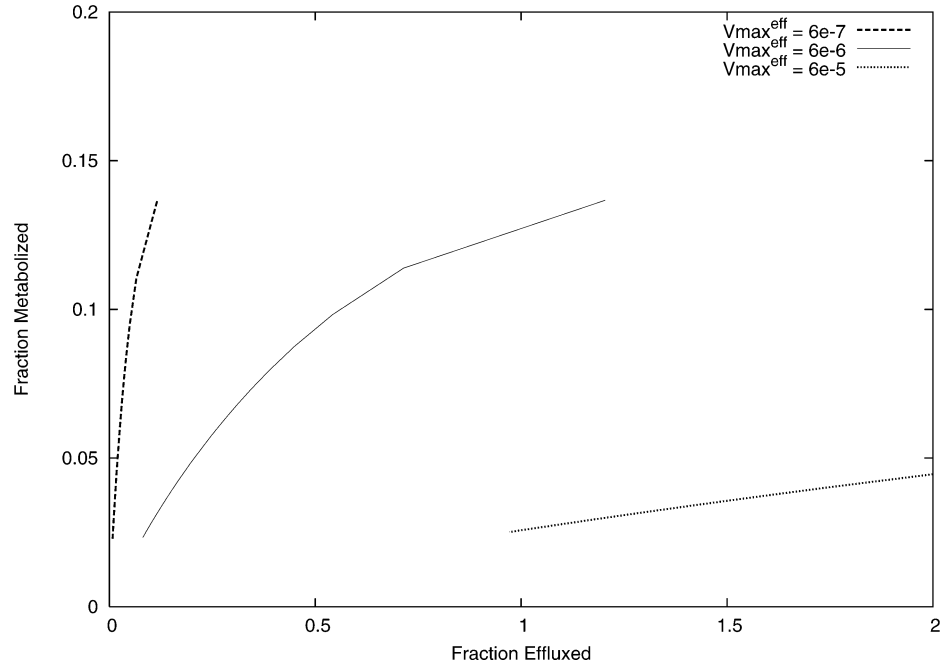

Figure 9. Fraction of drug metabolized vs fraction of drug effluxed by P-glycoprotein in the intestine. V_{max}^{met} is fixed at 3×10^{-6} mg/cm^2/s, and $P_{pass} = 1.2 \times 10^{-3}$ (cm/s), while V_{max}^{eff} varies along each of the curves.

lower, then the same amount of Pgp activity would have caused a significant reduction in the relative bioavailability as the dose decreased.

Figure 11 shows how the reduction in absorption due to transporters changes with the permeability of the drug. In the low-permeability region ($P_{pass} < 10^{-5}$), even a small amount of transporter activity can significantly reduce the bioavailability. For highly permeable drugs ($P_{pass} > 10^{-3}$), no V_{max}^{eff} values result in any reduction in bioavailability. In Figure 11, we include lines of constant $R_{Pgp} = V_{max}^{eff}/P_{pass}C_{mean}$. When R_{Pgp} is less than 0.05, then 90% of the bioavailability is retained.

4. Discussion

In the gastrointestinal drug absorption process there are two major mechanisms: passive diffusion driven by the drug concentration gradient and active transport via various transporters in the intestinal membrane. This absorption

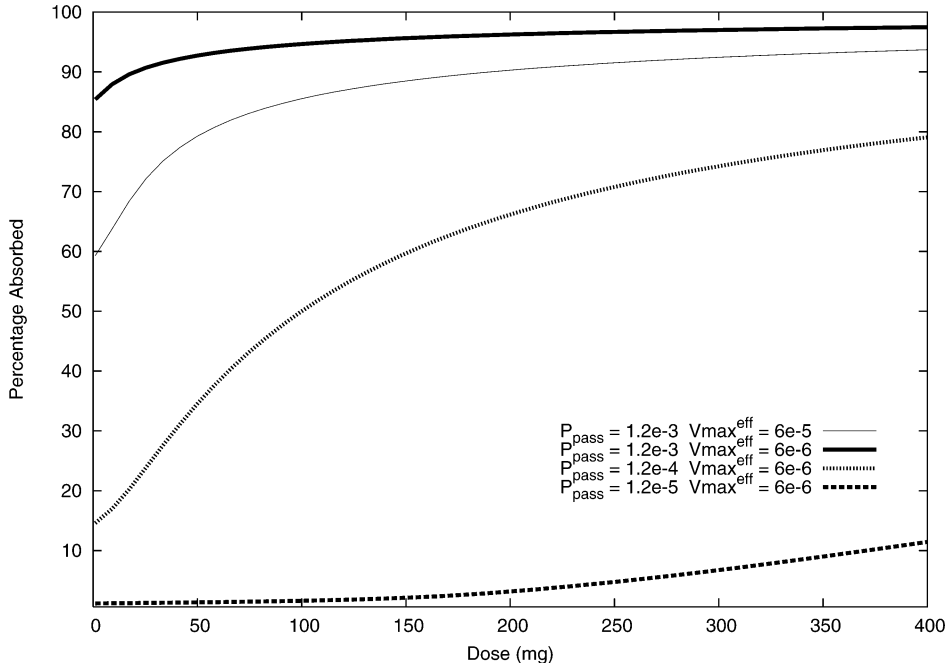

Figure 10. Percentage of drug absorbed relative to the absorption in the absence of transporters and metabolism vs dose of imatinib mesylate. For the curves $V_{max}^{met} = 3 \times 10^{-6}$ mg/cm^2/s, while V_{max}^{eff} has units of mg/cm^2/s and P_{pass} has units of cm/s.

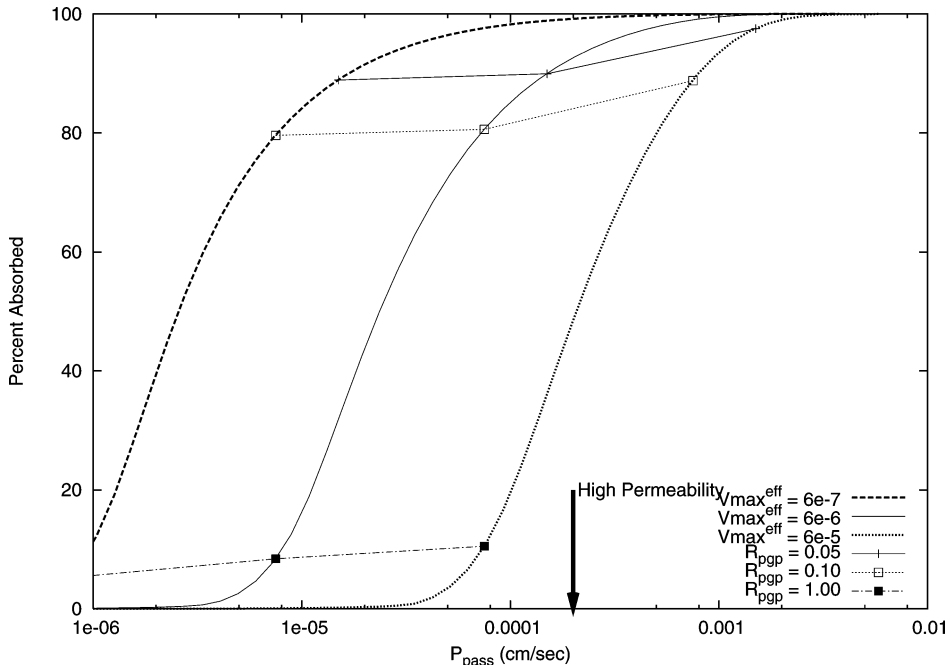

Figure 11. Percentage of drug absorbed relative to the absorption in the absence of transporters vs permeability. For the curves $V_{max}^{met} = 0$ mg/cm^2/s and the dose of imatinib mesylate is 400 μg.

process is one of the major factors that influence bioavailability of a drug. Pgp-mediated efflux has been invoked as an explanation for the low oral bioavailability of some drugs that are known to be Pgp substrates. In this paper, saturable Pgp-mediated efflux kinetics has been used to simulate the significance of Pgp efflux function as the drug concentration increases from the concentrations used in most in vitro or animal studies to the clinically relevant concentration for humans. In simulation II, the role of Pgp-mediated efflux on bioavailability of imatinib mesylate was explicitly studied. Even though imatinib mesylate is known as a Pgp substrate, the impact of Pgp on the intestinal absorption of imatinib mesylate was negligible in the clinical dose range. The ratio of active to passive transport as defined in the parameter R_{Pgp} provides an indication of when active transport will reduce bioavailability.

In this simulation, the evaluation of Pgp-mediated efflux was focused on intestinal drug absorption and bioavailability.

It is possible that the role of Pgp-mediated efflux on the drug absorption in tumor cells, blood−brain barrier, or other organs can be significant and relevant to drug efficacy in clinical application to the patients, especially when the drug concentration at the target organ is low.

Although numerous in vitro or in vivo experiments with animals have been performed to assess the role of Pgp-mediated efflux in oral bioavailability, the effect of Pgp on bioavailability may not be substantial. For most Pgp substrates, in vitro or animal studies for Pgp-mediated efflux on drug absorption were commonly carried out at very low drug concentrations, and therefore changes in clearance caused by suppression of Pgp transport are readily detected. Our simulations demonstrate that, for high-solubility drugs, even when Pgp transport is detectable at low concentrations, it may not be important at concentrations that occur in actual clinical practice. A low-dose study can identify whether a drug is a Pgp substrate during the drug development process; however, this study will not determine if the intestinal Pgp-mediated efflux will affect bioavailability. Therefore, an experimental design that includes the concentration range found in clinical applications should be considered if the intention is to apply the data from in vitro or in vivo animal studies to human bioavailability.

Simulation also shows the importance of the passive permeability in determining whether Pgp transport will affect bioavailability. The parameter R_{Pgp} provides a simple characterization of the effect of both passive permeability and dose on bioavailability for high-solubility drugs. Simulations now in progress are investigating low-solubility drugs to determine a similar simple characterization.

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