MODEL-BASED ANALYSIS OF THE PHARMACOKINETIC INTERACTIONS BETWEEN RITONAVIR, NELFINAVIR, AND SAQUINAVIR AFTER SIMULTANEOUS AND STAGGERED ORAL ADMINISTRATION

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ABSTRACT:

Eighteen healthy human immunodeficiency virus-negative subjects participated in an open-label, six-period, incomplete Latin-square crossover pharmacokinetic study. Each subject received two of the three possible pair-wise combinations of single-dose oral ritonavir (R) (400 mg), nelfinavir (N) (750 mg), and saquinavir (S) (800 mg), each pair on three occasions (simultaneous or staggered administration), each occasion at least 2 days after the last. A model-based analysis reveals the following major drug interactions under the conditions of this study: 1) R given simultaneously with S decreases S hepatic intrinsic clearance almost 50-fold relative to that predicted for S given alone and increases its gut bioavailability 90% (but decreases its rate of absorption 40%) relative to when N is given simultaneously; 2) N given simultaneously with S decreases S hepatic intrinsic clearance 10-fold relative to that predicted for S given alone; and 3) R inhibits S hepatic intrinsic clearance even after R plasma levels have become undetectable (>48 h after dosing), implying that R, when used as a pharmacokinetic enhancer, can be dosed less frequently than might be predicted from the duration of detectable systemic concentrations.

Protease inhibitors (PIs) \(^1\) ritonavir (R), nelfinavir (N), and saquinavir (S) are primarily metabolized by CYP3A4 (and partially by other cytochromes P450) in the liver (Eagling et al., 1997; Fitzsimmons and Collins, 1997; Hsu et al., 1998a; Kim et al., 1998; Washington et al., 1998). They exhibit extensive pharmacokinetic (PK) interactions (Merry et al., 1997; Hsu et al., 1998b; Jarvis et al., 1998), but the degree to which those interactions occur at the level of hepatic metabolism, gut metabolism, or gut efflux transporters is still uncertain. Adult AIDS clinical trial group study 378 (ACTG 378), involving staggered versus simultaneous administration of the three PIs, was designed to shed light on these issues. The findings with respect to changes of AUC (proportional to the ratio of systemic clearance to bioavailability) are reported elsewhere (C. B. Washington, C. Flexner, L. B. Sheiner, S. L. Rosenkrantz, M.A. Jacobson, T. F. Blaschke, submitted); they are considerable. This paper extends those findings by presenting a physiologically based population pharmacokinetic model applied to the full ACTG 378 data to assess and quantify the gut versus hepatic mechanisms responsible for the AUC changes and for any other PK interactions.

Materials and Methods

Data Source. ACTG 378 was an open-label, Latin-square design study of the effect of staggered versus simultaneous dosing on the PK profiles of the following three protease inhibitors: R, N, and S (we use the symbols R, N, S to refer not only to the drugs but to their concentrations; context should make clear which meaning is intended). A total of 18 human immunodeficiency virus-negative healthy volunteers participated in the study, and each was randomized to receive two of the three pairs (N + R, N + S, and R + S) in two series of three occasions. The three occasions for a given pair differed in whether the two drugs were given 1) simultaneously (denoted XY, in which X = N, R, or S, and likewise Y) or 2 and 3) separated by 4 h (staggered dosing), first one (X before Y, denoted X*Y) and then the other (Y*X). On a generic occasion, the first assigned dose(s) [400 mg R, 750 mg N, or 800 mg S (soft gelatin capsule)] was given 30 min after a standardized meal. Samples for PK analysis were drawn periodically for up to 28 h thereafter. With each subject, the two series of dosing occasions took place on successive weeks, and the three occasions within a series took place on Monday, Wednesday, and Friday. The sequence of series and occasions within series were assigned to subjects according to a Latin square. The study was approved by the Institutional Review Boards of Stanford University, Johns Hopkins University, and San Francisco General Hospital. Written informed consent was obtained from each subject.
Data Analysis. A hierarchical (population) PK model was fit to all data simultaneously with the program NONMEM (Beal and Sheiner, 1989–1998).

Pharmacokinetic (structural) model. A one-compartment model with first order absorption (and absorption lag time) is used for all three drugs. The key pharmacokinetic parameters for this model for a generic drug are the rate constant for absorption (k_{a,j}), volume of distribution (V), clearance (CL), and bioavailability (F). CL and F are further modeled as follows, corresponding to the “well stirred” liver model for a drug given orally and metabolized exclusively in the liver (Wilkinson and Shand, 1975), after possible absorption loss in the gut:

\[ F = F_{(\text{gut})} = F_{(\text{hep})} \frac{Q}{CL + Q} \]  
\[ CL = CL_0 \frac{Q}{CL_0 + Q} \]

where Q is hepatic blood flow, CL\_0 is intrinsic clearance of (total) plasma drug (= V_{max}/K_{m}, in which V_{max} is the maximal metabolic rate, and K_{m} is the drug-metabolizing-enzyme equilibrium constant), F_{(\text{gut})} is hepatic bioavailability (= 1 - extraction ratio across liver), and F_{(\text{hep})} is gut bioavailability (= 1 - extraction ratio across gut).

Using the symbols X and Y as drug variables (equal to N, R, or S, as circumstances dictate), a general competitive inhibition model is introduced to account for drug interaction effects on hepatic clearance (Segel et al., 1976):

\[ CL_{X} = \frac{CL_{X,0}}{1 + \sum Y_{i}(R,N,S)Y_{i}K_{i}} \]

where CL\_X\_0 is the uninhibited CL\_0 of X, Y is the concentration of the inhibitor drug, and K\_i is the inhibition constant of drug Y on drug X as substrate. Because Y varies in time, so will the CL\_0 and F_{(\text{hep})} (see eq. 1) of X. In eq. 3, concentrations and concentrations estimated are as micromolar free drug, computed assuming protein binding equals 98% for R, N, and S (Barry et al., 1998).

Another possible point of drug interaction, other than the liver, is the gut. Each of the three drugs are possible substrates for both gut CYP3A4 and P-gp (Wacher et al., 1995; Kim et al., 1998; Lee et al., 1998; Washington et al., 1998) and hence have the potential to inhibit their action on the other two drugs. Inhibition of CYP3A (P-gp) in the gut would be expected to increase the F_{(gut)} of a drug extensively metabolized (back-transported into the gut lumen) by it. Inhibition of P-gp can also increase k_{a} because back-transport should prolong absorption. Accordingly, we entertain the following equations for F_{(gut)} and k_{a}:

\[ F_{(\text{gut})}^{X} = 1 + g_{i}h_{i}(\text{codrug} = Y), \]
\[ k_{a}^{X} = 1 + h_{i}(\text{codrug} = Y), \]

where g and h are scalar parameters, X = R, S, or N, and so does Y, except Y \neq X, and I(\cdot) is the indicator function, taking the value 1 when its argument is true and 0 otherwise.

Because the magnitude of the drug interactions (see results, below) ascribable to gut effects is small relative to those ascribable to hepatic effects, model predictions, and hence goodness of fit, are relatively insensitive to variation in the form of eqs. 4 and 5, and therefore, although gut effects if present would almost certainly be nonlinear, a feature absent from eqs. 4 and 5, equations more complex than 4 and 5 cannot be estimated from our data.

Statistical model. At the first, within individual, level of the hierarchical model, residual (noise) variability is modeled with additive and proportional components:

\[ C_{e} = C_{e}(1 + e_{1}^{i} + e_{2}^{i}) \]

where C_{e} is the measured plasma drug concentration at time t in individual j, C_{e} is its prediction under the PK model, and the noise vector \( e = (e^1, e^2) \) is assumed to be independent, identically distributed normal with mean zero and the same diagonal variance-covariance for all three drugs.

At the second, interindividual, level of the hierarchical model, variability in the pharmacokinetic parameters is modeled generically as

\[ P_{a} = P_{a} \exp(\eta_{a}), \]

where, again using the subscript j to identify individuals, P_{a} is a pharmacokinetic parameter value (k, k_{a}, CL, V), for the jth subject, P_{a} is the (population) expected value of the parameter, and \eta_{a} is an independent random effect for the parameter. The random individual vectors \eta = (\eta_{a_1}, \eta_{a_2}, \ldots, \eta_{a_n}) are assumed independent identically distributed (multivariate) normal with mean zero and diagonal variance-covariance. Cov(\eta) = 0 assumed to be the same for all three drugs.

Inference. Although NONMEM can often produce standard errors of parameter estimates, for complex models with some poorly determined parameters (e.g., Q; see below), these often cannot be computed, or for other reasons in this particular analysis (see next subsection) are unreliable. Hence a different approach to inference is taken. The minimal value of the NONMEM objective function (approximately minus twice the log-likelihood of the data) can be used to test the merit of a more complex model (i.e., one with more parameters) over a less complex submodel. This is accomplished by computing the difference of minimized objective functions between the fits of the two models and referencing it to a \( \chi^2 \) distribution with degrees of freedom equal to the number of free parameters in the more complex model in excess of the number in the submodel (Cox and Hinkley, 1974).

Implementation details. The following additional details are noted: 1) to avoid nonidentifiability (“flip-flop”), all \( k_{i}^{X} \) are constrained to exceed \( k_{e} = CL_{X,0}^{Y}/V_{X} \), X = N, R, S; 2) to simplify computation, the concentrations of all drugs over time as they appear in the expression for CL\_0 are approximated by a step function, fixed locally constant at the average of the last previous and current observed concentration values; and 3) a minimal value for Q, if concentrations are expressed per liter of plasma, is hepatic plasma flow, ca. 50 l/h. Since red cells may transport some drug, however, effective Q, equal to plasma flow times blood/plasma partition coefficient, can be greater than plasma flow. Since partition coefficients were not measured, Q represents effective Q and could therefore be different for each drug. We nevertheless model it as identical for all drugs as model predictions (and hence goodness of fit) are very insensitive to its exact value whenever CL\_i < Q, as it is for both R and N (see Table 2, below); 4) the data from each individual appears three separate times in the data file, once for each drug (each individual receives all three drugs during the course of his six treatments). Each time, a different drug is considered to be the primary (modeled) drug and the other(s) the codrug. For example, the individual who received the sequence (NR, N*R, R*N, NS, N*S, S*N) appears in the data set three times with associated treatment data as in Table 1. Each individual thus appears to be three different individuals. This is done for convenience of data analysis so that the pharmacokinetic response can be treated as univariate. It has the effect of increasing the apparent number of individuals and hence independent observations, which may cause standard errors of parameter estimates to be underestimated. It is for this reason, among others, that no standard errors are reported herein.

Results

Preliminary analyses revealed no indication of nonlinear kinetics of N or S (i.e., no apparent change in their CL\_0 with changes in their own concentrations), a finding in accord with the literature (Faulds and Jarvis, 1998; Hsu et al., 1998b). Furthermore, no influence was apparent of 1) N on CL\_0 of R, 2) S on CL\_0 of N, 3) S or N on \( F_{(\text{gut})} \) or \( k_{a} \) of R, or 4) S or R on \( k_{a} \) of N. Thus, to obtain the results reported

<table>
<thead>
<tr>
<th>Modeled Drug</th>
<th>Codrug</th>
<th>Data from Treatments</th>
</tr>
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<tbody>
<tr>
<td>N</td>
<td>R/S</td>
<td>NR,N<em>R,R</em>N,N<em>S,N</em>S,N* N</td>
</tr>
<tr>
<td>R</td>
<td>N</td>
<td>NR,N<em>R,R</em>N</td>
</tr>
<tr>
<td>S</td>
<td>N</td>
<td>NS,N<em>S,S</em>N</td>
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</tbody>
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below, we fixed each of the parameters $K_{R}^{S}$, $K_{N}^{R}$, $K_{S}^{N}$, and $K_{S}$ to be sufficiently large so that its reciprocal is effectively zero, and we fixed both $g_{R}^{S}$ and $h_{R}^{N}$ for $Y = S, N$ and $h_{S}^{R}$ for $Y = S, R$.

The residuals from the fit of eqs. 1 to 7 to the data (with parameters fixed as just detailed) reveal that the model overestimates $S$ concentrations when the subject is $R$-naive and underestimates them when the subject has had prior exposure to $R$. To accommodate this, an empirical model for a “persistent (inhibitory) effect” of $R$ on $S$ intrinsic clearance is added to eq. 3 to produce the following eq. 8:

$$CL_{S}^{L} = \frac{CL_{S}^{L_{0}}}{1 + \sum_{Y=R,N,S}Y/K_{Y}^{S} + I(X = S \& Y = R)REFT/K_{R}^{S}}$$

where $REFT = W_{RS} \int R(t)e^{-k_{a}Rt}dt$ is the persistent effect. The expression for $REFT$ just given is a “leaky” integral of past $R$ exposure, i.e., it is proportional to the amount of (hypothetical) substance in a homogeneous compartment with input rate proportional (proportionality constant $= W_{RS}/K_{R}^{S}$) to current $R$ plasma concentration and first order loss with rate constant $k_{S}$.

To distinguish between hepatic and gut mechanisms of interaction and to assess the role of persistent inhibition of hepatic metabolism of $S$ by $R$, the following four successively more complex models were evaluated: model M1, neither persistent effect nor gut effect (eqs. 1–3, 6, 7); model M2, gut effect only (eqs. 1–7); model M3, persistent effect only (eqs. 1, 2, 6–8); and model M4, both persistent effect and gut effect (eqs. 1, 2, 4–8). Table 2 presents the parameter estimates and formal goodness of fit statistics for models M1–M4. Both models M2 and M3 provide significantly better fits than M1 but between the two, M3—persistent effect rather than gut effect—fits better. However, M4, which combines both persistent hepatic and gut effects, clearly fits better than either model with only one type of effect. This constitutes evidence for multiple levels of interaction, especially of $R$ on $S$.

Figure 1 shows the overall goodness of fit of M4 for the three drugs. Figure 2 shows this fit for three individual subjects. The six “peaks” in each panel of Fig. 2 are the six administrations of the modeled drug, the first three with one codrug and the second three with the other. Figure 3 shows simulated concentrations versus time for a typical individual according to M4, given a single dose (equal in magnitude to that used in this study) of each drug in the absence of any other codrug, and in the presence of a single dose of each other codrug. It also shows predicted concentrations versus time for single doses of $S$ (1200 mg) in the presence of steady-state average levels of $R$ (at 100 or 200 mg/day) under model M1 (no gut or persistent $R$ effect) and under model M4 (both gut and persistent effect present).

**Discussion**

The predictions of our final model M4 with respect to the effect on PI oral clearance (reciprocal dose-adjusted AUC) of coadministration of another PI agree in detail with the estimates from the noncompartamental analysis presented elsewhere (C. B. Washington, C. Flexner, L. B. Sheiner, S. L. Rosenkranz, M. A. Jacobson, T. F. Blaschke, submitted). 1) Simultaneous coadministration of $R$ with $S$ decreases $S$ clearance almost 50-fold relative to its clearance when given alone, whereas $R$ clearance decreases by only 30%; 2) simultaneous coadministration of $N$ with $S$ decreases $S$ clearance 10-fold, but $N$ clearance is unchanged; 3) simultaneous coadministration of $R$ with $N$ decreases $N$ clearance 2-fold, but $R$ clearance is unchanged; and 4) $R$ inhibits $S$ clearance even after $R$ plasma levels have become undetectable (~48 h after dosing). These results are also consistent with previous observations (Merry et al., 1997; Hsu et al., 1998b; Buss, 2000). The comparatively modest 30% increase of the AUC of $R$

<table>
<thead>
<tr>
<th>Parameter</th>
<th>M1 (Competitive Inhibition)</th>
<th>M2 (M1 + Gut Effects)</th>
<th>M3 (M1 + Persistent Effect)</th>
<th>M4 (M3 + Gut Effects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta$obj vs. (Mx) (ng/ml)</td>
<td>338 321 244</td>
<td>29 92 90 102</td>
<td>31 29 34 36</td>
<td>35 29 34 36</td>
</tr>
<tr>
<td>$f_{D}$ (gut) (%)</td>
<td>49 50 45 45</td>
<td>49 50 45 45</td>
<td>31 29 34 36</td>
<td>35 29 34 36</td>
</tr>
<tr>
<td>$f_{D}$ (gut) (%)</td>
<td>49 50 45 45</td>
<td>49 50 45 45</td>
<td>31 29 34 36</td>
<td>35 29 34 36</td>
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When $R$ is coadministered with $S$ (800 mg) the same order of magnitude as the 6.4% increase reported by Hsu et al. (1998b). The difference may be due to the higher dose of $S$ (800 mg) used in our study versus that (200–600 mg) used in the study of Hsu et al.

The analysis presented here was designed to elucidate the mechanisms of the above described findings. In so doing, we also uncovered an additional dynamic drug interaction on rate of absorption.

To comment first on the hepatic metabolic interactions, we find that the greatest effect (at least for all but $R$’s effect on $S$ metabolism) can be ascribed to classical (i.e., rapidly reversible) competitive inhibition. We estimate the $K_{i}$ for $N$ inhibition of $S$ metabolism to be higher (less potent) than the $K_{i}$ for $R$ inhibition of $S$ metabolism, 0.0052 versus 0.003 μM. This is consistent with the results (Eagling et al., 1997) using a CYP3A4 probe (inhibition of 6-β-hydroxylation of testosterone), in which the rank order of inhibitory potency was found to be ritonavir > indinavir > nelfinavir = saquinavir. In addition to the rank order, the absolute in vivo $K_{i}$ values we find and the in vitro values reported by others are of the same order of magnitude. For example, the in vitro $K_{i}$ (approximately equal to $K_{i}$ at low substrate concentrations) for $R$ inhibition of the metabolism of $S$ (3.8 μg/ml) has been estimated to be 0.029 μg/ml for total drug (A. Hsu, personal communication regarding Hsu et al., 1998b), or approximately 0.0006 μg/ml for free drug (assuming 98% binding), only ca. 3-fold less than the in vivo figure we find (0.003 μM–0.0018 μg/ml). In vivo $K_{i}$ values often do not agree exactly with in vitro ones, because in vivo
inhibitor concentrations at the cellular site of metabolite formation are not measured (Bertz and Granneman, 1997).

Our analysis provides strong support for the previously reported claim (Yuan et al., 1999) that R exhibits different $K_i$ values acting on different substrates' metabolism; goodness of fit significantly worsens (objective function increases more than 50 points) when all $K_i^R$ are required to be identical. Only a few exceptional drugs are metabolized exclusively by a single enzyme (Gorski et al., 1994). More commonly, multiple enzymes catalyze the formation of one or more metabolites, as is the case for the metabolism of the three PI s studied here. Thus the different “net” $K_i$ of R acting on different substrates may indicate differential relative inhibition by R of the enzyme isoforms predominantly responsible for metabolism of the different substrates.

Rapidly reversible competitive inhibition, however, cannot be the sole mechanism underlying the hepatic metabolic inhibition of the metabolism of S by R, as it persists well after plasma R from single-dose administration has declined to undetectable levels. Assuming that the persistent metabolic effect we estimate is real, one possible mechanism for it is irreversible inactivation of the CYP3A4 enzyme responsible for S metabolism by R, possibly through the formation of metabolic intermediate complexes (Koudriakova et al., 1998). Return of metabolic capacity with such a mechanism would occur at a rate governed by the resynthesis rate of the relevant CYP3A4, rather than by the disappearance rate of plasma R, and this is compatible with our estimated 30-h half-life of persistence (Barry and Feely, 1990; Li et al., 1997). Although R (and N) are known to be (rapidly) reversible competitive inhibitors of CYP3A4 (Kempf et al., 1997; Lillibridge et al., 1998), that does not rule out an irreversible component as well. However, irreversible inactivation of metabolizing enzyme would require that R permanently inactivate primarily an S-specific isoform of CYP3A4, because AUC increases of almost 50-fold—as seen for S when combined with R—are not seen for N or for R itself.

Another possible mechanism for the persistent effect, which does not involve irreversible inhibition of metabolizing enzymes, postulates that R and perhaps some of its unidentified metabolites, all acting only as rapidly reversible inhibitors, persist in liver tissue for a long time after the plasma concentration of the parent species has significantly declined. Due to the high affinity of R for CYP3A4 and the extreme sensitivity of S to CYP3A4 inhibition, even low concentrations of R or of putative inhibitory metabolites could significantly lower the intrinsic clearance of S.

The implications of the persistent effect are profound. They can be explored through extrapolation using model M4 because it is semimechanistic and can therefore accommodate dosages other than those actually used in this study. In particular, drug interactions between S

![Figure 1. Goodness fit of model M4 (see text) to R, N, and S data (left to right, as indicated).](image-url)
and mini-dose R (100 mg, or 200 mg/day)—currently popular as a “booster” for S concentrations because of its specific inhibition of hepatic CYP3A4—can be predicted (see Fig. 3) and compared with published data. In a recent study of coadministration of R (100 mg/day) and S-SGC (1200 mg/day), the AUC of S at steady state was 64,000 h · ng/ml (Kilby et al., 2000). That study also showed that further dose escalation of R to 200 mg/day did not increase steady-state AUC of S over that seen with 100 mg/day of R. Moreover, the trough concentrations of S (552 ng/ml) seen in that study at steady state with 100 or 200 mg/day of R are much higher than those predicted (by our model) for the single-dose situation if no persistent effect of R is included; model M1 predicts that the AUC of S (1200 mg/day) with 100 mg/day of R will be 20,000 (not 64,000) h · ng/ml and trough concentrations will be less than 1 (not 550) ng/ml. Moreover, increasing R to 200 mg/day under M1 causes the predicted AUC of S almost to double (relative to R at 100 mg/day), also contradicting the observations of Kilby et al. (2000). However, under M4 (or M3), the model with a persistent effect of R, 1) the predicted AUC of S at 1200 mg/day with 100 mg/day of R becomes 67,400 (remarkably close to 64,000) h · ng/ml, 2) the predicted trough concentrations are 176 ng/ml (the same order of magnitude as 550), and 3) the predicted AUC of S increases by only 18% (much less than double) when the dose of R is increased to 200 mg/day. Thus, our model M4 is qualitatively and quantitatively consistent with, and also provides a mechanistic explanation for, the findings of Kilby et al. This agreement also supports the conclusion that the persistent effect model presented here, based only on a very short sequence of single doses, is quantitatively applicable to the chronic dosing case of the Kilby et al. data as well. This suggests in turn that CYP3A4 induction by R (Hsu et al., 1998a; Greenblatt et al., 2000), likely not observed here due to the brevity of our study, does not markedly mitigate the persistent effect.

In vitro, PIs undergo metabolic extraction by CYP3A4 in the gut wall (Jarvis et al., 1998) and are also substrates for and inhibitors of intestinal P-gp (Kim et al., 1998; Lee et al., 1998; Washington et al., 1998; Shiraki et al., 2000). Our analysis of the ACTG 378 data (model M2 versus M1 or M4 versus M3) is compatible with gut-level interactions as well as hepatic ones. Of the two gut mechanisms, inhibition of gut CYP3A4 or P-gp, only the latter would likely affect rate of absorption, and such an effect is seen with S; according to M4, its absorption rate is 40% slower when it is given with R than when it is given with N. This is consistent with the two drugs’ relative (in vitro) P-gp inhibitory potencies (Shiraki et al., 2000; Huisman et al., 2001). In contrast, the effect of R versus N on the \( F_{in} \) of S is both greater (80%) and of opposite sign, suggesting that intestinal CYP3A4 is a more important factor for gut bioavailability of S than P-gp and that

**Fig. 2.** Fit of model M4 to concentrations of R, N, and S in three representative subjects.

Concentration of R, N, or S (as indicated) on the ordinate versus time (h) on the abscissa. Dashed line, population predicted concentration; solid line, individual maximal a posteriori Bayes prediction; •, observed concentrations. Subject 11 (subject numbers given in the upper right corner of each panel) took R with S in the first three periods and R with N in the next three periods. Subject 6 took N with R in the first three periods and N with S in the next three periods. Subject 16 took S with N in the first three periods, in the order S*N, N*S, and S*N, and then took S with R in the second three periods, in the order R*S, S*R, SR. Note the difference in S concentrations between the S*N and S*R administrations for this subject.
 inhibition of gut metabolism of S by R is much greater than such inhibition by N. This too is compatible with the results of others (Eagling et al., 1999; Huisman et al., 2001). Finally, the $F_{\text{gut}}$ of N is increased more by R than by S, but the increment is small (10%). The lack of a parallel effect on rate of absorption, argues, as above, for the mechanism of this $F_{\text{gut}}$ effect also being predominantly gut CYP3A4 inhibition, rather than P-gp inhibition. We tested whether concomitant versus subsequent administration of codrug was associated with quantitatively different “gut” effects on the modeled drug but did not find evidence for this, perhaps because the apparent gut effects are quantitatively so much less important than the hepatic ones.

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References


