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ORIGINAL PAPER

Understanding drug–drug interaction and pharmacogenomic changes in pharmacokinetics for metabolized drugs

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Abstract

Here we characterize and summarize the pharmacokinetic changes for metabolized drugs when drug–drug interactions and pharmacogenomic variance are observed. Following multiple dosing to steady-state, oral systemic concentration–time curves appear to follow a one-compartment body model, with a shorter rate limiting half-life, often significantly shorter than the single dose terminal half-life. This simplified disposition model at steady-state allows comparisons of measurable parameters (i.e., area under the curve, half-life, maximum concentration and time to maximum concentration) following drug interaction or pharmacogenomic variant studies to be utilized to characterize whether a drug is low versus high hepatic extraction ratio, even without intravenous dosing. The characteristics of drugs based on the ratios of area under the curve, maximum concentration and half-life are identified with recognition that volume of distribution is essentially unchanged for drug interaction and pharmacogenomic variant studies where only metabolic outcomes are changed and transporters are not significantly involved. Comparison of maximum concentration changes following single dose interaction and pharmacogenomic variance studies may also identify the significance of intestinal first pass changes. The irrelevance of protein binding changes on pharmacodynamic outcomes following oral and intravenous dosing of low hepatic extraction ratio drugs, versus its relevance for high hepatic extraction ratio drugs is re-emphasized.

Keywords Drug-drug interactions · Pharmacogenomics · Area under the curve · Operational half-lives · Maximum systemic concentrations

Tribute to Dr. Panos Macheras

Recently we derived the theoretical basis for the extended clearance model of organ elimination following both oral and intravenous dosing and critically analyzed the approaches previously taken [1]. Here in this special issue of the Journal honoring our friend and colleague, Professor Panos Macheras, we extend these analyses to understand and emphasize specific applications of these concepts, reflecting the approach taken by Professor Macheras in applying complex pharmacokinetic concepts and using them to elucidate the time course of various process in vitro and in vivo.

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The importance of changes or lack of change in volume of distribution

As our laboratory has pointed out [1, 2], drug–drug interactions and changes in disposition related to pharmacogenomic (PG) variance can potentially lead to changes in volume of distribution when transporters more than minimally affect drug disposition. Volume of distribution changes will not impede the ability to accurately predict changes in exposure (AUC, area under the systemic concentration–time curve) when transporters are involved. However, if both clearance and volume of distribution change as a result of transporters being significantly involved in a drug–drug interaction or as a result of a PG variance, it will be difficult to predict and understand the time-course of drug concentrations resulting from the modification, since mean residence time (MRT) is directly related to volume of distribution (V_{ss}, volume of

distribution steady-state) and inversely related to clearance (CL), as shown in Eq. (1) [3].

$$MRT = \frac{V_{ss}}{CL} \quad (1)$$

We use MRT here rather than half-life to obviate the necessity of discussing multicompartment systems.

Single dose terminal half-life versus operational half-life at steady state

It is important to note that many interactions are clinically relevant for drugs upon multiple dosing at steady-state, and as pointed out by Sahin and Benet [4], the elimination half-life of this steady-state disposition model will be less (and often markedly less) than the terminal half-life observed following a single dose. This is because at steady-state, distribution has less impact on the concentration time-course, and therefore a simple one-compartment disposition model can be used.

We illustrate this difference in single versus multiple dosing half-life in Fig. 1, where Fig. 1a depicts the logarithmic concentration–time curve following a single 100 mg oral dose of a low hepatic extraction drug with the following two compartment body model parameters: volume of the central compartment (V_1) is 100 L, the rate constant of elimination from the central compartment (k_{10}) is 0.1 h^{-1}, the distribution rate constants into and out of the peripheral compartment (k_{12} and k_{21}) are 0.06 $h^{-1}$and 0.08 h^{-1}, respectively (resulting in two-compartment exponential functions of $\lambda_1 = 0.2$ h^{-1} and $\lambda_2 = 0.04$ h^{-1}), an hepatic clearance of 10 L h^{-1}, a first order absorption rate constant (k_a) of 1.0 h^{-1} and a bioavailability (F) of 0.8 when $F_A \cdot F_G$ (as defined below) is 0.9. The equation describing this single oral dose concentration–time course is:

$$C = 0.750e^{-0.20t} + 0.208e^{-0.04t} - 0.958e^{-1.00t} \quad (2)$$

And the resulting single dose terminal half-life is 17.3 h. Above the single dose curve in Fig. 1a, we depict the concentration–time curve at steady-state where the 100 mg oral dose is given every 12 h. It is obvious in Fig. 1a that the concentration–time curves during a dosing interval at steady-state approximate a one-compartment body model, since with multiple dosing and accumulation the peripheral compartment becomes fuller and less distribution is evident, with a half-life that appears to be between 8.5 and 9 h. As pointed out by Sahin and Benet [4], it is the multiple dosing operational half-life that predicts accumulation, with no evidence that the 17.3 h terminal half-life is relevant.

Considerations of metabolic (vs transporter) drug–drug interactions and PG variance

Changes in drug metabolism related to drug interactions or PG variance have the potential to alter drug clearance, but not via any changes in transporter function. Therefore, it is expected that volume of distribution of drug should remain unchanged. Although we have not exhaustively analyzed the drug–drug interaction and PG variance database, we are not aware of any changes in drug volume of distribution that result from metabolic changes only. Further, changes in renal or biliary elimination are not expected, as they frequently are affected by transporters. Thus, the present analysis assumes that for metabolism-related changes resulting from drug interactions or PG variance there are no changes in volume of distribution, renal clearance or biliary clearance. Therefore, MRT and steady-state half-life are inversely related to clearance, and any observed changes in exposure (AUC), maximum concentration following an oral dose (C_{max}) and half-life result from metabolic changes only. The equations for AUC will all be analyzed assuming that the hepatic extraction ratio is determined as the ratio of hepatic blood clearance to hepatic blood flow as we recently reviewed [5], so that hepatic first pass bioavailability following oral dosing (F_H) is given by Eq. (3):

$$F_H = 1 - \frac{CL_H}{Q_H} \quad (3)$$

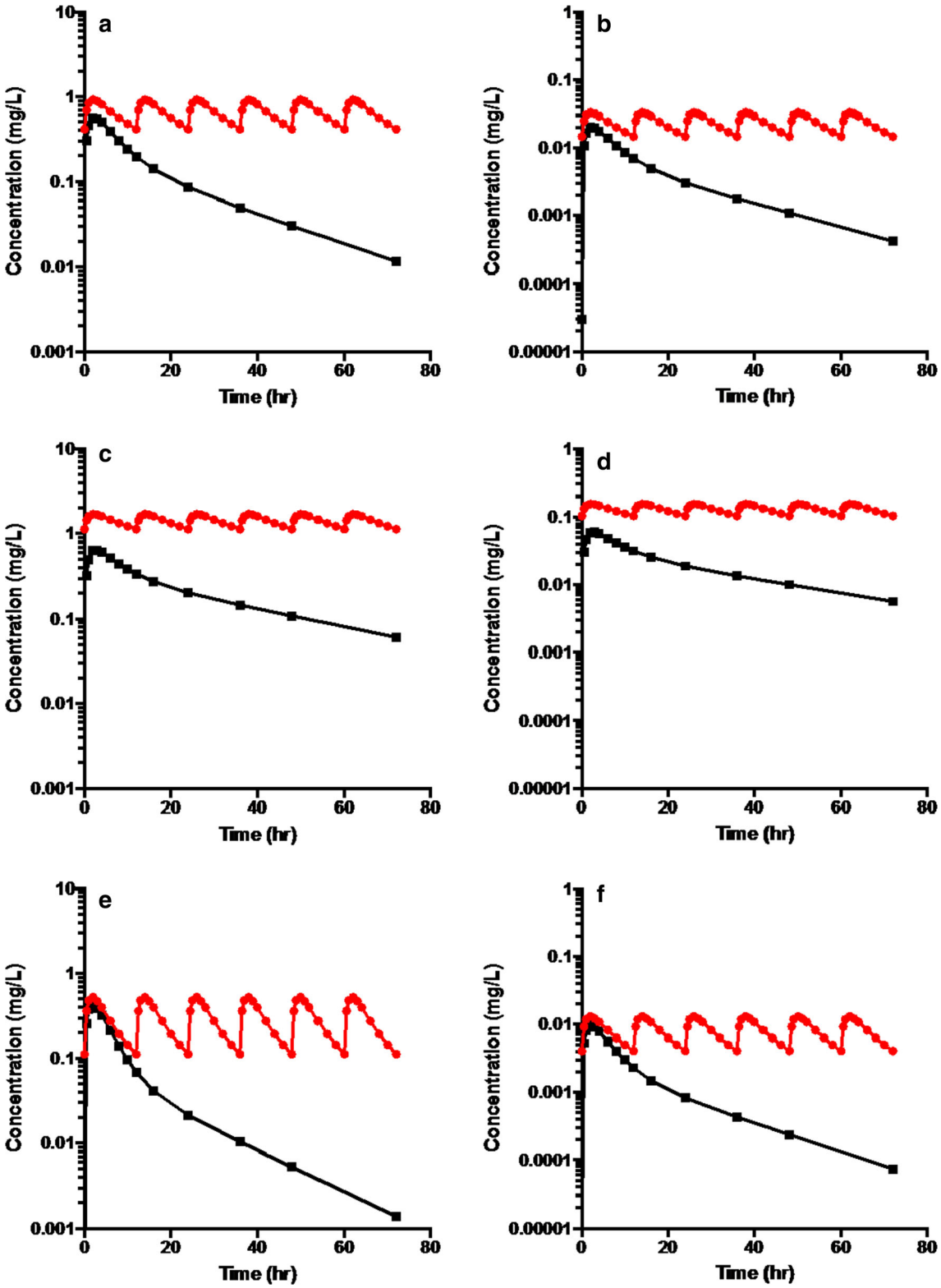
where CL_H is the hepatic metabolic blood clearance and Q_H is the hepatic blood flow.

Exposure following oral dosing and impact on pharmacodynamics

As shown in our recent publication [1] and by many others

$$AUC_{oral} = \frac{F_A \cdot F_G \cdot D}{f_{u,B} \cdot \sum CL_{int}} \quad (4)$$

where F_A is the fraction of the dose absorbed, F_G is the fraction of the dose escaping intestinal metabolism, D is dose, $f_{u,B}$ is the fraction of unbound drug in blood calculated as the fraction unbound in plasma divided by the blood to plasma concentration ratio, and $\sum CL_{int}$ is the sum of the irreversible elimination intrinsic clearances from the liver. Equation (4) is applicable to all oral dosing conditions where only metabolism is considered and volume of distribution is a constant. That is, Eq. (4) is valid for high hepatic extraction (ER_H), intermediate and low ER_H drugs. Thus, the exposure following oral dosing will change inversely with $\sum CL_{int}$ and $f_{u,B}$ and directly with $F_A \cdot F_G$.


a
b
c
d
e
f
Concentration (mg/L)
Time (hr)
0
20
40
60
80
10
1
0.1
0.01
0.001
0.0001
0.00001

◀**Fig. 1** **a** Log concentration–time plots for an orally dosed drug (100 mg) following two compartment disposition kinetics where volume of the central compartment (V_1) is 100 L, the rate constant of elimination from the central compartment (k_{10}) is 0.1 h^{-1}, the distribution rate constants into and out of the peripheral compartment (k_{12} and k_{21}) are 0.06 $h^{-1}$and 0.08 h^{-1}, respectively (resulting in two-compartment exponential functions of λ_1 = 0.2 h^{-1} and λ_2= 0.04 h^{-1}), an hepatic clearance of 10 L h^{-1}, a first order absorption rate constant (k_a) of 1.0 $h^{-1}$and a bioavailability (F) of 0.8 where the upper curve represents steady state dosing every 12 h and the lower curve depicts a single oral dose. The terminal half-life from the lower curve is 17.3 h, while $t_{1/2,op}$ for the multiple dosing upper curve is 8.8 h. **b** The log concentration time curves for a high extraction ratio drug where the values for dose, $F_A \cdot F_G$, distribution, elimination and absorption rate constants are unchanged from that in Fig. 1a but hepatic clearance is increased to 70 L h^{-1}, which results in F becoming 0.2. V_1 is increased to 700 L so that the terminal half-life for the single oral dose remains at 17.3 h, while $t_{1/2,op}$ from the multiple dosing upper curve is 7.8 h. **c** The single dose and multiple dose time curves for the low ER_H drug depicted in Fig. 1a when clearance is decreased by 50% to 5 L h^{-1}, which results in F becoming 0.85. From the upper steady state curve, $t_{1/2,op}$ = 17.2 h; from the lower single dose curve the terminal half-life is 28.9 h. **d** The single dose and multiple dose time curves for the high ER_H drug depicted in Fig. 1b when clearance is decreased by 50% to 35 L h^{-1}, which results in F becoming 0.55. From the upper steady state curve, $t_{1/2,op}$ = 17.2 h; from the lower single dose curve the terminal half-life is 28.9 h. **e** The single dose and multiple dose time curves for the low ER_H drug depicted in Fig. 1a when clearance is doubled to 20 L h^{-1}, which results in F becoming 0.70. From the upper steady state curve, $t_{1/2,op}$ = 4.7 h; from the lower single dose curve the terminal half-life is 12.4 h. **f** The single dose and multiple dose time curves for the high ER_H drug depicted in Fig. 1b when clearance is increased by 10L/hr to 80 L h^{-1}, which results in F becoming 0.1. From the upper steady state curve, $t_{1/2,op}$ = 6.2 h; from the lower single dose curve the terminal half-life is 14.1 h

Exposure following oral dosing can also be markedly affected by changes in F_G though inhibition, induction and/or genomic variance of intestinal enzymes. This will be particularly true for CYP3A substrates, since CYP3A4 is the major enzyme present in the intestinal epithelia. As will be addressed subsequently, the importance of F_G in changes of exposure following a single oral dose can be approximated by comparing the changes in AUC and C_{max} to the changes in half-life or MRT.

Clinically relevant changes, those where pharmacodynamics are altered, will be expected based on the extent of the exposure changes resulting from drug–drug interactions and PG variance. However pharmacodynamic changes will not be observed when total drug AUC varies due to $f_{u,B}$ changes. As emphasized by Benet and Hoener [6], Eq. (5) shows that the area under the concentration–time curve for unbound drug (AUC_u) following oral dosing will be unaffected by changes in protein binding.

$$AUC_{u,oral} = \frac{F_A \cdot F_G \cdot D}{\sum CL_{int}} \tag{5}$$

It is also possible to derive the relationship for the exposure within the liver following oral dosing ($AUC_{H,oral}$) as given in Eq. (6):

$$AUC_{H,oral} = \frac{F_A \cdot F_G \cdot D}{f_{u,H} \cdot \sum CL_{int}} \tag{6}$$

where $f_{u,H}$ is the fraction of drug unbound within the liver. Again, one can see by multiplying through by $f_{u,H}$ that changes related to intrahepatic unbound drug concentrations will have no effect on a pharmacodynamic outcome.

Using AUC, maximum concentrations and steady-state half-life to characterize extraction ratio following oral dosing

In understanding changes in pharmacokinetics for metabolized drugs, we concentrate on the ready measures that a clinician or scientist can observe following drug dosing. Following oral dosing, these include AUC, C_{max}, half-life and t_{max}, the time when C_{max} occurs. Most approved orally administered drugs have not been studied following intravenous dosing in humans and therefore as seen in Eq. (7), bioavailability (F, which equals $F_A \cdot F_G \cdot F_H$) cannot be distinguished from clearance.

$$\frac{D}{AUC} = \frac{CL}{F} \tag{7}$$

However, drug interaction and pharmacogenomic variance studies can provide useful information as to whether a drug is a high ER_H drug, where F is small, versus a low ER_H drug, where F approaches 1. As we demonstrate below, the analysis should consider AUC, C_{max} and apparent half-life at steady-state.

The data described in Fig. 1a represents a low ER_H drug for which all elimination is via metabolism, where F_H = 0.889 and $F_A \cdot F_G$ = 0.9, giving the F value of 0.8 for both single and multiple dosing. In Fig. 1b we depict the single dose oral concentration–time curve for a high ER_H drug, keeping the dose, $F_A \cdot F_G$, distribution, elimination and absorption rate constants unchanged, but hepatic clearance increased to 70 L h^{-1} and V_1 to 700 L. Above the single dose curve in Fig. 1b we depict the concentration time curve for every 12 h dosing. Here again the terminal half-life following oral dosing is 17.3 h and the half-life for steady-state dosing appears to be approximately 8 h.

Obviously, we could have chosen an infinite set of parameters to define the low and high extraction ratio drugs depicted in Figs. 1a and b, respectively, but to allow comparison of the effects of inhibition and induction on

low versus high ER_H drugs, we wanted to have control conditions and half-lives that were approximately the same.

Inhibition, induction and pharmacogenomic variance outcomes following oral dosing

In Fig. 1c and d we depict the concentration time curves when metabolism is inhibited, clearance is decreased by 50%, for both the low and high ER_H drugs. When metabolism is inhibited, for the low ER_H drug, CL_H = 5 L h^{-1}, which results in F becoming 0.85. For the high ER_H drug CL_H= 35 L h^{-1}, which results in F becoming 0.55.

In Fig. 1e we depict the concentration time curves when enzyme induction has occurred and have doubled the hepatic clearance of the low ER_H drug to 20 L h^{-1}, which results in F becoming 0.70. In Fig. 1f we have increased the hepatic clearance of the high ER_H drug to 80 L h^{-1}, which results in F becoming 0.1. It is obvious that the terminal half-life of the drug in each single dose plot is markedly different from the apparent one-compartment half-lives upon multiple dosing as noted in the figure legend.

Table 1 summarizes the ratios of the various parameters for the altered condition (either decreased-inhibited or increased-induced metabolism) relative to the control condition for both low and high ER_H drugs. The AUC ratio will be the same for the first dose and at steady-state, since the single dose $AUC_{0\rightarrow\infty}$ is equal to the multiple dose steady-state $AUC_{0\rightarrow\tau}$, during a dosing interval τ. The half-life value ratios reported in Table 1A are the multiple dosing values, the operational multiple dosing half-life, $t_{½,op}$, defined by Sahin and Benet [4]. The C_{max} ratios in Table 1B are for steady-state values ($C_{max,ss}$).

Table 1 Ratios (altered condition/control) of selected parameters for low and high ER_H drugs under inhibited (decreased) and induced (increased) conditions

A. More definitive ratios: altered condition/control

	AUC	$t_{½,op}$	$C_{max,ss}$
Low ER_H			
Inhibited	2.13	1.95	1.82
Induced	0.44	0.53	0.57
High ER_H			
Inhibited	5.50	2.20	4.71
Induced	0.44	0.80	0.39

B. Less definitive ratios: altered condition/control

	$C_{max,1st\ dose}$	$t_{½\ term,1st\ dose}$	$C_{min,ss}$	$t_{max,ss}$	$t_{max,1st\ dose}$
Low ER_H					
Inhibited	1.14	1.67	2.72	1.08	1.16
Induced	0.77	0.71	0.28	0.88	0.84
High ER_H					
Inhibited	2.61	1.67	7.05	1.08	1.16
Induced	0.47	0.82	0.28	0.95	0.93

A very useful relationship is observed when comparing the AUC, $C_{max,ss}$ and $t_{½,op}$ ratios. For low ER_H drugs, these three ratios are approximately the same for inhibited conditions and for induced conditions. In contrast, for high ER_H drugs, the AUC and $C_{max,ss}$ ratios are approximately the same but markedly different from the $t_{½,op}$ ratios. Thus, even without IV dosing it is possible from these interaction or PG variance studies to learn whether a drug is high or low ER_H. The marked difference in the operational half-life ratios versus AUC and C_{max} ratios for high versus low ER_H drugs is primarily due to the relative magnitude of change possible in F_H for high versus low ER_H drugs. For low ER_H drugs marked changes in clearance will have minimal impact on F_H (as evident in Eq. 3) and therefore on overall F. Since AUC and C_{max} can be influenced by changes in both clearance and F, and F is expected to be relatively unchanged for low ER_H drugs, it follows that changes in half-life related to clearance changes will be similar in magnitude to AUC and C_{max} changes. For high ER_H drugs, a small change in hepatic clearance can lead to a marked change in F_H (and therefore AUC and C_{max}), much larger in magnitude than the observed change in half-life. Additionally, on a percentage basis for high ER_H drugs a marked increase in clearance may not be possible, since clearance already approaches hepatic blood flow. Further, with a marked decrease in the hepatic clearance of a high ER_H compound, the drug would no longer be high ER_H.

Table 1B summarizes less definitive ratios, but some interesting outcomes should be noted. For a low ER_H drug, inhibition yields little change in C_{max} for a single dose study. This is true, since although AUC is the same for the first dose and the steady-state dosing interval, C_{max} accumulates during multiple dosing and little effect is seen for a single dose. In contrast for a high ER_H drug, there will be an observable first dose increase in C_{max} with inhibition, but not as much as the increase in AUC. Although mathematically we can calculate the first dose changes in C_{max} due to induction, and experimental studies can be designed to evaluate this ratio, this will not be useful in a relevant study or clinical situation since there will be little induction following the first dose of a concomitant inducer, and by the time induction has occurred, the subjects will be at steady-state. However, the first dose effect can be analyzed for increased PG metabolism. The $C_{min,ss}$ values do show differentiation between high and low ER_H drugs for inhibition and induction, however, the disadvantage is that there is no further confirming comparison as in the case of

the $C_{max,ss}$ ratios. The advantage of analyzing the $C_{max,ss}$ ratios is that they should be similar to the AUC ratios in discriminating high and low ER_H drugs. It will also be very difficult to make any conclusions based on t_{max} ratios either at steady-state or from a single dose inhibition study, since all of the ratio values are so close to 1.0. However, we will always expect the multiple dosing t_{max} to be smaller in magnitude than the single dose t_{max} for all situations. Similar to the $t_{½,op}$ ratios, the change in terminal half-life following a single dose will show the appropriate inhibition/induction effects, but it is often more difficult to determine these terminal half-life values versus the apparent $t_{½,op}$ values at steady-state. Yet, following single dose drug interaction or pharmacogenomic variance studies, high versus low ER_H can be discerned. Comparing AUC ratios with $t_{½term,1st\ dose}$ in Table 1 shows that the $t_{½term,1st\ dose}$ ratio approximates the AUC ratio for both inhibition and induction with low ER_H drugs, but not as close as the $t_{½,op}$ ratio (i.e., Inhibition, Low ER_H: AUC ratio 2.13, $t_{½term,1st\ dose}$ ratio 1.67, $t_{½,op}$ ratio 1.95; Inhibition High ER_H: AUC ratio 5.50, $t_{½term,1st\ dose}$ ratio 1.67, $t_{½,op}$ ratio 2.20; Induction, Low ER_H: AUC ratio 0.44, $t_{½term,1st\ dose}$ ratio 0.71, $t_{½,op}$ ratio 0.53; Induction, High ER_H: AUC ratio 0.44, $t_{½term,1st\ dose}$ ratio 0.82, $t_{½,op}$ ratio 0.80). One can readily see that high versus low ER_H can be determined following the single dose studies.

CYP3A substrates following oral dosing

Since CYP3A is the major cytochrome P450 enzyme in the intestine, inhibition or induction of this enzyme can have major effects on F_G. This results in greater effects on AUC and C_{max} ratios than for non-CYP3A substrates, but with essentially no additional effect on $t_{½}$ ratios. For CYP3A inhibition studies, we expect there to be less differential between the first dose and steady-state C_{max} ratios.

Inhibition, induction and pharmacogenomic variance outcomes following IV dosing

There are many fewer drug interaction (inhibition and induction) and PG variance (decreased and increased metabolism) data following IV dosing than for oral dosing. However, some general rules can be applied. For low ER_H drugs, changes in AUC and half-life will be similar to that for oral drugs, but of course, there will be no F related issues. For high ER_H drugs, AUC and half-life will change inversely with Q_H. Protein binding interactions will change pharmacodynamic effects. That is, if there is more free drug, a greater effect will be observed, in contrast to the lack of a pharmacodynamic effect for orally dosed drugs and low ER_H IV dosed drugs [1].

Comparison of pharmacokinetics in disease state patients versus healthy volunteers

The analysis presented here for analyzing pharmacokinetic changes in metabolic outcome due to inhibition, induction and PG variance assumes that volume of distribution remains constant, which we maintain is the condition for metabolic drug interactions and PG variance. As noted above if transporters are significantly involved the general trends discussed here may not be appropriate since transporter changes can also lead to volume of distribution changes in addition to clearance changes, both of which will affect half-lives. This may also be true for comparison of disease state versus healthy volunteer analysis, where the disease state may potentially change volume of distribution beyond simply changing the extent of protein binding. However, as seen below for propranolol, this does not appear to be a disqualifying situation.

Examples of metabolic drug interactions and pharmacogenomic variance from the literature

Alván et al. [7] reported the induction of alprenolol metabolism by pentobarbital treatment as depicted for one subject in Fig. 2. Subjects received oral (200 mg) and IV (5 mg) alprenolol, a high ER_H drug with a plasma clearance of 75 ± 10 L h^{-1} (blood to plasma ratio not given), before and after 10 days of nightly 100 mg oral doses of pentobarbital. As would be expected, no significant change

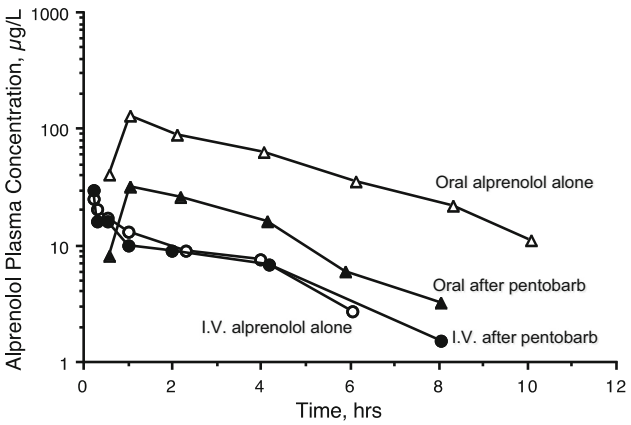


Fig. 2 Pharmacokinetics of alprenolol a high ER_H drug, before and after 10 days of nightly 100 mg oral doses of pentobarbital for 5 mg IV doses of alprenolol and 200 mg oral doses Adapted with permission from Ref. [7]

in AUC or $t_{½}$ was seen for the IV curves, since Q_H would not be expected to change with pentobarbital induction. However, there will be easily observable changes in AUC and $C_{max,ss}$ following oral dosing as per Eq. (4), and they are expected to change in parallel, as shown in Table 1A (High ER_H, Induced). As shown in Table 1, a decrease in $t_{½}$ would also be expected, but the change would be much less than the AUC and $C_{max,ss}$ changes and not as obvious. This appears to be the case in Fig. 2.

Blake et al. [8] carried out a meta-analysis of single oral doses of metoprolol in extensive, poor, intermediate and ultra-rapid CYP2D6 metabolizers of this high ER drug. The comparison of the ratios of mean values for AUC, $C_{max,1st\ dose}$ and terminal $t_{½1st\ dose}$ are given in Table 2. As seen in comparison with Table 1 High ER_H Inhibited, the AUC ratio (Poor/Extensive) in Table 2 is more than double the $C_{max,1st\ dose}$ ratio (4.86 vs 2.28) and the $t_{½term,1st\ dose}$ ratio (4.86 vs 2.28). The AUC ratio (Ultra-Rapid/Extensive) is less than the $C_{max,1st\ dose}$ ratio (0.37 vs 0.43) and the $t_{½term,1st\ dose}$ ratio (0.37 vs 0.90).These results follow the same pattern as the comparison in Table 1 for High ER_H Induced. At steady state the AUC and C_{max} ratios would be expected to be similar, but this is not the case following the first dose, which are often the only data available when sponsors are characterizing the relevance of potential drug–drug interactions and the importance of pharmacogenomic variance.

Kharasch et al. [9] investigated the effects of CYP2B6 polymorphisms on the pharmacokinetics of oral and intravenous methadone, a low ER_H drug. Only $AUC_{0\rightarrow\infty}$ values were reported together with figures depicting the average plasma concentration time curves. There was sufficient separation of the S-methadone plasma concentration curves that we were able to digitalize the data resulting in the outcomes presented in Table 3 for the measurements of relevance to this analysis. As can be seen, our calculated $AUC_{0\rightarrow\infty}$ values from the digitalized data are reasonably close to the published values, all within 7%. The ratios for the individual parameters we calculated from the digitalized data are presented in Table 3. There are no significant differences between the normal metabolizers (CYP2B*1/*1) and the intermediate metabolizers (CYP2B*1/*6). However, poor metabolizers (CYP2B*6/*6) yield comparable ratios for AUC and $t_{½term,1st\ dose}$ as would be suspected for a low ER_H drug following the pattern given in Table 1, with $C_{max,1st\ dose}$ not giving as big a change, again as reflected in Table 1 for inhibition of a low ER_H drug. The intravenous plasma concentration values in Kharasch et al. [9], corrected for a blood/plasma ratio of 0.79 [10], yield a blood clearance of 17.0 L h^{-1} for S-methadone, consistent with a low ER_H drug.

Table 2 Ratios of poor metabolizers to extensive metabolizers and ultra-rapid metabolizers to extensive metabolizers following oral dosing of metoprolol, a high ER_H CYP2D6 substrate [8]

	AUC ratio	$t_{½\ term,1st\ dose}$ ratio	$C_{max,1st\ dose}$ ratio
Poor/extensive	4.86	2.32	2.28
Ultra-rapid/extensive	0.37	0.90	0.43

There were only 4 rapid metabolizers in the study for two different genotypes as given in Table 3, and their average blood clearance was 27.2 L h^{-1}, approaching a doubling. The ratios of AUC and $t_{½term,1st\ dose}$ are quite similar to the values in Table 1 for a two-fold induction in clearance for a low extraction ratio drug, but the $C_{max,1st\ dose}$ ratio is lower than expected. This could be due to the limited number of subjects investigated, but it could also reflect the increase in clearance from the low ER_H range. Yet, it appears that it is probably easier to differentiate high versus low ER_H drugs based on inhibition drug–drug interaction or decreased pharmacogenomic activity studies than for induction or increased pharmacogenomic activity studies.

Rogge et al. [11] reported the effect of enoxacin inhibition on the metabolism of the low ER_H drug theophylline following 200 mg single oral doses. Following 9 enoxacin 25 mg doses every 12 h, a single 200 mg oral dose of theophylline (as Theo-Dur®) was compared with a 200 mg oral dose of theophylline prior to enoxacin administration resulting in the following ratios: $AUC_{inhibition}/AUC_{control}$ = 1.42; $t_{½inhibition}/t_{½control}$ = 1.35; $C_{max,inhibition}/C_{max,control}$ = 1.30, values that are similar to one another and consistent with what would be expected for a low ER_H drug.

Midazolam is a CYP3A substrate with an intermediate ER_H (plasma clearance hepatic = 46 L h^{-1}) and an F_G = 0.57 [12]. Concomitant dosing of 100 mg fluconazole with single oral 3 mg doses of midazolam yielded $AUC_{inhibition}/AUC_{control}$= 2.16; $t_{½inhibition}/t_{½control}$ = 1.25; $C_{max,inhibition}/C_{max,control}$ = 1.77 [12]. These data illustrate the point discussed above that for CYP3A substrates the effect of inhibition on F_G yields single dose C_{max} changes closer in magnitude to AUC changes than might be expected as given in Table 1. Backman et al. [13] investigated the inhibition and induction of midazolam, with concomitant multiple oral doses of itraconazole and rifampin, respectively, in 9 healthy volunteers noting that plasma concentration–time curves for oral midazolam may differ by 400-fold between the two interactions, as shown in Table 4. Here again, single dose C_{max} ratios for this CYP3A substrate are much closer to AUC changes, than $t_{½}$ changes.

Finally, Fig. 3 depicts the oral and IV propranolol blood concentration–time curves in 9 normal subjects and 7

Table 3 Measured AUC and parameters determined from digitalized data for oral doses of S-methadone, a low ER_H drug, in healthy volunteers exhibiting different CYP2B6 genotypes and the ratios of parameters from the study of Kharasch et al. [9]

A. Absolute values

Genotype	N	Phenotype	Published $AUC_{0\rightarrow\infty}$ (ng ml^{-1} h^{-1})	$AUC_{0\rightarrow96}$ (ng ml^{-1} h^{-1})	$AUC_{0\rightarrow\infty}$ (ng ml^{-1} h^{-1})	$t_{1/2\ term,\ 1st\ dose}$ (h)	$C_{max,1st\ dose}$ (ng ml^{-1})	t_{max} ($h_)$
CYP2B6*1/*1	21	Normal Metabolizers	620	546.6	612.8	29.3	13.3	8.0
CYP2B6*1/*6	20	Intermediate Metabolizers	734	630.1	714.9	30.8	19.1	3.0
CYP2B6*6/*6	17	Poor Metabolizers	1242	887.8	1164.7	45.5	18.7	3.0
CYP2B6*4/X (CYP2B6*1/*4 & CYP2B6*4/*6)	4	Rapid Metabolizers	155	152.2	156.5	17.7	5.7	6.0

B. Ratios versus normal metabolizers

Genotype	N:N	Phenotype	Published $AUC_{0\rightarrow\infty}$	$AUC_{0\rightarrow96}$	$AUC_{0\rightarrow\infty}$	$t_{½\ term,1st\ dose}$	$C_{max,1st\ dose}$	t_{max}
CYP2B6*1/*6	20:21	Intermediate Metabolizers	1.2	1.2	1.2	1.1	1.4	0.4
CYP2B6*6/*6	17:21	Poor Metabolizers	2.0	1.6	1.9	1.6	1.4	0.4
CYP2B6*4/X (CYP2B6*1/*4 & CYP2B6*4/*6)	4:21	Rapid Metabolizers	0.3	0.3	0.3	0.6	0.4	0.8

Table 4 Ratios of altered condition/control following oral dosing of midazolam, an intermediate ER_H CYP3A substrate, when inhibited by itraconazole and induced by rifampin [13]

	AUC ratio	$t_{½}$ ratio	$C_{max,1st\ dose}$ ratio
Inhibited/control	6.75	3.06	3.12
Induced/control	0.023	0.372	0.054

patients with cirrhosis observed during the seventh dosing interval for an oral 8 h dosing regimen measuring unlabeled drug with a simultaneous tritiated IV dose of propranolol as reported by Wood et al. [14]. For this intermediate-high ER_H drug, the change in AUC and half-life following IV dosing in the cirrhosis patients is not as great as following oral doses, since the AUC_{IV} Eq. (8) [1] is a function of both Q_H and CL_{int}, with the Q_H term markedly dampening the effect of decreased CL_{int} in the cirrhosis patients.

$$AUC_{IV} = \frac{D_{IV} \cdot (Q_H + f_{u,B} \cdot CL_{int})}{Q_H \cdot f_{u,B} \cdot CL_{int}} \quad (8)$$

However, following oral doses, Eq. (4) is the relevant relationship and the change of CL_{int} in the cirrhosis patients has a marked effect on AUC, C_{max} and $t_{½}$. As noted in Fig. 3 for the oral multiple doses, the data appear to follow a one-compartment body model with first order absorption as previously seen in the upper panels of Fig. 1.

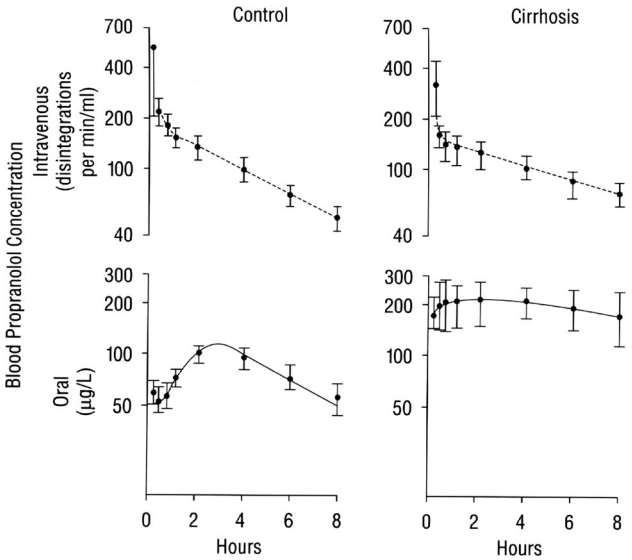


Fig. 3 In cirrhosis, the oral bioavailability of propranolol is greatly increased, as evidenced by comparison of the blood concentrations of unlabeled drug after oral administration (bottom panel) with that of tritiated drug after IV administration (top panel), following simultaneous determination of the kinetics of propranolol during the seventh dosing interval of an oral 8 h dosing regimen in 9 normal subjects and 7 patients with cirrhosis. Reproduced with permission from Ref. [13]

Conclusions

Following multiple dosing to steady-state, oral systemic concentration time curves appear to follow a one-compartment body model, but with the rate limiting half-life smaller, and often significantly smaller, than the single dose terminal half-life. This simplified disposition model at steady-state, as well as after single dose studies, allows comparisons of measurable parameters, AUC, C_{max}, $t_{½}$ and t_{max}, to be utilized following drug interaction or PG variance studies to characterize whether a drug is low versus high hepatic extraction ratio, even without IV dosing. We believe that such drug interaction and pharmacogenomic variance studies are the only means to characterize the relative magnitude of the extraction ratio for a drug in humans exclusively studied following oral doses. The characteristics of drugs based on ratios of AUC, C_{max} and $t_{½}$ are identified with the recognition that volume of distribution is essentially unchanged for these drug interaction and PG variance studies where only metabolic outcomes are changed and transporters are not significantly involved. Comparisons of C_{max} changes following single dose interaction and PG variance studies may also identify the significance of F_G changes. Pharmacodynamic changes would be expected to directionally follow pharmacokinetic changes for these metabolic drug interaction and pharmacogenomic variance studies, but not necessarily to the same extent. Once the relative magnitude of ER_H is determined, both drug development scientists and clinicians will recognize that for high ER_H drugs changes in exposure may be significantly more than estimated based on clearance and half-life changes.

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