The Impact of Ignoring Extraction Ratio When Predicting drug-drug Interactions, Fraction Metabolized and Intestinal First-Pass Contribution.
Brian J. Kirby and Jashvant D. Unadkat
Drug Metabolism and Disposition

Sensitivity/Error Analysis Results:

Figure S1 and S2 show the results of the sensitivity and error analysis. Notice the X axes (fraction of clearance remaining) in all Figures are on a logarithmic scale. The analysis presented below is conducted over the range of parameters (EH {0.1-0.9}, f_{hep} {0.5-1.0} and $f_{m,CYPi}$ {0.5-1.0}) that are observed for many of the commonly used victim drugs such as midazolam, alfentanyl and nifedipine for CYP3A and metoprolol and desipramine for CYP2D6. Most of these drugs have f_{hep} and $f_{m,CYPi}$ values close to or above 0.9 and EH values from 0.3 to 0.7 (see Table 1 for values). Therefore, these commonly observed ranges were used to highlight the sensitivity/error analysis.

The analysis below evaluates the sensitivity of EH, f_{hep} and $f_{m,CYPi}$ individually.

EH (Hepatic Extraction Ratio)

The true novelty of our model (Eq. 8) is that it affords the opportunity to quantify the error introduced into an AUC ratio prediction solely as a result of assuming that a drug is a low extraction ratio drug when in fact it is not. For all our simulations we assumed constant hepatic blood flow (Q =1.5 L/min), recognizing that variability in blood flow will change EH. The magnitude of change in EH will be most pronounced for highly extracted drugs and will affect the impact of ignoring EH.

Figure S1: Impact of EH When $f_{m,CYPi}$=1

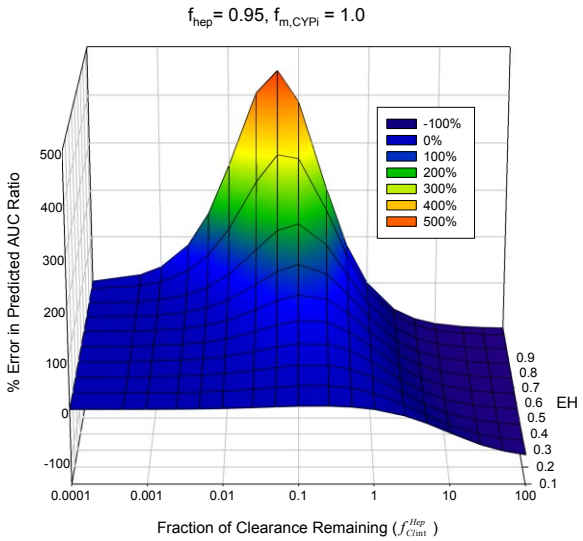
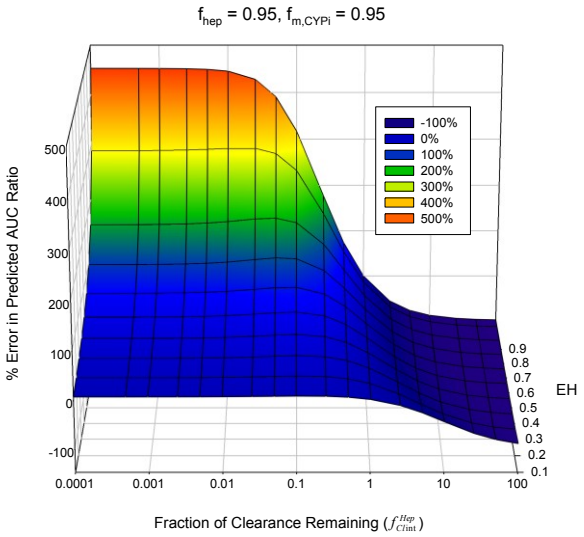


Figure S1 shows that the error is dependent on the magnitude of the DDI-induced fold-change in intrinsic clearance and $f_{m,CYPi}$. For a drug with an f_{hep} = 0.95 and $f_{m,CYPi}$ = 1.0, when the fold-change in intrinsic clearance (f_{Clint}^{Hep}) is in the range of 1 to 0.1 (0 to 90% inhibition), an error of as much as 20% is introduced into the predicted AUC ratio as a result of ignoring the EH of the victim drug even when the true EH is as low as 0.25 (a typically scenario). For a drug with EH of 0.9 ignoring the EH can result in an error that is as much as 300%. Interestingly, as the fraction of clearance remaining becomes very small (f_{Clint}^{Hep}<0.01, greater degree of inhibition), the error is significantly diminished as the AUC ratio is ultimately determined by non-hepatic clearance. This is because the inhibited enzyme is solely responsible for the hepatic clearance ($f_{m,CYPi}$ =1) and when that pathway is almost completely inhibited, the liver is no longer a clearing organ, and the resulting clearance is solely

determined by non-hepatic clearance. As a result, there is no effect of ignoring EH and the % error approaches 0%.

Figure S2: Impact of EH When $f_{m,CYPi}$=0.95



In contrast, for a drug with f_{hep} = 0.95 and $f_{m,CYPi}$ = 0.95 (Figure S2, above), as the fraction of clearance remaining becomes smaller (f_{CLint}^{Hep}<0.01), the % error in the AUC ratio plateaus at a constant value and this value depends on the EH. This is a result of the un-inhibited remaining fraction (0.05) of hepatic elimination constituting a larger fraction of the observed hepatic clearance than it did when the inhibited pathway was present. For example, a drug with an EH of 0.5 (total intrinsic clearance is equal to hepatic blood flow 1.5 L/min, but observed hepatic clearance is half of hepatic blood flow or 750 ml/min) if the drug has an $f_{m,CYPi}$ of 0.95, then 37.5 ml/min of observed hepatic clearance will be due to the minor pathway, which has an intrinsic clearance of 75 ml/min (1500ml/min * 0.05). When the major pathway is inhibited, the remaining observed hepatic clearance will be ~75 ml/min rather than 37.5 ml/min (750 ml/min *0.05) when not accounting for EH dampening of hepatic clearance. In figure S1 panel B, the point at which the maximum % error is achieved is shifted to the right for net inhibition (f_{CLint}^{Hep}<1) as the EH of the victim drug increases. This implies that as the victim drug EH increases, more potent inhibition is necessary to completely inhibit the clearance pathway. This phenomenon can be described by a hypothetical situation in which the clearance of two drugs (EH=0.1 and 0.9) are inhibited 99% (f_{CLint}^{Hep}=0.01). In this situation the hepatic clearance of the low EH drug would be 0.11% of blood flow whereas for the high EH drug it would be 9.0 % of blood flow. 99.99% inhibition (f_{CLint}^{Hep}= 0.0001or 100 times higher concentration of the inhibitor) would be necessary to inhibit the clearance of the high EH drug to 0.1% of blood flow.

The magnitude of percent error with respect to net induction (f_{CLint}^{Hep}>1) is not as prominent because it is artificially "capped" at -100% as a result of the AUC ratios being less than 1.0 and the method of calculation of % error. For a victim drug with EH = 0.25, f_{hep} = 0.95, $f_{m,CYPi}$ = 0.95 and modest induction of 2.5-fold, the % error is ~-25% or AUC ratios of 0.57 and 0.42 for EH and No EH model respectively (Figure S2). For victim drugs with higher EH, the error approaches -100% at much lower net induction (f_{CLint}^{Hep}>1). This shows that for

an IV administered victim drug in the presence of induction, the observed AUC ratio will be substantially higher (which will appear as less potent induction) than that predicted from a No EH model. This is a result of increasing the extraction ratio of the drug and thereby causing increased dampening on the decrease of the AUC ratio. As the EH of a drug increases, a larger degree of induction is necessary to have a comparable decrease in AUC ratio.

Looking at the vertical lines in Figure S2 (fixed degree of inhibition or induction) it is apparent that as the EH of the victim drug increases the % error in the AUC ratio increases. Therefore, for the same perpetrator drug the % error in the AUC ratio is dependent on the EH of the victim drug used and the error will increase as EH increases.

The surface in Figure S2 shows that the maximum difference between the predicted AUC ratios is seen when the fraction of clearance remaining is ~0.1 to 0.01, beyond which this value decreases somewhat and the % error stabilizes at a slightly lower plateau. This phenomenon is highlighted in Figure S3 in which the traces of predicted AUC ratio for a drug with f_{hep} of 0.95, $f_{m,CYPi}$ of 0.95 and EH of 0.25 or assuming the No EH model. A plot of the % error in AUC ratio is overlaid on the secondary y axis.

Figure S3: Impact of EH When $f_{m,CYPi}$=0.95

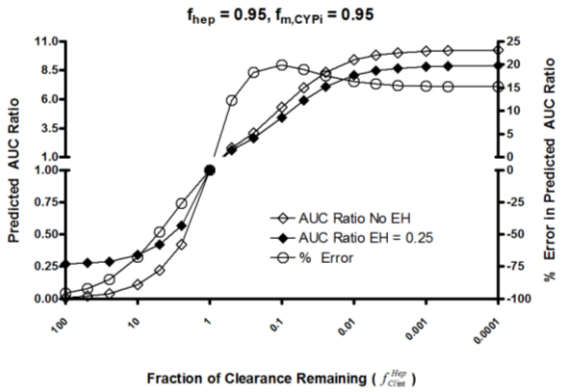


Figure S3 shows that the maximum % error is achieved not upon complete inhibition, but rather when ~90 % inhibition is seen (fraction of clearance remaining of 0.1). The % error after more potent inhibition plateaus at a slightly lower but constant value. The early maximum is a result of the change in the shape of the inhibition curve when the EH is accounted for and, arises as a result of evaluating the % change and not the absolute AUC ratio. The largest absolute difference in predicted AUC ratios is observed at maximum inhibition.

f_{hep} (the fraction of total clearance that is hepatic elimination)

To evaluate the contribution of f_{hep} (Figure S4) to AUC ratio prediction error we used a situation in which the EH is set at 0.5 and $f_{m,CYPi}$ is 0.95 and varied the f_{hep}.

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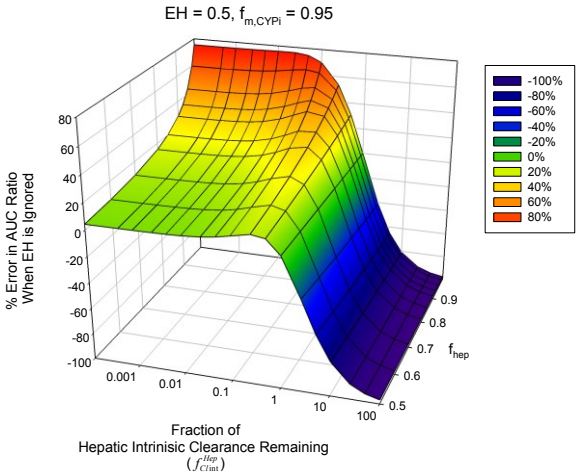
Figure S4: Impact of f_{hep}



As f_{hep} is increased from 0.5 to 0.99, the % error curves and maximum % error are shifted up and to the right. The rightward shift is similar to that described in the EH evaluation above and the magnitude of the upward shift is proportional to f_{hep}. This upward shift, or a greater % error as f_{hep} increases, is a result of the unaltered hepatic clearance pathway representing a larger fraction of the total clearance and that the contribution of this pathway is not adequately characterized by the No EH model as described in the EH evaluation above. A substantial f_{hep} ($\geq$ 0.90) is required for this effect to contribute more than 30% error in the AUC ratio.

$f_{m,CYPi}$ (the fraction of hepatic clearance by the affected pathway)

The contribution of $f_{m,CYPi}$ (Figure S5) was generated by setting the victim drug EH at 0.5 and f_{hep} at 0.95 while varying the value of $f_{m,CYPi}$ from 0.5 to 1.0.

Figure S5: Sensitivity/Error Analysis of $f_{m,CYPi}$

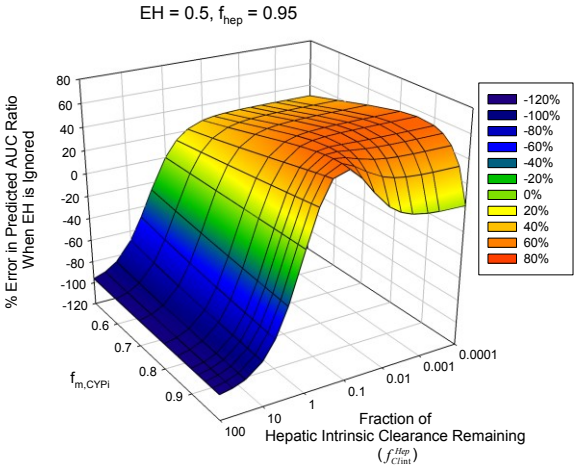


Figure S5 shows that the % error curves are slightly shifted vertically as $f_{m,CYPi}$ is increased showing that as $f_{m,CYPi}$ increases, the % error in the predicted AUC ratio increases when EH is not accounted for. Interestingly though, the shape of this surface changes as $f_{m,CYPi}$ is increased towards 1.0. In this plot, as the fraction of clearance remaining (f_{Clint}^{Hep}) decreases below 0.1(>90% inhibition), and $f_{m,CYPi}$ increases above 0.9, the % error begins to decrease until at $f_{m,CYPi}$ = 1.0 there is no difference between the two models at very high inhibition (f_{Clint}^{Hep}~0.0001). This again highlights the importance of hepatic blood flow dampening of hepatic clearance via the unaltered pathway which can contribute as much as 30% for a victim drug with EH $\geq$0.35 and $f_{m,CYPi}$ of $\geq$ 0.9.

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Summary of Sensitivity/Error Analysis

The impact of ignoring EH on the predicted AUC ratio of an IV administered victim drug is dependent on f_{hep}, $f_{m,CYPi}$, EH and the degree of the interaction (inhibition or induction). The minor non hepatic clearance mechanisms (f_{hep} > 0.9, which is the case for many victim drugs, See Table 1), have a measureable impact ($\geq$30% error), and should be taken into account when predicting IV AUC ratios especially for potent inhibition interactions ($f_{CL\text{int}}^{Hep}$<0.1, >90% inhibition). Likewise, ignoring the hepatic blood flow dampening of the unaffected hepatic clearance pathways (1-$f_{m,CYPi}$ $\leq$ 0.1) for drugs with EH $\geq$0.35 for potent inhibition interactions ($f_{CL\text{int}}^{Hep}$<0.1, >90% inhibition) will contribute greater than 30% error to the predicted IV AUC ratio. For net induction interactions, the effect of EH is substantial (-25% error for EH =0.25 and modest 2.5-fold induction), and should always be taken into consideration. For a specific inhibitor/inducer, as EH of the victim drug increases, the % error in the AUC ratio increases irrespective of whether or not the victim drug is moderate or high EH.