

A PBPK MODEL FOR COBICISTAT, A POTENTIAL STRONG CYP3A4 INHIBITOR FOR CLINICAL DDI STUDIES WITH CYP3A4 VICTIM DRUGS

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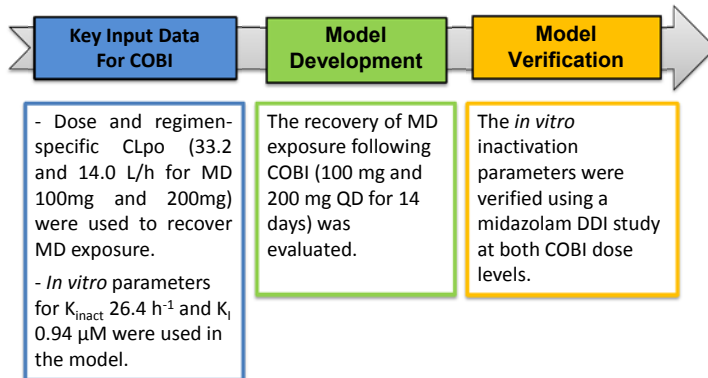
Background

- Since the use of ketoconazole was discontinued, investigators have assessed and proposed alternative strong CYP3A4 inhibitors for use in Phase I clinical DDI studies.
- One such alternative is Cobicistat (COBI), a potent CYP3A4 inactivator that was developed specifically as a pharmacokinetic booster.
- COBI exhibits non linear PK due to auto-inhibition of CYP3A4-mediated elimination routes. However, a quantitative estimate of the fractional contribution of CYP3A4 ($f_{m_{CYP3A4}}$) to the elimination of COBI, that would be required to model auto-inhibition, is currently unavailable in the literature.
- We present a PBPK model for COBI that can be used to assess the DDI liability of drugs in development that are metabolised by CYP3A4.

Methods

- A model workflow was devised to develop a PBPK model for COBI as a perpetrator using prior clinical and *in vitro* data to recover the multiple dose (MD) exposure after dosing of 100 mg and 200 mg QD (Figure 1).
- *In vitro* inactivation parameters², corrected for non-specific binding, were included in the model and the predicted interaction with midazolam (10 trials of age matched virtual subjects; Simcyp V15) was compared to corresponding observed data.

Figure 1. Workflow for COBI model development and verification



Results

- The developed model was able to recover the MD exposure of COBI after 100 and 200 mg QD; predicted and observed¹ AUC_(0,T) values were 3.44 and 3.41 and 16.1 and 16.2 mg/L.h, respectively (Figure 2).
- The predicted midazolam AUC_(0,∞) ratios were within 1.25 fold of the observed for both regimens; ratios were 13.4 and 12.9, and 19.0 and 20.7 for 100 and 200mg QD, respectively. The predicted midazolam C_{max} ratios were within 2-fold of observed¹ (Figure 3).

Figure 2. Simulated and observed¹ COBI concentration-time profiles following administration of a) 100mg QD and b) 200mg QD for 14 days. Data shown as the mean of each trial (n=15; grey lines) and the mean of the overall population (10 x n=15; black lines).

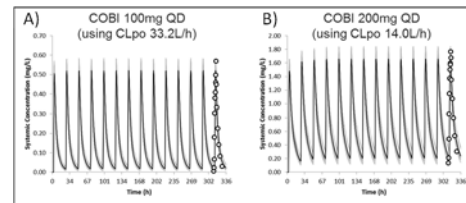
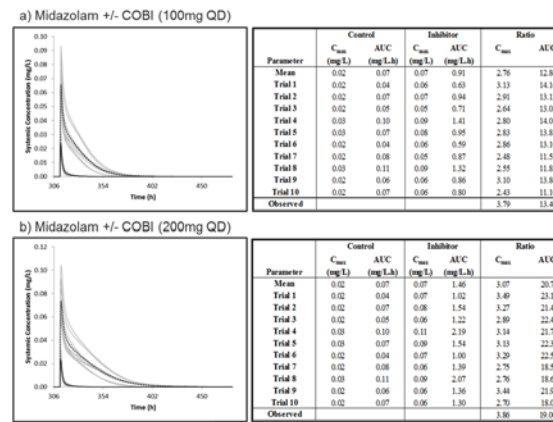


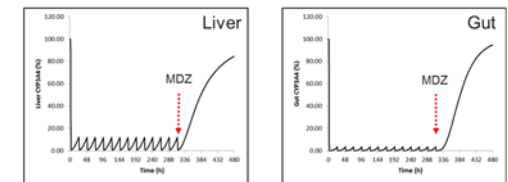
Figure 3. Simulated exposure and C_{max} & AUC ratios of midazolam before (solid line) and after (dashed line) MD COBI a) 100mg QD and b) 200mg QD for 14 days. Data shown as the mean of each trial (n=12; grey lines) and the mean of the overall population (10 x n=12; black lines).



AUC & C_{max} ratios = ratio of mean AUCs/C_{max} in line with those published

- Even at the lower dose (100mg), simulations indicated profound inactivation of CYP3A4 in the liver and gut (Figure 4).
- Although there were no clinical midazolam DDI data following single dose of COBI, use of the corresponding CL_{po} inputs into the model also recovered the single dose exposure of COBI (100-400 mg).

Figure 4 Simulated CYP3A4 inactivation in the liver and gut following administration of COBI (100mg QD, 14 days).



Conclusions

- Although the model presented here is not fully mechanistic, in that it does not consider auto-inhibition or other issues relating to its complex disposition, this “fit-for-purpose model” can be used to further investigate the potential of COBI as a perpetrator of CYP3A4-mediated interactions.
- Ongoing verification of the model using CYP3A4 substrate drugs and drugs in development can help ensure prediction accuracy of the DDI liability of COBI.
- Further work is required to derive and incorporate a quantitative estimate of $f_{m_{CYP3A4}}$. This would then allow auto-inhibition to be propagated into simulations, replacing the need to use dose and regimen-specific CL_{po} input data.

References

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