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Formulations can have an impact on intestinal drug-drug interactions: A PBPK study using oxybutynin as a model drug

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PURPOSE

A recently published absorption physiologically-based pharmacokinetic (PBPK) model was used and applied to mechanistically predict the oral bioavailability differences observed for R-oxybutynin's (R-OXY) OROS formulation compared to its immediate release (IR) tablet [**1**]. The PBPK model predictions suggested that the higher bioavailability observed for the OROS formulation was due to a reduced CYP3A-mediated intestinal metabolism (**Figure 1**). This highlighted the fact that while the distal absorption from the OROS formulation significantly reduced OXY's fraction absorbed (f_a), the decreased abundance of CYP3A enzymes in the distal gastrointestinal tract led to a "bypass" of the CYP3A-mediated first-pass metabolism and an increase on the intestinal availability (F_G)[**1**].

OBJECTIVE(S)

The aim of this work is to explore the implications that the aforementioned formulation-dependent differences in intestinal metabolism can have on drug-drug interactions (DDI), an aspect that is generally overlooked when investigating metabolic DDIs [**3**].

METHOD(S)

1. The Model

R-OXY's PBPK model was expanded to incorporate the different aspects of R-OXY's metabolism, as well as the formation of it's main metabolite N-desethyloxybutynin (R-DEOB) (**Figure 1**). The model was fit simultaneously to R-OXY's and R-DEOB's plasma concentration profiles obtained after IR administration using a pop-PBPK approach in NONEM 7.3. This model was then used to investigate the interplay between drug release, CYP3A-mediated metabolism and DDIs using R-OXY as a model drug.

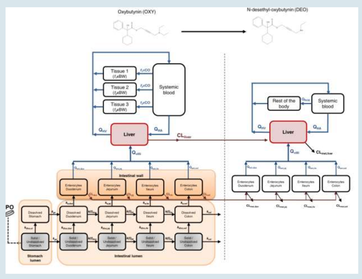

Figure 1: Schematic representation of the extended PBPK model for R-OXY and R-DEOB. The model was fit to R-OXY IR data using NONMEM and evaluations and model predictions were conducted in Matlab.

RESULT(S)

1. R-OXY/R-DEOB Pop-PBPK model fit

R-OXY's model performance was evaluated by visual predictive checks (VPCs) (**Figure 2**). The mechanistic model was subsequently validated by predicting the PK profiles of both R-OXY and R-DEOB obtained after administration of a 10 mg OROS formulation. For this simulation only the release profile of the OROS formulation was used as model input, while the parameters estimates from the IR fit were maintained (**Figure 3**).

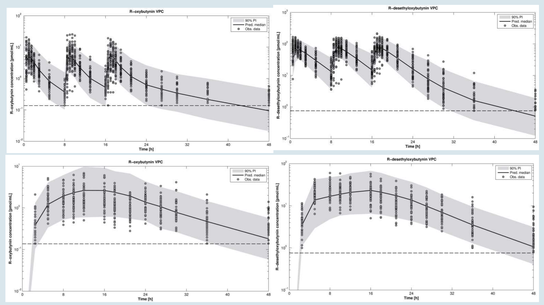

Figure 2: VPCs of R-OXY and R-DEOB PK profiles after the administration of a 3x5 IR mg tablets (left, OXY; right, DEOB)

Figure 3: VPCs of R-OXY and R-DEOB PK profiles after the administration of a 10 mg OROS formulation, observed data **not used** for model development (left, OXY; right, DEOB)

2. DDI simulations in the presence of ketoconazole

Additional model validation was conducted by simulating a DDI study between OXY OROS and ketoconazole (KTZ) 200 mg BID reported in product label (Ditropan XL [**2**]). KTZ profiles were simulated in SimCYP (v15) while OXY DDI simulations were conducted in Matlab. The DDIs were estimated mechanistically using standard equations for competitive inhibition (hepatic and intestinal). As shown in **Figure 4**, the model was able to capture the DDI magnitude (AUC and Cmax) reported in the label of both parent and metabolite.

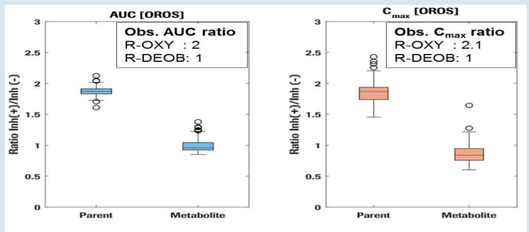

Figure 4: Box plot of population DDI of R-OXY and R-DEOB (simulated data) obtained after co-administering OXY OROS in the presence of KTZ 200 mg BID at steady state (left panel, AUC ratio; right panel, C_{max} ratio).

RESULTS(S)

3. Drug release and DDI magnitude

To evaluate the impact that release rates can have in R-OXY's DDI magnitude, simulations were conducted assuming different R-OXY formulations of varying release rates covering from IR tablets to extended release formulations (**Figure 5**). For each formulation a DDI study was simulated in the presence of ketoconazole. The ratios (with and without interaction) of AUC, oral bioavailability (**F**), hepatic availability (F_H) and F_G were then evaluated for each formulation. The simulations demonstrated that a variation of the release rate from rapid to slow release can reduce the DDI magnitude in the presence of strong CYP3A4 inhibitor by reducing the fold change in the AUC as shown in **Figure 6**.

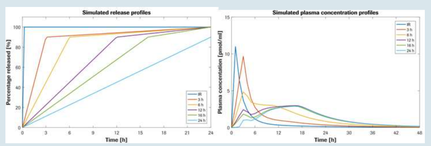

Figure 5: Simulated R-OXY PK profiles as function of the release rates (from IR to 24h release) used for DDI simulations.

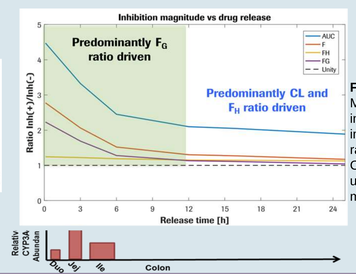

Figure 6: Mechanistic investigation of the impact of release rate on competitive CYP3A inhibition using OXY as a model drug.

CONCLUSION(S)

- The simulated changes in AUC ratio are mainly due to changes in the intestinal first pass between formulations given that only the F_G ratio varied significantly when switching from fast to slow release (**Figure 7**).
- This work highlights the importance that formulations can have when clinically-relevant DDI involving CYP3A substrates. This aspect is generally overlooked **[3]** when evaluating DDIs in drug development
- In addition, given that only the F_G ratios were affected by the change in formulation, this approach can be useful to gain information regarding F_G when IV data is not available. However, extended work needs to be conducted to corroborate this hypothesis.

REFERENCES

[1] Olivares-Morales A, et al. (2016) AAPSJ;18(6):1532-49
[2] U.S. Food and Drug Administration. Ditropan XL® Product Label.
[3] FDA Draft Guidance on Clinical Drug Interaction Studies - Study Design, Data Analysis, and Clinical Implications

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