Physiologically-based pharmacokinetic (PBPK) modeling of dronedarone and its main metabolite N-debutyldronedarone

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BACKGROUND AND OBJECTIVES

Dronedarone is described as the most potent P-gp (P-glycoprotein) inhibitor. The FDA (US food and drug administration) recommends dronedarone as a model perpetrator drug to evaluate the impact of P-gp inhibition on P-gp substrates (victim drugs) during co-administration [1]. Our objective was to establish a whole-body PBPK model of dronedarone including its main metabolite N-debutyldronedarone to explore and predict plasma concentrations of dronedarone and its metabolite and to use this model for drug-drug interaction prediction.

METHODS

A parent-metabolite PBPK model was built in PK-Sim® (version 7.1.0) and MoBi® (version 7.1.0). Drug-dependent parameters (e.g. lipophilicity, solubility) as well as plasma concentration-time profiles (dosing range 10-80 mg as intravenous and 100-1600 mg as oral administration) and study population demographic information (e.g. age, weight) from clinical studies with dronedarone were obtained from literature. Model parameters that could not be informed from literature, were optimized to accurately describe an internal dataset of plasma concentration-time profiles. Model evaluation was carried out by the prediction of an external dataset of clinical studies, followed by comparison of predicted versus observed plasma concentration-time profiles, AUC (area under the curve) and Cmax (peak plasma concentration) values.

RESULTS

Dronedarone and its metabolite both exhibit non-linear pharmacokinetics and their AUC and Cmax values vary greatly between different clinical studies with the same administered dose of dronedarone. The developed whole-body PBPK parent-metabolite model includes metabolism by CYP3A4 (cytochrome P450 3A4) and CYP2D6 to describe the elimination of dronedarone. The main metabolite is formed via N-debutylation by CYP3A4 and is eliminated through oxidation by MAO-A (monoamino-oxidase A) [2]. Furthermore, mechanism-based inhibition (MBI) of CYP3A4 by dronedarone and its metabolite was implemented [3]. The model structure is shown in Figure 1.

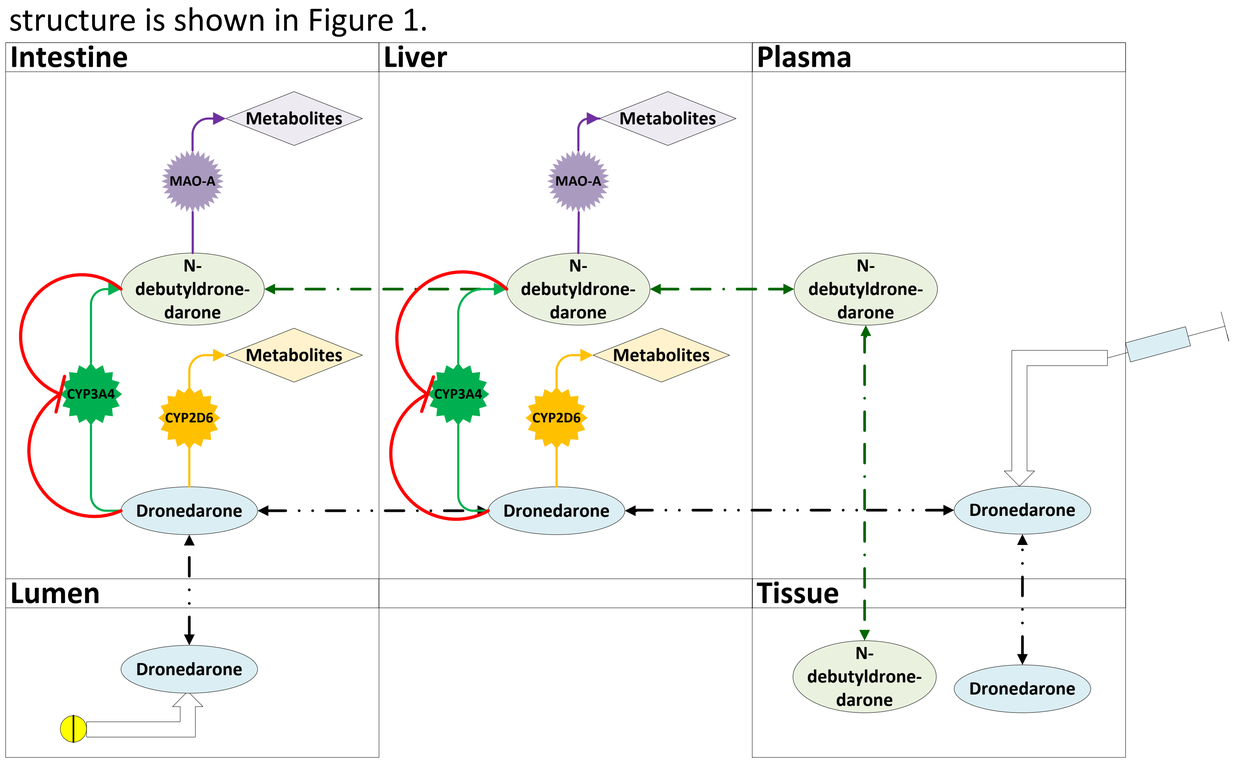

Figure 1: Model structure of the parent-metabolite PBPK model.

After oral administration, the MBI by dronedarone and N-debutyldronedarone leads to almost complete inhibition of CYP3A4 in the duodenal mucosa, already at low doses of dronedarone. In contrast, the MBI of CYP3A4 in the liver shows time- and dose-dependency (shown in Figure 2). The MBI had no impact on the CYP3A4 activity in duodenal mucosa or liver after intravenous administration.

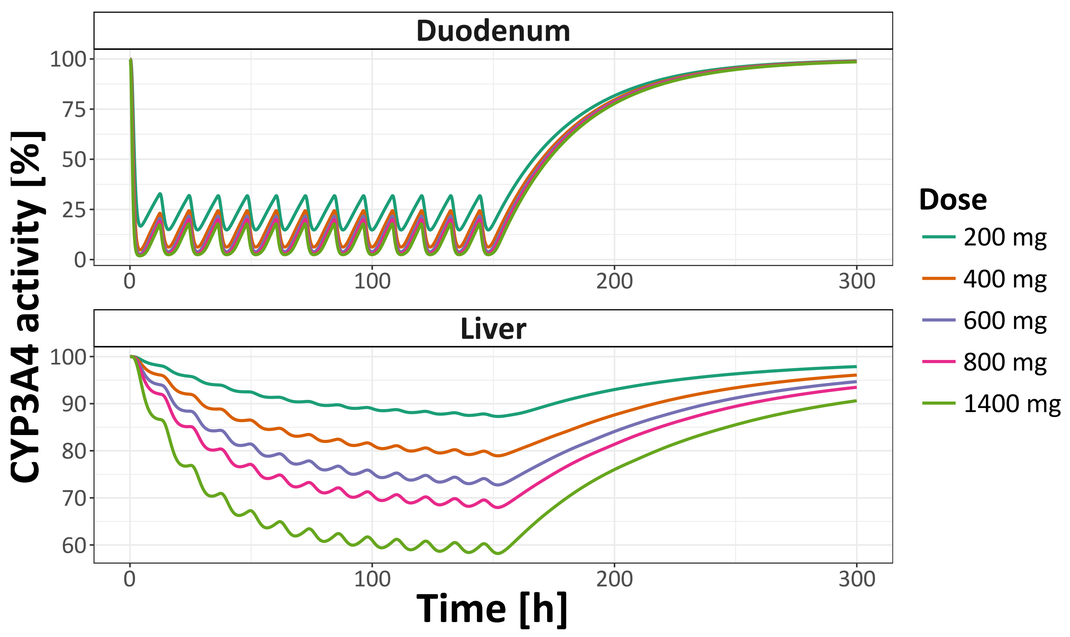

Figure 2: CYP3A4 activity. Simulation of CYP3A4 activity in duodenal mucosa and liver during twice daily administration of different doses of dronedarone over 7 days.

The parent-metabolite model predicts the observed plasma concentrations of dronedarone after intravenous and oral administration precisely (shown in Figure 3 and 4). The observed plasma concentrations of the metabolite N-debutyldronedarone were accurately described after oral administration. After intravenous administration the model predicts higher concentrations. The reason for this discrepancy might be the absent MBI of CYP3A4 after intravenous administration in the model.

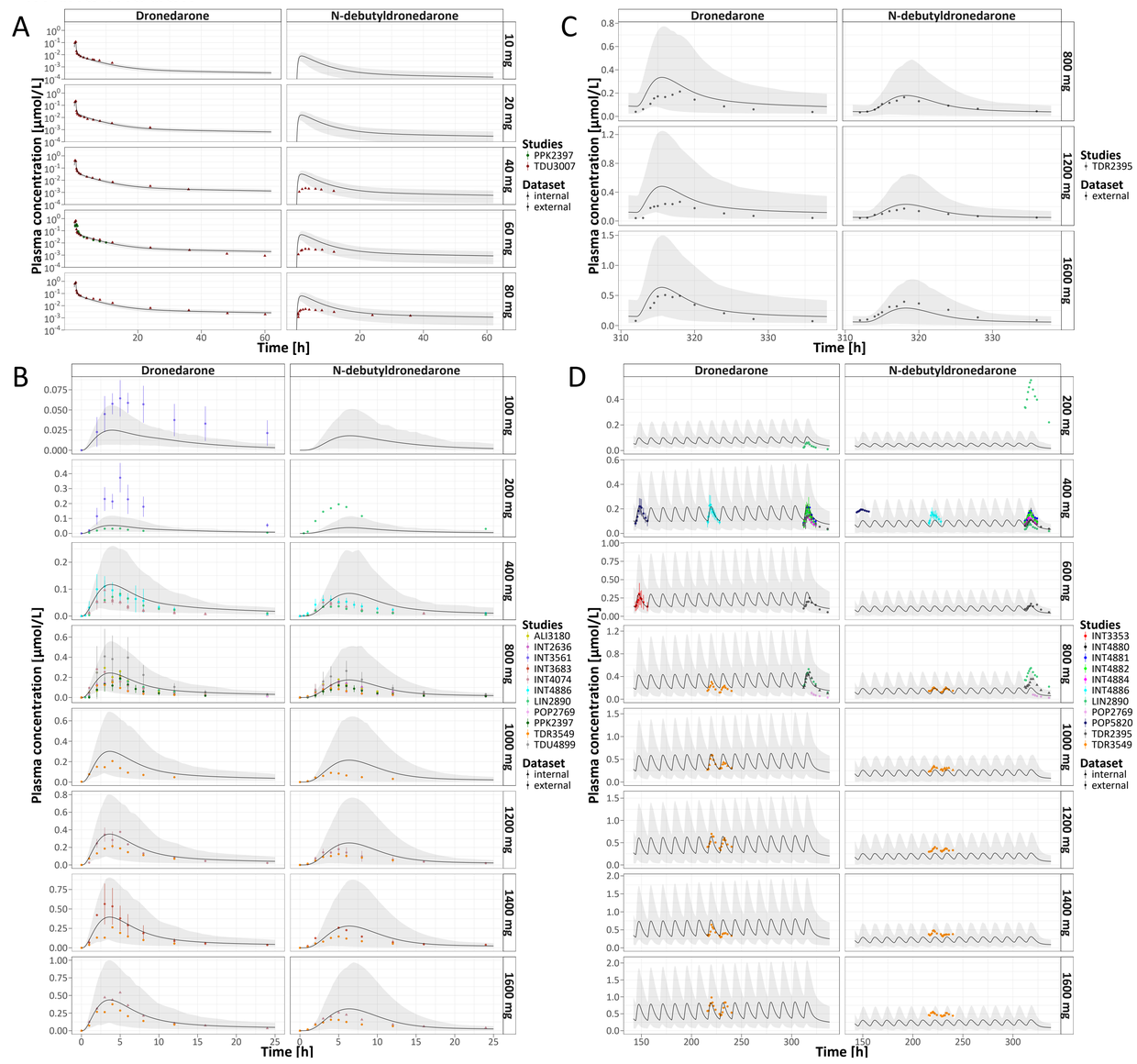

Figure 3: Plasma concentration. Population simulations of dronedarone and N-debutyldronedarone plasma concentration-time profiles compared to observed data following (A) intravenous administration (semilog scale), (B) single oral administration (linear scale), (C) once daily oral administration (linear scale) and (D) twice daily oral administration (linear scale). Observed mean values are presented as triangles (internal dataset) and circles (external dataset). Study names correspond to the FDA clinical pharmacology and biopharmaceutics review of dronedarone [4]. Population simulation means are shown as lines, the shaded areas depict the 5th – 95th percentile prediction interval.

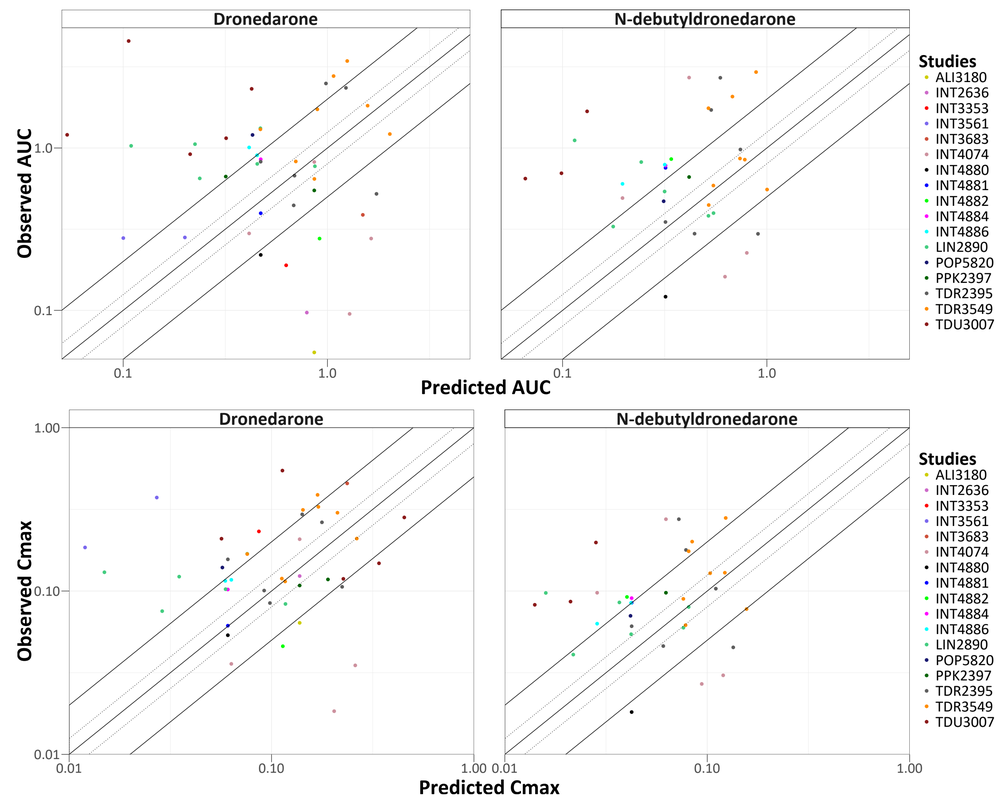

Figure 4: Correlation of observed versus predicted AUC and Cmax. Line of identity and 0.5- to 2.0-fold acceptance limits are shown as solid lines. 0.8- to 1.25-fold acceptance limits are shown as dotted lines. Correlated AUC and Cmax values are shown as dots.

CONCLUSION

The newly developed whole-body parent-metabolite PBPK model of dronedarone precisely describes plasma concentrations of dronedarone and its metabolite after intravenous and oral administration of dronedarone and is a valuable tool to predict the maximum impact of P-gp inhibition on the PK of P-gp victim drugs.

1. U.S. Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research (CDER): *Drug interaction studies – Study design, data analysis, implications for dosing, and labeling recommendations* **2012.** 2. Klieber, S. et al.: *Pharmacol. Res. Perspect.* **2014**, 2(3): 1-17. 3. Hong, Y. et al.: *Mol. Pharmacol*. **2016**, 89: 1-13. 4. U.S. Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research (CDER): *Clinical Pharmacology and Biopharmaceutics Review – Application Number: 22-425* **2009.**