PBPK Modelling of Ester-prodrugs:
Example of Oseltamivir for incorporating Organ and Plasma Esterase Metabolism and Assessing CES1 Population Genetic Impact

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Introduction

- Ester-prodrugs form an increasingly important part of rational drug-design for improving systemic availability of polar drugs following oral administration[1].
- Carboxylesterases (CES) present in organs and plasma are involved in esterase-prodrug activation[1].
- Mutations of CES1 results in dramatically reduced esterase metabolism *in vivo* and *in vitro* (2.6 to 9 fold)[2-5].
- The antiviral pro-drug oseltamivir phosphate (OP) (Figure 1) is a hepatic CES1 substrate used for treating influenza[2].
- A PBPK model for OP and the formation of its active metabolite oseltamivir carboxylate (OC) was developed in order to capture observed clinical data and to investigate the genetic impact for CES1 substrates.

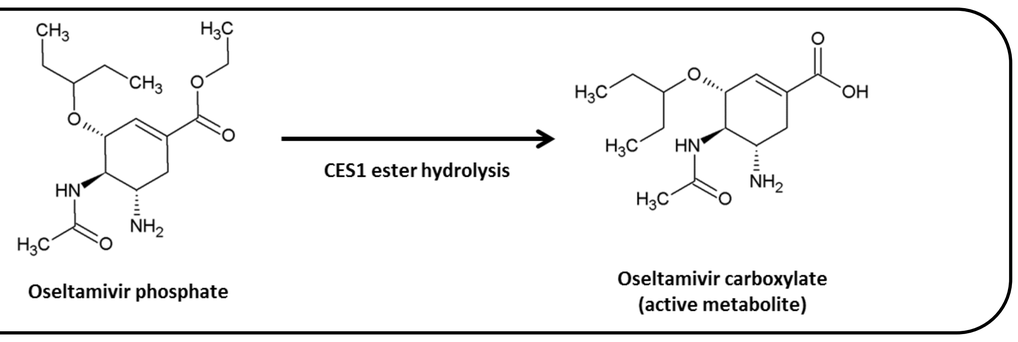

Figure 1| Ester-hydrolysis of oseltamivir phosphate to yield the active metabolite oseltamivir carboxylate by hepatic CES1

Aims

- Develop a population based PBPK model for OP and its active metabolite (OC) following oral administration.
- Use reported demographic and phenotypic data to predict the genetic impact of CES1 poor metaboliser status (PMs) relative to extensive metaboliser status (EMs) on oseltamivir metabolism within a population.

Methods

- Full-PBPK models were constructed for both OP and OC using the Simcyp Simulator (V15R1) (Figure 2)

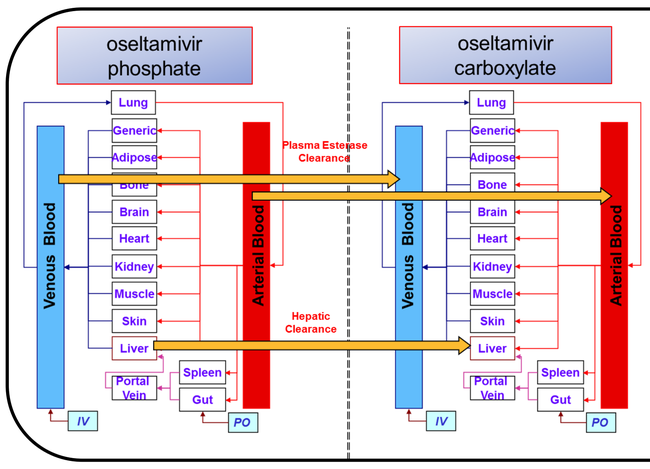

Figure 2| Full-PBPK model describing the distribution of oseltamivir and its conversion in to the active metabolite oseltamivir carboxylate in both the liver and plasma compartments respectively. Absorption of oseltamivir was described using the ADAM model. Oseltamivir carboxylate distribution was best described using the permeability limited liver model with low passive permeability.

- Tissue-to-plasma partition coefficients were predicted by the methods described by Rodgers and co-workers[6], using a Kp scalar of 0.6. Regional permeability was predicted using the MechPeff model[7]. Dissolution and absorption was described with the ADAM model[8].
- Metabolism of OP by CES1 was incorporated from reported hepatic S9 incubations[9,10]. An observed *in vitro* plasma half-life (44hrs)[11] was also included in the simulations, where plasma metabolism was accounted for in both arterial and venous compartments (Figure 2). CL_R was 29L/h[11] for OP and the only route of elimination for OC (16L/h)[11].
- A permeability-limited liver (PerL) model was used for OC using a fitted low passive permeability to match the observed slow distribution into the plasma.
- CES1 specific population variability was incorporated from meta-analysis of relative S9 liver abundances (n=23 donors)[12].
- The phenotypic activity for PMs for CES1 was based on the relative *in vitro* observed reduction for a diverse range of CES1 substrates [3-5].
- The PM phenotype frequency of 1 in 1000 was determined from meta-analysis of two large Caucasian population allele frequencies[2,3] assuming Hardy-Weinberg equilibrium.

Results

- Time concentration and urinary excretion profiles were well captured for OP after single doses of 75 and 150mg PO (Figure 3 A,C).
- The delayed T_{max} of OC was fitted using the PerL model, using a CL_{PD} of 2.5E-5 ml/min/10^6 cells (Figure 3 B,D). Urinary excretion was also well described at both oral doses.
- Further model validation using multiple dose administration studies following PO dosing BID for 7 days at 50, 100, 200, 500mg recovered the clinical profiles (Figure 3 E,F).

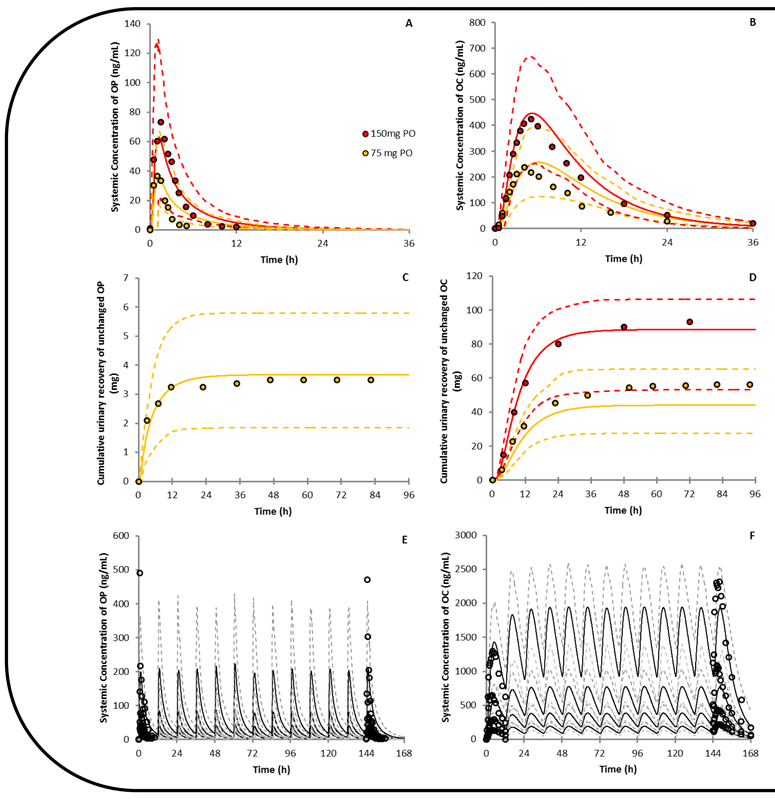

Figure 3| Plasma time concentration (A) and cumulative urinary elimination for OP (C) and OC (B,D) following 75 and 150mg single dose PO administration (Male HV 10x12, 20-50 years)[12]. Plasma concentration of OP (E) and OC (F) following BID OP dosing for 7 days (Male HV 10x6, 20-50 years)[11]. Dashed lines: 5 and 95% CI, solid lines: population mean.

- The impact of PM phenotype in a large population was simulated and this recovered well the increase in observed OP concentration for the single individual in the trial (Figure 4 A)[2].
- However the OC concentration was under-predicted for this individual (Figure 4 B).
- OC is a substrate for kidney OAT[13], however the individuals OAT phenotype was not available from this study.
- An improved approach for recovering the PM concentration for both OP and OC was to run an enriched PM population (Figure 4 C,D).

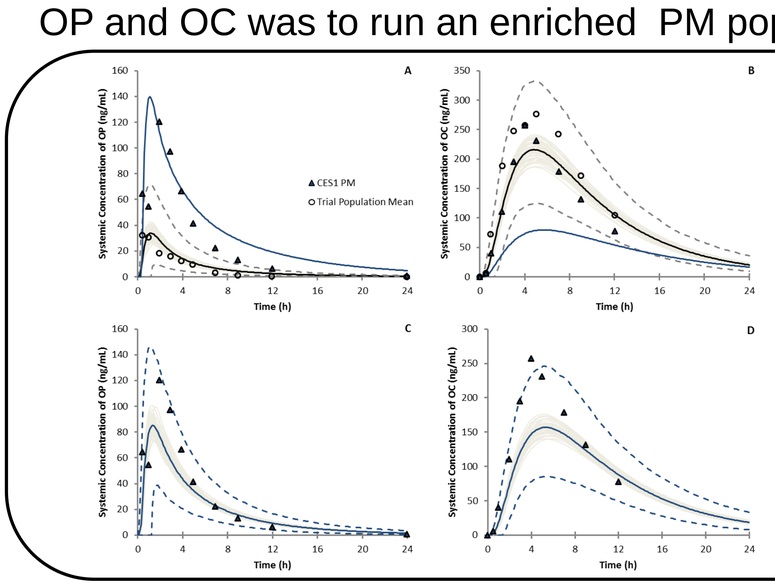

Figure 4| Plasma time concentration for OP (A) and OC (B) following 75mg single dose PO administration using CES1 PM population demographics (0.32 Female HV 50x22, 20-29 years)[2]. Plasma concentration of OP (C) and OC (D) using the same trial design, assuming a CES1 PM population.

Conclusions

- A PBPK model for OP CES1 mediated metabolism to the active metabolite OC was constructed and performance verified with clinical data.
- The impact CES1 polymorphism was investigated. OP concentrations were well predicted, but OC concentrations were not for a single individual in the trial *vs.* a single simulated individual.
- Given the low incidence of the PM phenotype in the Caucasian population, an improved approach in the absence of further mechanistic understanding (e.g. renal OAT component) is to simulate a PM population.

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