

Effects of probenecid on the pharmacokinetics of the neuraminidase inhibitor oseltamivir

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Introduction

- Oseltamivir is a potent, selective, oral neuraminidase inhibitor used worldwide in the treatment and prophylaxis of influenza in adults and children (aged > 1 year).
- It is administered as a prodrug, oseltamivir phosphate (OP), which is rapidly metabolized to active oseltamivir carboxylate (OC) by hepatic esterases and actively secreted by the kidney [1].
- In adults, recommended oseltamivir dosing regimens are 75 mg bid over 5 days (treatment of infection) and 75 mg daily over 5 days (prophylaxis).
- The uricosuric agent probenecid is a potent inhibitor of renal secretion and its dose sparing effects have been exploited for drugs actively secreted by the kidney, such as amoxicillin and cidofovir.
- Non-compartmental analysis demonstrated a 2.5-fold increase in systemic exposure of OC in the presence of probenecid (500 mg/6 hourly for 16 doses given 1 day before OP dose) [2].
- It has been suggested that such an approach could be applied to oseltamivir to extend stockpiles [3].

Objective

- To investigate potential dose sparing effects of oseltamivir when combined with probenecid (500mg/6 hourly) by model based simulation

Methods

- Data from four clinical studies (SAD and MAD [oral OP]; SAD [iv OP]; bioavailability [oral OP, iv OC]) were used to develop a population PK model for OP and OC. Between 8-31 PK samples were collected from each of 96 subjects.
- Single dose data from a probenecid interaction study [2] were used to assess potential probenecid effects on oseltamivir PK. Between 13-35 samples were collected from each of 19 subjects.
- The combined model for OP and OC was developed in NONMEM VI. PK data were log transformed and the distribution of random effects was log-normal.
- Parameter estimation methods FOCE (structural and final model) and FO (probenecid effect) were used.
- The structural model is illustrated in Figure 1.

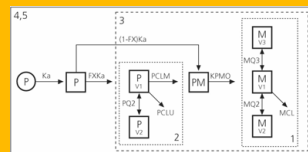
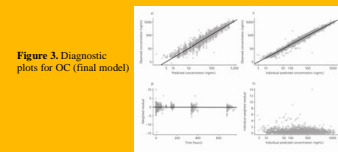
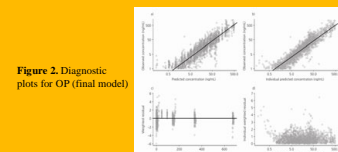


Figure 1. Population PK model for oseltamivir. Numbers reflect steps in the modeling process. (P: Prodrug, M: Metabolite)

- Probenecid effect was tested using treatment as a categorical covariate (probenecid on/off), on the oseltamivir PK parameters Ka, FX, PCLU, PCLM, PV1, KPMO, MCL, MV1.

- Stepwise covariate model building (FO): Sequential inclusion (P=0.05) followed by sequential deletion (P=0.01).
- Final model (FOCE): Minimization successful (see diagnostic plots in Figures 2 and 3); covariance step obtained (maximum relative SE = 34%; see Table 1 for probenecid effects).



Pharmacokinetic Parameter	Oseltamivir alone	Oseltamivir + Probenecid	Probenecid ratio (on/off)	SE (%)
PCLU	23.9 L/h	6.03 L/h	0.253	108 (%)
MCL	21.5 L/h	9.50 L/h	0.442	5

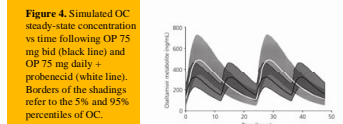
(*) upper 95% confidence limit = 0.96 (likelihood profiling)

- Simulations investigating oseltamivir dose sparing by probenecid through dose interval extension or dose reduction were carried out using Trial Simulator 2.2.
- OC AUC, Cmax and Cmin values matching at least those of oseltamivir alone were sought in tested combination regimens.

Results

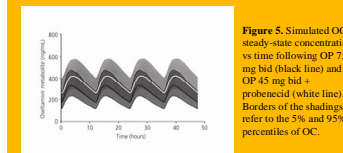
- The results of the dosing interval extension simulations are presented in Table 2 and Figure 4.

OP Regimen Simulation	Cmin	AUC	Cmax	OP Reference
QID 75 mg + Probenecid	1	1	1	BID 75 mg
QID 75 mg + Probenecid	1	1	1	QID 75 mg



- The results of the lower unit dose simulations are presented in Table 3 and Figure 5.

OP Regimen Simulation	Cmin	AUC	Cmax	OP Reference
BID 30 mg + Probenecid	1	1	1	BID 75 mg
BID 45 mg + Probenecid	1	1	1	BID 75 mg



Discussion/Conclusion

- Dosing interval extensions using oseltamivir 75 mg + probenecid are not advisable because exposure to OC (Cmin) is lower compared to oseltamivir 75 mg alone.
- Unit dose reduction to oseltamivir 45 mg but not 30 mg + probenecid achieved higher systemic OC exposure (AUC, Cmax and Cmin) than oseltamivir 75 mg alone.
- However, the potential for an oseltamivir-probenecid combination to compromise tolerability and to enhance drug interactions needs to be considered.
- Increased dosing requirements may also affect compliance and the attainment of optimal oseltamivir exposure.
- These factors, set alongside new increased capacity for oseltamivir production, should be carefully considered before an oseltamivir-probenecid combination is employed.

References

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