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 avidly 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.

Results

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

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


Table 1. Dosing interval extension simulations

<table>
<thead>
<tr>
<th>OP Regimen</th>
<th>Simulation Cmin</th>
<th>AUC</th>
<th>Cmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1D 75 mg</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>Q2D 75 mg</td>
<td>↓</td>
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<td>↑</td>
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<tr>
<td>BID 45 mg + Probenecid</td>
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