Pool Model versus Agonist-Antagonist Interaction Model for the Remoxipride Effect on Prolactin

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Objectives

The pool model [1] has previously been shown to be inferior to an agonist-antagonist interaction (AAI) model [2, 3] to describe prolactin response following administration of two antipsychotic drugs [3]. This study aimed to compare the pool model and the agonist-antagonist interaction (AAI) model to describe prolactin concentrations after administration of the antipsychotic drug remoxipride, i.e. the same data set as the pool model was originally developed from.

Methods

The remoxipride and prolactin concentration data were from 8 healthy male volunteers [1]. There were 5 study occasions and on each occasion two 0.5 h infusions of remoxipride were administered. The intervals between the first dose and the second dose on the 5 occasions were 2, 8, 12, 24 and 48 hours. Five models were compared in NONMEM and by visual predictive checks; (1) the original pool model [1], (2) a pool model with enforced mass balance, (3) a pool model with enforced mass balance and a circadian rhythm function for prolactin release [Figure 1], (4) the AAI model [2], and (5) the AAI model with circadian rhythm [3][Figure 2].

The pharmacodynamic parameters estimated by the circadian AAI model were in line with previous studies and current understanding about prolactin [Table 1]. The prolactin rhythm predicted by the circadian AAI model was close to reports in the literature [Figure 4]. The pharmacodynamic parameters estimated by the circadian AAI model were in line with previous studies and current understanding about prolactin. A VPC revealed that the circadian pool model was inferior to the pool model and the agonist-antagonist interaction (AAI) model to describe prolactin response following administration of two antipsychotic drugs [3].

Table 1. Estimated pharmacodynamic parameters for the evaluated prolactin models. For the AAI model the relative standard errors (RSE) could be estimated.

<table>
<thead>
<tr>
<th>Submodel</th>
<th>TV</th>
<th>INV</th>
<th>R</th>
<th>R2</th>
<th>R4</th>
<th>R8</th>
<th>R12</th>
<th>R24</th>
<th>R48</th>
<th>PK model (remoxipride concentrations)</th>
<th>PD model (Dopamine &amp; Prolactin)</th>
<th>UPDA</th>
<th>AIAPI (Mg/L)</th>
<th>AMS (µg/L)</th>
<th>OFV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circadian Pool Model</td>
<td>14.2</td>
<td>198</td>
<td>34</td>
<td>8.80(3)</td>
<td>11.17(9)</td>
<td>1.19(8)</td>
<td>0.145(4.2)</td>
<td>0.186(4.9)</td>
<td>-0.192(21)</td>
<td>0.08(3)</td>
<td>-0.32(12)</td>
<td>5.5(7.3)</td>
<td>1513.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circadian AAI Model</td>
<td>12(26)</td>
<td>54(23)</td>
<td>25(29)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1499.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

There are two periods, 24 and 12 hours, in the circadian sub-model. AMP1 and AMP2 are the amplitudes of each cosine functions. PK model and the agonist-antagonist interaction (AAI) model. A VPC revealed that the circadian pool model was inferior to the pool model and the agonist-antagonist interaction (AAI) model to describe prolactin response following administration of two antipsychotic drugs [3].

Conclusions

As previously observed for other antipsychotic drugs [3], the circadian AAI model was superior to the other investigated models in describing the prolactin response. The AAI model appears to work well across drugs and for a range of different types of administration schedules.

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References