Population pharmacokinetics of tribendimidine metabolites in adults with *Opisthorchis viverrini* in Laos

Fiona Vanobberghen,1,2 Melissa Penny,1,2 Urs Duthaler,1,2 Peter Odermatt,1,2 Somphou Sayasone,3 Jennifer Keiser,1,2 Joel Tarning4,5

1 Swiss Tropical and Public Health Institute, Basel, Switzerland; 2 University of Basel, Basel, Switzerland; 3 National Institute of Public Health, Vientiane, Laos PDR; 4 Mahidol-Oxford Tropical Medicine Research Unit, Bangkok, Thailand; 5 Centre for Tropical Medicine and Global Health, Oxford, UK

**Background**

In south-east Asia, an estimated 8-10 million people are infected with the liver fluke *Opisthorchis viverrini*.1 Praziquantel is the only drug currently available, therefore there is a pressing need to identify alternatives.2,3 Oral tribendimidine is a promising candidate, but its population pharmacokinetic (PK) properties are unknown.4,5

**Methods**

Within the framework of two phase IIa trials conducted in Laos, we enrolled *O. viverrini*-infected adults receiving single oral doses of 25-600 mg (study 1 used 200 mg tablets and study 2 used 50 mg tablets, with different absorption properties). Venous whole-blood, plasma and capillary dried blood spots (DBS) were sampled frequently. Concentrations of the tribendimidine metabolites dADT (deacetylated amidalen) and adADT (deacetylated dADT) were measured.6 Egg burden in stool was assessed at enrolment and at 21 days, with cure being no eggs. The two studies were pooled and population PK were assessed using nonlinear mixed-effects modelling with NONMEM, version 7. We assumed fixed renal dADT clearance of 35%, with the remainder metabolising into adADT.7 Values below the quantification limit were treated as missing data. We included body weight with allometric scaling and assessed other covariates by stepwise selection. We used bootstrapping to obtain confidence intervals and standard errors (200 reps). We used univariable logistic regression to assess the relationship between PK and cure.

**Results**

**Table 1. Patient demographics.** Results are n (%) or median (interquartile range).

<table>
<thead>
<tr>
<th>Enrolled study</th>
<th>N=37</th>
<th>P=0.37</th>
<th>Non-entrolled study</th>
<th>N=20</th>
<th>P=0.003</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose, mg</td>
<td>25</td>
<td>50</td>
<td>100</td>
<td>200</td>
<td>400</td>
</tr>
<tr>
<td>glm, female</td>
<td>9</td>
<td>9</td>
<td>10</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Age, years</td>
<td>45</td>
<td>(35, 56)</td>
<td>26 (22, 44)</td>
<td>44 (34, 51)</td>
<td>39 (23, 40)</td>
</tr>
<tr>
<td>Wt, kg</td>
<td>51</td>
<td>(49, 60)</td>
<td>48 (42, 54)</td>
<td>47 (44, 54)</td>
<td>55 (48, 58)</td>
</tr>
</tbody>
</table>

**Figure 1. Final structural PK model.** *F*o, bioavailability; *K*clear, renal clearance; *V*1, apparent central volume of distribution (subscript 1 for dADT and subscript 2 for adADT); *NTT*, mean transit time; *n*, total number of compartments (NTT = n + 1). *K*M/P, hepatic clearance.

**Figure 2. Model diagnostics (good of fit).**

A. dADT  
B. adADT

High cure rates (≥55% of participants) were observed with doses ≥100 mg. Higher dADT, but not adADT, Cmax and AUC were associated with cure (both p=0.003).

**Conclusions**

We have for the first time described the population PK of tribendimidine. Known differences in the 200 mg versus 50 mg formulations were captured by covariate modelling. Further studies are needed to validate the structural model and confirm covariate relationships.

**References**