BACKGROUND

- There is a tendency for under-prediction of in vivo clearance of UGT substrates using intrinsic clearance (CL\textsubscript{int,\textit{in}}) obtained from human liver microsomes (HLM) in vitro.
- There is increasing awareness of the importance of UGT2B7 as a major hepatic drug-metabolising enzyme, as it is one of the few UGTs with known probe substrates (Figure 1).
- Metabolic clearance, renal clearance, permeability, protein binding and physicochemical data were obtained from the literature and incorporated into the pharmacokinetic model within the Simcyp Simulator (Version 12 release 2).
- rUGT tissue scalars, calculated as the ratio of microsomal CL\textsubscript{int,\textit{in}} (from human liver, intestinal or kidney microsomes) to rUGT2B7 CL\textsubscript{int,\textit{in}} were incorporated into the prediction of in vivo oral clearance (Figure 2).

AIMS

- To use rUGT2B7 CL\textsubscript{int,\textit{in}} data and a tissue scalar approach to:
  - Predict in vivo clearance of carbamazepine (CBZ), diclofenac (DCF), gemfibrozil (GFZ) and zidovudine (AZT) and associated variability.
  - Consider kidney and intestinal metabolism in addition to hepatic UGT CL\textsubscript{int,\textit{in}}.
  - Estimate the contribution of UGT2B7 metabolism to total systemic clearance.

METHODS

- Recombinant human UGT microsomes (rUGT) are useful for assessment of UGT isoform specificity in vitro, particularly, to inform drug-drug interaction (DDI) studies involving UGTs.

RESULTS

Scaling of rUGT2B7 in vitro CL\textsubscript{int,\textit{in}}

- In vitro CL\textsubscript{int,\textit{in}} values obtained using rUGT2B7 ranged from 0.03 to 1145 µl/min/mg for CBZ and DCF, respectively (Table 1).
- Different baculovirus rUGT tissue scalars were obtained for GFZ and AZT. This may reflect different in vitro assay conditions or substrate differences; total maximum liver CL\textsubscript{int,\textit{in}} was 1000 L/h for GFZ and 123 L/h for AZT (Table 2).

<table>
<thead>
<tr>
<th>rUGT system</th>
<th>Liver</th>
<th>Intestine</th>
<th>Kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ</td>
<td>5.29</td>
<td>0.63</td>
<td>0.85</td>
</tr>
<tr>
<td>DCF</td>
<td>HEK293 cells</td>
<td>1.28</td>
<td>0.00</td>
</tr>
<tr>
<td>GFZ</td>
<td>Baculovirus</td>
<td>1.13</td>
<td>0.13</td>
</tr>
<tr>
<td>AZT</td>
<td>Baculovirus</td>
<td>3.12</td>
<td>1.36</td>
</tr>
</tbody>
</table>

Although CBZ, DCF, GFZ and AZT are glucuronidated mainly by UGT2B7, other non-UGT routes contribute to their elimination as well.

- The fraction metabolised by UGT2B7 (fmUGT2B7) was 7%, 62%, 85% and 69%, respectively (Figure 3).

In Vivo Clearance Prediction for the UGT2B7 Substrates Carbamazepine, Diclofenac, Gemfibrozil and Zidovudine Using a Mechanistic Population-Based Pharmacokinetic Model

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CONCLUSION

- rUGT tissue scalars in combination with rUGT CL\textsubscript{int,\textit{in}} data can be used to estimate the fraction metabolised by specific UGTs and incorporate extra-hepatic metabolism into predictions of in vivo clearance.
- Overall, prediction accuracy using rUGT2B7 CL\textsubscript{int,\textit{in}} was improved in comparison to predictions using HLM UGT CL\textsubscript{int,\textit{in}}.
- More investigation into the impact of experimental conditions on rUGT tissue scalars is required.

REFERENCES


Clinical data from meta-analysis of >20 clinical studies.