An Investigation into the use of an Empirical Scaling Strategy for the Prediction of In Vivo Aldehyde Oxidase Clearance

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BACKGROUND
- There is an increasing awareness of the importance of aldehyde oxidase (AO) to drug metabolism [1,2].
- In vitro assays and in vitro-in vivo extrapolation (IVIVE) strategies for AO are less robust than available for P450 and there is a need for further research and refinement [2,3].
- An under-prediction of in vivo clearance is often seen in vitro human liver data from cytosol (HLC), S9 (HLS9) or hepatocytes (HHEP) [3,4,5].
- Absolute AO protein abundance data for human liver cytosol (HLC) have recently been published [6]. However, the importance of extrahepatic AO to drug metabolism is still unclear.
- mRNA and relative protein abundance data indicate widespread distribution including liver, kidney, respiratory system and adrenal gland [7,8].

STUDY AIMS
- To assess published literature for AO substrates with available in vitro liver AO intrinsic clearance (CL\(_{H\text{LAO}}\)) and clinical intravenous and/or oral clearance (CL\(_{O\text{D}}\) or CL\(_{O\text{Do}}\) data).
- To compare in vivo AO clearance prediction accuracy from in vitro liver data obtained using HLC, HLS9 and HHEP systems.
- To investigate the benefits of an empirical scaling strategy to improve in vivo clearance prediction accuracy using in vitro liver data for AO substrates.

METHODS
- In vitro CL\(_{H\text{LAO}}\) data were used to predict in vivo hepatic AO blood clearance (CL\(_{H\text{LAO}}\)) using the well-stirred liver model and a simulated healthy volunteer population n = 1000 (Simcyp V13).
- Observed in vivo CL\(_{H\text{LAO}}\) values were obtained from CL\(_{IV}\) and CL\(_{O\text{D}}\) data, accounting for the fraction metabolised by AO (f\(_{\text{AO}}\)) and any renal or biliary excretory clearance (CL\(_{\text{excretion}}\)).
- CL\(_{O\text{Do}}\) data: f\(_{\text{A}}\) and f\(_{\text{F}}\) assumed to be 1 except where CL\(_{\text{CL,H\text{A0}}}\) is 2-fold higher than Q\(_{\text{h}}\). (Table 1)
- Comparison of predicted and observed CL\(_{H\text{LAO}}\) in order to assess if there is an empirical relationship.
- 3 approaches were assessed:
  1. CL\(_{IV}\) data only
  2. All CL\(_{IV}\) and CL\(_{O\text{D}}\) data
  3. Test set of CL\(_{O\text{D}}\) data (using CL\(_{IV}\) relationship)

RESULTS

1. CL\(_{IV}\) data only

- CHLAO ranged between 0.26 L/h (XK-469) and 156 L/h (BIBX1382)

2. All CL\(_{IV}\) and CL\(_{O\text{D}}\) data

3. Test set of CL\(_{O\text{D}}\) data (using CL\(_{IV}\) relationship)

Table 1. Observed clearance data for twelve AO substrates from clinical data

<table>
<thead>
<tr>
<th>Substrate</th>
<th>CL(_{H\text{LAO}}) (L/h)</th>
<th>CL(_{IV}) (L/h)</th>
<th>CL(_{O\text{D}}) (L/h)</th>
<th>CL(_{O\text{Do}}) (L/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BBX1390</td>
<td>2447</td>
<td>2447</td>
<td>426</td>
<td></td>
</tr>
<tr>
<td>O6-benzylguanine</td>
<td>58</td>
<td>0.83</td>
<td>0.83</td>
<td></td>
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<tr>
<td>Carbazol</td>
<td>154</td>
<td>0.52</td>
<td>0.52</td>
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<tr>
<td>DCA</td>
<td>78</td>
<td>0.65</td>
<td>0.65</td>
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<tr>
<td>FICD453</td>
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<tr>
<td>PF-4217903</td>
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<td>PF-49586</td>
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<tr>
<td>RS-482</td>
<td>330</td>
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<td></td>
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<tr>
<td>XK-469</td>
<td>1055</td>
<td>0.10</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Zaleplon</td>
<td>168</td>
<td>0.63</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>Zonisporide</td>
<td>96</td>
<td>0.60</td>
<td>0.60</td>
<td></td>
</tr>
</tbody>
</table>

There was a need for more CL\(_{IV}\) data, eg. CHLAO values for carbarzol and zonisporide were <10 clinical subjects

REFERENCES
[7] Simcyp Ltd (a Certara company)
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CONCLUSIONS
- CL\(_{H\text{LAO}}\) can be significantly > Q\(_{\text{h}}\), which suggests that extrahepatic AO metabolism is important.
- A preferred scaling strategy would incorporate extrahepatic AO abundance and activity. There is currently a lack of these data.
- In the meantime, the above relationships could be used to assess a potential range in predicted in vivo AO clearance for new compounds in development.
- However, there is a need for more in vitro and clinical AO data in order to improve the accuracy and validate the empirical scaling strategy before implementation in the simulator Can Consortium Members help with this?
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