Feasibility assessment of PBPK modelling for Endogenous Compounds: Baseline levels of endogenous compounds in the Caucasian population

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BACKGROUND

• There is increasing interest in the potential utility of Endogenous Compounds (EC’s) as biomarkers for assessment of drug-induced enzyme level/activity changes of (a) CYP3A or (b) UGT1A1 following chronic dosing of the drug of interest.

• In July 2013, Consortium Members were asked to identify a series of EC’s for further evaluation, with a view to implementation within the Simcyp Simulator.

• The two top ranked compounds and their proposed utility as biomarkers are given in Table 1.

AIMS

To evaluate the feasibility of developing the most popular EC’s (Table 1).

METHODS:

• A systematic literature search using representative key words in PubMed and the internet for the two EC’s was performed.

• Discussions were held with Consortium Members (e.g., webinar 1st August 2013) on their experiences with these biomarkers and potential data sharing opportunities.

• Key areas identified for investigation were baseline plasma levels of each biomarker in a Healthy Volunteer population and routes of biotransformation.

RESULTS

RESULTS (cont)

• Bilirubin and glucuronides

A schematic of the formation and breakdown of bilirubin is shown in Figure 4. Total serum bilirubin (bilirubin + bilirubin glucuronide), conjugated and unconjugated plasma levels reflect protein changes differently.

• Biliverdin reductase reduces Biliverdin to unconjugated, water-insoluble Bilirubin, which is carried in blood bound to serum albumin.

• Bilirubin is conjugated to glucuronic acids by uridine-diphosphoglucuronyl transferase (UGT1A1) and conjugated bilirubin (water-soluble) is transported into bile canaliculi by MRP2.

• Intestinal bacteria deconjugate and breakdown bilirubin into colourless urobilinojena, which are primarily excreted in faeces.

• Elevated conjugated, unconjugated and total serum bilirubin level (TSBL) are a marker for intrahepatic jaundice.

• In prehepatic jaundice the conjugated bilirubin and urinary bilirubin are absent. In post-hepatic jaundice, conjugated and total bilirubin levels are elevated.

• Baseline TSBL are given in Figure 5.

Table 1: The top 2 ranked endogenous compounds and their utility

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Utility</th>
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<tbody>
<tr>
<td>4-β-OH Cholesterol (4bOH-C)</td>
<td>Induction of CYP3A enzyme</td>
</tr>
<tr>
<td>Bilirubin; -conjugates</td>
<td>Induction and inhibition of UGT1A1, OATP2B1 and MRP2</td>
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 Baseline Population values

• The mean plasma level of 4bOH-C in Caucasians is 34 ng/mL (CV = 51%, n=374), which is higher than that reported for a Korean population (Figure 2).

• It should be noted that there is a high degree of inter-individual variability (Figure 3), and therefore, it may be more appropriate to represent [4bOH-C] levels relative to [cholesterol] levels. These ratios in the Caucasian population range between 0.06 and 0.26, n= 74 (2 references).

Figure 1 – Cholesterol metabolism

Figure 2 – Baseline population levels for plasma [4bOH-C] (Mean ± SD) in Healthy Volunteers.

Figure 3 – Frequency of the plasma [4bOH-C] in Caucasians. Each colour represents one reference.

Figure 4 – Bilirubin metabolism and elimination

Figure 5 – Baseline levels for total serum bilirubin in healthy Caucasians for UGT1A1 extensive and poor metabolisers (not separated by OATP1B1 phenotypes).

Challenges

• More information on the impact of OATP1B1 on levels of conjugated and unconjugated bilirubin is required.

• An induction model for UGT1A1 is needed, therefore turnover numbers for UGT1A1 are required.

Dear Consortium Member,

Initial baseline levels and the routes of biotransformation for the top 2 endogenous compounds have been collated. We would like to collate further data.

Please contact us, if you would like to contribute and discuss.