MICROSOMAL SCALING FACTORS AND THEIR VARIABILITY FOR USE IN THE PREDICTION OF HUMAN IN VIVO METABOLIC CLEARANCE

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In vitro - in vivo extrapolation (IVIVE) to assess variability in the clearances of drugs requires knowledge of the population values of several scaling factors, including the abundance of cytochrome P450s (CYPs) per milligram (mg) of microsomal protein and mg of microsomal protein per gram of liver (MPPGL). Previous studies have assumed fixed values and have not accounted for inter-individual variability. Reported mean values of CYP3A4 abundance and MPPGL vary widely (36 – 248 pmol CYP3A4 mg\textsuperscript{-1} and 7 – 77 mg g\textsuperscript{-1}, respectively). In addition, some MPPGL values used in IVIVE to assess human drug clearance are based on rat data (Houston, 1994). We evaluated representative values of CYP3A4 abundance and MPPGL together with measures of inter-individual variability.

Triplicate samples from 52 livers (22 – 80 years) held within the Sheffield Human Liver Bank, established with the approval of the Royal Hallamshire Hospital Ethics Committee and the local coroner, were used to determine values of MPPGL and microsomal CYP3A4 abundance. CYP3A4 abundance was measured by competitive ELISA, and MPPGL values were determined as described previously (Wilson \textit{et al.}, 2003). Repeated measurements of the liver sample allowed the estimation of inter-individual variability in MPPGL and CYP3A4 abundance using ANOVA. In addition, values of human MPPGL (9 sources; 132 livers) and CYP3A4 abundance (11 sources; 235 livers) were also collated from a number of published and unpublished sources.

Weighted mean values of CYP3A4 abundance and MPPGL were 91 pmol mg\textsuperscript{-1} (range 5 – 199 pmol mg\textsuperscript{-1}) and 29 mg g\textsuperscript{-1} (range 15 – 54 mg g\textsuperscript{-1}), respectively, for the 52 livers and 144 pmol mg\textsuperscript{-1} and 37 mg g\textsuperscript{-1}, respectively, for the combined data. A one-way ANOVA indicated significant inter-individual variability in both parameters (CVs of 53% and 25%, respectively, \( p < 0.001 \)). The findings indicate more accurate estimates of population means and inter-individual variability of key scaling factors than those commonly used in IVIVE.