VALUES OF HUMAN HEPATOCELLULARITY PER GRAM OF LIVER AND ASSOCIATED VARIABILITY FOR USE IN THE PREDICTION OF HUMAN IN VIVO METABOLIC CLEARANCE

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INTRODUCTION

Extrapolation of data from human hepatocytes to predict in vivo drug clearance (IVIVE) invariably assumes a fixed value of hepatocellularity per gram of human liver (HPGL) without accounting for inter-individual variability.

The most commonly used value of 120 x 10^6 cells g^-1 [1] (Figure 1) was not determined experimentally and, from personal communication with the original source, appears to have been only a guess.

The aim of this study was to provide researchers with experimentally determined values of human HPGL together with a measure of inter-individual variability.

MATERIALS & METHODS

In order to calculate the number of hepatocytes accurately in a given mass of liver, corrections must be made for the incomplete yield of cells following perfusion of the liver sample (Figure 2).

Values of HPGL (n=24) were determined after accounting for the fractional loss of hepatocytes during processing. Fractional loss was corrected by measurement of the hepatocyte specific marker, CYP450 in homogenates prepared from matched liver tissue and hepatocyte suspensions [2] (Figure 3).

Repeated measurements (n=3) of the liver samples allowed separation of experimental variability and thus estimation of inter-individual variability in HPGL (ANOVA).

RESULTS

The geometric mean value of HPGL was 86 x 10^6 cells g^-1 (95% CI mean geo: 72 – 102 x 10^6 cells g^-1; 95% CI of observations: 36 – 201 x 10^6 cells g^-1).

Inter-individual differences in HPGL between livers were significant (ANOVA p < 0.05) with values ranging from 35 – 184 x 10^6 cells g^-1 (Figure 4).

No relationship was found between HPGL and donor sex, smoking or drinking habits (p > 0.05).

However, donor age was found to be a significant covariate of HPGL, with values decreasing with age (p = 0.018) (Figure 5).

CONCLUSIONS

The findings provide more accurate estimates of population mean and inter-individual variability of a key scaling factor used in IVIVE.

REFERENCES