Letter to the Editor

PREDICTING THE CLEARANCE OF CYP2C9 SUBSTRATES

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Recently, Andersson et al. (2004) reported that quantitative predictions of hepatic clearance from in vitro CL_{int} values using the “well-stirred liver” model were not useful. Over-prediction of in vivo clearances of four CYP2C9 substrates was found when plasma binding and nonspecific microsomal binding were ignored, and under-prediction when both were accounted for. We have reanalyzed these data showing that reasonably accurate predictions can be obtained in the latter case, when appropriate binding parameters are applied and all metabolic pathways are considered.

Use of f_{ub} Instead of f_{up}

Andersson et al. (2004) used the fraction unbound in plasma (f_{ub}) instead of the fraction unbound in blood (f_{up}). It is necessary to use the latter when relating clearance to hepatic blood flow (Rowland and Tozer, 1995). The blood to plasma ratio for fluvastatin was cited to be 1.8, but, in fact, this is the plasma to blood ratio; an independent report confirms this (Tse et al., 1993). If these corrections are applied, three of the four (diclofenac, fluvastatin, and ibuprofen) hepatic blood clearance estimates for the CYP2C9 substrates fall within 2.5-fold of the observed in vivo clearances. In the case of tolbutamide, a low-clearance drug, the predictions are very sensitive to f_{ub} and f_{up}. Therefore, it is important to consider a range of values for these parameters; reported values for f_{ub} range from 0.02 to 0.084 (Rostami-Hodjegan et al., 1998). Using the weighted mean of 0.056 (and blood to plasma ratio of 0.55), the clearance estimate for tolbutamide now lies within 2.5-fold of the observed clearance. Hepatic clearance estimates of 191, 13, 26, and 449 ml/min were calculated for diclofenac, tolbutamide, ibuprofen, and fluvastatin, respectively.

Metabolism Pathways

The acyl glucuronidation of diclofenac was not considered in the estimate of its clearance. Kumar et al. (2002) have reported that diclofenac clearance was accurately predicted (within 1.25-fold) only when both acyl glucuronidation and diclofenac 4-hydroxylation were considered. Using the CL_{int} value of 74,913 ml/min/liver (Kumar et al., 2002) for the combined pathways, in addition to the corrections described above, the hepatic clearance is calculated to be 321 ml/min (within 1.3-fold of the in vivo value).

For ibuprofen, the principal metabolite is 3-hydroxyibuprofen, which is formed mainly by CYP2C9. 2-Hydroxylation is also considered to play a significant role in the metabolism of this drug, yet Andersson et al. (2004) focused only on the 3-hydroxylation pathway for their prediction. Hamman et al. (1997) have reported enzyme kinetic data for both pathways. Using a combined CL_{int} of 3024 ml/min/liver, in vivo clearance is now estimated at 53 ml/min (within 1.5-fold).

Clearly, the predictions of clearance and drug-drug interaction potential are now compatible when the appropriate calculations are made, and it is unreasonable to question the reliability of in vitro-in vivo extrapolation without adequate in cerebro input.

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