A NEW METHOD FOR THE PREDICTION OF CLINICAL CYP3A INDUCTION
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Quantitative prediction of in vivo CYP3A induction from in vitro studies using hepatocytes has not been established because of the variability among experiments. The variability among the lots of hepatocytes is sometimes great and, even within the same lot, maximum induction ratios may differ and at a high concentration of exposure, induction activity sometimes decreases. Therefore, we attempted to correct for variability among experiments and developed a new prediction method to rank induction potency. In this method, the activity ratio (R) was adopted to reduce variation among experiments. R(RIF) or R(PB) was defined as the concentration ratio that showed the same induction as typical inducers such as rifampicin (RIF) or phenobarbital (PB). R of several inducers—RIF, PB, carbamazepine, dexamethasone, phenytoin, sulfinpyrazone, and omeprazole—was calculated from in vitro data using a human hepatoma cell line (HepaRG). The R at high concentration exposure had large variations, but R at a concentration showing 2- to 3-fold induction had small variations, so we enabled reduced variability among experiments by using R at 2- to 3-fold induction. With the application of R, the clinical exposure level of inducers is converted into RIF concentration expressed by C(RIF) = (Css,u/R (RIF)) and PB concentration expressed by C(PB) = (Css,u/R(PB)). A good correlation between C(RIF) or C(PB) and the clinical induction ratio was obtained: inducers that have over 7.29 nmol/L of C(RIF) or 6.69 μmol/L of C(PB) induced CYP3A, but inducers that have less than 0.32 nmol/L of C(RIF) or 0.13 μmol/L of C(PB) did not induce CYP3A. In conclusion, with this method, the variability among experiments was reduced, and thus the prediction ranking the potency of in vivo CYP3A induction was possible.

Evaluation of CYP3A4 induction using long term cultured human hepatocytes
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We investigated CYP3A4 induction using long term cultured human hepatocytes in vitro. The relative induction score (RIS) was calculated using $E_{\text{max}}$ and $EC_{10}$ values obtained in the hepatocytes study and the free plasma concentration of the compound in the clinical study. The extent of clinical drug-drug interaction was evaluated by determining the decreased percent of plasma concentration of ethinylestradiol or midazolam as a result of the compounds concomitantly administered. The value of RIS and the extent of clinical drug-drug interaction were well correlated. Considering the level of drug-drug interaction in the clinical study, the RIS value of troglitazone was estimated to be very low. Thus, we investigated the CYP3A4 induction level of troglitazone-sulfate of which plasma concentration was 6 times higher than that of troglitazone. The CYP3A4 induction level of troglitazone-sulfate was the same as that of troglitazone.