Oral

[O25-2] O25-2: CNS and miscellaneous

Chairs: Koichiro Tsuchiya, Japan / Yasuo Takeda, Japan
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[O25-2-4] CYP activity in paired human liver and jejunum samples

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Background

The bioavailability of orally administered drugs is restricted by first-pass metabolism in the gut wall and the liver. This is largely due to cytochrome P450 (CYP) enzymes expressed in both intestinal mucosa and hepatocytes. However, there is limited data describing the relative contribution of the hepatic and intestinal CYP activity to the overall first-pass metabolism in individual patients. In a clinical study in patients with morbid obesity undergoing gastric bypass surgery, paired biopsies from jejunum and liver were obtained from each patient. The aim of this project was to analyse *ex vivo* activities of seven CYP enzymes in individually prepared jejunum and liver microsomes using a cocktail of CYP probes.

Methods

Liver and jejunum samples from 14 patients were analysed. The tissue samples were homogenized and individual microsomal fractions were prepared. The microsomes were incubated for 20 minutes with a cocktail of substrates (bupropion (CYP2B6), midazolam (CYP3A), bufuralol (CYP2D6), amodiaquine (CYP2C8), diclofenac (CYP2C9), phenacetin (CYP1A2) and S-mephenytoin (CYP2C19)) in eight concentrations. The chosen metabolite for each substrate was quantified with UPLC-MS/MS. The enzyme kinetic parameters were obtained from untransformed data by nonlinear regression using GraphPad Prism.

Results

The liver microsomes showed considerable activities of all seven CYP enzymes, whereas the jejunum microsomes mainly showed CYP3A and CYP2C9 activities. Interestingly, the intestinal microsomal fractions also showed CYP2C8 activities. Interindividual variability of the various CYP activities ranged from 6 to 26-fold and 3 to 47-fold in liver and jejunum, respectively. As expected, the hepatic CYP activities were overall higher than respective intestinal CYP activities when normalized to total protein content, varying from 1.5-fold (CYP3A) to 300-fold (CYP2C8). The paired tissue samples showed poor correlation in CYP-activities, except for a significant positive correlation in CYP2C9 activities ($r= 0.62$, $P=0.022$).

Conclusions

Activities of seven CYP enzymes assessed in paired samples from jejunum and liver from patients with morbid obesity showed considerable interindividual variability. The results provide important information about the impact of liver- and intestinal CYP metabolism on first-pass metabolism and can be utilized in physiology-based pharmacokinetic modelling in this patient population.