O1.5

Potentiation of CYP inhibition during CYP3A-mediated imatinib biotransformation in human liver

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Objective: The tyrosine kinase inhibitor imatinib (glivec) undergoes cytochrome P450 (CYP)-dependent oxidative biotransformation to its N-demethylated metabolite. During prolonged cancer chemotherapy with imatinib the clearance of the drug is altered, which may precipitate toxicity or impaired pharmacological effects. This study tested the hypothesis that potent inhibitory metabolites are generated during imatinib biotransformation and evaluated the specificity of CYP inhibition by imatinib.
Methods: The role of individual CYPs in imatinib N-demethylation was assessed using cDNA-expressed enzymes, microsomal fractions (n=24) and CYP-specific inhibitors. Inhibition selectivity was tested using several CYP-specific substrate oxidations. Preincubation of imatinib in NADPH-supplemented (1 mM) microsomes for varying periods was used to evaluate inhibition in relation to biotransformation.
Results: CYPs 3A and 2C8 were the principal imatinib N-demethylases in human liver. Imatinib preferentially inhibited CYP3A-dependent midazolam 1'-hydroxylation and testosterone 6β-hydroxylation in human liver microsomes (IC_{50} ranges 22±2 μM and 15±5 μM, respectively; n=4-6). CYP3A inhibition was intensified 2.2±0.3-fold after preincubation of imatinib with NADPH-supplemented microsomes prior to estimation of IC_{50}s. In time-dependence studies 50% of microsomal CYP3A activity was lost during imatinib oxidation every 7.3±0.8 min (n=3). In contrast, minimal inhibition of the specific activities of alternate drug-metabolising CYPs 1A2, 2B6, 2C8, 2C9 and 2D6 was observed at therapeutically relevant drug concentrations.
Discussion: These findings indicate that CYP3A enzymes in human liver both mediate imatinib biotransformation and are susceptible to inhibition by the drug. Imatinib biotransformation generated metabolites with greater inhibition potency against CYP3A activity. These metabolites may contribute to the impaired clearance of imatinib that occurs in patients during prolonged therapy with the drug.

O1.6

Serum salbutamol enantiomer levels and extra pulmonary effects during disease exacerbation of COPD

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Objective. This study was designed to investigate the relationship between serum levels of salbutamol enantiomers and the potential extra-pulmonary side effects, among patients with COPD exacerbation presenting to the emergency department.
Methods. Blood samples were collected during routine initial assessment at the emergency department, and serum levels of (R)- and (S)-salbutamol enantiomers were determined by LC-MS/MS assay. Extra-pulmonary effects measured at presentation included ECG measurements (QTc interval), serum potassium level and blood sugar level, which were collected from the hospital medical records. Subjects with medical or medication history that may interfere with the measurement(s) were excluded from the corresponding analysis.
Results. Thirty seven subjects were recruited for the study. The mean (± SD) serum level of salbutamol were 2.7 ± 3.3 and 7.1 ± 8.9 ng/mL for (R)- and (S)- salbutamol respectively. Weak association between total salbutamol levels and the measured QTc intervals (p=0.05) were observed. However, similar relationship were not observed between subjects with prolonged QTc interval (>440 ms and >450 ms for males and females respectively) and subjects with 'normal' QTc interval (p>0.05). The serum salbutamol levels were also not found to be associated with other potential extra-pulmonary effects.
Discussion. Some high serum levels of salbutamol were observed in COPD patients presenting to the emergency department (up to 16.7 and 36.3 ng/mL for (R)- and (S)- salbutamol respectively). Previous studies have shown that the serum salbutamol levels were associated with the changes in some extra-pulmonary measurements. However, the levels were not found to be associated with any clinically significant extra-pulmonary cardiac adverse effects (determined by 'normal' range of the measurements in current practice standard), when the drug was administered by inhaler in the emergency department setting. Long term effect(s) of continuous high serum salbutamol enantiomer concentrations remain unknown and further investigations are required.