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Simultaneous evaluation of the activity of five cytochrome P450 enzymes by a cocktail study in healthy volunteers

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A “cocktail” approach involving the simultaneous administration of multiple cytochrome P450 (CYP)-specific probes concurrently detects the activity of multiple CYP enzymes. We developed and validated a rapid and selective liquid chromatography tandem mass spectrometry (LC-MS/MS) method to determine the plasma concentrations of 5 CYP probe drugs and metabolites (caffeine/paraxanthine, CYP1A2 substrate; losartan/losartan carboxylic acid (E3174), CYP2C9 substrate, omeprazole/5-hydroxy omeprazole, CYP2C19 substrate; dextromethorphan/dextrorphan, CYP2D6 substrate; and midazolam/1'-hydroxymidazolam, CYP3A4 substrate) by a single-step extraction followed by a single LC-MS/MS run. The assay had high accuracy and reliability for plasma samples. Next, we clarified the chronological changes in rifampicin-induced CYP enzyme activity after rifampicin discontinuation because the time course after drug treatment discontinuation has received little attention. Thirteen volunteers were administered rifampicin (450 mg) once daily, and the cocktail method was repeatedly performed. A 7-day rifampicin administration increased CYP2C19 and CYP3A enzyme activities. The induced CYP2C19 and CYP3A activities remained elevated at 4 days after rifampicin discontinuation and returned to baseline levels 8 days after rifampicin discontinuation. However, CYP1A2 and CYP2D6 enzyme activities showed no significant changes and CYP2C9 enzyme activity increased with rifampicin with a tendency toward statistical significance. These results suggest that drug interactions can occur even after rifampicin discontinuation. In conclusion, the advantage of our cocktail approach is that it enables *in vivo* assessment of the activity of various drug-metabolizing enzymes and the detection of potential drug interactions in a single assay.

Biography

Shinya Uchida received his PhD degree from the University of Shizuoka in 1999. He served as a Clinical Pharmacist at the University Hospital of Hamamatsu School of Medicine. At present, he is an Associate Professor at the University of Shizuoka and his major interests include clinical pharmaceutical science, clinical pharmacology and pharmacokinetics. He has published 69 papers in peer-reviewed journals.

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