일반연제

"Inje Cocktail" for High-throughput Evaluation of Five Human Cytochrome P450 Isoforms in *in-vivo*

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Background: Cocktail method is a useful tool to phenotype the various CYP enzymes in in-vivo. However, some limitations such as poor specificity, side effects and complexity of phenotyping procedures make it difficult to use cocktail method.

Objectives: Our objectives were (1) to determine whether the drugs caffeine, losartan, omeprazole, dextromethorphan and midazolam can be given simultaneously as a cocktail for the phenotyping of cytochrome P450 1A2, 2C9, 2C19, 2D6, 3A, respectively, and (2) to design an administration schedule to give as few sampling occasions as possible.

Methods: Twelve subjects received oral midazolam (2 mg), losartan (50 mg), caffeine (93 mg) + omeprazole (20 mg) + dextromethorphan (30 mg) and a cocktail of oral midazolam + losartan + caffeine + omeprazole + dextromethorphan. Blood samples were collected at 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12 hours for midazolam, caffeine, omeprazole and their metabolites. 0, 0 to 4 hour, 4 to 8 hour, 8 to 12 hour urine samples were collected for analysis of dextromethorphan, losartan and their metabolites.

Results: The CYP2C9 metabolic ratio (losartan/E-3174 in 0 to 8hr urine) after administration of losartan was not significantly different from that obtained with the cocktail (P=.583). Likewise, the CYP2C19 (omeprazole/5-OH omeprazole in 3hr plasma), CYP1A2 (paraxanthine/caffeine in 4hr plasma), and CYP2D6 (Log[dextromethorphan/dextrophan] in 0 to 8hr urine) metabolic ratios were not significantly different after cocktail administration (P=.284 for CYP2C19; P=.583 for CYP1A2; P=.136 for CYP2D6). Also, midazolam plasma clearance (CYP3A) was not significantly different after cocktail administration compared with that after administration of midazolam alone (P=.480). No side effects were observed through the whole clinical trial periods.

Conclusions: These results show that there are no pharmacokinetic or pharmacodynamic interactions in this 5-drug cocktail. This cocktail approach could be used as a valuable phenotyping tool for simultaneous measures of the activity of multiple CYP enzymes.