Oral

[O26-4] O26-4: Pharmacogenomics (2)

Chairs: Tsuyoshi Fukuda, USA / Taisei Mushiroda, Japan
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[O26-4-1] Small-dosing clinical study: pharmacokinetic, pharmacogenomic (SLCO2B1 and ABCG2), and interaction (atorvastatin and grapefruit Juice) profiles of five probes for OATP2B1 and BCRP

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Background

The aims of the present human study were (1) to investigate the effects of atorvastatin (10 mg, therapeutic dose) and grapefruit juice (GFJ), inhibitors of OATP2B1, on the pharmacokinetics of some substrates of OATP2B1 and BCRP (sulfasalazine, rosuvastatin, glibenclamide, celiprolol, and sumatriptan), and (2) to evaluate the contribution of *SLCO2B1* c.1457C>T (*SLCO2B1*3*) and *ABCG2* c.421C>A polymorphisms to the pharmacokinetics of the five test drugs. In order to evaluate these issues safely and efficiently, we applied the small-dosing cocktail approach to the protocol; the cocktail included dual substrates (sulfasalazine, rosuvastatin, and glibenclamide), an OATP2B1 substrate (celiprolol), and an unknown substrate (sumatriptan). We administered the five test drugs at less than 25% of the individual therapeutic dose.

Methods

Twenty-three healthy volunteers with genotypes for *SLCO2B1*3* and *ABCG2* c.421C>A were enrolled in this study. In a single-arm and three-phase study, the test drugs (300 μg sulfasalazine, 250 μg rosuvastatin, 300 μg glibenclamide, 1200 μg celiprolol, and 600 μg sumatriptan) were administered to volunteers with either water (control phase), 10 mg atorvastatin, or GFJ. The plasma concentrations of the drugs were quantified by LC-MS/MS. Non-compartmental pharmacokinetic analysis was performed using WinNonlin 6.4. The $AUC_{0\text{-}24}$ of the test drugs was calculated by the linear trapezoidal rule. C_{max} and T_{max} values were obtained directly from data.

Results

GFJ, but not atorvastatin reduced the exposure of the test drugs significantly more than the control phase, suggesting that all five test drugs are substrates for OATP2B1. The *SLCO2B1*3* genotype had no effect on the pharmacokinetics of the test drugs. In contrast, the exposure of sulfasalazine and rosuvastatin was significantly higher in *ABCG2* 421C/A than in *ABCG2* 421C/C individuals at all three phases, even under small-dosing conditions.

Conclusions

The results of the present study suggest that (1) 10 mg atorvastatin does not exert inhibitory effects on

OATP2B1 functions in humans, (2) GFJ decreases the exposure of OATP2B1 substrates, and (3) *ABCG2* 421C>A is associated with changes in the pharmacokinetics of sulfasalazine and rosuvastatin, even under small-dosing conditions.