Poster

[P27-10] P27-10: Pharmacokinetics and pharmacogenetics

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[P27-10-6] In vivo phenotyping for CYP3A by a single-point determination of plasma concentration ratio of endogenous 6β-hydroxycortisol to cortisol

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Background

Cytochrome P450 3A (CYP3A) is involved in the metabolism of approximately 50% of all drugs currently used in humans. CYP3A phenotyping is important for personalized pharmacotherapy since genetic polymorphism of CYP3A cannot explain the variability in CYP3A mediated metabolism. We have previously developed cortisol 6β-hydroxylation clearance ($CL_{m(6\beta)}$) as an index for *in vivo* CYP3A phenotyping, which requires a 2-hour urine collection and 1 or 2-point blood sampling (*Drug Metab. Dispos.*, 2013). In this study, we developed a simple method for phenotyping *in vivo* CYP3A activity by a single-point determination of plasma 6β-hydroxycortisol/cortisol ratio. We then compared the plasma 6β-hydroxycortisol/cortisol ratio with the clearance $CL_{m(6\beta)}$ as endogenous markers of CYP3A activity in 3 women after administration of oral contraceptives. We demonstrated that the plasma 6β-hydroxycortisol/cortisol ratio can be used for the *in vivo* CYP3A phenotyping in humans.

Methods

Three healthy women aged 28~33 years were participated in this study. Oral contraceptive containing ethinylestradiol (30~40 μg) and levonorgestrel (50~150 μg) were taken at 10:00 for 21 consecutive days. Blood sampling: day 0 (predose), 1, 21 and 28. 6β-Hydroxycortisol and cortisol in plasma were assayed as the corresponding picolinyl derivatives by LC–MS/MS. $CL_{m(6\beta)}$ was calculated according to our previous study (*Steroids*, 2014). This study was approved by Tokyo University of Pharmacy and Life Sciences Human Subjects Review Boards and written informed consent was obtained.

Results

The endogenous plasma 6β-hydroxycortisol/cortisol ratio were decreased by 39% (Subject A), 61% (Subject B), 50% (Subject C) during the oral contraceptive treatment period (21 days). The $CL_{m(6\beta)}$ were decreased by 41% (Subject A), 59% (Subject B), 54% (Subject C). A significant correlation ($r = 0.9053$) was found between the endogenous plasma 6β-hydroxycortisol/cortisol ratio and the clearance $CL_{m(6\beta)}$.

Conclusions

The present study demonstrates that the endogenous plasma 6β-hydroxycortisol/cortisol ratio is a simple and reliable index for *in vivo* CYP3A phenotyping. The method requires only a single blood sample and should be useful for evaluating the CYP3A activity even in the patients, such as children, pregnant women, and the elderly with renal failure.