PARTIAL METABOLIC CLEARANCE OF CAFFEINE TO PARAXANTHINE FOR IN VIVO CYP1A2 PHENOTYPING WITH CAFFEINE AS A PROBE

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The partial metabolic clearance of caffeine (CA) to paraxanthine (PX) has been suggested as the ‘gold standard’ for CYP1A2 phenotyping with caffeine as a probe. However, this approach requires multiple blood sampling to estimate the conversion of CA to PX in vivo. In this study, we developed a simple and reliable procedure for evaluating the partial metabolic clearance (CLCA-PX), based on the concentration of CA in plasma and the total amount of five caffeine metabolites in urine. Six healthy adult subjects (five males and one female, age 22-53 years) received a single 200-mg oral dose of caffeine. Twenty-seven blood samples were obtained over a 30 h-period after dosing. Urine samples were obtained at 2h- or 4h-intervals. Plasma concentrations of CA and PX and urinary excreted amounts of CA and its five metabolites (PX, 1-MX, 1-MU, 1,7-DMU, and AFMU or AAMU) were analyzed by HPLC. The study was approved by the Ethics Committee of Tokyo University of Pharmacy and Life Science, and written informed consent was obtained from the subjects. The partial metabolic clearance (CLCA-PX-ref), calculated from plasma concentration-time data, was used as the reference for CYP1A2 phenotyping. It was found that there was an approximately 2.4-fold interindividual variability (1.93-4.57 L/hr for 6 subjects). The partial metabolic clearance (CLCA-PX) was also calculated from plasma and urine data, as the total amount of five caffeine metabolites in urine (2h-urine collection) divided by the AUC value of CA in plasma (one blood sampling). The values in a period of 8 ~16 hr after dosing most closely correlated to those obtained from the reference method, as an index for CYP1A2 phenotyping.