PHARMACOKINETICS OF CYCLOSPORINE A IN RENAL ISCHEMIA-REPERFUSION INJURY MODEL RATS
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Cyclosporine A (CyA), a potent immunosuppressant, has been widely used for the prevention or treatment of graft rejection after organ transplantation. The large inter-individual variability in CyA pharmacokinetics (PK) led to the development of a strategic therapeutic drug monitoring method that could optimize and individualize the immunosuppressive therapy. With the PK profiles of CyA obtained after cadaveric and living related renal transplantation (CRT and LRT, respectively) at Kyoto Prefectural University of Medicine in recent 3 years, Cmax in CRT was approximately 40% lower than that in LRT, and Tmax in CRT delayed about 2 hr as compared to LRT. Generally, in the case of CRT, it takes at least 2 weeks to recover the renal function. In this study, to elucidate the PK behavior of CyA under renal failure (RF) condition after CRT, we performed a PK study of CyA in the RF rat model made by renal ischemia-reperfusion. In this model rats, both plasma creatinine concentration and urea nitrogen level were 5 times, and ureic acid level was 11 times higher than the control level. In addition, area under the blood CyA concentration vs. time curve (AUC) after oral administration significantly decreased (90.5%). Moreover, the AUC significantly decreased (31%), and the distribution volume significantly increased (29%) after intravenous administration. These results suggest that the PK of CyA is strongly affected by the renal damage derived from long time ischemia.

EPIGENETIC REGULATION OF CYP1A2 IN MOUSE LIVER
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Cytochrome P450 1A2 (CYP1A2) is tissue-specifically regulated in the mammalian liver by arylhydrocarbon receptor (AhR)-dependent and -independent pathways. Compared to lung and kidney, the CYP1A2 promoter is undermethylated in the liver in a promoter domain-specific manner. The CYP1A2 promoter showed a similar methylation pattern in wild-type and AhR-null liver. At birth, the promoter was hypermethylated and CYP1A2 was negligibly expressed in the liver. However, CYP1A2 expression increased following birth, coincident with the demethylation of the promoter. In diethylnitrosamine-induced liver tumors less expressing CYP1A2, the promoter was hypermethylated at specific CpG sites. In isolated hepatocytes, CYP1A2 expression declined over time and the degree of CYP1A2 methylation increased, albeit only after a delay. Exposure to 5-aza-2'-deoxycytidine did not induce CYP1A2 in Hepa1c1c7 cells and hepatocytes. In addition, CYP1A2 was induced in hepatocytes exposed to the histone deacetylase inhibitors trichostatin A (TSA) and sodium butyrate (SB), but only well after constitutive CYP1A2 expression was silenced. However, cotreatment with the arylhydrocarbon receptor ligand 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and either TSA or SB reduced the induction of CYP1A2 with the same time course as TSA or SB increased its induction. Our findings suggest that CpG methylation is involved in the tissue-specific and developmental regulation of CYP1A2, but the de novo methylation of the CYP1A2 promoter is induced by the silent state of the gene rather than causing it and also that histone modification is involved in CYP1A2 regulation in hepatocytes through pathways that are independent of AhR. (Supported by Korea Institute of Environmental Science and Technology)