quite fast, but faster in plasma and even faster in blood. It was found that the fraction of systemic clearance of triflusal (Fmi) was 0.9573. These results showed that triflusal was metabolized by 95.73% in rats and the residue would be hydrolyzed via the other route. Therefore, it would be necessary for the investigation of metabolite kinetics of triflusal to HTB to incorporate the degradation process of triflusal in blood into the pharmacokinetic model.

[PE2-5] [10/19/2000 (Thr) 15:00 - 16:00 / [Hall B]]

Effects of rehydration on the pharmacokinetics of chlorzoxazone in water deprivated rats

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In rats with water deprivation (DH, 72-hr water deprivation), hepatic cytochrome P450 2E1 levels was induced markedly and cytochrome P450 2E1 mRNA increased significantly compared with those in control rats, however, the values were completely returned to control levels by water supplementation (from 48 hr after water deprivation, rats with RH) (Kim, Kim et al., J. Appl. Toxicol., in press). Chlorzoxazone (CZX), which is extensively metabolized to 6-hydroxychlorzoxazone (OHCZX) by cytochrome P450 2E1, was administered intravenously in 1-min to control rats and rats with DH and RH. In rats with DH, the plasma concentrations of OHCZX was significantly higher, and AUC increased significantly (15%) compared with that in control rats. The 24-hr urinary excretion of OHCZX and total body clearance of CZX also increased (28% and 55%, respectively) in rats with DH. Above data suggested that the metabolism in rats with DH increased by induction of CYP2E1 and this supported by previous study (Kim, Kim et al.). In rats with RH, however, most of altered pharmacokinetic parameters in rats with DH restored to the leve in control rats; AUC (38% increase), total body clearance (28% decrease) and 24-hr urinary excretion of OHCZX (14% decrease) were returned to control level compared with those in rats with DH. Above data suggested that increased metabolism of CZX in rats with DH decreased by water supplementation and this might be due to altered expression of CYP2E1 and this was supported by previous molecular biological study (Kim, Kim et al.).

[PE2-6] [10/19/2000 (Thr) 15:00 - 16:00 / [Hall B]]

EFFECTS OF CYSTEINE ON THE PHARMACOKINETICS OF INTRAVENOUS ADRIAMYCIN IN RATS WITH PROTEIN-CALORIE MALNUTRITION

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In rats with protein-calorie malnutrition (PCM, 5% caseine diet for 4 weeks), hepatic cytochrome P450 levels suppressed markedly and cytochrome P450 mRNAs decreased significantly compared with those in control rats (23% caseine diet for 4 weeks), however, the values completely (or partially) returned to control levels by a week (from fourth week) of cysteine supplementation (rats with PCMC) (Cho, Kim et al., Arch. Biochem. Biophys. 1999, 372: 150-158). The formation of aglycone metabolites of adriamycin and adriamycinol, M3 and M4, respectively, seemed to be induced (Lee and Lee, Res. Commun. Mol. Pathol. Pharmacol. 1999, 105: 87-96) by pretreatment with dexamethasone (possibly by hepatic cytochrome P450 RL 33/cDEX, Komori and Oda, J. Biochem. 1994, 116: 114-120) in rats. Adriamycin, 16 mg/kg, was administered intravenously in 1-min to control rats and rats with PCM and PCMC. In rats with PCM, the plasma concentrations of adriamycin was higher (the area under the plasma concentration-time curve from time zero to 12 hr, AUC0-12 hr, tended to be higher) and 24-hr urinary excretion of M3 (including its 'conjugates') seemed to increase than those in control rats, suggested that the formation of M3 was inhibited in rats with PCM. In rats with PCMC, the plasma concentrations of adriamycin were

lower (the AUC0-12 hr was significantly smaller) and 24-hr urinary excretion of M3 (including its 'conjugates') were significantly greater than those in rats with PCM, suggested that the formation of M3 increased significantly by cysteine supplementation by restoring the enzyme system(s) that metabolize adriamycin to M3. The altered pharmacokinetic parameters of adriamycin mentioned above in rats with PCM returned to greater than those of control rats after cysteine supplementation (rats with PCMC). Above data suggested that other hepatic cytochrome P450 isozyme(s) which catalyze(s) the formation of M3 from adriamycin could be induced by cysteine supplementation.

[PE2-7] [10/19/2000 (Thr) 15:00 - 16:00 / [Hall B]]

Tissue Distribution and Urinary Excretion of Nifedipine Orally Given to Rats: Administration Time Dependency

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Administration time dependency of tissue distribution and urinary excretion of nifedipine (NFP) were investigated in rats orally given to rats at three different administration times (08:00, 16:00, 00:00). At 30min after dosing, the highest plasma concentration was observed when given at 08:00 followed by 16:00 and 00:00. Drug concentrations were relatively higher in stomach and intestine but lower in liver. The drug concentration orally given at 08:00 was higher in most tissues except liver and pancreas when compared with 00:00 and 16:00. At 2hr after dosing, tissue distribution of NFP was irregularly changed and reversed when compared with 30min. Generally, the drug concentration orally given at 00:00 was significantly higher in most tissues (heart, kidney, spleen, pancreas and plasma) except liver and stomach when compared with 08:00 and 16:00. Drug concentration in stomach was invariably the highest at 30 min and 2h after dosing when given at 08:00. It was noted that decreasing power of drug concentration from 30 min to 2h in tissues was relatively higher when given at 08:00 compared with 00:00 and 16:00. The amount of NFP excreted as unchanged drug was so low and gave less than 0.03-0.013% of the dose. The cumulative urinary excretion of NFP orally given at 08:00 was significantly higher when compared with 16:00 and 00:00. It was evident that there was an administration time dependency of tissue distribution and urinary excretion of NFP. However, tissue distribution was quite variable by the collection time of organs. Both timing of administration and NFP dosage formulations must be simultaneously considered in clinical studies to efficiently control the blood pressures.

[PE2-8] [10/19/2000 (Thr) 15:00 - 16:00 / [Hall B]]

Pharmacodynamics of cyclosporin A in lymph on rats

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Cyclosporin A (CSA) is a potent immunosuppressive drug in transplantation medicines and for the treatment of autoimmune disease. The mechanism of CSA is that CSA inhibits selectively the interleukin-2 (IL-2) driven proliferation of activated T lymphocytes (CD4 T-cells) at the transcription levels. The target of CSA is activated T lymphocytes which are distributed highly to the lymphoid organ such as lymph node, spleen and so on. So, we attempted to investigate the pharmacodynamic characteristics of CSA in lymph on rats after CIPOL Inj.® (Chong Kun Dang Pharm., Seoul, Korea) was administered (10 mg/kg). The lymphocyte suspensions (106 cells/ml) were prepared from the isolated lymph node and spleen and whole blood, the CD4 T-cell counts were measured by the flowcytometer (Becton Dickinson Immunocytometry System, Mountain View, CA, U.S.A.) with the fluorescein isothiocyanate (FITC)-conjugated mouse anti-rat CD4 monoclona