Technology, Daejeon 3Dongbu Hannong Chemical Co., Daejeon

The in vitro and in vivo metabolism of the new proton pump inhibitor DBM-819, 1-(2-methyl-4-methoxyphenyl)-4-[(3-hydroxypropyl)amino]-6-methyl-2,3-dihydropyrrolo-[3,2c]quinoline in the rat were identified using LC/MS/MS. Four metabolites (M1, M2, M3 and M4) were produced using rat liver microsomes in the presence of NADPH-generating system. They were identified as desmethyl-DBM819 (M2), 8-hydroxy-DBM-819 (M3), 1-(2-methyl-4-methoxy-phenyl)-4-amino-6-methyl-2,3-dihydro-pyrrolo-[3, 2c]-quinoline (M4) and hydroxylated DBM-819 (M1), respectively. The metabolites M1-M3 obtained from in vitro studies were also confirmed in the bile after an oral administration of DBM-819 to rats. Enzymatic hydrolysis of the bile samples suggested that those metabolites were excreted as glucuronic acid-conjugated forms as well. Based on the results obtained metabolic map of DAM-819 is proposed.

[PE2-3] [10/19/2000 (Thr) 15:00 - 16:00 / [Hall B]]

Pharmacokinetics of cyclosporin A in lymph on rats

Kim SJ°, Suh SP* and Lee YB

College of Pharmacy and Research Institute of Drug Development, Chonnam National University, Kwangju 500-757, Korea, *Medical School, Chonnam National University, Kwangju 501-757, Korea.

Cyclosporin A (CSA), a cyclic endecapeptide with potent immunosuppressive activity, was derived from extracts of Tolypolcladium inflatum Gams. CSA inhibits lymphocyte proliferation at the cytokine transcription levels. CSA has large molecular weight, is highly lipophilic and virtually insoluble in water, because of these properties, oral and intravenous formulations of CSA are available as an oil-based solution or a microemulsion. Lipid-soluble vitamins and other lipophilic compounds are generally transported in the lacteals of the mesenteric lymphatic system in association with the chylomicron, and liposome, emulsion, macroconjugate and so on have been used for lymphatic delivery. So, we attempted to investigate the pharmacokinetic characteristics of cyclosporin in rat lymph node and blood after CIPOL Inj. (Chong Kun Dang Pharm., Seoul, Korea), intravenous commercial product as a microemulsion formulation, was administered (10 mg/kg). We measured simultaneously the CSA concentrations of mesenteric, brachial node, spleen and whole blood using TDxFLx (Abott Labaratores, Abott Park, U.S.A.). The pharmacokinetic parameters were evaluated by fitting the proposed catenary model with WinNonlin. The profiles of CSA concentrations in lymph node and whole blood were well fitted to this pharmacokinetic catenary model.

[PE2-4] [10/19/2000 (Thr) 15:00 - 16:00 / [Hall B]]

Metabolite kinetics of triflusal to 2-hydroxy-4-trifluoromethyl benzoic acid in rats

Jeong TJ°, Lee YB

College of Pharmacy, Chonnam National University, 300 Yongbong-Dong, Buk-Gu, Kwangju, 500-757, Korea

In order to elucidate the fraction of hydrolysis in the over all in vivo metabolism of triflusal, the hydrolysis of triflusal to 2-hydroxy-4-trifluoromethyl benzoic acid (HTB) was studied in rats. Triflusal and HTB were injected into the rat femoral vein, respectively. And the pharmacokinetic parameters were obtained from the plasma concentration-time profiles of triflusal and HTB determined by the simultaneous analysis using high-performance liquid chromatography. It was supposed that triflusal was almost metabolized in vivo because the total excreted amounts of triflusal via urinary route were elusive. And also triflusal hydrolysis to HTB in aqueous media is

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

Kim YC°, Kim YG, Kim EJ, Kim EJ, Kim SG and Lee MG

College of Pharmacy, Seoul National University

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

Kim YG°, Cho MK, Kwon JW1, Kim SG and Lee MG

College of Pharmacy, Seoul National University and 1Research Laboratory, Dong-A Pharmaceutical Company, Ltd.

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