volumetric flasks made of glass, the percent adsorbed of CsA adsorbed on glassware were about 30-40% of the total CsA. In the Snapwell™and side-by-side diffusion chamber, about 50% and 40% of CsA were adsorbed respectively. In order to solve the adsorption problem of the drug for accurate monitoring of the drug transport, the amount of transported CsA across Caco-2 cell monolayers was determined with the modified Augustijns et al (1993) method and the permeability of CsA across Caco-2 cell monolayers in the Snapwell™ was also investigated. At 0.5μM CsA, average permeability coefficient (Papp) value obtained in the apical (AP) to basolateral (BL) direction was 20-fold lower than the reverse (BL to AP) process. The results indicated that the modified method of Augustijns et al. (1993) was effective in evaluating the transport of CsA across Caco-2 cell monolayers.
Key Words: cyclosporin A; Caco-2 cell; adsorption; permeability.

[OE-3] [04/20/2001 (Fri) 14:00 - 14:15 / Room 4]

Membrane- and substrate selective damage in the hepatobiliary transport of drug by carbontetrachloride

Hong SS°, Chung SJ, Shim CK

College of Pharmacy, Seoul National University

The purpose of the present study was to investigate the effect of the CCl4-EHF on unit processes for the hepatobiliary transport of Organic Cations(OCs). TEMA and TBuMA were selected as model OCs, because they are not protein bound in either plasma or liver cytosol and are not metabolized. The study was performed using an isolated hepatocyte preparation as well as in vivo experimental systems.
AUCs up to 3 hr were increased slightly by the CCl4-EHF, although no significance was observed for the increase. Cumulative biliary excretion were decreased by the CCl4-EHF to 13.2 % (60 % decrease) for TBuMA, but not for TEMA. As a consequence, a 66 % decrease in the CLb of TBuMA, but not for TEMA, was observed by the CCl4-EHF. An apparent decrease in the uptake rate by the CCl4-EHF was observed for both compounds. And the Vmax, efflux, but not the Km, efflux or CLlinear, efflux, of TEMA was decreased significantly (81.9 % decrease) by the CCl4-EHF. On the other hand, the CCl4-EHF had no significant effect on any of the kinetic constants for the efflux of TBuMA from hepatocytes. Also the transport of both OCs across the bile canalicular membrane was not influenced by the CCl4-EHF, which is contrary to the case for the sinusoidal membrane (i.e., uptake and efflux). In conclusion, the membrane- and substrate selective damage should be kept in mind in utilizing the CCl4-EHF as a model for the liver diseases.

[OE-4] [04/20/2001 (Fri) 14:15 - 14:30 / Room 4]

POPULATION PHARMACOKINETICS OF LOXOPROFEN

Yun JH°, Cho HY, Kim SJ, Ahn MR*, Choi SO*, Chung HJ*, Yang JS*, Lee YB

College of Pharmacy and Research Institute of Drug Development, Chonnam National University, Kwangju 500-757, Korea; *Department of Pharmacology, National Institute of Toxicology Research, KFDA, Seoul 122-704, Korea

The purposes of this study were to evaluate the population pharmacokinetics of loxoprofen according to several pharmacokinetic (PK) models and to investigate the influence of characteristics of subjects such as body weight, age and creatinine on the pharmacokinetics of loxoprofen. Plasma data from 98 healthy male subjects who participated in several different studies were used for this analysis under the assumption that all data were distributed as a log-normal pattern. After overnight fast, each subject received a single 60 ㎎ oral dose of loxoprofen; blood samples were collected for 8 hours.

Plasma loxoprofen concentrations were measured using HPLC with UV detector and analyzed by standard two-stage (STS) method. The population pharmacokinetic parameters of loxoprofen were evaluated according to several PK models such as 1-compartment model without lag time, 2-compartment model without lag time and noncompartmental method using WinNonlin. In the case of 2-compartment model without lag time, population mean Volume/F, K_{01}, K_{10}, T_{max} and C_{max} were 64.53 ×102 ㎖, 2.79 hr^{-1}, 0.90 hr^{-1}, 0.52 hr and 4.73 ㎍/㎖, respectively. The coefficient of variation (CV) of the parameters ranged from 9.5 to 143.37%. Based on the noncompartmental methods, mean loxoprofen $t_{1/2,\lambda}$, Volume/F, $AUC_{0-\infty}$, CL/F, MRT, T_{max} and C_{max} were 1.74 hr, 1.44 ×104 ㎖, 10.5 ㎍·hr/㎖, 5.74 ×103 ㎖/hr, 2.19 hr, 0.5 hr and 6.27 ㎍/㎖, respectively. Loxoprofen data were well fitted to 2-compartment model without lag time rather than other PK models. And also, weight, age and creatinine were not correlated with the pharmacokinetic parameters obtained from 2-compartment model without lag time.

[OE-5] [04/20/2001 (Fri) 14:30 - 14:45 / Room 4]

Effect of Prokinetic Agents, Cisapride and Metoclopramide, on the Bioavailability in Humans and Intestinal Permeability in Rats of Ranitidine, and Intestinal Charcoal Transit in Rats

Lee HT°, Chung SJ, Shim CK

Department of Pharmaceutics, College of Pharmacy, Seoul National University

To investigate the effect of cisapride and metoclopramide on the bioavailability of drugs, ranitidine was administered to healthy volunteers following pretreatments with or without the prokinetic agents. Cisapride or metoclopramide was administered orally 30 min prior to an oral administration of ranitidine. The serum concentrations of ranitidine were determined by an HPLC method and the bioavailability parameters of the groups with the prokinetic agent pretreatment were compared with those of the control group. The effects of these prokinetic drugs on the in vitro apparent permeability of ranitidine across the rat jejunum, and on the in vivo intestinal charcoal transit in rats were also examined. Either of the pretreatments shortened the Tmax of ranitidine in humans significantly. The AUC of ranitidine in human subjects was also decreased significantly in the case of cisapride pretreatment. However, no changes were observed for the Cmax and T1/2. Rat studies revealed that cisapride and metoclopramide had no influence on the in vitro permeability of ranitidine or the in vivo intestinal charcoal transit. These data indicated that the changes in the Tmax and AUC in humans are not related with the intestinal permeability or intestinal transit of ranitidine. The shortened Tmax of ranitidine appears to be due to accelerated gastric emptying of the drug. However, underlying mechanisms for the decreased AUC of ranitidine in the case of cisapride pretreatment are currently unclear.

Oral Presentations - Field F

[F1. Clinical Pharmacy] [F2. Social Pharmacy]

[OF-1] [04/20/2001 (Fri) 14:45 - 15:00 / Room 4]

Evaluation of Influencing Factors on Theophylline(TP)

Lee HJ, Jung SH, Lee YH, Kim KS, Park KH, Lee HK, Son IJ