Hepatic and Intestinal First-Pass Effects

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The purpose of this study was to report dose-independent pharmacokinetics of KR-31543, a new neuroprotective agent for ischemia-reperfusion damage, after intravenous and oral administration and first-pass effects after intravenous, intraportal, intragastric, and intraduodenal administration in rats. After intravenous (10, 20 and 50 mg/kg) and oral (10, 20 and 50 mg/kg) administration, the pharmacokinetic parameters of KR-31543 were dose-independent. The extent of absolute oral bioavailability (F) was 27.4% at 20 mg/kg. Considering the amount of unabsorbed KR-31543 from gastrointestinal tract at 24 h (4.11%), the low F value could be due to the hepatic, gastric, and/or intestinal first-pass effects. After intravenous administration of three doses, the total body clearances were considerably slower than the reported cardiac output in rats suggesting almost negligible first-pass effect in the heart and lung in rats. The areas under the plasma concentration-time curves from time zero to time infinity (AUCs) were not significantly different between intragastric and intraduodenal administration of KR-31543, 20 mg/kg, suggesting that gastric first-pass effect of KR-31543 was almost negligible in rats. However, the values were significantly smaller (305 and 318 μg · mL/min) than that after intraportal administration (494 μg · mL/min) indicating considerable intestinal first-pass effect of KR-31543 in rats, approximately 40% of the oral dose. Approximately 50% of KR-31543 absorbed into the portal vein was eliminated by the liver (hepatic first-pass effect) based on intravenous and intraportal administration (the value, 50%, was equivalent to approximately 30% of oral dose). The low F value of KR-31543 after oral administration, 20 mg/kg, to rats was mainly due to considerable intestinal (approximately 40%) and hepatic (approximately 30%) first-pass effects.

[PE2-19] [04/18/2003 (Fri) 09:30 - 12:30 / Hall P]

Drug-drug interaction with DA-125 and the other anticancer drugs

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DA-125, a novel anthracycline analog containing fluorine with decreased cardiotoxicity and increased antitumor activity of adriamycin (ADM), developed by Research Laboratories of Dong-A Pharmaceutical. DA-125, water soluble prodrug of M1, is a β-alanine derivative of M1 (FT-ADM). DA-125 was rapidly hydrolyzed to M1, and M1 was metabolized to both M2 and M3. Both M2 and M3 were further metabolized to M4. The purpose of this study is to investigate the drug-drug interaction with DA-125 and the other anticancer drugs (prednisolone, 6-thioguanine, cytarabine, vincristine) using in vivo and in vitro assay. In vitro assay, when we used rat liver homogenate S9, the pattern of DA-125 metabolism was changed a little by prednisolone and 6-thioguanine. After oral administration of DA-125 and the other anticancer drugs to rats, we examined the changes of M1, M2, M3 and M4 plasma concentration. When DA-125 was co-administrated with prednisolone to rats, AUC of M4 was increased compared with control group. Therefore, it is considered that DA-125 has the possibility of the drug-drug interaction with prednisolone.

[PE2-20] [04/18/2003 (Fri) 09:30 - 12:30 / Hall P]

The pharmacokinetics of tramadol hydrochloride in Korean healthy volunteers

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This study was conducted to investigate the pharmacokinetic characteristics of a synthetic opioid, Tridol?Capsule (tramadol hydrochloride from Yuhan Pharmaceutical Co., Ltd., Korea) in 24 healthy Korean volunteers after a single dose administration. The volunteers received two capsules of 50 mg dose. Plasma samples were obtained over a 24-hour interval, and tramadol concentrations were determined by validated HPLC methods with a fluorescence detector. From the plasma tramadol concentration vs. time curves, the areas under the plasma concentration curves of tramadol (AUC) were 2731 ± 1210 ng h/ml and peak serum concentrations of 321.6 ± 123.6 ng/ml were reached 2.3 h after oral administration of two Tridol capsules. The half-lives of absorption were 0.80 ± 0.68 h and the lag-time 0.14 ± 0.12 h. In the terminal phase the biological half-lives of tramadol were 6.6 ± 2.2 h.

[PE2-21] [04/18/2003 (Fri) 09:30 - 12:30 / Hall P]

Identification of urinary metabolite(s) of CKD-712 by gas chromatography/mass spectrometry in rats

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Examination was made of the urinary metabolite(s) of CKD-712, which is a chiral compound, named S-YS49 derived from higenamine (one component of *Aconite spp.*) derivatives. First of all, to analyze the metabolite(s) of CKD-712, a simple and sensitive detection method for CKD-712 was developed by using gas chromatography-mass spectrometry(GC/MS). Urine was collected from adult male Sprague-Dawley rats(250±10g) in metabolic cage for 24hr after oral administration of 100 mg/kg of CKD-712. The recovery of CKD-712 after extraction and concentration with AD-2 resin column was above 90 % from rat urine. The detection limits of CKD-712 in urine was approximately 0.1 ng/mL. It has well been suggested that isoquinoline possessing catechol moiety such as CKD-712 should be subjected to the catechol-O-methyl transferase activity in vivo. We detected three major peaks of presumed CKD-712 metabolites in the total ion chromatogram obtained from the rat urine sample after oral administration of CKD-712. From these results, it is assumed that the urinary metabolites are mono-methylation in the naphthyl moiety (metabolite I), methylation at the C-6 or 7 hydroxy group in the isoquinoline moiety and hydroxylation at in the naphthyl moiety (metabolite II), and methylation at the C-6 or 7 hydroxy group in the isoquinoline moiety (metabolite III).

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Kinetic behavior of sophoricoside by gas chromatography/mass spectrometry in rats

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