Prediction of in vivo human hepatic clearance of CW529 from in vitro data by use of human liver microsome

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In this study, we predicted the hepatic clearance of human of CW529. The area under the blood concentration-time curve(AUC) and the steady-state blood concentration(Css) are pharmacokinetic paramerter considered to be directly related to the pharmacological effects of side effects of a drug. Therefore, in the processes of drug discovery and development, it is very important to have information on the total body clearance (CLtot) and hepatic availability(Fh), which govern these values. CLtot is expressed as the sum of the clearances of tissues that are connected via blood flow. Prediction of hepatic(CLh) and renal(CLr) clearance is very important for drugs eliminated by hepatic metabolism and urinary excretion, respectively. As far as renal clearance is concerned, many successful attempts have been made to predict this in humans from animal data using animal scale-up methods. However, in the case of CLh, there are limitations to the application of animal scaling because of the large inherent species differences involved. For that reason, we previously compared the intrinsic clearance(1589ml/min/kg) obtained from in vitro experiments using rat liver microsomes with those(327ml/min/kg) obtained in vivo, and then calculated scaling factor(0.206). Furthermore, we determined in vitro hepatic intrinsic clearance(1646ml/min/kg) using human liver microsome. Based on the scaling factor estimated from rats data, in vivo human hepatic intrinsic clearance of CW529 was predicted(339ml/min/kg). When we extrapolate this data using dispersion model, the human hepatic clearance and availability is 13.4ml/min/kg and 0.417.

[PE2-5] [04/19/2001 (Thr) 15:30 - 16:30 / Hall 4]

POPULATION PHARMACOKINETICS OF FLUOXETINE

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The purposes of this study were to evaluate the population pharmacokinetics of fluoxetine 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 fluoxetine. Plasma data from 92 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 of one group received 80 ㎎ oral dose of fluoxetine and that of the other group received 60 ㎎; blood samples were collected for 72 hours. Plasma fluoxetine concentrations were measured using HPLC with UV detector and analyzed by standard two-stage (STS) method. The population pharmacokinetic parameters of fluoxetine 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 1-compartment model without lag time, population mean Volume/F, K_{01}, K_{10}, T_{max} and C_{max} were 99.67 ×104 ㎖, 0.35 hr^{-1}, 0.02 hr^{-1}, 8.54 hr and 67.04 ㎍/㎖ in group received 80 ㎎, respectively. The coefficient of variation (CV) of the parameters ranged from 0.43 to 21.86%. Based on the noncompartmental methods, mean fluoxetine $t_{1/2,\lambda}$, Volume/F, $AUC_{0-\infty}$, CL/F, MRT, T_{max} and C_{max} were 34.89 hr, 10.53 ×105 ㎖, 38.24 ×102 ㎍·hr/㎖, 20.92 ×103 ㎖/hr, 53.31 hr, 5 hr and 68.38 ㎍/㎖, respectively. In the other group received 60 ㎎, population mean Volume/F was 74.76 ×104 ㎖ and all the other parameters were the same. The CV of the parameters ranged from 6.72 to 21.86%. Based on noncompartmental methods, mean fluoxetine $t_{1/2,\lambda}$, Volume/F, $AUC_{0-\infty}$, CL/F, MRT, T_{max} and C_{max} were 34.89 hr, 79.00 ×104 ㎖, 38.24 ×102 ㎍·hr/㎖, 15.69 ×103 ㎖/hr, 53.31 hr, 5 hr and 68.38 ㎍/㎖, respectively. Fluoxetine data were well fitted to 1-compartment

model without lag time rather than the other PK models. And also, weight, age and creatinine were not correlated with the pharmacokinetic parameters obtained from 1-compartment model without lag time.

[PE2-6] [04/19/2001 (Thr) 15:30 - 16:30 / Hall 4]

Effects of cysteine on the pharmacokinetics of intravenous phenytoin in rats with protein-calorie malnutrition

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The effects of cysteine on the pharmacokinetics of phenytoin and one of its metabolites, 5-(p-hydroxyphenyl)-5-phenylhydantoin (pHPPH) were investigated after intravenous administration of phenytoin, 25 mg/kg, to control rats (4-week fed on 23% casein diet) and rats with PCM (4-week fed on 5% casein diet) and PCMC (PCM with oral cysteine supplementation, 250 mg/kg, twice daily starting from the fourth week). In rats with PCM and PCMC, the phenytoin hydroxylation (to form pHPPH) activities were significantly smaller (164, 103 and 95.3 pmol/min/mg protein for the control rats, and rats with PCM and PCMC, respectively) than that in control rats. In rats with PCMC, the intrinsic clearance of phenytoin, CLint, was significantly slower than those in control rats and rats with PCM (0.175, 0.131 and 0.044 ml/min). The above data suggested that the formation of pHPPH could be reduced in rats with PCM and PCMC. This was supported by significantly smaller 24-h urinary excretion of pHPPH (54.7, 35.6 and 32.5% of intravenous dose of phenytoin) in rats with PCM and PCMC than that in control rats. In rats with PCM, the maximum velocity (0.344, 0.203 and 0.196 mg/min), apparent volume of distribution in central compartment (44.4, 65.4 and 72.2 ml/kg) of phenytoin, and total area under the plasma concentration-time curve from time zero to time infinity (609, 714 and 1210 ug min/ml), renal clearance (20.5, 13.4 and 4.67 ml/min/kg) and 24-h urinary excretion (54.7, 35.6 and 32.5% of intravenous dose of phenytoin) of pHPPH were not returned to control levels by cysteine supplementation (rats with PCMC). This could be mainly due to the fact that the phenytoin hydroxylation activity in rats with PCMC was not returned to control level.

[PE2-7] [04/19/2001 (Thr) 15:30 - 16:30 / Hall 4]

Bioavailability of new matrix metalloproteinase inhibitor SS11 series in rats

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We studied pharmacokinetics for the new sulfonamide derivatives, SS11 series, recently developed as a matrix metalloproteinase inhibitor(MMP) by Samsung Ad. Ins. Technol.. An high-performance liquid chromatography(HPLC) system with UV detection was employed for the determination of SS11 compounds in the rat plasma. Most of the compounds were well separated from the plasma with the retention times of <10 min and the recoveries of >75%. The limits of quantitation were 10-30 ng/ml. Of the new 24 sulfonamide derivatives investigated in the current study, only SS11-197, 229, 248, 299, 397 and 246 showed oral bioavailability. The plasma concentration-time data could be adequately described by an one or two-compartment open model. From the i.v. kinetic study at a dose of 10 mg/kg, the CLt of the bioavailable derivatives were 10-100 ml/hr/kg. The bioavailability of SS11-197, 229, 248, 299, 397 and 246 were approximately 78, 21, 26, 41, 59 and 68%, respectively. Moreover, these compounds have shown a selective activity against MMP-2 and MMP-9 enzymes associating with tumor metastasis and angiogenesis. Therefore, we will discuss possibility as new anti-tumor lead compounds for the new sulfonamide derivative SS11s.