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.

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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