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Carvedilol is a nonselective β -adrenoblocking agent with vasodilating activities. The pharmacokinetics and pharmacodynamics of carvedilol were studied in healthy volunteers following single oral administration. After oral administration of carvedilol 25mg, blood samples were collected for a period of 30 hours. Plasma concentrations of carvedilol were determined by HPLC with spectrofluorometric detection. The effects of carvedilol on systolic and diastolic blood pressure (BP) and heart rate (HR) were measured during the same period. The time courses of the plasma concentration of carvedilol and the cardiovascular effects (BP and HR) were analyzed with PK/PD modeling using ADAPT II program.

The estimated C_{max} , T_{max} , CL/F (apparent clearance), V/F (apparent volume of distribution) and half-life of carvedilol were 66.43 ± 2.86 ng/L, 1.13 ± 0.08 hrs, 92.26 ± 5.32 L/hr, 663.31 ± 34.10 L, and 5.48 ± 0.24 hr, respectively. The maximal decrease in SBP was 11.70% and in DBP was 28.89% at and in HR was 15.22%. Both the maximum change in SBP and HR were detected at 3hr after administration of the drug. But the maximum change in DBP were observed at 6hr. Direct response model was tested for the change in SBP, DBP and HR. Plasma drug concentrations were linked to the observed effects via an effect compartment model with a sigmoid E_{max} model. These PK/PD model could describe the relationship between carvedilol plasma concentration and cardiovascular effects.

[PE2-9] [10/18/2002 (Fri) 13:30 - 16:30 / Hall C]

Pharmacokinetic Scaling of SJ-8029, a Novel Anticancer Agent Possessing Microtubule and Topoisomerase Inhibiting Activities, by Species-Invariant Time Methods

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This study examined the pharmacokinetic disposition of SJ-8029, a novel anticancer agent possessing microtubule and topoisomerase inhibiting activities, in mice, rats, rabbits and dogs after i.v. administration. The serum concentration-time curves of SJ-8029 were best described by tri-exponential equations in all these animal species. The mean Cl , V_{SS} and $t_{1/2}$ were 0.3 L/h, 0.1 L and 63.2 min in mice, 1.5 L/h, 1.6 L and 247.7 min in rats, 13.8 L/h, 39.6 L and 245.9 min in rabbits, and 29.2 L/h, 44.6 L and 117.4 min in dogs, respectively. Based on animal data, the pharmacokinetics of SJ-8029 were predicted in humans using simple allometry and also by several species-invariant time transformations using kallynochron, apolysichron and dienetichron times. The species-invariant time transformations showed that all animal data from four species were superimposable. The human pharmacokinetic parameters of Cl , V_{SS} and $t_{1/2}$ predicted by the simple allometry and various species-invariant time methods ranged from 50.4-145.0 L/h, 369.0-579.8 L and 242.0-1448.3 min, respectively. These preliminary parameter values may be useful in designing early pharmacokinetic studies of SJ-8029 in humans.

[PE2-10] [10/18/2002 (Fri) 13:30 - 16:30 / Hall C]

Kinetic Analysis of the Hepatic Uptake and Biliary Excretion of IH-901, a Potential Anticancer Agents, in Rats

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The purpose of the present study was to investigate the hepatic uptake and biliary excretion of IH-901, a potential anticancer agents, in rats. IH-901 was mainly distributed into the liver after its iv administration at the dose of 10-30 mg/kg. The liver concentration of IH-901 at 7 min after its iv administration was comparable with its initial concentration of the plasma. Moreover, recovery ratio of IH-901 in the bile for 6 hr was more than 40% after its iv administration. The early phase (0-5 min) of the plasma concentration was disappeared by exponentially. The hepatic recovery ratio (Rh) was estimated by comparing the liver concentration and that disappeared from the circulation. The Rh value was about more than 30%, indicating that the liver is one of the

responsible organ in the distribution of this drug. The slope of the integration plot was linear up to 5 min after its iv administration. The CLuptake value for IH-901 was thus calculated as 0.262 ml/min/g liver. Furthermore, we determined the CLbiliary by measuring the plasma concentration, bile concentration and liver concentration, after its iv infusion at the infusion rate of 40–400 ug/min/kg. Both the plasma and the bile concentration of IH-901 were reached at steady-state at 45 min (5 times of $t_{1/2}$) after its iv infusion. The CLbiliary value for IH-901 was 0.85 ml/min/g liver. The liver concentration of IH-901 was higher by 23 times than that of plasma at steady-state. In conclusion, IH-901 was mainly distributed in the liver, followed by being excreted into the bile as a intact form. The mechanism by which IH-901 uptakes into hepatocytes requires further in vitro studies such as isolated hepatocytes and cultured hepatocytes.

[PE2-11] [10/18/2002 (Fri) 13:30 - 16:30 / Hall C]

New Analytical Method of Cyclosporine A in Human Serum by High-performance Liquid Chromatography/Diode Array Detector and Its Application to Pharmacokinetics of Cyclosporine A in Human Volunteers

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A simple, specific and sensitive method for the determination of cyclosporine A (CsA) in human serum has been developed by a high performance liquid chromatography/diode array detector (DAD) and applied to pharmacokinetic study of CsA. This method involves the use of solid phase extraction procedure following rapid protein precipitation with zinc sulphate from 1 ml of human serum, using a disposable C₁₈ extraction cartridge. Two different kinds of HPLC column (XTerra RP₁₈ (2.1 x 150 mm, 5 μ m) vs. Symmetry 300 (3.9 x 150 mm, 5 μ m)) and mobile phases (acetonitrile:H₂O (65:35, v/v%) vs. acetonitrile:methanol:H₂O (50:15:35, v/v/v%)) were used for comparison of peak areas and linearity of CsA and CsD. Effects of pressure setting of a vacuum manifold on cumulative peak areas of CsA and CsD were compared. As a result, XTerra RP₁₈ column, low pressure (-4~-9 inch Hg), and acetonitrile/H₂O (62/38, v/v%) as mobile phase were selected for the assay. CsA and CsD showed good resolutions in this conditions and no significant interfering peaks were observed. The detection limit is less than 50 ng/ml. A good linearity ($r > 0.9986$) was obtained in the range of 50–500 ng/ml CsA. Intra-day accuracy and precision (CV%) were 94.3–113.3% and 4.3–10.1% and inter-day accuracy and precision were 85.9–110.8% and 6.5–15.5%, respectively. The developed method was applied on the pharmacokinetic study of CsA after oral administration of CsA (200 mg) to 8 healthy human volunteers. The principal pharmacokinetic parameters resulted in 602.5 ± 250.9 ng-hr/ml of AUC_{0→8hr}, 270.0 \pm 82.7 ng/ml of C_{max}, 1.69 \pm 0.26 hr of T_{max}, 0.4627 \pm 0.2331 hr⁻¹ of Ke, and 1.88 \pm 0.99 hr of $t_{1/2}$.

[PE2-12] [10/18/2002 (Fri) 13:30 - 16:30 / Hall C]

In vivo kinetics and biodistribution of a HIV-1 DNA vaccine after administration in mice

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The present study evaluates the pharmacokinetics and tissue distribution of GX-12, a multiple plasmid DNA vaccine for the treatment of HIV-1 infection. PCR analysis after i.v. injection in mice showed that plasmid DNA was rapidly degraded in blood with a half-life of 1.34 min and was no longer detectable at 90 min post-injection. Plasmid DNA concentration also rapidly declined at the injection site after i.m. injection, with less than 1% of the initial concentration remaining at 90 min post-injection. However, sub-picogram levels (per mg tissue) were occasionally detected until 14 days post-injection. The ratios of the individual plasmids remained approximately constant at the injection site until 90 min post-injection. Plasmid DNA levels in various organs other than the injection site peaked at 90 min post-injection but was not detected after 8 h. The rapid in vivo degradation of GX-12 and low persistence in nontarget tissues suggest that the risks of potential gene-related toxicities by GX-