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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 Cmax, Tmax, 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 Emax model. These PK/PD model could describe the relationship between carvedilol plama 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