antibody (PharMingen, A Becton Dickinson Co., San Diego, CA, U.S.A.). We established the four modified indirect pharmacodynamic model (A~D) to estimate the parameters of CD4 T cell counts in lymph nodes and whole blood. We used the estimated concentration of CSA derived from the proposed pharmacokinetic model in lymph node and blood. The profiles of CD4 T cells were well fitted to these four pharmacodynamic models. So, in order to identify the pharmacodynamic model having physiological meaning from the above pharmacodynamic models, it was suggested that the pharmacological response in lymph was needed to be investigated *in vitro*.

[PE2-9] [10/19/2000 (Thr) 15:00 - 16:00 / [Hall B]]

Pharmacokinetics of Diltiazem and Deacetyldiltiazem after Oral Administration of Diltiazem in Mild and Medium Folate-Induced Renal Failure Rabbits

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Diltiazem inhibits calcium channels and leads to vascular smooth muscle relaxation and negative inotroic and chronotropic effects in the heart. Diltiazem is almost completely absorbed after oral administration, but its bioavailability is reduced because of considerable first-pass hepatic metabolism. The main metabolite of diltiazem is deacetyldiltiazem. Diltiazem is able to dilate renal vasculature and can increase the glomerular filtration rate and renal sodium excretion.
The purpose of this study was to report the pharmacokinetic changes of diltiazem (DTZ) and the metabolite, deacetyldiltiazem (DAD) after oral administration of diltiazem to control rabbits and mild and medium folate-induced renal failure rabbits (FIRRs).
The AUC and Cmax of DTZ were significantly increased in mild and medium FIRRs. The metabolite ratio of the DAD to DTZ were significantly decreased in mild and medium FIRRs. The Volume of distribution (Vd) and total body clearance (CLt) of DTZ were significantly decreased in mild and medium FIRRs. The elimination rate constant (β) of DTZ was significantly decreased in FIRRs, but that of DAD was significantly increased. These findings suggest that the hepatic metabolism of diltiazem was inhibited and Vd, CLt and β of DTZ were significantly decreased in mild and medium folate-induced renal failure rabbits.

[PE2-10] [10/19/2000 (Thr) 15:00 - 16:00 / [Hall B]]

Distribution of AG-60, a Potential Anticancer Agent, in Tissues and Platelets of the Rat.

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The purpose of the present study was to investigate the distribution of AG-60 in rats. For this purpose, the distribution of AG-60 in tissues and platelets for 48hr was measured after its im administration. Pharmacokinetics of AG-60 was reported in a our previous presentation. AG-60 is a potential anticancer agent which is a 1:1 complex of acriflavine (ACR) and guanosine. ACR is a 1:2 mixture of proflavine(PRF) and tripaflavine (TRF). The distribution of TRF and PRF was relatively high in the kidney, lung and liver, low in the intestine and the muscle. The tissue concentration of TRF was higher compared with that of PRF. The tissue concentration of both TRF and PRF was not detected after 24hr. On the other hand, we measured distribution of AG-60 in plasma, blood cells and platelets. The concentration of PRF and TRF in plasma and blood cells were not detected after 6hr, and blood cells concentration was similar to plasma concentration. We also measured the concentration of PRF and TRF in platelets and found that 0.183x10E8 platelets existed in 1 mL blood. Amount of PRF and TRF per 1.0x10E8 platelets was calculated. PRF concentration levels were two times higher than TRF concentration level at 1hr after im

administration of AG-60. PRF was not detected after 24hr, but TRF concentration in platelets was maintained by 48hr.

[PE2-11] [10/19/2000 (Thr) 15:00 - 16:00 / [Hall B]]

Pharmacokinetics of Gentamycin After intravenous Administration in Acute and Chronic Alloxan-Induced Diabetes Mellitus Rabbits

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Many diabetic patients develop serious complications during the course of the disease, including cardiovascalar disorders, nepropathy,neuropathy, and retinopathy. Because some physiological changes occurring in diabetes mallitus patients could alter the pharmacokinetics of the drugs to treat the disease.
Pharmacokinetics of gentamycin was investigated after intravenous administration of the drug (2mg/kg) to control rabbits and acute or chronic alloxan-induced diabetes mellitus rabbits(AIDRs).

After intravenous administration, the serum concentrations of gentamycin were significantly higher in AIDRs compared with these in control rabbits. This resulted in significant increase in AUC in acute (26.04±3.01 ㎍/㎖·hr) and chronic (31.91±3.76 ㎍/㎖·hr) AIDRs than that in control rabbits. This could be due to decrease of gentamycin by kidney excretion in the both AIDRs, since gentamycin in essentially excreted in kidney. Impaired kidney function in AIDRs were based on blood chemistry and tissue microscopy. Biological half-life ($t_{\frac{1}{2}}$) in AIDRs were significantly longed compared with that in control rabbits. Total body clearance(CLt) in AIDRs were significantly decreased compared with that in control rabbits. Cumulative urinary excretion of gentamycin were decresed in AIDRs compared with that in control rabbits.

[PE2-12] [10/19/2000 (Thr) 15:00 - 16:00 / [Hall B]]

PHARMACOKINETIC DISPOSITION AND TISSUE DISTRIBUTION OF BISPHENOL A IN RATS AFTER INTRAVENOUS ADMINISTRATION

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This study examined the dose-linearity pharmacokinetics of bisphenol A, an EPA classified endocrine disruptor, in rats following i.v. administration. Upon i.v. injection of 0.2, 0.5, 1 or 2 mg/kg, serum levels of bisphenol A declined bi-exponentially, with mean initial distribution and elimination half-lives ranging from 4-8.2 min and 38.6- 62.2 min, respectively. There were no significant alterations in the systemic clearance rate (mean range, 90.1-123.6 ml/min/kg) and the steady-state volume of distribution (mean range, 4.6-6.0 l/kg) as a function of the administered dose. In addition, the area under the serum concentration-time curve linearly rose as the dose was increased. In a second study, bisphenol A was given by simultaneous i.v. bolus injection plus infusion to steady-state and levels were measured in serum and various organs. When expressed in concentration terms (e.g., amount accumulated per gram organ weight), bisphenol A was found predominantly in the lung, followed by kidneys, thyroid, stomach, heart, spleen, testes, liver and brain. Ratios of the organ to serum bisphenol A concentrations exceeded unity for all the organs examined (ratio range, 2.0-5.8) except for brain (ratio 0.75). Given the high systemic clearance and short elimination half-life, bisphenol A is unlikely to accumulate significantly in the rat.