lower (the AUC0-12 hr was significantly smaller) and 24-hr urinary excretion of M3 (including its 'conjugates') were significantly greater than those in rats with PCM, suggested that the formation of M3 increased significantly by cysteine supplementation by restoring the enzyme system(s) that metabolize adriamycin to M3. The altered pharmacokinetic parameters of adriamycin mentioned above in rats with PCM returned to greater than those of control rats after cysteine supplementation (rats with PCMC). Above data suggested that other hepatic cytochrome P450 isozyme(s) which catalyze(s) the formation of M3 from adriamycin could be induced by cysteine supplementation.

[PE2-7] [10/19/2000 (Thr) 15:00 - 16:00 / [Hall B]]

Tissue Distribution and Urinary Excretion of Nifedipine Orally Given to Rats: Administration Time Dependency

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Administration time dependency of tissue distribution and urinary excretion of nifedipine (NFP) were investigated in rats orally given to rats at three different administration times (08:00, 16:00, 00:00). At 30min after dosing, the highest plasma concentration was observed when given at 08:00 followed by 16:00 and 00:00. Drug concentrations were relatively higher in stomach and intestine but lower in liver. The drug concentration orally given at 08:00 was higher in most tissues except liver and pancreas when compared with 00:00 and 16:00. At 2hr after dosing, tissue distribution of NFP was irregularly changed and reversed when compared with 30min. Generally, the drug concentration orally given at 00:00 was significantly higher in most tissues (heart, kidney, spleen, pancreas and plasma) except liver and stomach when compared with 08:00 and 16:00. Drug concentration in stomach was invariably the highest at 30 min and 2h after dosing when given at 08:00. It was noted that decreasing power of drug concentration from 30 min to 2h in tissues was relatively higher when given at 08:00 compared with 00:00 and 16:00. The amount of NFP excreted as unchanged drug was so low and gave less than 0.03-0.013% of the dose. The cumulative urinary excretion of NFP orally given at 08:00 was significantly higher when compared with 16:00 and 00:00. It was evident that there was an administration time dependency of tissue distribution and urinary excretion of NFP. However, tissue distribution was quite variable by the collection time of organs. Both timing of administration and NFP dosage formulations must be simultaneously considered in clinical studies to efficiently control the blood pressures.

[PE2-8] [10/19/2000 (Thr) 15:00 - 16:00 / [Hall B]]

Pharmacodynamics of cyclosporin A in lymph on rats

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Cyclosporin A (CSA) is a potent immunosuppressive drug in transplantation medicines and for the treatment of autoimmune disease. The mechanism of CSA is that CSA inhibits selectively the interleukin-2 (IL-2) driven proliferation of activated T lymphocytes (CD4 T-cells) at the transcription levels. The target of CSA is activated T lymphocytes which are distributed highly to the lymphoid organ such as lymph node, spleen and so on. So, we attempted to investigate the pharmacodynamic characteristics of CSA in lymph on rats after CIPOL Inj.® (Chong Kun Dang Pharm., Seoul, Korea) was administered (10 mg/kg). The lymphocyte suspensions (106 cells/ml) were prepared from the isolated lymph node and spleen and whole blood, the CD4 T-cell counts were measured by the flowcytometer (Becton Dickinson Immunocytometry System, Mountain View, CA, U.S.A.) with the fluorescein isothiocyanate (FITC)-conjugated mouse anti-rat CD4 monoclona

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