After 4-week treatment with control(23% protein diet) and PCM(5% protein diet)diets, the expression of P-gp in the liver was determined by Western blot.Also hepatic ATP level was measured.The canalicular transport of H^3-daunomycin and H^3-taurocholate measured. The pharmacokinetics of daunomycin,H^3-TBuMA, substrates of P-gp and C^{14}-TEA after intravenous infusion was also measured.
The expression of P-gp in the liver was suppressed(30-40% by Western blot analysis) and the hepatic ATP level was decrease in PCM rats. The kinetic analysis of the transport of H^3-daunomycin into cLPM vesicles revealed that the function of P-gp was decreased. Moreover, the biliary excretion was significantly decreased after intravenous infusion of daunomycin, this imples that hepatic ATP depletion may deteriorates hepatic activity of the P-gp,one of the hepatic ABC transporters.

[PE1-25] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Hydrolysis of coprecipitate from Coptidis Rhizoma and Scutellaria Radix by β-Glucuronidase

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Precipitation was formed during the preparation of decoction from the mixture of Coptidis Rhzoma and Scutellariae Radix. Berberin and baicalin were identified in coprecipitated products and these compoments were the active ingredients of two herbal medicine. The coprecipitated products were very slightly soluble in water and sparingly soluble in ethanol. The content of berberin and baicalin in the coprecipitated products were 26.8% and 23.1% but the content of active ingredients in supernatants were 0.3% and 0.7% respectively. For the purpose of hydrolyze the coprecipitate, some kinds of the intestine bacterias and these enzymes were tested and compared the rate of hydrolysis under various conditions. β-Glucuronidase from Escherichia coli hydrolyzed the coprecipitated product to berberin glucuronide and baicalein. The berberin glucuronide was absorbed rapidly in the small intestine of rats and maintained more higher serum level than the coprecipitated products.

[PE1-26] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Transport mechanism of berberine across Caco-2 cell monolayers

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Berberine, a quarternary isoquinoline alkaloid, is frequently utilized in the diarrheal treatment. In previous study, in vitro absorption of berberine across rat colonic segments was non-saturable and equal in both

directions(the apical-to-basolateral (A-to-B), basolateral-to-apical(B-to-A)),suggestive of a passive diffusional process. However, the transport mechanism of berberine is not yet studied using in vitro cell line . Also in another previous study, berberine modulates expression of P-glycoprotein. This result implies that berberine may be transported in carrier-mediated system. Therefore we elucidated the transport mechanism of berberine using in vitro absorption model, Caco-2 cell monolayers.
Caco-2 cells were grown to confluency on a polycarbonate membrane inserts to permit loading of berberine on either the apical or basolateral side of the cell monolayer. we performed concentration and temparature dependency and inhibition studies.
Polarized transport of berberine was observed with B-to-A permeability being 20-fold greater than A-to-B permeability. B-to-A transport of berberine was concentration and temperature dependent, and was reduced by P-glycoprotein inhibitor such as verapamil.
In summary this study demonstrated that berberine is secreted across the Caco-2 cell monolayers via P-glycoprotein-mediated efflux. Thus this study provide that berberine can be substrates of P-glycoprotein.

[PE1-27] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Preparation and properties of mono-PEG modified interferon-a having different molecular weight of the PEG portion

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Pegylation, conjugation process with poly(ethylene glycol) (PEG), may be an effective method for delivering therapeutic proteins and modifying their pharmacokinetic properties. PEG-protein conjugates exhibit: (1) enhanced solubility (2) decreased antigenicity (3) decreased proteolysis and (4) reduced rate on kidney clearance. These effects are mostly dependent on the molecular weight of the attached PEG. The attachment of PEG to the proteins might result in decreasing the biological activity by masking the active site of protein.
The present studies investigated the effects of PEG molecular weight size on the properties of PEG modified interferon-a (IFN-a). Mono-PEGylated IFN-as were prepared by conjugation with various PEGs of different size and purified. Their physico-chemical properties, biological activities and the pharmacokinetics were examined.
The results showed that the covalent attachment of PEG into IFN-a did not change the protein conformation, and endowed with increased stability against temperature and enzyme digestion. Depending on the increase in PEG size, their biological activity decreased due to the stearic hindrance, whereas phamacokinetic parameters such as circulating half-life increased. And it is expected that these circulating half-life extension would give rise to increase in overall in vivo biological activity of PEGylated-IFN-a even though its bioactivity itself decreases.

[PE1-28] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Sustained Release of Recombinant Human Growth Hormone From Biodegradable Polymer Matrices

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Sustained-acting formulations for recombinant human growth hormone (rhGH) were prepared by a phase separation (dispersion/solvent evaporation-extraction) method from hydrophilic 50:50 poly(D,L-lactide-co-glycolide) (PLGA) polymers, MW 5 000 and MW 10 000.
The rhGH-loaded PLGA 5K (Formulation I) and 10K (Formulation II) microspheres showed similar particle