[PE1-22] [10/19/2000 (Thr) 15:00 - 16:00 / [Hall B]]

The transport of a reversible proton pump antagonist, YH1885, across Caco-2 cell monolayers

Li H°, Chung SJ, Kim HS, Lee JW, Lee MH, Shim CK

College of Pharmacy, Seoul National University and Yuhan Research Center

5.6-Dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinoline-2-yl) pyrimidine hydrochloride (YH1885) is under development as a novel proton pump antagonist by Yuhan Research Center. Previous studies have suggested that the AUC and C_{max} of orally dosed YH1885 are dose-dependent in the range of 2-500mg/kg. The objective of the present study was to investigate the absorption mechanism of YH1885 using a human colon carcinoma cell line, Caco-2. The cells were grown to confluency on a permeable polycarbonate membrane insert to permit loading of YH1885 on either the apical or basolateral side of the cell monolayer. The flux across the monolayer from the apical to basolateral side was 3-5 times greater than that from the basolateral to apical side. The uptake of YH1885 into the Caco-2 cell monolayer was saturable and appeared to be mediated by a high affinity transporter, with an apparent K_m of 1.47±0.21μM and a V_{max} of 25.14 ±1.16pmol/cm^2/40sec. The apical to basolateral transport across the monolayer was Na^+-independent, H^+-sensitive and energy-dependent. The transport was significantly inhibited by the presence of structure analogues of YH1885 (e.g., YH957, YH1070 and YH1041), some pyrimidine nucleobases (uracil and 5-methyluracil) and nucleobase transport inhibitors (e.g., papaverine, dipyridamole and phloridzin). These results demonstrate that the transport of YH1885 across the Caco-2 cell monolayer is partially mediated by a nucleobase transport system, which exhibits high affinity properties. Saturation of this transport system, in addition to the limited solubility of YH1885 (i.e., ~ 5.3μM), appears to contribute to the dose-dependent bioavailbility of the drug.

[PE1-23] [10/19/2000 (Thr) 15:00 - 16:00 / [Hall B]]

Properties of a newly synthesized H+/K+ ATPase inhibitor, DBM -819, In vitro biochemical properties

Hyae Gyeong Cheon*#, Hong Lim, Dong Ha Lee, and SangSook Lee°

Pharmaceutical Screening Center, Korea Research Institute of Chemical Technology

DBM-819 inhibited rabbit gastric H+/K+ ATPase (EC 3.6.1.3) with an IC50 value of 5 μM. On the other hand, DBM-819 was a weak inhibitor for dog kidney Na+/K+ ATPase, indicating the selectivity for gastric H+/K+ ATPase. The inhibition was reversible, and noncompetitive with respect to the activating cation K+. The presence of DTT did not protect H+/K+ ATPase from the inactivation. The inhibition by DBM-819 was potentiated by acid pretreatment of the compound, suggesting the structural conversion of DBM-819 into a more active intermediate under acidic condition. The results suggest that DBM-819 is a potent, selective and reversible inhibitor of gastric H+/K+ ATPase, and that the essential cysteine residue may not be involved in the DBM-819-mediated inactivation of gastric H+/K+ ATPase.

[PE1-24] [10/19/2000 (Thr) 15:00 - 16:00 / [Hall B]]

Properties of a newly synthesized H+/K+ ATPase inhibitor, DBM -819, In vivo pharmacological properties

Hyae Gyeong Cheon*#, Sang Sook Lee°#, Hong Lim and Dong Ha Lee

Pharmaceutical Screening Center, Korea Research Institute of Chemical Technology

DBM-819, given intraduodenally, inhibited basal acid secretion with an ED50 value of 3.5 mg/kg. In addition, DBM-819 reduced either histamine or pentagastrin-stimulated gastric acid secretion with ED50 values of 4.0 and 5.1 mg/kg, respectively. Duration of the anti-secretory effect was about 18 h upon oral administration. Oral administration of DBM-819 dose dependently protected the gastric lesions induced by ethanol, NaOH, indomethacin and aspirin, and the duodenal ulcer induced by cysteamine, with ED50 values of 7.0, 20, 3.1, 4.0 and 6.0 mg/kg, respectively. Taken together, these results suggest that DBM-819 acts as an orally effective anti-ulcer agent in vivo, and that DBM-819 could be developed as a new therapeutic agent for peptic ulcer disease.

[PE1-25] [10/19/2000 (Thr) 15:00 - 16:00 / [Hall B]]

Effect of the pretreatment with prokinetic agents on gastric emptying as estimated from serum concentrations of orally administered ranitidine in humans

Lee HT, Chung SJ, Lee MH, Shim CK

Department of Pharmaceutics, College of Pharmacy, Seoul National University

To comparatively investigate the effect of two prokinetic drugs, cisapride and metoclopramide, on gastric emptying and intestinal transit by assessing the serum concentration of ranitidine following oral administration to healthy volunteers. Six healthy male subjects participated in a three-way cross-over study. Cisapride or metoclopramide was administered orally 30 min prior to an oral administration of ranitidine. Serum concetrations of ranitidine were determined by an HPLC method, and compared with the control group of no receiving the pretreatment. Pharmacokinetic parameters, including AUC_{inf}, C_{max}, T_{max} and $T_{1/2}$ were obtained by standard methods. In addition, the effects of these prokinetic drugs on the in vitro apparent permeability of ranitidine across the rat jejunum in the Ussing chamber, and on the in vivo intestinal transit of charcoal meals in rats were also examined. T_{max} of ranitidine in human subjects was shortened significantly by the either of the pretreatments. Even the AUC_{inf} of ranitidine was also decreased significantly in the case of cisapride pretreatment. However, no changes were observed for the values of C_{max} and $T_{1/2}$ by the pretreatments. Rat studies revealed that cisapride and metoclopropamide had no influence on the in vitro permeability of ranitidine or the in vivo intestinal transit of charcoal meals. We conclude that these prokinetic agents accelerate the gastric emptying of ranitidine, thereby decreasing the AUC_{inf} of ranitidine in the case of cisapride pretreatment. We hypothesize that the saturation of the carrier system, which is responsible for the intestinal absorption of ranitidine, is responsible for the decrease in the AUC_{inf}.

[PE1-26] [10/19/2000 (Thr) 15:00 - 16:00 / [Hall B]]

Inhibitory Effect of Curcumin on Experimental Hepatic Fibrosis <I>in vivo </I>and <I>in vitro</I>.

Kang HC°, Nan JX, Kim JY, Park EJ, Kim HJ, Woo SW, Zhao YZ, Ko GI, Sohn DH.

Medicinal Resources Research Center, College of Pharmacy, Wonkwang University, Iksan, Cheonbuk, 570-749

Background/Aims. : In an earlier our report, we reported Curcumin had the protection effects on acute or subacute Carbon tetrachloride-induced liver damage in rats. In this present study, the