[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

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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

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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