[S9-5] [10/18/2002(Fri) 17:20-17:40/Hall A]

Pharmacokinetic and Pharmacodynamic Modeling of a Proton Pump Inhibitor

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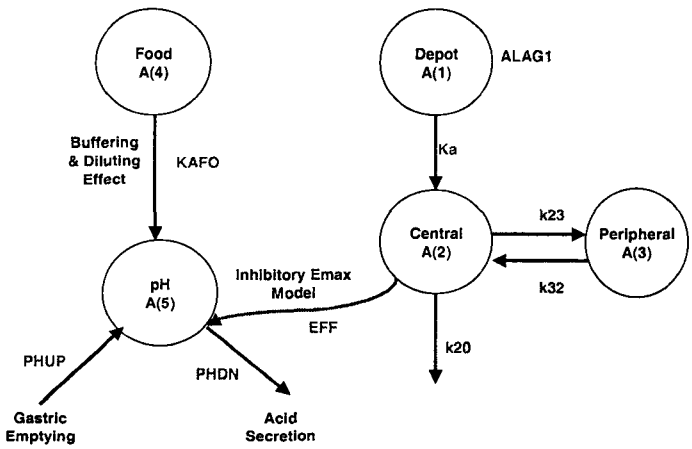
Pharmacokinetic (PK) and pharmacodynamic (PD) study of a new reversible proton pump inhibitor (YH1885, Yuhan Pharmaceutical Co.) was done as a phase 1 clinical trial in Seoul national UniversityHospitalClinicaltrialcenter.Singledoseof60,100,150,200,and300mgwereadministered to total 20 healthy subjects under fasting state. Six subjects were given 100 mg after food and 12 subjects were given multiple doses of 150 and 300 mg every day for 7 days under fasting state. PK samples were drawn before and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours after dose. For PD effect intragastric pH was measured for 24 hours before and after dose.

PK/PD modeling was done using NONMEM V level 1.1. PK data were 643 plasma concentrations from 52 subjects. For PK modeling ADVAN4, TRANS4 subroutines and absorption lag were applied. PD model was developed from baseline pH data before drug administration. PD model assumed 2 compartments, pre-stomach and stomach, to model food effect on gastric pH using logit function. Drug effect on the pH was modeled using inhibitory Emax model. The link between PK and PD was established sequentially.



PK modeling revealed 2-compartment model with lagged 1st order absorption and was the most appropriate one. Age, body weight, and height were not significant covariate for the clearance or volume of distribution. Clearance and inter-compartment clearance showed strong correlation. Food increased absorption rate and lag time by 30%, respectively. Modeling the baseline pH using logit function fit the food effect on pH fairly well. The PK model attached to baseline PD model affecting pH as inhibitory Emax explained drug effect without having to incorporate direct link or indirect response model. The performance of this PK/PD model was checked by simulating a phase 2 clinical trial.