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POPULATION PHARMACOKINETICS OF ESOMEPRAZOLE IN ADULT PATIENTS WITH GASTROESOPHAGEAL REFLUX DISEASE. J. Li, PhD, T. Lind, MD, PhD, T. Tzeng, PhD, B. Birmingham, PhD, J. Zhao, MD, PhD, T. Andersson, PhD, P. Martin, MD, P. Lundborg, MD, PhD, AstraZeneca LP, Kärnsjukhuset, AstraZeneca LP, Wilmington, DE.

PURPOSE: To establish a population pharmacokinetic (PK) model of esomeprazole (ESO), a proton-pump inhibitor, in 36 adult patients with gastroesophageal reflex disease (GERD) symptoms following an oral administration of 40 mg ESO (AstraZeneca study SH-QBE-0008).

METHODS: Blood samples for ESO plasma concentration measurements were obtained from 0 to 8 hours post dosing. The absorption model of ESO was identified by a semi-parametric deconvolution approach with the input function represented by a piece-wise linear spline. Identification of the disposition model of ESO and covariate evaluation was performed by population PK analysis using NONMEM.

RESULTS: A one-compartment open model with sequential zero- and first-order absorption described the data best. Estimated population means for apparent clearance, apparent volume of distribution, first order absorption rate constant, duration of zero order input and the absorption lag time are 8.66 (L/hr), 18.7 (L), 2.0 (1/hr), 0.32 (hr) and 0.46 (hr), respectively. Covariate evaluation indicated that apparent clearance in female was about 81% of that in male. Body weight exhibited a slight impact on the first-order absorption rate constant.

CONCLUSIONS: The absorption of 40 mg ESO in GERD patients could be described by a sequential zero- and first-order absorption model. Slight effects of gender on clearance and of body weight on the first order absorption rate constant are unlikely to be clinically significant.

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NEURAL NETWORK MODEL OF ORBOFIBAN PHARMACODYNAMICS FROM SPARSE PHASE-II DATA. D. E. Mager, PharmD, PhD, J. D. Shirey, MS, D. Cox, PhD, D. J. Fitzgerald, MD, D. R. Abernethy, MD, PhD, University at Buffalo, SUNY, National Insitute on Aging, NIH, Royal College of Surgeons in Ireland, University College Dublin, Buffalo, NY.

BACKGROUND/AIMS: The purpose of this study was to develop a neural network (NN) pharmacodynamic (PD) model that correlates the inhibition of ex vivo platelet aggregation by orbofiban, an oral GPIIb/IIIa antagonist, with the administered dose and patient characteristics.

METHODS: Data were obtained from a Phase-II dose-finding study in patients presenting with acute coronary syndromes. A back-propagation NN was designed to predict drug effect measured at pre-dose and 4 and 6 hours on treatment days 1, 28, and 84 (9 responses/patient). The training set (TS) consisted of patients for whom complete response profiles were reported (n=67), and remaining patients were included in the validation data set (VS; n=47). The concentration-effect relationship was described also using a population inhibitory sigmoidal model, and a comparison of the predictive performances of both models was performed.

RESULTS: The final NN reasonably described orbofiban PD from sparse data sets (r^2=0.83 & 0.61; TS & VS) without specifying a structural model or drug concentrations. Despite considerable inter-patient variability in response-time profiles, the population model revealed a strong correlation between drug concentration and effect and exhibited greater precision than the NN model.

CONCLUSIONS: Although the population model showed greater precision, these results suggest that NNs may be useful for predicting drug PD when plasma concentrations are relatively unpredictable or unavailable.

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A POPULATION PHARMACOKINETIC/PHARMACODYNAMIC MODEL FOR THE MOBILIZATION OF PROGENITOR CELLS BY AMD3100. B. Green, MSc DPh, H. Lee, MD, PhD, N. Lack, BSc, D. Dale, MD, G. Calandra, MD, PhD, R. MacFarland, PhD, K. Badel, BSc, W. Liles, MD, PhD, G. Bridger, PhD, C. Peck, MD, Center for Drug Development Science, AnorMED Inc, University of Washington, Washington, DC.

BACKGROUND: AMD3100 is a small molecule CXCR4 antagonist that has been shown to induce the mobilization of hematopoietic stem cells (CD34+) from the bone marrow to peripheral blood. The purpose of this study was to characterize the exposure-response (ER) relationship of AMD3100 in mobilizing CD34+ cells.

METHODS: AMD3100 concentrations and CD34+ cell counts obtained from 29 healthy subjects in a single dose, intensively sampled PK-PD study were analyzed using nonlinear mixed effects regression with the software NONMEM. FOCE with interaction was the estimation method and simultaneous PK-PD fitting was adopted.

RESULTS: The PK of AMD3100 was described by a two compartment model with first order absorption. The population estimates for clearance (CL) and central volume of distribution (V) (± SE) were 5.17 L/hr (0.49) and 16.9 L (3.79) respectively. CD34+ cell mobilization was best described by an indirect effect model that stimulates the entry process of CD34+ from the bone marrow to peripheral blood in the form of sigmoid E_{max} model. The population estimates of E_{max}, EC_{50} and equilibration time (± SE) were 12.6 (4.89), 53.6 mcg/L (11.9) and 5.37 hours (1.31) respectively.

CONCLUSIONS: The ER relationship of AMD3100 in mobilizing CD34+ cells following subcutaneous administration was adequately characterized. Experimentation in patient populations is required to characterize the ER relationship further.

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POPULATION PHARMACOKINETIC-PHARMACODYNAMIC (PK-PD) MODELING OF ETANERCEPT IN PATIENTS WITH JUVENILE RHEUMATOID ARTHRITIS (JRA) USING A DICHOTOMOUS CLINICAL ENDPOINT. D. Yim, MD, PhD, H. Zhou, PhD, C. C. Peck, MD, H. Lee, MD, PhD, Center for Drug Development Science, Wyeth Research, Washington, DC.

BACKGROUND: Realistic PK-PD models should incorporate the perceived clinical outcome of drug treatment. In the case of JRA, therapeutic outcome is judged according to a dichotomous scale (improved or not). We developed a PK-PD model for etanercept using six clinical component variables, which comprise the definition of improvement (DOI), assessed as "improved" if three or more of the components decrease by more than 30% of baseline values.

METHODS: Clinical trial data of etanercept in 69 patients with JRA were used. The six component variables were percentage changes from baselines of global assessments by the physician (MDGA), patients or guardians (PTGA), functional ability (FA), number of active joints (AJC), number of joints with limitation of motion (LOM) and erythrocyte sedimentation rate (ESR). Each variable was fitted using the E_{max} model with individual predicted etanercept concentration or cumulative AUC. (NONMEM Ver. 5.1.1.) The dichotomous DOI was determined according to the criterion of 30% improvement in at least 3 of the 6 individual predicted variables.

RESULTS: E_{max} and EC_{50} estimates are shown in the table.

Three hundred and thirty eight points out of 422 (80.1%) individual predicted DOI values matched with the observed DOI values.

CONCLUSIONS: A PK-PD model for a dichotomous PD parameter was developed using component variables. This approach will help researchers to quantify the pharmacologic effects assessed by dichotomous clinical outcome variables.

Estimated Emax and EC50

Component Variable	Pharmacokinetic Parameter Used	Estimated E_{max} (%)	Estimated EC_{50}
MDGA	Cumulative AUC	63.5	1510 mg/L × h
FA	Cumulative AUC	55.2	5250 mg/L × h
AJC	Cumulative AUC	54.5	1750 mg/L × h
LOM	Cumulative AUC	50.7	1260 mg/L × h
PTGA	Serum concentration	52.3	904 μg/L
ESR	Serum concentration	44.2	98.8 μg/L