

TITLE: A Three-Stage Hierarchical Bayesian Mechanism-based Population Exposure/Interleukin-6 Response Model of Drug X in Patients with Immunological Disease

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OBJECTIVES: The objective of this study is to develop a three-stage hierarchical bayesian mechanism-based population exposure-response (E-R) model to describe the relationship between the drug exposure and interleukin-6 (IL-6) response in patients with immunological disease.

METHODS: A total of 2148 serum drug concentrations (from 388 subjects) and 1894 IL-6 serum concentrations (from 799 subjects) were included in the analysis. A two-compartment linear PK model was used to describe the drug exposure. An indirect-response model was developed to describe the serum IL-6 concentration-time profiles. The drug affected the synthesis of IL-6 through an inhibitory Emax model. First, the E-R model was developed using two-stage hierarchical Monte-Carlo parametric expectation maximization (MCPEM) method implemented in the S-ADAPT program and fit simultaneously to both PK/PD data [1]. A novel three-stage hierarchical Bayesian estimation method was implemented in S-ADAPT and used to develop the final model. In brief, the maximum likelihood estimate of the population parameters obtained from two-stage MCPEM method was used to construct full conditional distributions for the Bayesian-analysis [2]. Then the Gibbs sampling method was used to create samples of population parameters including inter- and intra-subject variances from these full conditional distributions [2]. For a given set of population parameters, proposed parameters for each individual are generated by the Metropolis-Hasting Markov Chain Monte Carlo Stochastic Approximation Expectation Maximization (MCMC SAEM) method [3].

RESULTS: Based on the initial information provided by the final population parameters estimated from the two-stage MCPEM algorithm, mechanism-based population E-R model developed using a novel three-stage hierarchical bayesian model was stable and generated reasonable final parameter estimates (Table 1). A total run time for the final model in a single HP Pentium 4 2GHz computer is about 7 hours.

CONCLUSIONS: To our knowledge, this is the first case study to demonstrate the feasibility of using a novel three-stage hierarchical Bayesian model that combined Gibbs sampling and MCMC SAEM method to develop complex mechanism-based population E-R model from a real clinical data.

REFERENCES:

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Table 1: Summary of Posterior Distribution for Population Parameters in the Final PKPD Model

	5 th Percentile	Median	Mean	95 th Percentile
Population Parameters				
CL (L/day)	0.596	0.622	0.621	0.645
Vc (L)	3.33	3.47	3.48	3.62
CLd (L/day)	1.71	2.28	2.28	2.87
Vp (L)	6.47	7.10	7.10	7.68
Ksyn (pg/mL/day)	2.15	2.60	2.61	3.04
Kdeg (1/day)	0.114	0.138	0.138	0.161
E _{max}	0.760	0.788	0.788	0.816
EC ₅₀ (µg/mL)	2.28	2.95	2.97	3.58
Inter-subject Variability				
CL	0.199	0.213	0.213	0.227
Vc	0.136	0.147	0.147	0.159
CLd	0.328	0.356	0.356	0.387
Vp	0.332	0.359	0.359	0.388
Ksyn	0.409	0.442	0.442	0.479
Kdeg	0.675	0.730	0.730	0.785
E _{max}	0.0251	0.0272	0.0272	0.0295
EC ₅₀	2.87	3.10	3.11	3.37
Intra-subject Variability				
Proportional Error (PK)	0.310	0.323	0.323	0.337
Proportional Error (PD)	0.540	0.564	0.565	0.591