Three-Stage Hierarchical Bayesian Analysis For Population Analysis of Complex PK/PD Models In S-ADAPT

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ABSTRACT

Objective: Time-course hierarchical Bayesian analysis has been recently implemented within the S-ADAPT program, which provides a convenient interface for complex PK/PD population analysis. While WinBUGS offers a general environment for Bayesian analysis, in interface does not allow one to easily perform PK/PD model analysis on population data. Here we compare the results of a Bayesian analysis performed in S-ADAPT 1.55 with those of WinBUGS/Blacklives 14.4 data simulated using a receptor-mediated clearance and indirect response model typically used in antibody therapeutics.

Methods: As a first step, a maximum likelihood estimate of the population model parameters is obtained using the standard MCPEM algorithm in S-ADAPT [1]. The S-ADAPT program automatically formats the MCPEM output as input for a subsequent Bayesian analysis. The maximum likelihood estimates from the first step serve as estimates of the model of the Bayesian distributions we want to generate. The Bayesian analysis example, containing prior information was supplied for the three-stage hierarchical Bayesian analysis. S-ADAPT uses a Gibbs sampler [2] or Metropolis-Hastings algorithm [3] to carry out the Markov chain Monte Carlo (MCMC) procedure to generate a large sample of the distribution.

Results: A data set was simulated using a typical PK/PD model often used in antibody therapeutics (antibody-receptor). The data set consisted of 50 patients each with a rich sampling of 17 PK and 18 PD observations per individual, sampled over a period of 50 days after receiving a bolus dose of 1 mg/kg Ab one week later. Individual parameters were generated from a normal distribution, and individual PD parameters were modeled as an indirect response model. Standard deviation of the observed response levels were selected at random from a univariate normal distribution with a mean of 5% and a standard deviation (SD) of 10%. The ratio of the squares of the pre-t diluted on the square of the predilection value. A typical PK/PD profile is shown.

METHODS

MODEL

The PK/PD model is described by the following mass transfer equations:

\[ \frac{dC}{dt} = \frac{Q}{Vc} \left( \text{infusion rate} - \frac{C}{Kmc} \right) - \frac{C}{\tau} \]

Peripheral Ab (Ab)

Central Ab (Vc)

(1)

Receptor

Gibbs Sampling of Population Parameters in S-ADAPT

A full description of the Bayesian analysis methods in S-ADAPT are given in [4]. Briefly, at each iteration, a new set of individual model parameters for each subject, receptor-mediated clearance and indirect response model typically used in antibody therapeutics. Population parameters, inter-subject variances, and intra-subject variances were for obtained as parameters. Two Markov chain Monte Carlo (MCMC) algorithms were used, one with a normal distribution and the other with a t-distribution.

RESULTS

METHODS


REFERENCES

