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22S: 138 Final Project Report
12/10/2007
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Introduction:

For our project we conducted a (hierarchal) nonlinear mixed effects Bayesian analysis of a real data set from population pharmacokinetics. The data set consisted of plasma theophylline concentration-time profiles from 12 subjects for approximately 25 hours following a single oral administration of theophylline (Upton et. al, 1982). The data was modeled using an open 1-comparment pharmacokinetic (PK) model with 1st order absorption as given by:

$$y_{i,j} = f(t_{i,j}, \underline{\theta}_i) + \varepsilon$$

$$f(t_{i,j}, \underline{\theta}_i) = \frac{D_i \cdot ka_i}{\left(V/F\right)_i \cdot (ka_i - ke_i)} \left[exp(-ke_i \cdot t_{i,j}) - exp(-ka_i \cdot t_{i,j})\right]$$

$$ke_i = \frac{\left(Cl/F\right)_i}{\left(V/F\right)_i}$$

where $y_{i,j}$ is the observed plasma theophylline concentration in the i^{th} individual at the j^{th} observation, $f(t_{i,j}, \underline{\theta}_i)$ is predicted plasma concentration, t is the time of the observation, $\underline{\theta}$ is a vector of subject specific random effects, D is the theophylline dose, ka is the first-order absorption rate constant, V/F is the bioavailability (F) normalized volume of distribution, Cl/F is the bioavailability normalized clearance, and ke is the first-order elimination rate constant. As is convention, the subject specific random effects (i.e. ka, V/F, and Cl/F) were assumed to follow a multivariate lognormal distribution since the parameter values must be positive by definition and for computational convenience. Specifically:

$$\underline{\theta}_i = \left(log\left(\left(Cl/F\right)_i\right), log\left(\left(V/F\right)_i\right), log(ka_i)\right)^T$$

$$\underline{\theta}_i \mid \underline{\mu}, \Omega \overset{ind}{\sim} N(\underline{\mu}, \Omega^{-1})$$

With prior distributions:

$$\underline{\mu} \sim N\left\{log\left(\left(Cl/F\right)_0\right), log\left(\left(V/F\right)_0\right), log(ka_0), \Lambda^{-1}\right\}$$

$$\Omega^{-1} \sim W(R, \nu)$$

It should be noted that all normal distributions were parameterized in terms of mean and precision. Finally, residual error ε was modeled with an additive (normally distributed) model. Specifically:

$$y_{i,j} - f(t_{i,j}, \underline{\theta}_i) \sim N\left(0, 1/\sigma^2\right)$$

With prior distribution:

$$1/\sigma^2 \sim G(a,b)$$

The effect of different priors on the parameters (i.e. mean and variance-covariance parameters) was also explored, comparing the results obtained using informative priors from the literature to using noninformative priors. Finally the Bayesian analysis results were compared to the results obtained using a frequentist maximum likelihood approach.

Materials and Methods:

Data

The data set consisted of plasma theophylline concentration-time profiles from 12 subjects for approximately 25 hours following a single oral administration of theophylline (Upton et. al, 1982). The complete data set is displayed in Appendix A.

Model Fitting

The Bayesian PK model was created using WinBUGS (Version 1.3)/PKBUGS (Version 1.1) with prior distributions of the parameters obtained from other literature sources (Ohnishi et. al 2003, see below) and then the model was exported to WinBUGS (Version 1.4.3)/Pharmaco (PKBUGS Version 2.0) interface to fit the published data set. The fitted model WinBUGS code is displayed in Appendix B. Three MCMC chains of 10,000 iterations were run for each model fitting from different overdispersed initial values for each chain. The first 4,000 iteration in each chain were excluded as the Metropolis algorithm acceptance rate is tuned to a value between 0.2 and 0.4 during the first 4,000 iterations. The convergence and mixing was assed from the history, autocorrelation, and BGR diagnostic plots. To determine model fit to the plasma concentration over time, custom plots were created in R displaying the observed data, the 95% point-wise confidence intervals (CI), and the 95% prediction intervals (PI) for each subject for both the informative and non-informative Bayesian data

analysis.

The frequentist maximum likelihood approach was conducted using the SAS® NLMIXED procedure (SAS® for Windows 9.1.3, Service Pack 4, SAS® Institute, Cary, NC). The procedure maximizes the marginal likelihood of $y_{i,j}$ using adaptive Gaussian quadrature integration approximation of the marginal likelihood, integrating out the random effects ($\underline{\theta}$, which enter the model nonlinearly) from the joint distribution of y and $\underline{\theta}$. The fitted PK model was identical to that used for the Bayesian analysis, except obviously there were no prior distributions specified for $\underline{\mu}$ and Ω^{-1}, and the variance-covariance matrix (Ω) was simplified to only a diagonal matrix. This matrix had to be simplified to a diagonal matrix due to numerical optimization issues. The fitted model SAS® code is displayed in Appendix C.

Bayesian Prior Distribution Construction:

Relationship between Log-Normal and Normal Distribution

Due to the relationship between the log-normal and normal distribution, it is realized that if $Y \sim N\left(\mu_N, {}^{1}\!/\!_{\sigma_N^2}\right)$ and $X = exp(Y)$, then:

$$\mu_N = log(E(X)) - \frac{1}{2} log\left(1 + \frac{Var(X)}{(E(X))^2}\right)$$

$$\sigma_N^2 = log\left(1 + \frac{Var(X)}{(E(X))^2}\right)$$

Therefore, priors for μ_N and σ_N^2 can be analytically calculated from papers where the sample mean and variance (standard deviation) of the parameters are given on the linear scale (i.e. NOT the log-scale).

INFORMATIVE PRIORS

Population mean priors ($\underline{\mu}$)

Consider the prior for the population mean parameters to be distributed multivariate normal with mean vector $\left[log\left(\left({}^{Cl}\!/\!_{F}\right)_0\right) log\left(\left({}^{V}\!/\!_{F}\right)_0\right) log(ka_0)\right]^T$ and diagonal precision matrix Λ^{-1}, for simplicity. The bioavailability of theophylline is near 100%. Therefore, for $log\left(\left({}^{Cl}\!/\!_{F}\right)_0\right)$ and $log\left(\left({}^{V}\!/\!_{F}\right)_0\right)$ the F value was fixed to 1.0. The clearance ($ {}^{Cl}\!/\!_{F}$) and