Neonatal Gentamicin Population Pharmacokinetics

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Abstract

Introduction. Individualized, predictive dosing of gentamicin for neonates has been an important goal for many years. Previous approaches have been limited by populations that had limited ranges of gestational and post natal ages.

Objective. To develop a predictive pharmacokinetic model for accurately dosing gentamicin in newborns across broad ranges of gestational and post natal ages.

Methods. Study approval was obtained from our institution's IRB. Demographic, clinical and gentamicin dosage regimen and serum concentration information was gathered on all NICU patients known to have received gentamicin from September 2009, through July 2014. After collection, data were subjected to cross-checking, error correction, and validation. After validation in Excel, gentamicin dosage regimen information and clinical covariates were placed in Pmetrics format. We used the Pmetrics iterative 2-stage Bayesian population pharmacokinetic modeling program to estimate population parameter values for the one compartment model with multiple infusion inputs.

Results. We collected and analyzed data for 163 neonates (105 males). Their gestational ages ranged from 22 to 42 weeks (73 of 163 were less than 27 weeks). At the time of gentamicin administration ages ranged from day of life (DOL) 2 through DOL 125 (76 of 163 were less than 29 days) while weights were between 395 and 4,930 grams. Only 9 had serum creatinines exceeding 0.8 mg/dl. Good estimates of each patient's individual parameters were obtained; regression of observed gentamicin serum concentrations on those predicted from the individual's estimated distribution volume and elimination rate constant yielded an r^2 of 0.998. Our predictive model, based on dosing weight, DOL, and serum creatinine yielded an r^2 of 0.885.

Conclusion. Our predictive model for serum gentamicin levels in neonates appears useful in neonates of GA greater than 23 weeks who have serum creatinines that are age appropriate and who are DOL up to 70 days.

Background

The goal of covariate analysis in pharmacokinetic (PK) and pharmacodynamic modeling (PD) is to find physiologically plausible descriptors of drug behavior. When such descriptors are found, they may be used alone or in combination to provide a useful, prospective dosage regimen for individuals who will not be the subjects of intensive study. Population pharmacokinetic analysis can be used to develop such a model from individually sparse data across a broad range of individuals. Application of this method is especially suited to modeling in groups wherein individual data will be inherently scanty, such as newborns.

Methods

- Study population: hospitalized infants receiving gentamicin
- Study design: retrospective data collection
- Study samples: routine blood samples for gentamicin therapeutic drug monitoring
- Data collection: for all gentamicin doses we recorded date, time, infusion duration and dose. For all measured concentrations we recorded the sample time. Individual subject post-natal age (days), gestational age (weeks), weight (kg), length (cm), and serum creatinine (mg/dL) were collected.
- Sample analysis: gentamicin concentrations were measured using fluorescence polarization immunoassay.
- Data analysis:
  - -We tested one compartment models having differing covariates using the iterative 2-stage Bayesian parametric population PK modeling program in Pmetrics [1].
  - -We compared model observed vs. predicted fits and likelihoods
  - -We calculated prediction bias as the mean (pred - obs), and prediction imprecision as the root mean squared error (pred- obs)^2
  - - All analyses and plots were made with Pmetrics, R 3.2.0 [2], and Stata 11 [3].

Results

Data were available from 163 infants, whose characteristics are as noted in the abstract Results. There were 2 samples from 154 (94%) subjects, 3 samples from 7, and one and four samples from 1 subject each.

Figures 1 – 4 illustrate increasing potential utility for various models derived from our population. Figure 5 shows the additional gain in explained variance when the individual's elimination is incorporated, and Figure 6 shows the degree to which the derived parameters fit the data.

Results

Figure 1. Serum gentamicin concentrations, observed vs predicted, from weight formula-adjusted individual's covariates

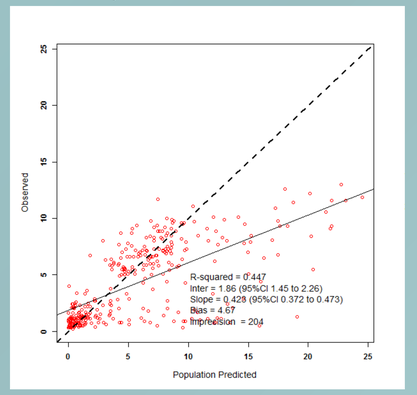


Figure 2. Serum gentamicin concentrations, observed vs predicted, from equation-adjusted elimination and weight-adjusted volume

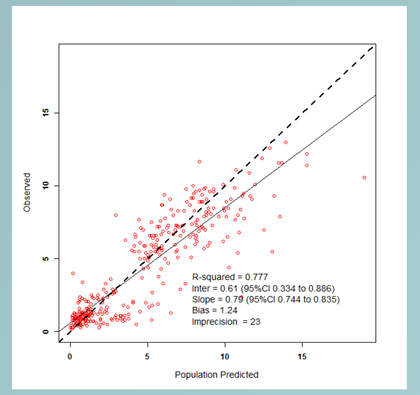


Figure 3. Serum gentamicin concentrations, observed vs predicted, from individual elimination and weight-adjusted volume

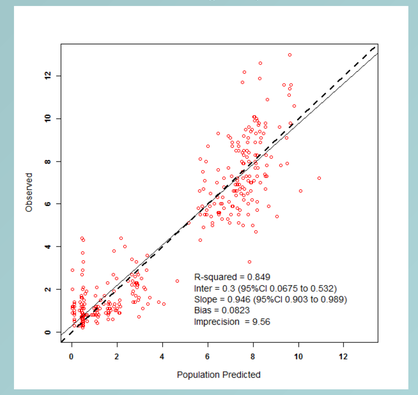


Figure 4. Serum gentamicin concentrations, observed vs predicted, from equation-adjusted elimination and volume

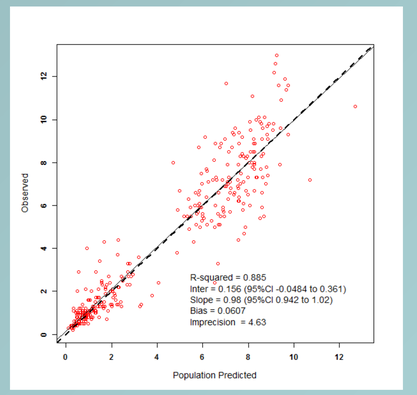


Figure 5. Serum gentamicin concentrations, observed vs predicted, from equation-adjusted elimination and volume, <28 weeks

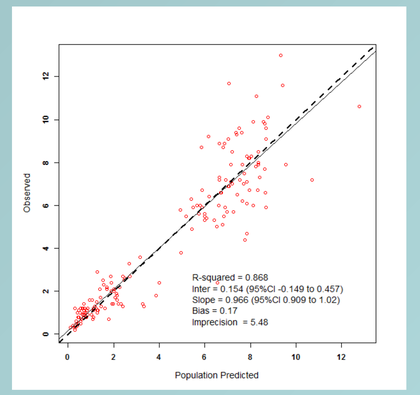
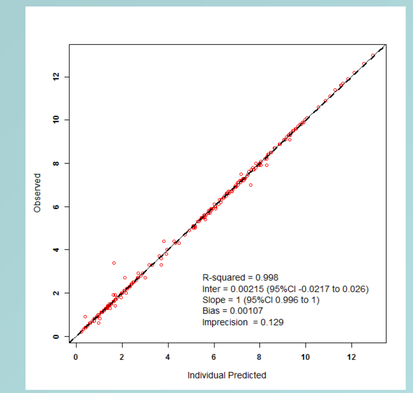


Figure 6. Serum gentamicin concentrations, observed vs predicted, from individual elimination and individual volume



References

[1] Neely MN, van Guilder MG, Yamada WM, Schumitzky A, Jelliffe RW. Accurate detection of outliers and subpopulations with Pmetrics, a nonparametric and parametric pharmacometric modeling and simulation package for R. Ther Drug Monit 2012; 34:467-476.
[2] http://www.R-project.org/.
[3] StataCorp LP, College Station, Texas 77845

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