Collaborative Grant Writing Example Statistical Plan

BIOS 352

March 31, 2014

Pharmacokinetic Modeling

The two-compartment model is expressed by a system of two coupled ordinary differential equations as follows

$$\begin{array}{lll} \frac{dC_1}{dt} & = \frac{R}{V_1} & -\frac{k_n+k_x}{V_1}C_1 \quad -\frac{k_d}{V_1}C_1 \quad +\frac{k_d}{V_2}C_2 \\ \frac{dC_2}{dt} & = & +\frac{k_d}{V_1}C_1 \quad -\frac{k_d}{V_2}C_2 \end{array}$$

where C_1 and C_2 represent drug concentration (μg/ml) in the central (blood) and peripheral compartments, repspectively. The parameters V_1 and V_2 are the corresponding compartment volumes (ml). Intercompartmental clearance is given by k_d (ml/hr). First-order intravenous dosing is represented by the known quantity R (μg/hr). In order to account for CRRT removal of antibiotic, the central compartment clearance is expressed as the sum of endogenous (k_n) and exogenous (k_x) clearances. The exogenous (CRRT) clearance will be estimated directly for each study subject by direct measuremnt of drug concentrations in CRRT effluent (spent dialysate and ultrafiltrate). For the porposes of model fitting, numerical solutions to this system will be obtained using a fourth-order Runge-Kutta method.

Statistical Methods

The unknown parameters of the modified two-compartment model will be fitted to data using nonlinear mixed effects regression. Each of the four unknown PK parameters (i.e., V_1, V_2, k_d, and k_n) will have a random component indexed by subject, and a fixed component. For Aim 1, the fixed effect associated with endogenous clearance will be modeled as a linear combination of candidate clinical variables. For Aim 2, the central compartment volume will be modeled in a similar manner. Polynomials up to third order, and all possible first order interactions of the candidate variables will be considered. We will use a forward stepwise algorithm to identify the linear combination of predictors that optimize the Akaike information criterion (AIC). The AIC is a measure of model fit that incorporates a penalty for model size. The forward stepwise method sequentially adds predictors to the model in the order that results in the largest incremental improvement in AIC. No additional predictors are included when the AIC cannot be improved. A parametric bootstrap method will be used to characterize the uncertainty associated with the stepwise procedure. Conditional on the selected model, 95% confidence intervals will be computed for all PK parameters. Confidence intervals that exclude the appropriate null value will be considered statistically significant. As an exploratory analysis, we will further examine the unexplained random effect variability in each PK parameter using a battery of visual and analytical techniques.

Secondary outcomes will be assessed using a suite of statistical procedures. The utility of extended infusions will be evaluated using the fitted pharmacokinetic models for piperacillin. The average incidence of target attainment under each dosing scheme will be estimated, with 95% confidence interval. Nonlinear mixed effects regression will be used to identify relationships between clinical factors and the endogenous clearance of tazobactam, as described above for piperacillin. Generalized multiple linear regression methods will be used to evaluate (1) the associations between clinical factors and attainment of published pharmacodynamic targets, (2) the associations between pharmacodynamic target attainment and survival, ventilator- and pressor-free days, predicted mortality risk (Dermirjian's score), and (3) the association between drug exposure and adverse drug reactions. All statistical analyses will be implemented using the statistical software package R version 3.0.1 and the add-on package NLME.

Decision Support Tool Evaluation

The random effects portions of the fitted model will be used to characterize the individual pharmacokinetics for each study participant. These data will be used to estimate the proportion of the dosing interval where

antibiotic plasma concentration was greater than four times the MIC (fT>4×MIC; aim 1), or the area under the concentration-time curve (AUC; aim 2) during a single dosing interval. The fixed effects portion of the model will be used to make predictions about individual pharmacokinetics, including fT>4×MIC or AUC, for each study participant, given the combination of clinical factors that were selected by the stepwise algorithm. In this way, the model will act as a clinical decision support tool (DST). The quality of fT>4×MIC and AUC predictions will be evaluated against the corresponding individual estimates using the mean absolute error. In addition, for each drug type, we will simulate a clinical decision process where the predicted fT>4×MIC and AUC are used to make a dose titration decision (increase, decrease, or hold current dose and frequency). The effect of this decision will be evaluated using individual PK estimates. In particular, we will estimate the frequency of underdosing (relative to established efficacy criteria) with and without the DST. A boostrap validation technique will be used to assess the optimism associated with these measures of model and DST quality.

Sample Size & Precision Analysis

The primary goal of the proposed work is to construct a clinical decision tool with utility in making predictions about individual antibiotic parmacokinetics. There are two facets of this approach that are affected by the study sample size. First, there must be broad variability within the sample cohort on the clinical factors that become part of the decision tool. As a rule-of-thumb, 20 samples should be collected per clinical factor. Hence, by this rule, 100 study subjects per aim and site permits consideration of five predictors. However, the stepwise selection algorithm is self-limiting, in that redundant or irrelevant predictors are automatically excluded. Secondly, and more importantly, we will evaluate the tool's utility in predicting the relevant PK parameters (fT>4×MIC or AUC) using the mean absolute error (MAE) between predictions and individual estimates. Among many other factors, the size of the study cohort affects the standard error of the estimated MAE. Hence, we have selected a sample size of 100 participants per participating institution and study aim to ensure, under a priori assumptions, that the precision in this estimate is clinically relevant.

In order to assess the MAE precision associated with fT>4×MIC for piperacillin, we implemented a simplified simulation of the proposed design and statistical analysis plan, using estimates of pipercillin pharmacokinetics and population variability available in the literature, and under the assumption that no clinical factor improves PK predictions, relative to the population average (i.e., a worst-case scenario). Where each participant is sampled 16 times over a single six hour dosing period (3g IV bolus), the mean and standard deviation of the absolute prediction errors associated with T>64 μg/ml were 32 and 15 minutes (9 and 4% of the dosing period), respectively. Hence, for sample sizes 25, 50, and 100, the approximate standard error for the estimated MAE is 3.0, 2.1, and 1.5 minutes, respectively. That is, recruiting 100 participants per aim and study site ensures, with 95% confidence, that the estimate of mean absolute error in predicting T>64 μg/ml will be precise to within 3 minutes.

In Aim 1, we focus on a common time-dependent antibiotic, piperacillin-tazobactam. This drug is used extensively at both centers, but administered sufficiently differently as to warrant separate pharmacokinetic analyses. At Vanderbilt, it is infused over four hours in critically ill inpatients, whereas at University of Alabama, Birmingham (UAB), it is given as a 30 minute bolus. While the covariates that drive drug disposition are likely the same regardless of administration time, the different administration methods warrant independent pharmacokinetic modeling. Consequently, for Aim 1, we will enrol 100 subjects at Vanderbilt and 100 subjects at UAB.

For Aim 2, we focus on two commonly used fluoroquinolones, ciprofloxacin and levofloxacin. Both drugs are used at both institutions, although regional prescribing habits vary. Ciprofloxacin is thought to undergo more extensive hepatic metabolism than levofloxacin, so, again, while the patient factors that influence peak drug concentrations are likely highly similar between the two drugs, they will require independent pharmacokinetic models. We will enrol 100 subjects for each drug.