A Framework for Meta-Analysis of Veterinary Drug Pharmacokinetic Data Using Mixed Effect Modeling

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ABSTRACT: Combining data from available studies is a useful approach to interpret the overwhelming amount of data generated in medical research from multiple studies. Paradoxically, in veterinary medicine, lack of data requires integrating available data to make meaningful population inferences. Nonlinear mixed-effects modeling is a useful tool to apply meta-analysis to diverse pharmacokinetic (PK) studies of veterinary drugs. This review provides a summary of the characteristics of PK data of veterinary drugs and how integration of these data may differ from human PK studies. The limits of meta-analysis include the sophistication of data mining, and generation of misleading results caused by biased or poor quality data. The overriding strength of meta-analysis applied to this field is that robust statistical analysis of the diverse sparse data sets inherent to veterinary medicine applications can be accomplished, thereby allowing population inferences to be made. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

Keywords: meta-analysis; nonlinear mixed-effect modeling; pharmacokinetics; population pharmacokinetics; veterinary medicine; drug depletion; drug withdrawal time; clearance; distribution; formulation

INTRODUCTION

In both human and veterinary medicine, pharmacokinetics (PKs) describes the absorption, distribution, metabolism, and elimination (ADME) of drugs in the body. Unlike human PKs, which focuses primarily on differences between individuals, veterinary medicine also gives consideration to differences between species and breeds.[1] Veterinary and human PK also differ in the extent and variety of data collected from clinical trials that is much less comprehensive in veterinary studies. Another major difference is that a drug's depletion must be studied in the edible tissues of food-producing animals to ensure that human consumers of meat, eggs, and milk are not exposed to harmful drug residues. Moreover, PK studies in exotic animals are lacking, and therefore, the dosage regime for those species is mostly based on empirical knowledge.

Statistically, meta-analysis is a tool designed to summarize the results of multiple studies.[2] It has been utilized in human drug development to assess the clinical effectiveness of healthcare interventions by combining data from different trials.[3,4] For veterinary medicine, it is, however, impossible to accomplish this because of the lack of available data. Meta-analysis may only be performed based on the average reported data.[5] However, combined data can be analyzed using nonlinear mixed effect (NLME) modeling approaches not specifically designed for this purpose. This review outlines the procedures and some of the differences and challenges in studying the PKs of drugs in veterinary species. We also discuss several advanced PK techniques that can be used to conduct meta-analysis and improve the interpretation of these data combined from several studies.

Abbreviations used: AD, aggregate data; ADME, absorption, distribution, metabolism and elimination; AMDUCA, Animal Medicinal Drug Use Clarification Act; BSV, between-subject variability; CIs, confidence intervals; FARAD, Food Animal Residue Avoidance Databank; IPD, individual participant data; NCA, noncompartmental analysis; NLME, nonlinear mixed effect; PBPK, physiologically based pharmacokinetic modeling; PDs, pharmacodynamics; PKs, pharmacokinetics; WDI, withdrawal interval; WDT, withdrawal time.

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DEVELOPING A META-ANALYSIS AND NLME MODEL FRAMEWORK

A framework is needed to describe the performance of PK data in veterinary medicine. Figure 1 illustrates the basic components of such a framework for data collection, modeling, and interpretation.

Data Collection

There are two kinds of data amenable to meta-analysis: individual participant data (IPD) and aggregate data (AD). It is easier to obtain IPD from human clinical trials, whereas AD is more common for veterinary studies. For PK studies, AD represents the mean value of concentration at different time points from a group of animals with standard deviation. In fact, for most cases, we cannot get standard deviation as the sample sizes of most PK studies are relatively small, and we do not know the true population mean. Instead, we use standard error to describe how far our sample mean is likely to be from the true population mean. Generally, we can get such information from tables or graphs of time–concentration profiles in the literature using available software such as UN-SCAN-IT (Silk Scientific, Inc., Orem, Utah). Collected data should be clarified into corresponding groups such as control versus experimental variable. One should collect as much available supplementary information as possible about the data. Supplementary information includes variables such as dosage, dosing routing, drug formulation, matrix and animal conditions (species, weight, age, sex, and disease), and so on.

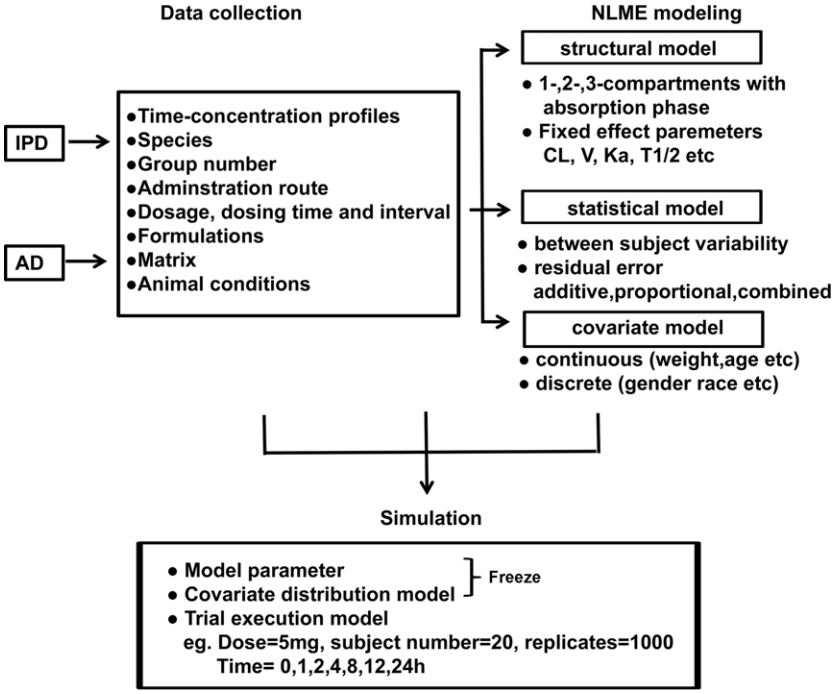

Figure 1. The workflow of meta-analysis and population-based NLME modeling for veterinary drug development.

NLME Modeling

The difference between PK and clinical trial data is PK data consist of a set of dependent variables determined by a function of time. But for most meta-analysis, clinical trial data means single individual data from treated or untreated group. Therefore, when dealing with PK data, we need a time-dependent structure model to describe the kinetic process of the drug. NLME modeling is the primary technique available for the analysis of integrated PK data.[6] "Nonlinear" implies that the dependent variable is nonlinearly related to the model parameters and independent variables. "Fixed effect" refers to the parameters that do not vary across individuals, whereas "random effect" refers to those parameters that vary across individuals.[7] Basically, a NLME model contains three components: (1) structural model, (2) statistical model, and (3) covariate model as depicted in Figure 1.

The structural model is developed to describe the PKs of a drug after dosing. A typical structural model is represented by one, two, or three compartments (depending on the time–concentration profile) with an absorption compartment for extravascular administration. The statistical model explains the variability around the structural model. There are two major sources of variability: between-subject variability (BSV) and residual variability. BSV is the variance of a parameter across individuals and would be represented as:

$$\log(P_i) = \log(P_{\text{pop}}) \exp(\eta_i) \tag{1}$$

where P_i is the parameter of the ith subject, P_{pop} is the population parameter, and η_i is the deviation from the population value for the ith subject and is assumed to be normally distributed with a mean of 0 and variance ω^2 for parametric methods. It should be noted that there are also nonparametric approaches to mixed-effect modeling.[8] Residual variability, also referred to as residual error, generally arises from assay variability or model misspecification. There are several functions for describing residual errors. Additive, proportional, or combined additive and proportional error model functions are the most commonly used in NLME model. Covariate model specification is important for developing the correct population PK model as it identifies which covariates are highly correlated with PK parameters. Potential covariates can include any available physiological parameters influencing ADME process such as weight, age, gender, liver enzyme activity, and so on. The covariates are classified into continuous or discrete. The typical continuous covariates are expressed using functions as:

$$\log(P_i) = \log(P_{\text{pop}}) \left(\frac{\text{Cov}_i}{\text{Cov}_{\text{avg}}}\right)^{\theta} \exp(\eta_i) \tag{2}$$

where P_i is the parameter of the ith subject, P_{pop} is the population parameter, Cov is a covariate factor centered by average mean or a reference value, and η_i is the deviation from the population value for the ith subject. In some situations, θ can be fixed to a certain value to account for changes in PK parameters. The discrete covariates are separated as dichotomous (gender) or polychotomous covariates (race). The values of such covariates are usually set as 0 for reference and 1 or more for the other classification. The typical discrete covariate is set as following:

$$P_i = \theta_i (1 + \theta \text{Cov}) \exp(\eta_i) \tag{3}$$

Simulation

Simulation is used to assess the effect of individual independent variability in each separate PK parameter on the overall model output. We obtain the PK model from the NLME model. This model is then used to simulate data that is an

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