Discrimination Between Rival Dosing Histories

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Purpose. In population pharmacokinetic studies, the dosing history is sometimes recorded in more than one way. The purpose of this study was to develop and evaluate a procedure for discriminating between rival dosing histories, i.e., for each individual in a data set, identify the dosing history that is the most plausible.

Methods. The procedure consists of four steps. In the first step we identify individuals whose dosing histories produce predictions that are consistent. In the second step these individuals are used to build a population pharmacokinetic model which is used, in step three, to select the dosing history for the individuals not identified in step one. In step four the population model is refined using the best available dosing histories for all individuals. The proposed procedure was evaluated using both simulations and a real data set, in which two dosing histories, based on patient diaries and electronic monitoring devices (MEMS) were available.

Results. In the real data set, estimated variabilities were almost always lower when the selected dosing histories were used compared to when no selection procedure was used. The diary dosing histories were selected more often than the MEMS dosing histories. In the simulations, the parameter estimates obtained using the selection procedure were closer to the true parameter values compared to when only one of the dosing histories was used.

Conclusions. The proposed procedure appears to be robust and should be beneficial in at least two respects: improved parameter estimation of population pharmacokinetic and PK/PD models and objective information by which dosage recording methodologies can be compared and patient dose recording behavior can be assessed.

KEY WORDS: compliance; dosing history; NONMEM; population pharmacokinetic analysis.

INTRODUCTION

Population pharmacokinetic analysis has proven able to generate useful information from sparse data (1), for example, with data from outpatient studies, but a poor knowledge of the dosing history will severely diminish the trustability of the result (2). Therefore knowledge of the dosing history, or a fair estimate of it, is required when analyzing this type of pharmacokinetic/pharmacodynamic (PK/PD) data. In phase I single dose studies this is routinely obtained since the dose intake is supervised by the staff at the clinic. However, in outpatient studies with multiple dosing, e.g., phase II and III clinical studies, the assessment of the correct dosing history can be more problematic. Not only are the doses taken without the detailed control (with respect to the actual intake of the dose as well as the time of intake) present in phase I studies, it is usually also necessary to have correct information from more than one dosing occasion prior to blood sampling or PD measurement. The issue of dose intake information is therefore a crucial part of the study design.

It should be noted that we do not use the term dosing history in the same sense as the term compliance is often used in the literature. The latter usually refers to the way patients adhere to a prescribed dosage regimen while the first refers to the actual dose intakes leading to the observations to be analyzed, regardless of whether the doses were taken as prescribed or not. Obviously there are connections between the two, for example one of the often seen compliance patterns, “white-coat compliance”, where the compliance to a prescribed dosage regimen often increases in the days prior to a visit to the clinic (3), will directly affect the dosing history of any observations made during the visit to the clinic. On the other hand, “drug holidays”, defined as a period of several days without drug intake (3), will not have the same consequences to the analysis of pharmacokinetic data unless it occurs just prior to (relative to the half-life of the drug) the time-point of the pharmacokinetic observations. Of course, drug holidays will have a large importance when trying to relate a side-effect event, occurring between two clinic visits, to the exposure to the drug, or for that matter, to the success or failure of the treatment as a whole. However, in the present paper we concentrate on, from a data analysis point of view, the problems that arise when there are uncertainties in the dosing history.

The methods to record dosing histories can be broadly divided into being either subjective or objective (4). Subjective methods are those that rely on the information provided by the patient, by, for example, interviews or patient diaries. Objective methods, on the other hand, rely on sources of information other than the patient. Staff supervised intake is an example of a method that is usually considered to give an objective measure of dose intake, electronic monitoring devices is another. An example of the latter is MEMS (Medication-Event-Monitoring System APREX Corporation, Fremont, CA). These are special drug containers that record when the drug is dispensed. There are a number of variants these, e.g., eye-drop containers, containers for drugs that are to be inhaled, and special lids for pill bottles (3). The idea is that the recorded time of dispensing should give an estimate of the time of drug intake. Pill counts have also been used to provide a rough estimate of overall compliance, but for pharmacokinetic analysis purposes, do not provide the necessary information about the dosing history.

None of these methods is ideal. Dose intake information given by the patient can be biased towards what is “expected.” Electronic monitoring devices can cease to function due either to hardware failure or mishandling (5). The recording may be inaccurate if the patient does not take the dose immediately after he opens the pill bottle or that more or less than the required amount is dispensed during a single pill bottle opening. Staff supervised intake may not be feasible in an outpatient study. Pill counts do not reflect the total number of doses taken and times of dose intake are not provided.

From a data analysis point of view, one practical consequence of having patients in which the quality of the dosing history is variable is that the data analyst is likely to face the
problem of handling outliers with the knowledge of an unknown contribution from a possibly inaccurate dosing history. If an individual dosing history is clearly incorrect then the decision to exclude the individual is easily made. If the dosing history does not result in observations that are distinguishable from the bulk of the data, then the individual will be retained in the data set. Between these two extremes, when the observations are slightly out of line, but not more so than they may be normal observations from an odd individual, the data analyst will have to make a more or less subjective decision whether to retain the individual in the data set or not. The influence that an individual with an incorrect dosing history will have, if retained in the data set, on the results of the analysis depends on whether the retained observations have a high influence and/or leverage on the calculations involved in the analysis of the data. In any event, it is likely that retaining individuals with incorrect dosing histories will increase the imprecision and, possibly, introduce bias in the estimated parameters.

It is obvious that the dosing histories provided by various methods differ from studies where one recording method has been employed (5,6). Although it is sometimes believed that one method is preferable to the other, the problem is then that one method of recording the dosing history might not provide an adequate dosing history for all individuals in the data set. We will describe one approach that can be taken, if two (or more) parallel dosing histories are available for each patient. First, individuals are identified for which the dosing histories are consistent, that is, give rise to, for all practical purposes, the same results. Then we address the subsequent question of how to treat the individuals that do not have consistent dosing histories. For illustration, we use data from an outpatient Phase II study, where sparse plasma concentration data were collected and dosing histories were recorded both by patient diaries and MEMS lids. This study was originally designed to be analyzed using population analysis (7) and we will present the suggested approach in this context. However, there is nothing inherent in the approach that necessitates this type of analysis, except perhaps that the data from outpatient studies are often sparse and population analysis is commonly used to analyze such data (1).

**MATERIALS AND METHODS**

**Dosing History Selection Algorithm**

The proposed selection procedure for discriminating between two dosing histories is depicted in Figure 1. In step 1 predictions for the data using each of the two dosing histories are obtained using a basic model that is consistent with the expected pharmacokinetic characteristics of the drug. The resulting predictions are compared and the individuals that have similar predictions are considered to exhibit consistent dosing histories (CDH). Such a procedure will down weight differences in the dosing history that occurred so long before the time of the observations that they will have no influence on the estimation of pharmacokinetic parameters. On the other hand, if the observation is made relatively close to the dosing event, even small differences in dosing history may result in different predictions. The individuals with non-consistent dosing histories (non-CDH) are retained in both of two separate data sets, one for each method of dosing history assessment. In step 2, the CDH data set is used to build a population model for the data.

In step 3, using the population model developed in step two, we perform two empirical Bayes estimations (8) (hereafter called Bayesian analysis) for each individual belonging to the non-CDH data set, one for each dosing history. To decide which of the two dosing histories is the most plausible for that patient, the likelihood of these individual analyses are compared. The most plausible dosing histories are retained in the selected dosing histories (SDH) data set. This SDH data set is then merged with the CDH data set and the population model is refined with the data from all individuals (step 4).

During the dosing history selection algorithm, two subjective choices have to be made. The first is which basic model to use in step 1 and the second is the cut-off value below which we say that the dosing histories are consistent, also step 1. In addition, choices are always part of population model building.