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, occuring 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

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problem of handling outliers with the knowledge of an unknown contribution from a possibly inaccurate dosing history. If an individuals 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 more than 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).

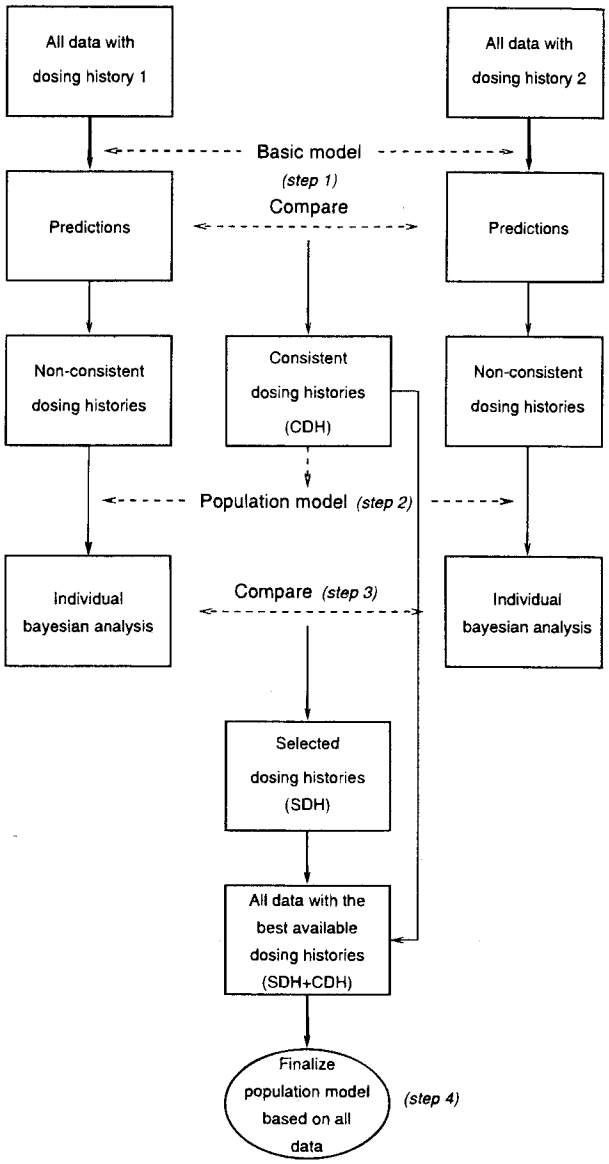

Fig. 1. The proposed procedure for discriminating between two dosing histories.

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

(step 2). In step 3, we used NONMEM (9) for performing the Bayesian analysis and the objective function value, which is −2 times the log likelihood, provided by NONMEM, and it is an appropriate criteria for the selection between the two non-CDH dosing histories. However, the sum of the squared weighted residuals (WRES) constitutes a more easily accessible means of comparison. Although these two measures can be expected to perform similarly in the present situation, the two were compared.

Real Data Set

The real data set was collected as a part of a double-blind, parallel multi-national, multi-center study comparing the investigational drug to placebo. Doses were taken orally twice daily for six months. Each patient was scheduled for five visits to the study clinic. Blood samples for pharmacokinetic analysis were taken at two of the study visits in selected clinics in five of the ten participating countries. The study was performed in accordance with the principles stated in the Declaration of Helsinki and approved by local Ethics Committees. Two blood samples, approximately one hour apart, were taken at each sampling visit. Visits could either be in the "morning" (0–4 hours post-dose according to the protocol) or in the "afternoon" (5–8 hours post-dose according to protocol) depending on when the patient was scheduled for a visit. Compliance was monitored using MEMS lids (MEMS-1®) during the whole study period. The patients were not actively informed about the monitoring by the MEMS. The dosing history was also recorded in patient diaries (the week immediately before a visit to the clinic) combined with any additional information the patient provided during the clinic visit (which was noted in the case record form). In addition to concentration-time data, a number of covariates were available for each patient: age, height, weight, gender, serum creatinine, creatinine clearance (calculated from the other covariates according to the Cockroft and Gault equation (10)), smoking and drinking habits. Patients with a pill count of less than 70% were excluded from the pharmacokinetic analysis.

Pharmacokinetic information for population model building was available from 222 visits of 120 patients. Dosing histories from the diaries were available from all these visits, compared to MEMS, where information was available from 180 visits of 92 patients. The difference occurs from MEMS not being returned by some patients and by inability to retrieve the information stored by some MEMS. Only the visits for which both MEMS and diary data were available were included in the selection procedure, i.e. 180 visits of 92 patients. Each patient visit was treated as a separate individual during the course of the dosing history selections (steps 1 and 3 in Figure 1). During population model building (steps 2 and 4 in Figure 1), both visits were recognized as coming from the same individual.

When the real data set was used to test the selection procedure, we had to make the choices about the form of the basic model and the size of the cut-off limit in step 1. For constructing the basic model, we used two pieces of prior knowledge: that absorption was rapid and that the terminal half-life was 6 hours. The resulting model was a one-compartment model with first-order absorption (absorption half-life 30 minutes). As expected from this rather crude information, the basic model was not in agreement with the results obtained from later stages population modeling. In a separate run, we investigated whether a more appropriate choice of basic model (a two-compartment model with parameter estimates close to those obtained from the present data) would result in different selection procedure. As cut-off limit in step 1, for what could be considered consistent predictions, we chose an average relative difference of 5% between the predictions as the default value, but also investigated the outcome of the selection procedure when up to a 20% difference was considered consistent.

The population model building was performed using the non-linear mixed effects modeling software NONMEM (9). We tried different structural, covariate, and statistical (correlations between the parameters, inter-individual, inter-occasion, and residual variability components (11)) sub-models as indicated appropriate from complementary graphical analyses.

Dose Recording Behavior

We also examined the differences between the diary and MEMS dosing histories for the patients in the non-CDH data set. Here we looked only at the two last scheduled dosing occasions before blood samples were taken. The (last) morning dose prior to sampling was defined as being the dose(s) taken after midnight the evening before sampling. The (second-to-last) evening dose prior to sampling was defined as being the dose(s) taken between noon and midnight on the day before sampling.

In step 3 the dosing histories of the non-CDH patients were compared using Bayesian analysis. To assess whether the decision to use one of the dosing histories instead of the other, for a specific patient, led to a marked improvement, we compared the objective function values (the objective function value is calculated by NONMEM and is proportional to −2 log likelihood) for the two analyses. We defined a marked improvement to be a difference of more than 4. This is loosely based on the fact that for two hierarchical models, one with one more parameter, a difference of 4 is significant at $p < 0.05$.

One possibility is that there might be a systematic difference between the patients in the CDH data set compared to the patients in the non-CDH data set. To study this we tested for any differences in patient characteristics (demographic data and habits) using unpaired t-test ($p < 0.05$).

Simulations

Although the analysis of real data can illustrate the selection procedure and provide information about recording behavior, it cannot demonstrate that the procedure chooses the (more) correct dosing history. To evaluate this point we used simulations. The way we simulated data is depicted in Figure 2. We started with two different dosing histories. These could have been arbitrarily chosen, but we chose to use the two sets of dosing histories (and the sampling history) that were available from the real data set. To stress that there is no necessary connection to the real data set, we have denoted them dosing history 1 and 2, rather than diary and MEMS. For each individual we randomly selected one of the two dosing histories for generation of data. The result was a data set with true (known) dosing histories. From the true dosing histories data set we simulated data using a one-compartment model with first order absorption and with three sets of population parameters (again no necessary connection with the real data set although there

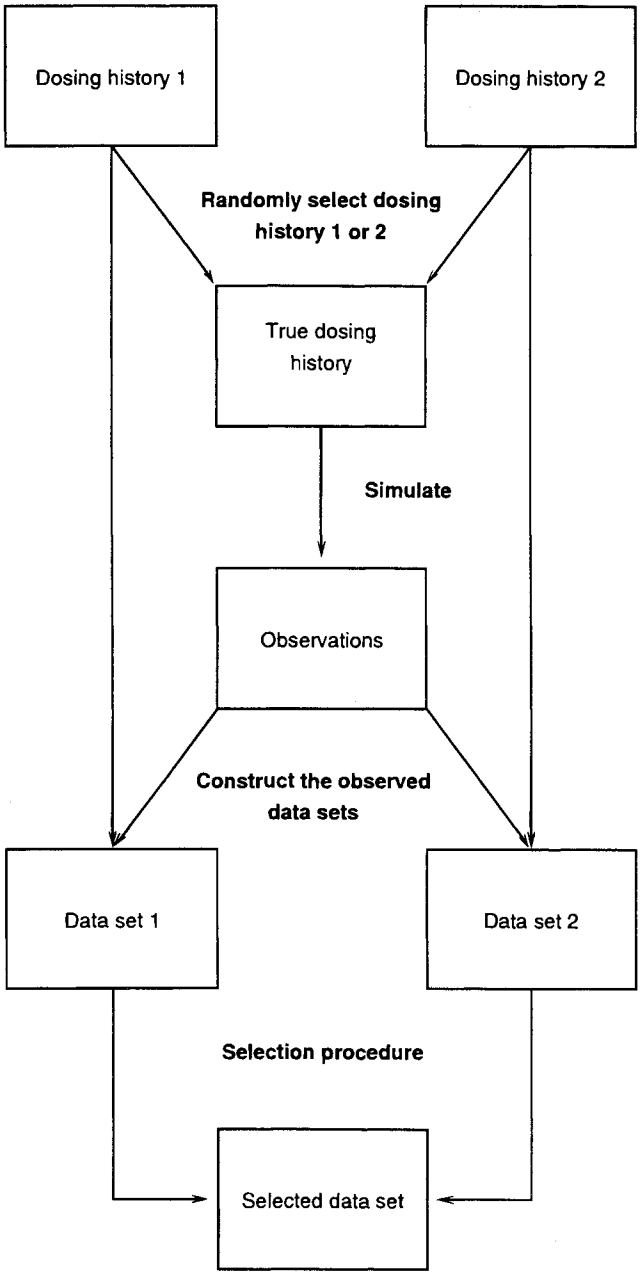

Fig. 2. Data simulation algorithm.

are some similarities). The first parameter set (Model A) had a rapid absorption and a terminal half-life of 10 hours. The second parameter set (Model B) had a rapid absorption and a terminal half-life of 20 hours, and the third parameter set (Model C) had a slow absorption and a terminal half-life of 10 hours. The three sets of parameter values used in the simulation are given in Table I.

Through the simulations we created a situation similar to that of our real data set, i.e., we had one set of observations together with two dosing histories. By applying the selection procedure to these data sets, we obtained a selected data set. It was then possible to compare the population as well as the individual parameter estimates obtained using the selected data set and the data sets with only dosing history 1 or 2 to the true parameter values.

RESULTS

Real Data Set

The plot of observed concentration versus time after dose for the selected dosing history obtained using the default conditions is displayed in Figure 3. Each line joins the two concentrations obtained on one visit. When the selection procedure was applied using default conditions, 37% of the total number of visits were included in the CDH data set. Forty seven percent of the total number of visits were in step 3 selected to the diary dosing history. The remaining 16% were in step 3 selected to the MEMS dosing history. For the higher cut-off value (20%) in the initial selection these values were 61%, 27%, and 12%. The same values when using the two-compartment model in step 1 were 19%, 48%, and 33%. The last model led to a smaller number of visits being regarded as having CDH compared to the default conditions, which it is likely to be because the dosing history that affects the predictions are longer with the two compartment model.

There were no differences in demographic indices or habits between the patients with consistent and non-consistent dosing histories, neither between patients selected to diary and to MEMS.

The non-CDH data, from the selection based on the basic one-compartment model with 5% cut-off, consisted of 114 visits. Among the 114 visits, 25 had a marked difference (objective function value difference >4) between the dosing histories. In step 3, all of these 25 visits were selected to the same dosing history, regardless of which basic model, cut-off value, or criteria for selection in step 3 was used. Of the 89 non-CDH visits that were not markedly different according to the objective function value, nine were selected differently when the sum of the weighted squared residuals was used as the selection criteria in step 3. The largest difference in the objective function value between MEMS and diary dosing histories for these nine visits was 0.4.

A two-compartment model with a first-order absorption and a linear relationship between CL and creatinine CL was found to best describe the data. The statistical model consisted of inter-individual variability in V/F, a fully correlated inter-occasion (11) variability in CL/F and V/F (this is denoted in Table II as inter-occasion variability in F) and inter-occasion variability in Ka. The data were log-transformed before analyses and the residual error was additive in the log domain (i.e., approximately proportional for untransformed data). The population parameter estimates obtained using the selected dosing histories from the three conditions tested, together with the estimates from when only diary and only MEMS dosing histories were used, are given in Table II. The parameter estimates obtained using the three different conditions for the subjective choices are similar and appear not to be dependent on these settings in the range that we tested. The estimated variabilities were almost always lower for the selected data sets compared to when no selection procedure was used to define the dosing history. In general, the population parameter estimates obtained when the selected dosing histories and when only the diary dosing history were used showed greater similarity than those estimates obtained when only the MEMS dosing history was used.

For 24 of the 25 visits showing marked difference between the dosing histories, the diary dosing history was superior. In

Table I. Parameter Estimates Obtained with the Simulated Data Sets

	True values	True dosing history	Selected dosing history	Dosing history 1	Dosing history 2
		Model A – tl/2 = 10 h, rapid absorption			
CL[a] (L/h)	14.5	14.9	14.3	15.6	14.2
V (L)	210	180	209	194	282
Ka[b] (h^{-1})	3.0	2.1	1.7	>10	1.9
θ CRCL[c]	0.008	0.007	0.009	0.002	0.006
IIV[d] CL (%)	35	42	41	0	0
IIV V (%)	35	31	57	142	142
IIV Ka(%)	35	48	0	>1000	108
ϵ[e] (%)	10	11	13	21	20
		Model B – tl/2 = 20 h, rapid absorption			
CL (L/h)	7.0	7.1	7.0	7.3	6.9
V (L)	210	170	210	940	268
Ka (h^{-1})	3.0	1.7	1.1	0.9	0.8
θ CRCL	0.008	0.007	0.011	0.009	0.011
IIV CL (%)	35	42	39	48	48
IIV V (%)	35	33	77	733	733
IIV Ka(%)	35	53	157	710	710
ϵ (%)	10	10	10	13	13
		Model C – tl/2 = 10 h, slow absorption			
CL (L/h)	14.5	15.0	15.0	15.2	14.2
V (L)	210	189	210	439	314
Ka (h^{-1})	0.8	0.8	1.0	>10	0.8
θ CRCL	0.008	0.007	0.004	0.010	0.005
IIV CL (%)	35	42	38	57	57
IIV V (%)	35	23	43	303	303
IIV Ka(%)	35	59	130	>1000	117
ϵ (%)	10	10	11	20	18

[a] For a subject with creatinine clearance of 84 ml/min.
[b] Absorption rate constant.
[c] Parameter relating creatinine clearance to CL.
[d] Inter-individual variability.
[e] Residual variability.

only one case was the MEMS history superior. For 23 of the 25 visits the major difference between the two dosing histories was that the diary data (and the measured concentration level) indicated that a morning dose was taken, whereas no corresponding MEMS record existed of dose intake.

Figure 4 shows how the selection was made in step 1 and step 3. The data is from a representative individual with the major difference between the two dosing histories being that the diary dosing history reports a morning dose while the MEMS dosing history does not. The top panel shows the predicted concentration-time profiles from the basic one compartment model for the day before and the day of sampling. The lower panel shows the predicted concentration-time profiles from the population model built in step 2. Also indicated in this panel are the observed concentrations. Clearly, for this individual, the diary recordings give the most likely dosing history.

Simulated Data Set

The parameter values obtained from the true dosing history, the selected dosing history, and dosing histories 1 and 2 are given in Table I. The parameter estimates from the selected data set were almost always closer to the estimates obtained when the true dosing history was used than the estimates obtained when either dosing histories 1 or 2 were used for the whole data set. Focusing on two important parameter estimates: CL and inter-individual variability in CL, it can be seen that the former is robust and exhibits the same value regardless of dosing history. The inter-individual variability in CL, on the other hand, is highly dependent on the dosing history. For Model A, it is driven to zero when either dosing history 1 or 2 alone is used. For Models B and C these dosing histories show inflated values of inter-individual variability in CL. The true and selected dosing histories show minor overestimations of the parameter regardless of condition. The root mean squared errors of the individual CL estimates obtained (with Model A) when using the true, the selected and dosing histories 1 and 2, were 17%, 33%, 33%, and 65% respectively. The corresponding values for V (volume of distribution) were 42%, 57%, 194%, and 313%.

DISCUSSION

When more than one dosing history record is available it opens up the possibility for the data analyst that would not be accessible with only a single dosing history. As a first step, individuals with consistent dosing histories can be identified. One option is to consider only the dosing histories for these

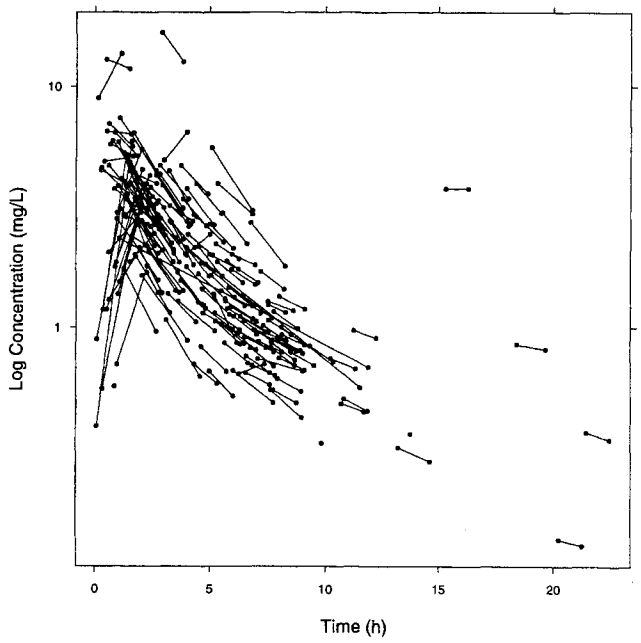

Fig. 3. Observed concentrations vs time. Times are based on the selected dosing history using the default values (5% and one compartment model for cut-off and model respectively) for the subjective choices in step 1. Each line connects the individual observations made at one visit.

patients to be of high enough quality for being included in the analysis. This alternative is attractive for obtaining basic pharmacokinetic information from a relatively large data set. However, if the data set is not large enough to exercise this option, or if information about subgroups is required, there may be a need to use as much of the data as possible.

In the present study, we have presented a method to discriminate between rival, or parallel, dosing histories. The procedure can be used to increase the number of evaluable patients from a clinical trial and to decrease the noise introduced by using incorrect dosing histories. Only two, predefinable, subjective choices have to be made and the selection procedure appears to be robust to both. A possibility to further robustify the approach, not explored by us but straightforward in theory, is to allow a partial iteration of the outlined scheme. After having gone through the entire scheme in Figure 1, one could return to step 3 and based on the "final" population model, all data would be selected to either dosing history and a new "final" model would be constructed based on those data. Such a scheme can be expected to lessen the influence of the original choices in step 1 even further. Another situation when such an iteration procedure may become useful is when the data set is so small that the cut-off value of step 1 has to be set to a relatively high value in order to include sufficient data to be able to build the population model of step 2. It should be noted that the 5% level for considering two predictions to be similar would, in most situations, be considered very strict and is certainly much smaller than the magnitude of the residual error, which in population analyses not seldom exceeds 25% (12).

The simulations show that the selected dosing history produced parameter estimates that were closer to the parameter estimates obtained when the true dosing history was used, compared to if either dosing history alone was used for all individuals. Especially, using either dosing history on its own resulted

Table II. Parameter Estimates from the Real Data Obtained When Altering the Subjective Choices in the Selection Procedure

	Selection				
	Basic one compartment model cutoff = 5%	Basic one compartment model cutoff = 20%	Basic two compartment model cutoff = 5%	Only MEMS	Only diary
CL[a] (L/h)	14.3 (3)	14.3 (4)	14.4 (3)	13.1[j]	14.7 (4)
Vc[b] (L)	57.7 (8)	62.9 (9)	57.9 (7)	92	66 (12)
Q[c] (L/h)	9.7 (12)	8.9 (14)	9.9 (11)	26	10 (23)
Vss[d] (L)	122.1 (18[k])	129.9 (22[k])	128.7 (15[k])	830	132 (24[k])
Ka[e] (h^{-1})	1.6 (20[l])	1.8 (24[l])	1.5 (20[l])	2.3	2.3 (26[l])
θ CRCL[f]	0.008 (20)	0.008 (23)	0.008 (19)	0.010	0.009 (23)
IIV[g] V (%)	38 (63)	34 (94)	29 (90)	95	31 (177)
IOV[h] F (%)	32 (23)	39 (29)	35 (20)	60	42 (33)
IOV Ka (%)	297 (33)	261 (33)	283 (26)	431	356 (58)
ε[i] (%)	6 (21)	7 (35)	5 (26)	23	10 (40)

Note: Figures in parentheses are %CV.
[a] For a subject with creatinine clearance of 84 ml/min.
[b] Central compartment volume of distribution.
[c] Inter-compartment clearance.
[d] Volume of distribution at steady-state.
[e] Absorption rate constant.
[f] Parameter relating creatinine clearance to CL.
[g] Inter-individual variability.
[h] Inter-occasion variability.
[i] Residual variability.
[j] It was not possible to estimate the standard errors in the data set with only MEMS dosing histories.
[k] The value refers to Vp = Vss − Vc.
[l] The value refers to θ = Ka − α, where α is the exponent of the first term in the bi-exponential model.

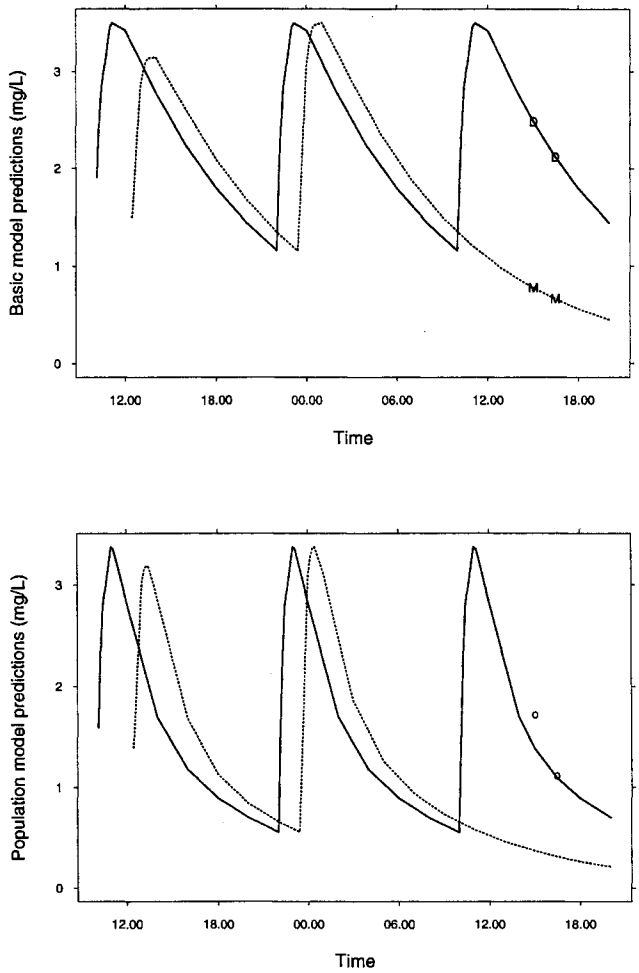

Fig. 4. The plot illustrates the selection in step 1 and step 3. The data is from a representative individual with the main difference between the two dosing histories being that the diary dosing history reports a morning dose the day of sampling while the MEMS dosing history does not. The top panel shows the predicted concentration-time profile (diary dosing history = solid line, MEMS dosing history = dashed line) from the basic one-compartment model for the day before and the day of sampling. Shown is also the predictions that are compared in this step (D = predictions based on the diary dosing history, M = predictions based on the MEMS dosing history). The lower panel shows the predictions based on the two-compartment population model built in step 2. The "o's" are the observed concentrations.

in considerably biased estimates for the variability in drug exposure (CL). Although the typical value for the pharmacokinetic behavior (including the covariate relationship) may be identifiable in the presence of noise from a partly erroneous dosing history, the same may not be true for identification of the concentration-response relationship. Large errors in individual pharmacokinetic parameter values, as seen in the simulations when only a single dosing history was available, may mask the relationships between exposure and response.

An implicit assumption in the suggested approach, is that the patients selected to CDH have similar pharmacokinetic characteristics to those in the non-CDH data sets. In other words, is there a correlation between true pharmacokinetic characteristics and dose history recording? Although this cannot be ruled out, it seems unlikely that the difference between the two groups should be so large that it resulted in erroneous selection. Further, at least in the real data set explored in this study, the demographic characteristics were similar for the two groups.

It is easy to envisage that an erroneous dosing history would increase the magnitude of the residual variability, but, in addition, it may also inflate inter-individual variability components due to the difference between the perceived and true intake. Since the selection in step 3 favors the dosing history that results in predictions that are the closest to the predictions from the typical individual in the population one could argue that the variability estimates could be shrunk not only to the true values but beyond. However, this was not observed in the simulations. Neither does it seem likely that the number of occasions is large where a considerably erroneous dosing history would be selected because the individual exhibits near-typical pharmacokinetic parameter values. However, the risk of such downward bias would be appreciable if the scheme was used to select between many, possibly hypothetical, dosing patterns.

An alternative strategy, if the analyst has enough previous knowledge to use a population model as starting point, is to start at step 3, with selection based on objective function value (or sum of weighted squared residuals) for the entire data set. A further possibility would be to use a mixture model (9,13), where both dosing histories were part of the model. Such a model includes a parameter for the fraction of the population for which the dosing history is best described by one of the dosing histories. It would also be possible to obtain individual estimates of the most plausible dosing history from such a model.

When two dosing histories are available, the dose recording behavior can be studied. Hypotheses about this behavior can be made based on differences between the records. If one method is assumed to provide the true dosing history, the errors made by the recording method can be clarified. However, as pointed out in the introduction, all methods have their drawbacks and none of them can be expected always to perform well. Using the proposed scheme yields information about which of two conflicting recordings that is the most believable. The limitation is, of course, that the method can only provide guidance when differences in recordings have an impact on the concentration predictions.

When discussing the relative performance of the dosing histories provided by the diaries and the MEMS, it is worth noting that the objective with the MEMS monitoring was to assess the compliance over the entire study period. The patients were not actively informed about the monitoring in an attempt to avoid affecting the compliance (the patients were, however, told about the nature of the MEMS lids if they asked). The diaries, on the other hand, were handed out to the patients the week before sampling to ensure a good dosing history for the analysis of the data. Nevertheless, the MEMS did not perform as well as could be expected in this study: information was not available from many of the visits and when the dosing histories conflicted, diary data proved more reliable. The most common reason seems to have been that morning doses taken were not recorded by MEMS. Although information about MEMS handling was not collected, one patient had a note in the case record form that she used to take out the morning tablet in the evening. This and other "mistakes" in MEMS handling by the

patients could probably have been avoided if they had been thoroughly informed about the recording system. The use of MEMS by uninformed patients seems not to provide a correct dosing history. The results we obtained during the analysis our real data set should not be extrapolated to the use of MEMS by informed patients, where the quality of the recording could be quite different. What can be concluded is that the MEMS and the true dosing histories are different in many uninformed patients.

When using the proposed method it is easily assumed that at least one of the two dosing histories provides a good estimate of the true dosing history. This is obviously not the case, e.g., consider two dosing histories that are both, to a large extent, incorrect. In that situation the selection procedure would tell us which of the two is the least incorrect, according to the selection criteria, which do not necessarily mean that the same selected dosing history will provide correct (or sufficient) information about the dose intake of the patient. In other words, the proposed method is not a substitute for careful recording of the dose intake and is not intended to reconstruct poorly documented doing histories.

In summary, we have presented a method for selection between rival dosing histories that can have a dual benefit: 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 assessed.

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