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Research Paper

Methods to Account for Inaccuracies in the Dosing History When Performing Population Pharmacokinetic Analysis

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Purpose. To develop and assess methods to account for missing dose history (MDH).
Methods. A simulation study was performed with different doses, dose times and formulations using NONMEM. Four methods were used to account for MDH, these were the ideal dose method (IDM) which uses the actual dose history, the concentration minimum method (CMM) which assumes that the nominal dose history is accurate, the extrapolation subtraction method (ESM) which estimates the residual concentration at the time of the study dose and the concentration time method (CTM) where the time of the previous dose event is estimated. The CTM is a new method.
Results. The CTM was superior to ESM and CMM and provided parameter estimates that were comparable in accuracy to the IDM.
Conclusions. When the nominal dosing history is available then the CTM is a simple and effective method to account for potential inaccuracies in the dose history.

KEY WORDS: missing dose history; population pharmacokinetics.

INTRODUCTION

The primary objective of pharmacokinetic-pharmacodynamic (PKPD) models is to provide a biologically plausible description, and prediction of future time course of drug effects. Understanding the time course of drug effects will provide the necessary knowledge about optimal doses and dosing regimens. One of the major hurdles in achieving this objective is inaccuracies in the data used to create PKPD models. In particular this relates to inaccuracy in the reported dosing histories (1).

In some circumstances a full dosing history may be present but inaccurate as a function of misinformation, due to accidental or deliberate non-compliance, or be missing either completely or partly due to poor record keeping or inability to locate the (appropriately kept) records. The latter censored dose records may occur after a deliberate overdose in circumstances where the patient may be unable to provide/recall information about their previous dosing record. For the purposes of this work we lump these two types, misinformation and missingness and refer to them collectively as *missing dose history* (MDH). It should be noted that all clinical PK studies are likely to incur some level of MDH.

In the case of outpatient clinical studies various methods are generally used to assess a patients' compliance to a prescribed dosage regimen, including pill counts and electronic monitoring systems (MEMs) (2,3). However, only MEMs provides an accurate measure of dosing history and then only for accidental non-compliance (4). Such systems are not common place for most clinical studies.

Remedies have been proposed to deal with MDH. Friberg *et al.,* Soy *et al.* and Gupta *et al.* illustrated methods to determine unbiased PK parameter estimates for data where MDH was identified (5–7). A limitations of these methods is the assumption that the drug input (e.g. via absorption) is complete before the reference/study dose is administered. This may not be true in all clinical settings. This is particularly true case of studies of deliberate overdose, where the dose event is an impulsive act that may occur any time after the regular dose (5). So, if the overdose is consumed before absorption of the regular dose is complete the assumption made in the existing methods would lead to biased estimates of the PK parameters. This limitation is also likely to be true for therapeutic use of extended release (XR) formulations.

The aim of the current study is to develop and assess a general method to account for missing dose history allowing accurate estimation of parameters in population pharmacokinetic studies.

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ABBREVIATIONS: BSV, between subject variability; *CL*, clearance; CMM, concentration minimum method; CTM, concentration time method; D_o, over/study/reference dose; D_p, prescribed dose; ESM, extrapolation subtraction method; IR, immediate release; IDM, ideal dose method; K_a, absorption rate constant; MDH, missing dose history; MEM, electronic monitoring systems; PE, percentage error; PKPD, pharmacokinetics pharmacodynamics; RUV, residual unexplained variability; T_o, over/study/reference dose time; T_p, prescribed dose time; *V*, volume of distribution; XR, extended release; τ, dose interval.

MATERIALS AND METHODS

We approached our goal through simulation. In this section we detail the simulation plan, methods of accounting for MDH and measures of method performance.

The motivating example for this work was the analysis of PK data for venlafaxine that arose after an overdose event. Most of the patients were on long term treatment with venlafaxine and would be expected to have reached steady state when the overdose event took place. Patients were either receiving immediate release (IR) or XR formulations of venlafaxine. Similarly both formulations were represented in the overdose event. The key feature of overdose, which makes it an ideal test case for these methods, is the lack of certainty about the amount and timing of the study dose in relation to the previous therapeutic regimen. The only information available about the MDH was the nominal prescribed dose and dosing interval. It is believed under these circumstances that standard methods handling missing dose data, e.g. ESM (6) or assuming the exact dose history may perform poorly. Hence a new method where the time of study dose with respect to previous dose is estimated as a parameter was developed. All of these methods are described in detail in section "Accounting for missing dose history".

Simulation Plan

The simulation plan included the assumed clinical scenario, structural and statistical models used for simulation, and the values of parameters used for simulation.

Clinical Scenario

A hypothetical drug was chosen. It was assumed to be available in two different formulations *viz*., IR and XR. In case of IR formulations the (over)dose is generally ingested in the disposition phase of the previous dose, whereas in XR formulation the (over)dose may be ingested during the absorption phase of the previous dose. The defined daily dose of the drug was D_p (100 U) to be administered once daily orally (the dose interval (τ)=24 h) at the nominal prescribed times (T_p). All patients were assumed to be at steady state before the study dose event occurred. On the day when the study dose is self-administered, which in this case happens to be an overdose event, the patient may have consumed a nominal dose (D_o) that could be same or many times bigger than D_p. We considered four different dose levels 1, 5, 10 and 20 times D_p. A nominal dose $D_o=1\times D_p$ refers to a therapeutic dosing (for example as may be the case in a clinical trial). While 5, 10 and $20\times D_p$ represents the overdose. We also considered that the patient ingested the (over)dose at any time (T_o) in the previous dose interval i.e. $T_{p(i-1)}<T_o<T_{p(i)}$. We studied four different times at which the (over)dose was ingested at each of the above dose levels. These were at 1/4, 1/2, 3/4 and 1 times T_p. At $1\times T_p$ the (over)dose would have been taken at exactly the time when the next dose would have been due. Note also that the methods provided could easily be extended to give a general solution for unknown dose time; e.g. when $T_o=0\times T_p$ the patient would have taken 2 doses at the same time, conversely when $T_o=2\times T_p$ the patient would have missed the previous dose.

Thus a total of 32 different case scenarios were studied which differed at three levels in terms of formulation, dose and dosing time. Fig. 1 represents the factorial design of the simulations.

Population PK Model

In this section we describe the structural and statistical models used for simulation.

Structural Model

The drug was assumed to follow a one-compartment PK model with first-order absorption and elimination. The PK parameters that describe the time course of drug concentration were the clearance (CL), volume of distribution (V) and absorption rate constant (K_a).

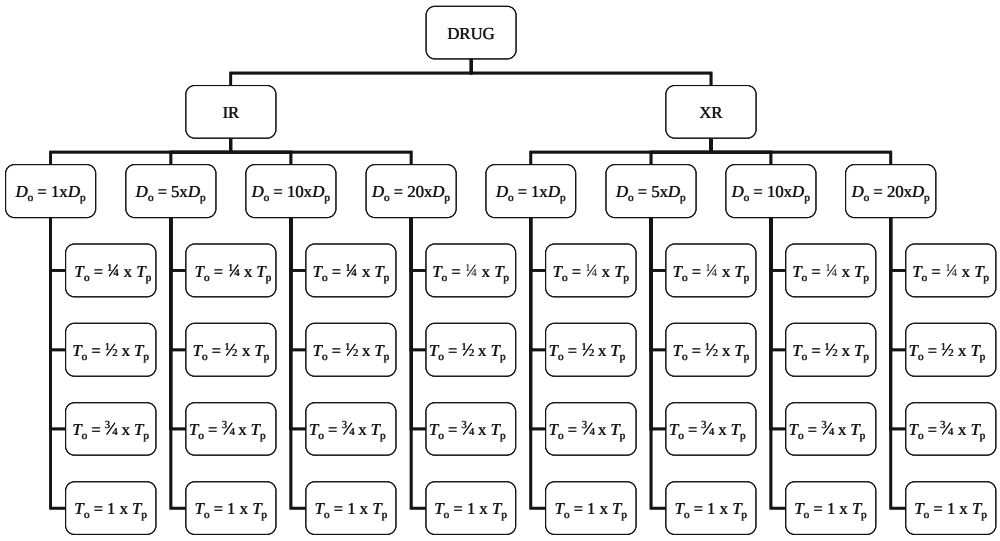

Fig. 1. A factorial design of all simulation conducted.

Statistical Model

For each of the studies, the model for the residual variability in the observed drug concentration was assumed to be mixed error with an additive and exponential component as shown in Eq. 1:

$$y_{ij} = \hat{y}_{ij} \times \exp(\varepsilon_{ij,1}) + \varepsilon_{ij,2} \quad (1)$$

where, y_{ij} was the observed concentration for jth observation and ith subject and $\hat{y}_{ij}$ was the corresponding model predicted concentration; and ε_{ij} was the difference between the observed and predicted concentration. It is assumed that $\varepsilon_{ij,1}$ and $\varepsilon_{ij,2}$ were independent and identically distributed and described by a normal distribution with a mean zero and variance σ_1^2 and σ_2^2, respectively.

An exponential between subject variability model was used to describe the individual PK parameters $\boldsymbol{\theta}_i$. These were described as a function of population average value θ and between subject difference $\boldsymbol{\eta}_i$:

$$\boldsymbol{\theta}_i = \boldsymbol{\theta} \times \exp(\boldsymbol{\eta}_i). \quad (2)$$

Simulation Parameters

The structural parameters for the simulation were selected in such a way that the overall accumulation was close to two when the concentrations after a single dose were compared to those at steady state for both IR and XR formulations. The half-life of the drug was equal to the dosing interval τ. The K_a of the drug was assumed to be 1 for the IR formulation and 0.1 for the XR. The between subject variability (BSV) was assumed to be 25% of population mean parameter value and residual unexplained variability (RUV) was 15% and 30% for exponential component and additive component of the RUV, respectively as per Soy *et al.* (6). Here the additive component is expressed as a percent of the average concentration. The correlation between the parameters was assumed to be 50%. The additive component of RUV was fixed and was not estimated. All parameters used for simulation are listed in Table I.

The number of individuals per study, number of samples per individual and the schedule of sampling points were determined using WinPOPT (8). Effort was made to make the design equally informative for both the formulations. The upper bound of the criteria used to choose the design was that the percent standard error of the fixed and random effects parameters was less than or equal to 10% and 30%, respectively for both the IR and XR formulations. This will result in a design that is similarly informative for parameter estimation for both formulations. The design was constrained to have the same sampling times for both formulations. From the results of the study, the number of individuals per study was 50 and 100 for IR and XR formulation respectively. The number of sampling points was 6 samples at 0.01, 0.5, 4, 8, 24 and 48 h post dosing.

All the data sets were simulated and estimated using NONMEM V (level 1.1) with first order conditional estimation and interaction (9). We replicated each study 200 times. Using 200 replicates will give a standard error of 3% (approx) on 25th and 75th percentiles of parameter estimates. All simulations were done using IDM (described in the methods of analysis section), but analysed using different methods. (All methods are described in the next section). A single control stream was used for both simulation and estimation.

Table I. Parameter values used in simulation of data

Parameter	IR	XR
CL	1	1
V	34.2	34.2
K_a	1	0.1
ω^2_{CL}	0.0625	0.0625
ω^2_{V}	0.0625	0.0625
$\omega^2_{K_a}$	0.0625	0.0625
Cov (CL,V)	0.03125	0.03125
Cov (CL,K_a)	0.03125	0.03125
Cov (V,K_a)	0.03125	0.03125
σ_1^2	0.0225	0.0225
σ_2^2	0.09	0.09

Cov: covariance

Accounting for Missing Dose History

The nominal dose (D_o) was considered to be known in all the methods. This is because there are methods available to deal with uncertainty in dose. Friberg *et al.* has used veracity scale on reported dose to calculate the uncertainty in the dose to estimate the overdose PK parameters of citalopram (5).

We used three general methods to account for the MDH. All the methods are shown in Fig. 2. The figure depicts how each method analyses the observed data when $D_o = 1 \times D_p$ and $T_o = 1/4 \times T_p$ in case of XR formulation. The study dose was ingested in the absorption phase (6 h after the prescribed dose) of the previous dose (K_a for XR formulation is 0.1 h. So, absorption half life $= 0.693/K_a = 6.93$ h). A clear description of all the methods is given in the following text.

1. *Complete information about dose history is known*: When complete information about the dose history is known, an ideal dose method can be used.

Ideal dose method (IDM) (6). The ideal dose method uses the true dose history of the patient i.e. in this case simulated values of T_p, D_p, T_o and D_o. This is not a "true" method, since the exact dose history is never known. Here the IDM will be the reference method. This method is also used to simulate all data. The method is shown in Fig. 2a. In this method the complete (and exact) information about dose history is know. When exact dose history is used unbiased estimate of parameters is possible.

2. *Partial information about dose history is known:* When dose history is known to extent of knowledge of the prescribed but not actual dose and dosing interval, the concentration minimum method (CMM) or concentration time method (CTM) can be used.

Concentration minimum method (CMM). This method is depicted in Fig. 2b. The method assumes that study dose was

ingested at the time the next dose was due, i.e. $T_o = T_p$. Hence the residual concentration from previous doses at the time of overdose is equal to the minimum concentration at steady state and is estimated for each individual. The residual concentration was then allowed to change at the same rate as would be predicted by the model for each individual i.e. the residual concentration followed a standard absorption and disposition phase. The observed concentrations are then modelled as the sum of the model predicted residual concentration and the model predicted concentrations after the study dose D_o.

This method is the IDM when $T_o = T_p$ and hence represents the normal assumption in clinical practice. However when $T_o \neq T_p$ it is expected that the method will experience some level of bias.

Concentration time method (CTM). This is a new method. In this method the study dose was assumed to occur at an unknown time T_o. This time is estimated for each individual during the modelling process. The residual concentration (C_T) in each compartment from any of the previous therapeutic dose at this time T_o is then estimated. Then C_T was allowed to increase and/or decay as per the model prediction for each individual. The observed concentrations are then modelled as the sum of the model predicted residual concentration and the model predicted concentration after the study dose D_o.

The method estimates the time at which study dose was ingested (T_o) in relation to the previous dose history, where $T_{p(i-1)} < T_o < T_p$. The method also allows for the remaining amount of drug from the depot compartment to be absorbed.

This method is depicted in Fig. 2c. A control stream for CTM is shown in Appendix.

3. *No information about dose history is known:* When no information is known about the MDH the extrapolation subtraction method can be used. The method ignores the unknown dose history.

Extrapolation subtraction method (ESM) (5). In the ES method the details of unknown dose history is completely ignored. Instead, the residual concentration (C_T) from any previous therapeutic dosing at T_o was estimated as a parameter in the modelling process. The residual concentra-

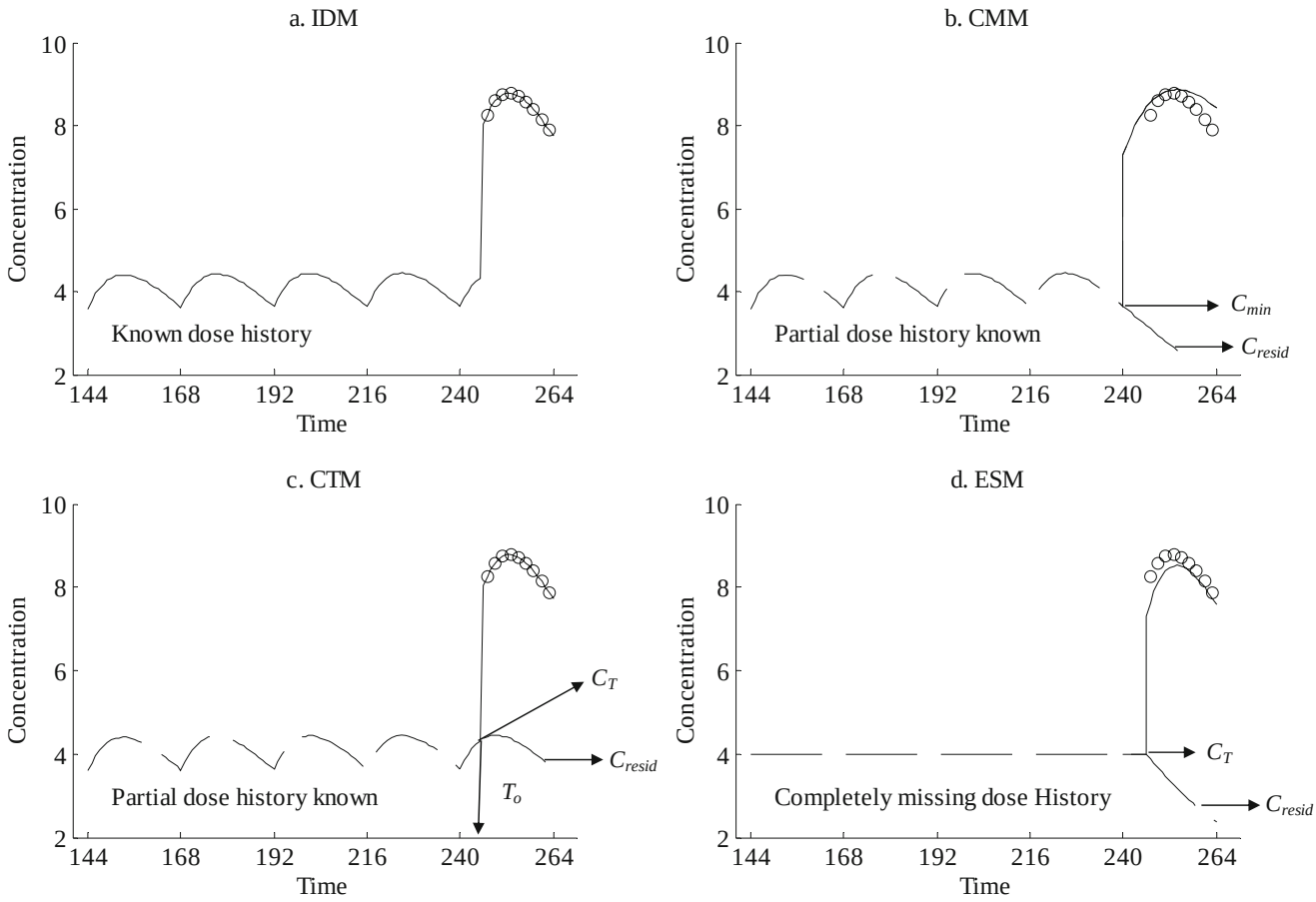

Fig. 2. The four different methods IDM, ESM, CMM and CTM are represented. In all the graphs $D_o = 1 \times D_p = 100$; T_p=24 h; $T_o = 1/4 \times T_p$. The *solid line* is the model fit, the *open circles* are the observed data; the *dashed line* represents the imputed data. **a** IDM; the dose history is known. **b** CMM. The method assumes $T_o = T_p$, partial information about previous dose history is used to impute C_{min}. C_{resid} is the change in C_{min} calculated using parameters from fitting the observed data. **c** CTM. The method estimates the time of dose after the previous dose (T_o) as a parameter. C_T is the concentration in the plasma (amounts in other compartments are also imputed but not shown here) at T_o predicted from the prescribed dose and dose time. C_{resid} is the change in C_T using estimated parameters from observed data. **d** The ESM method ignores the dose history. The concentration is estimated in the plasma at the time of the study dose as a parameter (C_T). C_{resid} is the decay phase of C_T.

tion was then allowed to decay according to model prediction for the disposition phase for each individual i.e. in this case curve equal to $C_{resid} = \widehat{C}_T \times \exp((-CL/V) \times (t - T_o))$. The observed concentrations are then modelled as the sum of model predicted residual concentrations and the model predicted concentrations after the study dose D_o. This model is shown in Fig. 2d.

In all cases subtraction of the predicted residual curves from the total predicted curve provides the apparent real predicted concentration *vs* time curve.

Criterion for Estimating Method Performance

The bias of the estimates of population PK parameters is expressed in terms of percentage error (PE); the PE is calculated using Eq. 3:

$$\mathrm{PE} = \frac{\widehat{P} - \overline{P}}{\overline{P}} \cdot 100 \tag{3}$$

where $\widehat{P}$ and $\overline{P}$ are the estimated and true values, respectively of the parameter.

In each of the 32 cases, the bias of estimate of all the population PK parameter was calculated as percentage error. Population parameters obtained from all the data sets were used in calculation of PE value.

RESULTS

All the 200 replicated data sets of the 32 case scenarios were estimated using the four different methods to account for missing dose history (IDM, CMM, CTM and ESM). For each parameter the percentage error (PE) values obtained from the IDM were used as a reference with which all the other methods were compared. IDM uses the exact dose history and hence gives the best possible estimate of parameters for the given design.

Figs. 3, 4, 5 and 6 provide estimates of the prediction error for CL, V, K_a, ω^2_{CL} , ω^2_v , $\omega^2_{K_a}$ and σ^2_1 (σ^2_2 is fixed and hence not shown) for all methods with IR and XR formulations at different dose levels and dose times when

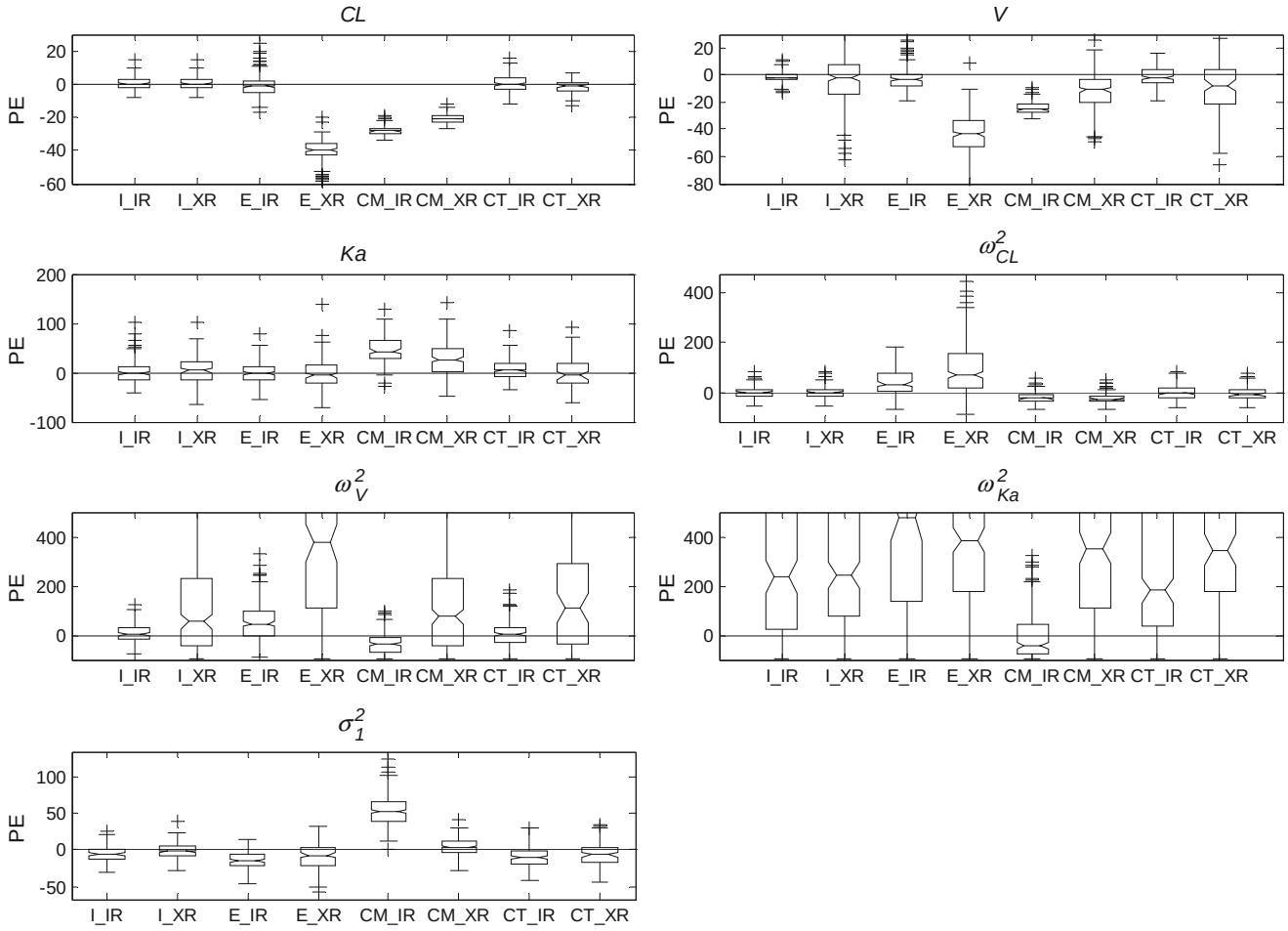

Fig. 3. Boxplots of percentage error for all parameters for IR and XR formulation at $D_o = 1 \times D_p$ *and* $T_o = 1/4 \times T_p$. *Structural parameters* clearance (CL), volume of distribution (V), absorption rate constant (K_a). *Statistical parameters* between subject variability (BSV) for CL $\left(\omega^2_{CL}\right)$, V $\left(\omega^2_V\right)$ and K_a $\left(\omega^2_{K_a}\right)$. Residual unexplained variability (RUV) for data $\left(\sigma^2_1\right)$. The *horizontal line* within each subplot is the zero percentage error line. The *notch* in the centre of each box marks the median (50th percentile), the *box boundaries* are at the 25th and 75th percentile, and the *limits of the whiskers* are at the 10th and 90th percentiles (not all whiskers are shown). I ideal dose method, E extrapolation subtraction method, CM concentration minimum method, CT concentration time method, IR immediate release, XR extended release.

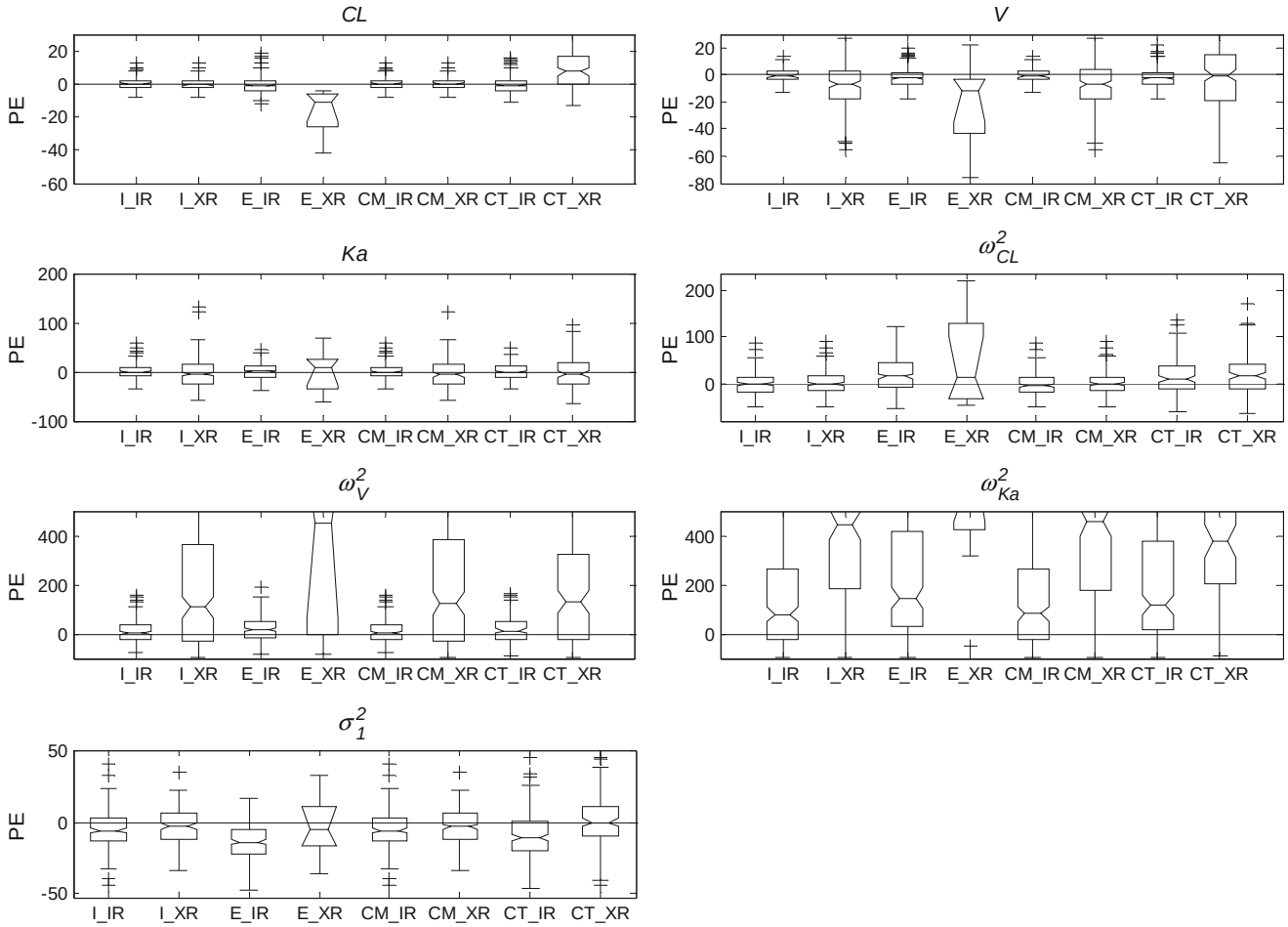

Fig. 4 Boxplots of percentage error for all parameters for IR and XR formulation at D_o=1×D_p and T_o=1×T_p. *Structural parameters* clearance (CL), volume of distribution (V), absorption rate constant (K_a). *Statistical parameters* between subject variability (BSV) for CL $\left(\omega^2_{CL}\right)$, V $\left(\omega^2_V\right)$ and K_a $\left(\omega^2_{K_a}\right)$. Residual unexplained variability (RUV) for data $\left(\sigma^2_1\right)$. The *horizontal line* within each subplot is the zero percentage error line. The *notch* in the centre of each box marks the median (50th percentile), the *box boundaries* are at the 25th and 75th percentile, and the *limits of the whiskers* are at the 10th and 90th percentiles (not all whiskers are shown). I ideal dose method, E extrapolation subtraction method, CM concentration minimum method, CT concentration time method, IR immediate release, XR extended release.

$D_o = 1 \times D_p$ and $T_o = 1/4 \times T_p$; $D_o = 1 \times D_p$ and $T_o = 1 \times T_p$; $D_o = 20 \times D_p$ and $T_o = 1/4 \times T_p$ and $D_o = 20 \times D_p$ and $T_o = 1 \times T_p$ respectively. Where, D_p and T_p are the prescribed dose and dose time, D_o and T_o are the study/reference dose and dose time. The extreme doses and dose times are shown here as they represent the boundary conditions of the simulated scenarios, the results of other combinations of doses and dose times fall in between these findings (results not shown).

When compared for dose times, all the methods perform better when T_o=1×T_p, when compared with T_o=1/4×T_p. We observe from the complete set of results of other intermediate dose times (not shown here) that as T_o approaches T_p performance of all the methods improve. The performance of CTM and ESM improved significantly as T_o approaches T_p. Whereas CTM performed well in all circumstances and hence showed minimal improvement under this condition. Note that the CMM makes the assumption that the time of the study dose (T_o) occurs at the time it was expected to occur (T_p) and hence when T_o=T_p, CMM=IDM (Figs. 3 and 4 and Figs. 5 and 6).

When we compare the results at different doses (Figs. 3 and 5 and Figs. 4 and 6), it is evident that all the methods perform better (including IDM) when D_o=20×D_p (Figs. 4 and 5) compared to D_o=1×D_p (Figs. 3 and 4). This was seen irrespective of the method and irrespective of the formulation (IR or XR).

If we consider, therefore the most challenging scenario, when $D_o = 1 \times D_p$ and $T_o = 1/4 \times T_p$, then significant differences are evident between the methods (Fig. 3). The CTM performs well with both IR and XR formulation. The CMM which is the common clinical assumption gives biased estimates of parameters with both the formulations. ESM performs well with IR formulation, but gives a biased estimate of parameters with XR formulations. Identical findings can be observed with all the methods when $D_o = 20 \times D_p$ and $T_o = 1/4 \times T_p$, except that ESM performs better with XR formulations at higher dose.

It is noted that all methods performed poorly for estimation of the between subject variance of K_a, including the IDM.

DISCUSSION

Accurate estimation of PK parameters from multiple dose PK data in theory requires complete knowledge of dose history. But unfortunately all clinical PK studies are subject to some level of inaccuracies in the dosing history. Here we use a general

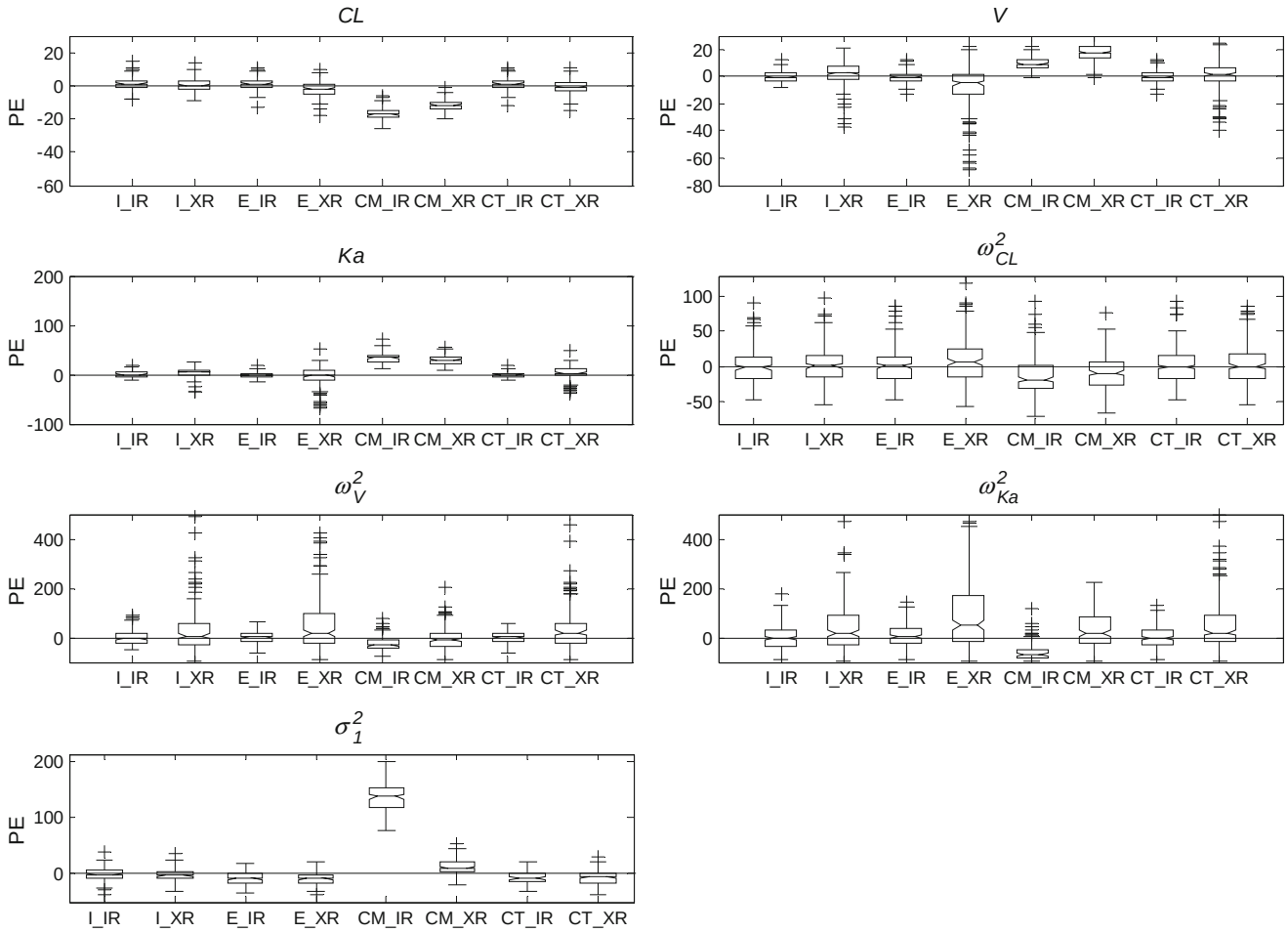

Fig. 5 Boxplots of percentage error for all parameters for IR and XR formulation at $D_o=20\times D_p$ and $T_o=1/4\times T_p$. *Structural parameters* clearance (CL), volume of distribution (V), absorption rate constant (K_a). *Statistical parameters* between subject variability (BSV) for CL $\left(\omega^2_{CL}\right)$, V $\left(\omega^2_V\right)$ and K_a $\left(\omega^2_{K_a}\right)$. Residual unexplained variability (RUV) for data $\left(\sigma^2_1\right)$. The *horizontal line* within each subplot is the zero percentage error line. The *notch* in the centre of each box marks the median (50th percentile), the *box boundaries* are at the 25th and 75th percentile, and the *limits of the whiskers* are at the 10th and 90th percentiles (not all whiskers are shown). I ideal dose method, E extrapolation subtraction method, CM concentration minimum method, CT concentration time method, IR immediate release, XR extended release.

phrase, missing dose history, to include partial or complete loss of the dosing history (whether the loss is accidental or purposeful). In this report we illustrate the use of methods that are tailored to the amount of information available about the MDH. We show how the performance of each method is dependent on the dose, dosing regimen and formulation. The results from this work shows the proposed CTM provides acceptable estimates of parameters in all the scenarios studied.

The CTM is new method to this work. The requirement of this method is knowledge of the prescribed (nominal) dose history, rather than the actual dose history. The method then allows for uncertainty in the dose time. This is achieved by estimating the study dose time (T_o) as a parameter for each individual. The method then accounts for drug remaining in the depot compartment from any previous doses to be absorbed during the current dose. These properties of the method allow it to find wide application in outpatient clinical trials, in the overdose setting and in those circumstances where extended release formulations have been taken. It should be noted here that as T_o approaches T_p then this is equivalent to the patient having taken 2 doses simultaneously, while as T_o approaches 0 then the previous dose would have been missed.

The usual method used in most modelling projects relies on the assumption that the patient is compliant and the next dose was taken at the nominal dose time (CMM). Results from the simulation studies show that when $T_o<T_p$, the CMM performs poorly in both IR and XR formulations. This is because the method always assumes that the T_o occurs at T_p, and calculates the amount of drug in the central and depot compartments at the this time. This amount will be much less than the actual amount in the central compartment when $T_o<T_p$. The most commonly used method to formally handle MDH is the ESM. The ESM performs well for IR formulations but, as expected, poorly with XR formulations. The reason for this is that in case of XR formulations ($K_a=0.1$ in our example) the time taken for 50% of the drug to reach the central compartment is a considerable proportion of the dose interval (in our case approximately 7 h). So, when the next dose is administered at 6 h after the previous dose is administered (i.e. $T_o=1/4\times T_p$) almost 50% of drug from previous dose remains in the depot compartment when D_o is administered, and this amount of drug is not accounted for in the model.

The performance of all the methods improved when $D_o>D_p$. The reason for this may be because the baseline

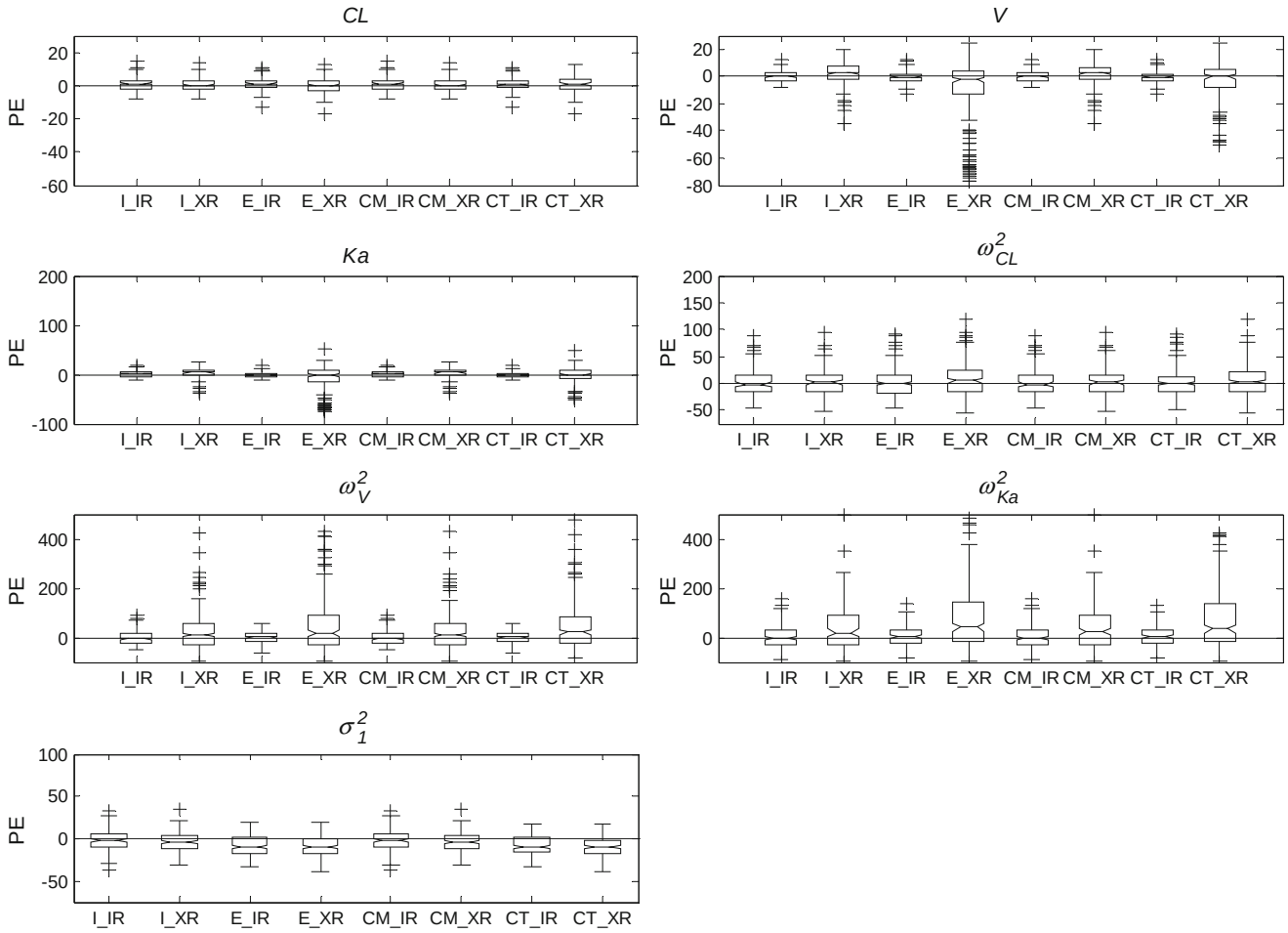

Fig. 6 Boxplots of percentage error for all parameters for IR and XR formulation at $D_o=20\times D_p$ and $T_o=1\times T_p$. *Structural parameters* clearance (CL), volume of distribution (V), absorption rate constant (K_a). *Statistical parameters* between subject variability (BSV) for CL $\left(\omega^2_{CL}\right)$, V $\left(\omega^2_V\right)$ and K_a $\left(\omega^2_{K_a}\right)$. Residual unexplained variability (RUV) for data $\left(\sigma^2_1\right)$. The *horizontal line* within each subplot is the zero percentage error line. The *notch* in the centre of each box marks the median (50th percentile), the *box boundaries* are at the 25th and 75th percentile, and the *limits of the whiskers* are at the 10th and 90th percentiles (not all whiskers are shown). I ideal dose method, E extrapolation subtraction method, CM concentration minimum method, CT concentration time method, IR immediate release, XR extended release.

concentrations from the previous doses are negligible in comparison with the observed concentrations after a large study dose. In addition the effect of any additive residual error is minimized when the dose is large.

Both the CTM and ESM include the estimation of an additional fixed effect parameter with associated random effect. The disadvantage of the ESM method is that the single parameter corresponds to the central compartment and ignores other compartments that are not at equilibrium. It is of course possible to generalise the ESM method to include other disposition compartments under the assumption of equilibrium with no additional cost of extra parameters to estimate. A logical extension of the ESM method would include estimation of the amounts of drug in the central and depot compartment as parameters and assume equilibrium for the disposition compartments. Under these conditions (of steady state), this would be expected to be as flexible as the CTM. The benefit of an extended ESM method is the applicability to settings where there is a complete absence of previous dosing history although at the added cost of at least two additional parameters more than CTM.

The common clinical practice is to use the CMM (which is equivalent to IDM when $T_o=T_p$), i.e. to assume that the patient has accurately followed the prescribed dosage regimen. This method would on average be expected to work acceptably when the missing dose history is due to random inaccuracies and accidental missing dose histories. In this case the dosing errors would be incorporated into the residual uncertainty. But, when the missing dose history is not random (e.g. deliberate) as is in the scenarios considered here then CMM will yield biased parameter estimates. In contrast, the CTM would be expected to be less affected by non-random deviations in the dosing history, since the timing of the study dose is estimated. Empirically this finding is supported by the study results shown here.

CONCLUSION

In summary, when the nominal dosing history is available then the CTM is a simple and effective method to accommodate for potential inaccuracies in the dose history. In the event where ever the nominal dose history is missing the ESM can be used.

APPENDIX

```
$PROB Missing dose data
$INPUT ID TIME AMT DV MDV FLAG TP                  ;TP is time passed dose
$DATA ..\filename.csv IGNORE=#
$SUBR ADVAN2 TRANS2
$PK
IF(AMT.GT.0.AND.FLAG.EQ.3) THEN                    ;Uses the dose history during
   DOSE=AMT                                        ;simulation and ignores during
ENDIF                                              ;estimation
IF(FLAG.EQ.1.AND.ICALL.NE.4)THEN
   F1=0
ENDIF
IF(FLAG.EQ.2.AND.ICALL.NE.4)THEN
   F1=1
ENDIF
IF(FLAG.EQ.3.AND.ICALL.NE.4)THEN
   F1=0
ENDIF
IF(ICALL.EQ.4)THEN
   F1=1
ENDIF
CL=THETA(1)*EXP(ETA(1)
V=THETA(2)*EXP(ETA(2))
KA=THETA(3)*EXP(ETA(3))
DT=THETA(4)*EXP(ETA(4))                            ;DT is the time of ;dosing of
                                                   ;study dose
K=CL/V
ND=11                                              ;Number of previous doses
S2=V
TAU = 24                                           ;Dose interval
IF(ICALL.EQ.4) THEN                                ;During simulation CT is zero,
   CT = 0                                          ;during estimation CT is
ELSE                                               ;estimated from the equation
   A=(DOSE*KA)/(V*(KA-K))
   B=(1-EXP(-ND*K*TAU))/(1-EXP(-K*TAU))
   C=(1-EXP(-ND*KA*TAU))/(1-EXP(-KA*TAU))
   CT = A*(EXP(-K*(DT+TP))*B-EXP(-KA*(DT+TP))*C)
ENDIF
S2=V
$ERROR
Y=(F+CT)*EXP(EPS(1))+EPS(2)
IPRED=F
$THETA
(0.1,1)
(1,34.2)
(0.001,0.1)
(0.001,6)
$OMEGA BLOCK(4)
0.0625
0.03125 0.0625
0.03125 0.03125 0.0625
0.03125 0.03125 0.03125 0.0625
$SIGMA
0.0225
0.09 (FIXED)
$SIMULATION
(6457503)
SUBPROBLEMS=200
$ESTIMATION
MAXEVAL=9999 METHOD=1 PRINT=1 SIG=3 NOABORT
INTERACTION
$TABLE
ID TIME AMT DV IPRED CL V KA
NOPRINT ONEHEADER FILE=data.fit
```

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