Modelling pre-dose concentrations in steady-state data in presence of between-occasion variability and poor adherence.

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Background and Objectives

In large Phase III/IV studies, data are often obtained from outpatients and record of previous doses are missing or based on patient-reported times, which may be imprecise or unreliable.

The PK of many drugs is subject to diurnal variation, meal-dependent absorption, BOV , etc.

This leads to large variability in pre-dose sample concentrations, which needs to be properly accounted for.

In this work we evaluate several methods to do so.

Methods

A published model [1] was used to simulate nevirapine concentrations after a once daily 400 mg dose of nevirapine, a drug used in HIV treatment, in 250 patients with samples at -0.5 (pre-dose), 0.5, 1, 2, 3, 5, 8, and 12 hours.

The majority of simulated patients were adherent (dose within 3 hours from declared time), but commonly encountered scenarios were simulated:

- poor or no adherence to protocol (e.g. 1 or more missed doses),
- incorrect reported dosing times (e.g. evening instead of morning)
- and BOV in bioavailability (F) (i.e. ~20%).

Different approaches to model such data were tested:

- assuming steady-state and adherence to protocol (C_0=C_{24}) and excluding (P1) or including (P2) pre-dose concentrations in the fit
- using BOV for F and treating each dose as a separate occasion (P3)
- modelling the pre-dose concentrations as baseline [2]:
  - distributed in the population with Typical Value (TV) and BSV [3] (P4),
  - each one distributed with RUV around the measured concentration (P5)
  - distributed between a TV and the observed concentrations, taking into account both BSV and RUV (P6)
  - assuming the measured pre-dose value as correct (P7)

A "cheater" model – knowing the correct dosing information - was also fitted for comparison (P0).

Results

Population Parameters. When adherence to protocol and steady-state is assumed (P1-P2-P3), the BSV for the PK parameters is not well estimated and an inflated level of additive RUV is detected in the data.

The naive inclusion of pre-dose samples in the fit (P2), with respect to their exclusion from the dataset (P1), further overestimates the additive RUV, and the BSV of CL/F. The introduction of BOV in F (P3) absorbs part the BSV of the PK parameters (especially V/F), but does not improve the results.

The baseline approaches (P4-P5-P6-P7) provide more accurate estimates of both TV and BSV and often approach the performance of P0 – which "knows" the actual time of all doses and can thus be considered as a lower bound. P4 and P7 overestimate the additive RUV, and P4-P5-P6 slightly underestimate the BSV of ka and CL/F.

	ka	CL/F	V/F	ADD	PROP	BSV ka	BSV CL/F	BSV V/F	corr CL-V
P1	-6%	6%	-2%	60%	-3%	29%	29%	8%	84%
P2	-8%	7%	-2%	173%	-14%	13%	40%	-4%	13%
P3	-7%	8%	-1%	151%	-13%	12%	31%	-25%	27%
P4	3%	-2%	3%	89%	-6%	-10%	-16%	5%	13%
P5	2%	1%	3%	7%	1%	-11%	-11%	-1%	9%
P6	2%	-1%	0%	60%	-7%	-11%	-11%	-3%	-22%
P7	2%	4%	4%	8%	1%	-4%	2%	11%	48%
P0	-2%	1%	-1%	-22%	2%	-7%	2%	-4%	0%

Table 1. *Accuracy (bias) of the population parameter estimates obtained from simulation and estimation of 500 datasets.*

	ka	CL/F	V/F	ADD	PROP	BSV ka	BSV CL/F	BSV V/F	corr CL-V
P1	8%	6%	5%	64%	5%	34%	29%	16%	88%
P2	9%	7%	3%	173%	14%	21%	40%	8%	21%
P3	8%	9%	3%	152%	13%	20%	32%	28%	37%
P4	6%	5%	5%	91%	7%	19%	28%	8%	52%
P5	6%	4%	4%	29%	3%	19%	18%	7%	36%
P6	5%	4%	4%	62%	8%	21%	28%	8%	68%
P7	5%	6%	5%	29%	3%	15%	11%	13%	54%
P0	5%	3%	3%	27%	3%	15%	6%	8%	19%

Table 2. *Precision (RMSE) of the population parameter estimates obtained from simulation and estimation of 500 datasets.*

Individual Parameters. The individual results confirm the trends previously found.

P1-P2 and P3 yield the least precise results, while the baseline estimation techniques (P4-P5-P6-P7) approach the performance of the "cheater" method (P0) for ka and V/F, and they also provide more reliable estimates of CL/F.

	ka	CL/F	V/F
P1	31%	35%	30%
P2	31%	41%	22%
P3	31%	37%	24%
P4	29%	26%	21%
P5	29%	23%	19%
P6	29%	23%	24%
P7	29%	22%	21%
P0	29%	12%	19%

Table 3. *Precision (RMSE) of individual parameters obtained by averaging the results on 3 randomly selected datasets.*

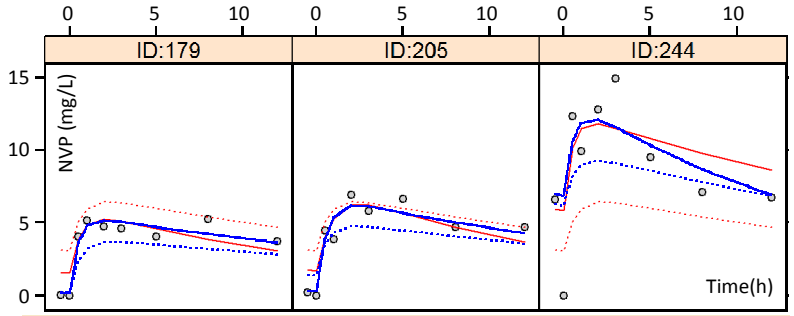

Figure 1. *graphical depiction of the model fit for selected non-adherent patients. Individual (solid line) an d population predictions (dotted) for P2 (red) and P5 (blue).*

Conclusions

Variability in pre-dose concentrations should be appropriately accounted for.

Naive approaches (P1-P2) lead to poor estimation of the level of error in the data (RUV), and BSV of the PK parameters.

The pre-dose concentration is not informative enough to allow estimation of BOV (P3), whose introduction does not solve the estimation problems.

Baseline estimation methods (P4-P5-P6-P7) can overcome these estimation problems and greatly improve the fit, especially for poorly adherent subjects.

P4 has been suggested as golden standard before [3], but P5 performs just as well (if not better), while using only 1 parameter and without making assumptions on the population distribution of the pre-dose concentrations. P7 also performs well, but it is expected to be sensitive to error in the pre-dose values. P6 is complicated to implement, not computationally robust and does not seem to offer advantages over the other alternatives.

Further investigation will be necessary to compare the proposed methods and fathom the effect of factors such as the size of measurement error and the sampling schedule.

References and Acknowledgements

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