

SHORT STUDY REPORT

Title: Retracing compliance patterns from blood samples: a comparison with medication event monitoring system recordings

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Objectives

We developed a method that attempts to retrieve how patients have used their medication from blood samples. We wished to evaluate the performance of our method by comparing its output to data from Medication Event Monitoring System (MEMS, AARDEX Ltd, Union City, CA, USA). If possible, we further wished to improve the performance of the method by: 1) testing various blood sampling strategies from the study's data points, or 2) using basic patient characteristics to narrow down the method's level of uncertainty due to inter-individual variability.

The obtained data from Abbvie

Data was collected during a phase II, multi-country and multi-center trial. The aim of the study was to evaluate the safety, tolerability and pharmacokinetics of Kaletra, a drug combining Lopinavir and Ritonavir. There was a total of 35 participants, separated in 2 groups, one group taking 800/200 mg qd and the other taking 400/100 mg bid. The pills were self-administered with food. Dense and trough blood samples were obtained. A total of 7 blood samples were taken for those in the qd regimen, at day 21, at 0, 2, 4, 6, 8, 12 and 24 hours post-dose. All participants provided trough concentrations at weeks 8, 16, 24 and 48. Adherence was measured by a device monitoring the opening of bottles containing the drug (MEMS, AARDEX). The device returned the date and time the bottles were opened.

Method and analysis

The method that allows to retrace how individuals used their medication before a blood sample is described in Barriere *et al.*[1] The procedure relies on a population or individual-specific PK model. We planned on using the dense concentration data to obtain a first population-PK model. We also planned on using Bayesian estimates of individual parameters in order to obtain individual-specific PK models. As an alternative population-PK model, we chose one which was reported in the literature and which was developed with the same drug formulation of Kaletra as was used in the study mentioned above (Crommentyun 2005). The procedure would then be applied to retrace the drug intake pattern from trough concentrations.

We fitted the dense profiles using NLMIXED procedure from SAS to obtain a first PK model. We performed sensitivity analyses for the concentration values which were inconsistent with the sampling design (e.g. a peak of concentration for the pre-dose sample, negative concentration values, etc.).

The dense profiles were inspected to gather a priori knowledge on drug concentration variability. The retracing procedure is sensitive to the extent of this variability. A population PK model exhibiting low inter-individual variability would allow that model to be used to retrace the drug intake patterns of patients without requiring any additional individual-specific data. On the contrary, a high inter-individual variability could indicate that individual-specific pharmacokinetic modelling was required to obtain accurate predictions. Furthermore, a high intra-individual variability in concentration that is mainly due to adherence would enable the retracing procedure to perform well. On the contrary, a high intra-individual variability that is not due to adherence is likely to increase the uncertainty in the procedure's results.

The retracing procedure was then applied on each individual trough concentrations. The output of the procedure is a probability value of drug intake pattern preceding blood sample. These probabilities were compared to MEMS bottle opening data, which were first inspected for inconsistencies. We inspected if the procedure could accurately retrace whether a dose was incorrectly taken before blood sampling (few hours before the blood sample). Depending on these results, we planned on looking back farther in time (e.g. did the individual take a dose at the last nominal time of drug?).

Results/Discussion

Dense concentration data: observations and model fit

We inspected the dense profiles visually. We were mainly concerned by the apparent absorption of the drug. The absorption process appeared to largely differ between individuals. In some cases, a delay of absorption and two peaks of concentration were observed, while in other cases, there seemed to be no delay and a single peak only. This variability in absorption was also observed in Crommentuyn *et al.* reporting a coefficient of variation of 98% for the inter-individual variability in absorption for their model fit.[2] We tried to obtain a pop-PK model using these dense profiles, using the NLMIXED SAS procedure. We chose a model with 1 compartment, linear absorption and elimination, as was used in other articles about this drug (Crommentuyn). [2]. Pharmacokinetic data only allowed to model a limited number of parameters. Inter-individual variability parameters could only be estimated for clearance and volume of distribution. We could not obtain an adequate fit using all dense profiles, even when allowing the baseline value (predose sample) to vary. Most individual fit of dense profiles were inadequate, with auto-correlating residuals with time. We attributed this lack of fit to the high inter-individual variability in absorption. This variability made it almost impossible task to obtain Bayesian individual parameters to reproduce the concentration profile. There were few exceptions for which the model seemed to fit the data well (4 profiles). Overall, residual variability was high (coefficient of variation of around 40%).

Sparse concentration data: main observations

There was a large variability of trough concentrations in the data. In particular, the intra-individual variability largely varies between individuals, especially for the 800mg qd regime. The intra-individual variability is of special importance for the performance of the procedure we wish to apply, and could explain the results we obtained for the retracing procedure (see below).

Application of the procedure: retracing the dose intake from single blood samples

Because we could not obtain an adequate model fit using dense profiles, we used the Population-PK model reported in Crommentuyn *et al.* in order to retrace the dose intake. We also used the individual PK models for 4 individuals, namely those for which the model seemed to correctly fit the data. As was mentioned earlier, we used the trough sample data points to evaluate how individuals used their medication preceding the blood sample.

The procedure based on the Pop-PK model

We first inspected the retracing procedure predictions without comparing them to MEMS data. The method inputs a drug concentration and outputs a probability of drug intake pattern. For those in the qd regimen, the procedure highlighted a moderately large area of trough concentration values (between 4.5mg / L and 6.5mg / L) for which there was high uncertainty in whether a dose was taken or not, few hours before blood sampling. More precisely, an individual who had a trough concentration below 4.5 mg/L was assessed to have a 30% chance or less of having taken a dose in the last few hours. Those who had a trough concentration above 6.5mg/L were assessed to have 70% or more of a drug intake few hours before the blood sampling. Intermediary concentrations led to a 30 to 70% chance of previous dose intake. For those in the bid regimen, the equivalent range of trough value was from 4 to 8.5 mg/L. A great proportion of the trough concentrations fell into these intermediate ranges. Based on these results, we expected it to be quite difficult to detect whether or not the person had taken a dose within a few hours before the blood test.

We then inspected MEMS data. A fairly large proportion of individuals (84/167) opened their vial within the few hours preceding the blood test. In principle, these people were not supposed to take the drug before their appointment. Without relying on the retracing procedure, we inspected the relationship between trough concentration values of those who opened vs those who did not open their flask. There were no significant differences in the trough concentration values, indicating that it was quite likely that no one took a pill few hours before blood sampling, independently of whether the pill bottle had been opened or not. We hence expected that most individuals would have smaller trough concentration values linked to the absence of dose intake based on the retracing procedure. However, the retracing procedure was not in agreement with this finding, rather reporting that 41% of the trough concentrations were more likely to have been obtained when a pill was taken a few

hours before blood sampling. Furthermore, there was no relationship between the opening of a vial few hours before drug intake and whether it was more likely that a dose had been taken or not based on the procedure. (Kappa measure < 0.15)

We further analyzed the data on those we were more certain that they had not taken a dose in the hours before the blood sample (83 observations where the vial had not been opened within the few hours preceding blood sample). We then applied the tracing method to investigate whether we could correctly assess if a dose had been taken at the last nominal dose intake time. We created variables to perform comparisons between the retracing procedure results and the MEMS data: 1) an indicator of the number of doses that were most likely taken based on the procedure (zero, one, or two), and 2) the probability of having taken zero, one or two doses based on the procedure. When we compared the indicator values with the number of bottle opening at the last nominal time, we obtained very low agreement (Kappa < 0.1). There seemed to be a small relationship between the assessed probability of dose intake and the number of bottle openings, a relationship which was, however, not statistically significant.

The procedure based on the Individual-specific PK models

We finally inspected the performance of the method using the 4 individual specific PK models. Again, there was a low agreement between assessed probabilities of dose intake and whether or not the pill bottle had been opened previously (more than 65% unsuccessful predictions).

Conclusions

In general, the procedure used to retrace the drug intake pattern proved ineffective. The potential reasons are: 1) the large intra-individual variability in trough concentrations which was noticed even when bottle opening conditions were similar, indicating that this variability is likely due to other than drug adherence; 2) The inadequacy of the population PK models that were obtained which, in turn, could be due to the high inter-individual variability in drug absorption, and 3) The non-correspondence between the opening of a bottle and an actual drug intake. We suspect that the data did not lend themselves to the exercise of tracing of dose intake. It might be possible for a drug with little intra-individual variability, for which a Bayesian fit of individual parameters could generate a sufficiently accurate model to track individual drug intake patterns. This was not the case for the data we accessed.

References

- [1] Barrière O, Li J, Nekka F. A Bayesian approach for the estimation of patient compliance based on the last sampling information. *Journal of Pharmacokinetics and Pharmacodynamics*, 38.3 (2011): 333-351.
- [2] Crommentuyn, K. M. L., Kappelhoff, B. S., Mulder, J. W., Mairuhu, A. T. A., Van Gorp, E. C. M., Meenhorst, P. L., ... & Beijnen, J. H. (2005). Population pharmacokinetics of

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