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Identifying and minimizing major sources of variability in population pharmacokinetic studies

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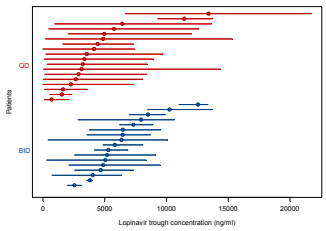
INTRODUCTION

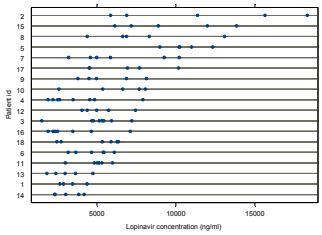
Occasional sampling of the concentrations of drug in plasma is used to study the pharmacokinetics of the drug in question, and to determine whether or not dosing is optimal. Both purposes are compromised by variance in the concentration of plasma, the origins of which include variations in both the sources and sinks for drug in the body. The main variation in the source of drug in ambulatory patients is variable execution of the prescribed regimen. The main variations in the sinks for drug arise from food- and/or drug-induced changes in pharmacokinetic parameters, changing the relation between dose and concentration. To minimize these variations, sampling is routinely done at a 'trough' point in an interval between scheduled doses, i.e., just prior to the next scheduled dose in the prescribed dosing sequence.

Trough Concentration variability in clinical studies [1,2,3]

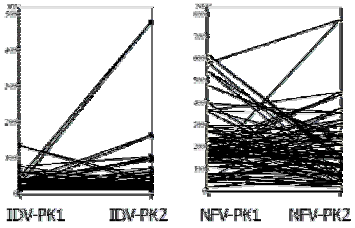
Trough concentrations may vary markedly among patients as exemplified by the following studies [1,2,3]



(1)	QD	BID
Between-patient	64 %	34 %
Within-patient	84 %	35 %



(2)	BID
Between-patient	40 %
Within-patient	38 %



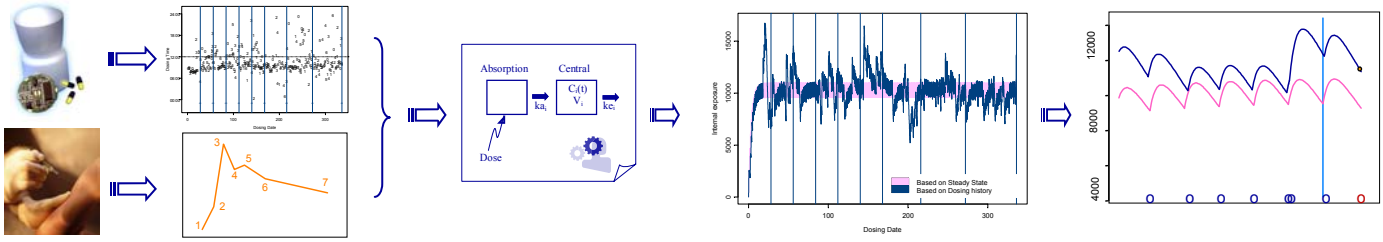
(3)	IDV	NFV
Between-patient	73 %	73 %
Within-patient	80 %	74 %

Objectives

If the existence of a large between-patient variability justify the use of TDM, the presence of a large within-patient variability may undermine its use. The main objective of this research is to determine the magnitude and sources of variability in trough concentrations collected during ambulatory care. This research focus on non adherence to the planned therapy as potential source of variability.

Material and Method

Therapeutic drug monitoring data issued from a very well controlled study were combined in order to quantify the within- and between-patient variability in trough concentrations and to identify major sources of PK variability. Electronically compiled dosing histories data were used to identify the proportion of variability that could be attributed to patient non adherence to prescribed therapy. The steps used to quantify the variability are

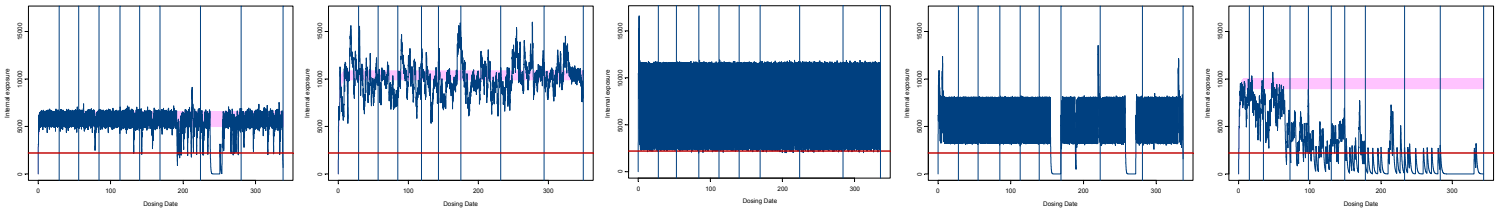


Results:

When therapeutic drug monitoring is used, many samples turned out not to be taken at the trough, but at some other point in the dosing cycle, and, furthermore, many samples turned out to be taken during an inter-dose cycle when the assumption of a steady-state is not justifiable, because of prior irregularities in dosing times. Those deviations result in considerable within-patient variability inducing sometimes difficult clinical interpretation of the results. Surprisingly, in some circumstances, the within-patient variability exceeds the between-patient variability. Through projections we were able to show that electronically compiled times of dose taken prior to blood sampling can explain more than 50% of the residual, within-patient variability in trough concentrations.

TDM : dosing histories bring valuable information in the decision process

The results show the importance of non adherence to the prescribed therapy as source of variability in trough concentration. The decision process should be adjusted for this source of variability. As self-reported adherence poorly correlates with plasma drug level [4], continuous assessment of adherence brings reliable and valuable information in the decision process. As illustrated below, the decision can be secured in the light of this new dimension.



Concentrations in the target range at steady state. Deterioration of the adherence during the second part of the follow-up.

Concentrations rarely at steady state. Very loosy BID patient. The adherence should be improved. A switch to a QD regimen may also be considered.

Concentrations constantly close to the target trough. This patient has an excellent adherence. A BID regimen instead of a QD treatment may be more appropriate.

Concentrations in the therapeutic range. This patient has an good overall compliance but presents several drug holidays.

Concentrations in the target range at steady state. However, this patient is a poor adherer with a decrease over time. An improvement in adherence is clearly needed

Conclusion

These results suggest that electronically-compiled dosing histories may greatly improve information derived from both population PK studies and therapeutic drug monitoring. Non adherence to the protocol and to the therapy are two important sources of variability in trough concentrations. Measuring patient's dosing history may bring a valuable information in decision process involved by therapeutic Drug Monitoring.

References :

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