In silico evaluation of the estimation of patient compliance based on limited pharmacokinetic information

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Purpose

Develop and evaluate *in silico* a method to estimate patient compliance to an oral chemotherapy from :

(i) an *a priori* population pharmacokinetic (PK) model,
(ii) limited optimal PK information collected on day 1,
(iii) a single PK sample collected after multiple doses.

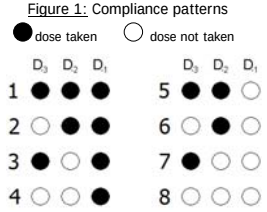
Methods

Idea of the compliance estimation method

Extract the compliance information from a single PK sample by comparing it to corresponding predicted concentration computed with a pop PK model and Bayesian individual parameters

- 8 compliance patterns were defined as the sequence of last 3 doses taken or not (Figure 1)
- Key step was to impute the dosing pattern to the one minimising the "distance" between observed and predicted concentration
- This classification algorithm was evaluated by repeated simulations

Figure 1: Compliance patterns



Simulation procedure

- 1000 PK parameter sets drawn according to *a priori* population distributions and each simulated patient assumed to have a given compliance pattern
- Simulation of sparse conc. on day 1 and one conc. on day 10
- Re-estimation of individual Bayesian PK parameters based on day 1 sparse samples
- Comparison of the actual concentration versus the predicted ones computed according to each pattern
- Choice of the compliance profile which minimises the distance between actual and predicted value

Performance of the compliance estimation

Evaluation at several time points after last taking on day 10

- Last1T: % patients for which last taking is well predicted
- Last2T: % patients for which last 2 takings are well pred.
- Last3T: % patients for which last 3 takings are well pred.

In silico evaluation

Population PK models:

Imatinib ($t_{½}/\tau = 0.625$) †

- One compartment pop PK model published by Widmer et al[1] with first order absorption and elimination
- Residual variability modelled with an exponential error model with CV 31%
- 500 mg once daily
- 4 PK samples taken on day 1 at 0.1, 1.6, 7.1 and 18 h
- 1 PK sample taken on day 10

Capecitabine/FBAL ($t_{½}/\tau = 0.25$) †

- Cascade model for capecitabine and metabolites published by Gieschke et al[2]. FBAL is capecitabine metabolite with the longest plasma half-life (approx. 3 hours)
- Residual variability modelled with an exponential error model with CV 20%
- 2000 mg twice daily for 14 days / 1week rest
- 4 PK samples taken on day 1 at 4.5, 6, 13.5 and 18 h
- 1 PK sample taken on day 10

† $t_{½}$ is the drug plasma elimination half-life, τ is the interdose interval

Results

Evolution of performance through time

The best estimation is obtained for a sample collected 5 hours after last dose taking on day 10 in both examples:

- but performance is quite stable through time
- compliance over the 2 last takings is correctly estimated (Table I – CV 31%)

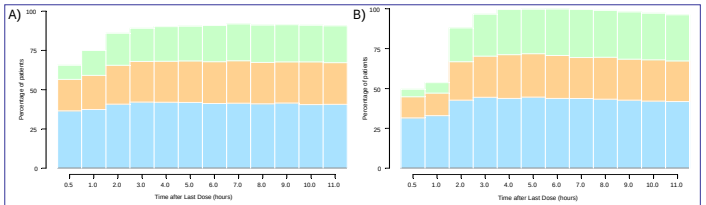


Figure 2: Evolution of the percentage of patients whose compliance is well estimated
A) in imatinib example B) in capecitabine/FBAL example
Last3T (blue), Last 2T (blue+orange), Last 1T (blue+orange+green)

Results (cont.)

Impact of the CV of the residual error model

Table I: Performance of the estimation method at the best sampling time in the imatinib example

Res. Error CV	Sampling time at day 10	Last 1T (%)	Last 2T (%)	Last 3T (%)
31%	5 hours	91.8	69.6	44.4
1%	Any	100	100	100
5%	2 hours	99.8	99.1	89.0
10%	3 hours	99.1	92.9	70.5
20%	5 hours	94.4	77.6	51.0
30%	5 hours	90.9	68.9	42.6
40%	5 hours	87.1	63.3	37.8
50%	5 hours	83.9	58.9	34.5

Comparison of both examples

Performance in both examples are compared using the same magnitude of CV (20%)

Table II: Performance of the estimation method in both examples

Run	$t_{½}/\tau$	Sampling time at day 10	Last 1T (%)	Last 2T (%)	Last 3T (%)
Imat. 20%	0.625	5 hours	94.4	77.6	51.0
FBAL	0.25	5 hours	99.8	71.9	44.6

The performance of the estimation method is better with:

- smaller error CV in the pop PK model
- greater ratio $t_{½}/\tau$ (plasma half-life / interdose interval)

Conclusions and perspectives

- 2 parameters have an effect on the method performance
  - ratio $t_{½}/\tau$
  - σ the magnitude of the error model
- In both examples, compliance was correctly estimated over the 2 last scheduled doses
- PK method is not informative enough and should be associated to electronic monitoring in a future clinical study (*OCTO – Compliance to an oral chemotherapy*)

References

1. Gieschke R et al, *J Pharmacokinet Pharmacodyn* 29(1): 25-47, 2002
2. Widmer et al, *Br J Clin Pharmacol* 62: 97-112, 2006