Handling inter-occasion variability in model-based therapeutic drug monitoring

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Background

The potential of dose individualization using model-based therapeutic drug monitoring (TDM) is known to be challenged by high magnitudes of inter-occasion variability (IOV) [1, 2].

Currently, it is not clear which is the preferred method to individualize dosing regimens in the presence of IOV.

Objective

To compare different approaches to handle IOV in a TDM context, using a population PK model for coagulation factor VIII (FVIII) as example.

Methods

This simulation-based study consists of a chain of steps for a number of simulated scenarios, as represented below:

STEP 1
Simulation from a population pharmacokinetic model
➢ Observed factor VIII activity (simulated) data

STEP 2
Bayesian forecasting using a population pharmacokinetic model varying the number of observations (occasions) included
➢ Individual PK parameters

STEP 3
Dose calculation to reach pre-defined target [FVIII of 0.01 IU/mL at 48 h post-dose]
➢ Dose required to achieve target on next occasion

STEP 4
Calculation of FVIII 48 h post-dose on next occasion using dose from step 3 and true PK parameters from step 1
➢ Expected FVIII activity on next occasion

STEP 5
Comparison between expected FVIII activity and target
➢ Accuracy and precision in target attainment

Simulations were based on a PK model for FVIII activity following i.v. administration to hemophilia A patients (**ORIG model** [3])**,** and alternative models with none (0%) to large (50%) IOV on CL or V1 (**IOV models**):

- ORIG model: 2-compartment model, IIV on CL (28%) and V1 (17%, correlation CL-V 0.64), IOV on CL (13%) and V1 (10%), combined residual error (8.5 %, 0.012 IU/mL)
- Simulated steady-state FVIII activity at 4, 24 and 48 h following FVIII administration of 30 IU/kg to 1000 patients on 4 occasions

Alternative models without IOV were estimated based on real or simulated data (**IIV models**).

The following approaches were explored to calculate the individual dose:

- **Approach IIV**, Bayesian forecasting based on an IIV model
- **Approach IOV1**, Bayesian forecasting based on an IOV model; IOV etas were not included in the calculation of the individualized dose
- **Approach IOV2**, Bayesian forecasting based on an IOV model; IIV and IOV etas were included in the calculation of the individualized dose

All procedures were carried out in NONMEM 7.3 assisted by PsN 4.6.16 and R 3.3.1.

Results

The performance of the explored approaches to predict an individualized dose that aims to result in the target FVIII activity (0.01 IU/mL) on the next occasion is depicted in **Figure 1**.

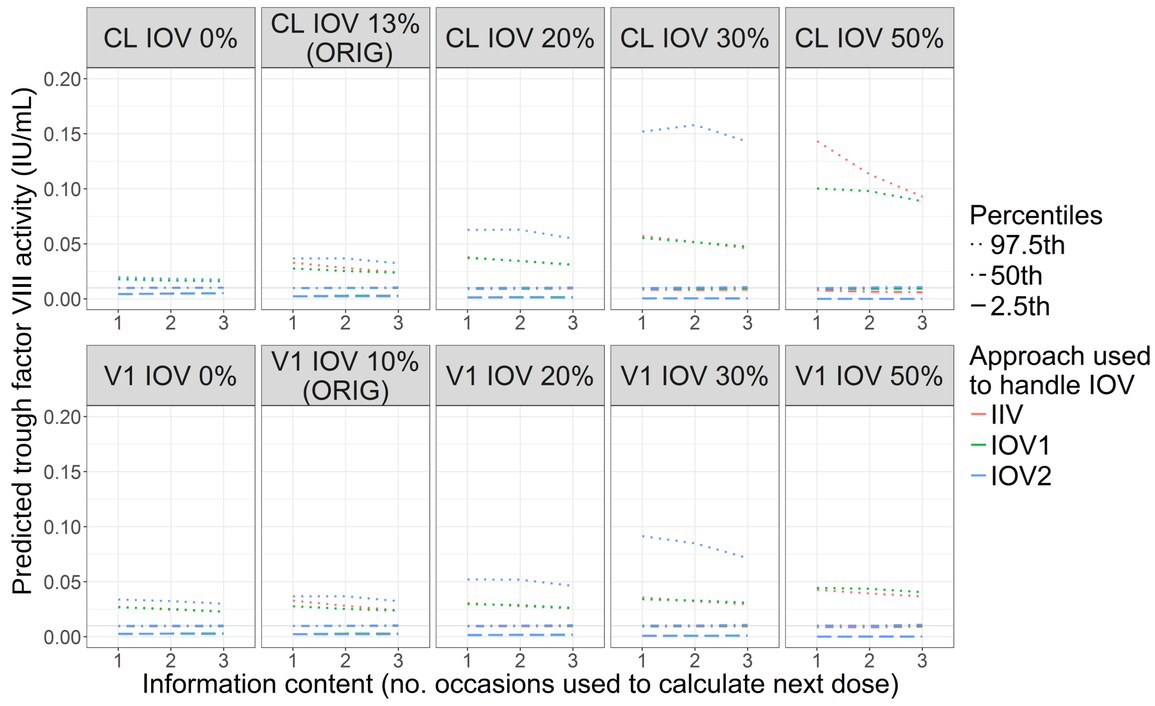

Figure 1 – The 2.5th, 50th and 97.5th percentiles of predicted FVIII trough activity at 48 h post-dose when aiming at a target of 0.01 IU/mL, using information from 1, 2 or 3 occasions to predict the subsequent occasion, according to different approaches (IIV, IOV1 and IOV2).

In general, the individual predicted doses resulted in low bias in the predicted FVIII activity. As expected, the imprecision of the predictions increased with increasing magnitude of IOV, and IIV and IOV1 resulted in the most precise predictions.

The percent of values predicted to be below 0.0025 IU/mL (1/4 of target) and in the interval [0.0025, 0.005) IU/mL (1/4-1/2 of target) for approaches IIV and IOV1 are presented in **Table 1**.

Table 1 – Percent of predicted FVIII trough activity values <0.0025 and [0.0025, 0.005) IU/mL when aiming at a target of 0.01 IU/mL, using information from 1 or 3 occasions to predict the subsequent occasion, according to approaches IIV and IOV1 for the simulated scenarios.

		Approach used for dose calculation			
		IIV		IOV1	
Simulated scenario	FVIII activity (IU/mL)	1 occasion	3 occasions	1 occasion	3 occasions
CL IOV 13% V1 IOV 10% (ORIG)	<0.0025	2.7	2.2	2.8	2.1
	[0.0025, 0.005)	11.7	11.0	12.0	10.7
CL IOV 0%	<0.0025	0.3	0.0	0.3	0.0
	[0.0025, 0.005)	3.8	2.3	3.9	2.3
CL IOV 20%	<0.0025	7.5	7.2	7.2	6.4
	[0.0025, 0.005)	16.0	14.6	14.4	12.7
CL IOV 30%	<0.0025	15.5	14.6	13.4	11.9
	[0.0025, 0.005)	17.5	18.4	15.6	14.4
CL IOV 50%	<0.0025	28.7	31.1	24.2	22.6
	[0.0025, 0.005)	12.5	14.4	11.6	12.3
V1 IOV 0%	<0.0025	2.2	1.6	2.2	1.3
	[0.0025, 0.005)	10.5	8.2	10.3	7.7
V1 IOV 20%	<0.0025	5.6	4.6	5.3	4.5
	[0.0025, 0.005)	14.4	13.4	13.2	12.3
V1 IOV 30%	<0.0025	10.1	9.8	9.2	8.5
	[0.0025, 0.005)	15.1	13.3	13.5	12.4
V1 IOV 50%	<0.0025	19.9	19.1	17.1	16.5
	[0.0025, 0.005)	13.7	14.2	13.2	11.7

In scenarios with low IOV (<20%), IIV and IOV1 had a similar performance when predicting low FVIII activity, but increasing IOV lead to a higher percent of very low values (<0.0025 IU/mL) with the IIV approach, regardless of the information content considered.

Conclusion

The IIV and IOV1 approaches showed a similar performance to individualize doses when IOV was low (<20%), and IOV1 was superior for the remaining scenarios of IOV.

If employing an IOV model in Bayesian forecasting, the IOV etas should not be used in the calculation of the individualized dose.

References

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