In silico evaluation of limited blood sampling strategies for individualized factor IX prophylaxis in hemophilia B patients

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Introduction

- Severe hemophilia B patients administer prophylactic intravenous doses of recombinant clotting factor IX (rFIX) concentrate in order to prevent spontaneous joint bleeds.
- Current guidelines recommend a plasma trough FIX concentration of >0.01 IU mL^{-1} (1%).
- rFIX doses can be individualized using PK analysis.
- Currently, individual PK parameters are still assessed by taking multiple (>10) blood samples.
- Limited sampling and Bayesian *a posteriori* estimation can be used to reduce the number of samples.

Objectives

- To develop practical limited sampling strategies (LSSs).
- To evaluate *in silico* how the predictive performance is influenced by the number and timing of blood samples.

Methods

Simulation

- Dataset with 5000 patients simulated in R, with median age 25 years (range 10 – 70 years) and median body weight 75 kg (range 35 – 130 kg).
- Simulation of rFIX concentration-time profiles (figure 1) after i.v. bolus-infusion of 100 IU kg-1 in NONMEM® using a prophylactic population PK model from literature [1].

Bayesian estimation

- Eleven LSSs in a 80-hour period were evaluated (table 1).
- Predictive performance was evaluated for all PK parameters, trough concentration on day 3 (72h-80h), and calculated dose.
- All subjects with one or more simulated observations below LLOQ were censored from further analysis.

References

1. *Björkman S. Population pharmacokinetics of recombinant factor IX: Implications for dose tailoring. Haemophilia. 2013;19(5):753–7.*

Figure 1. Simulated observations

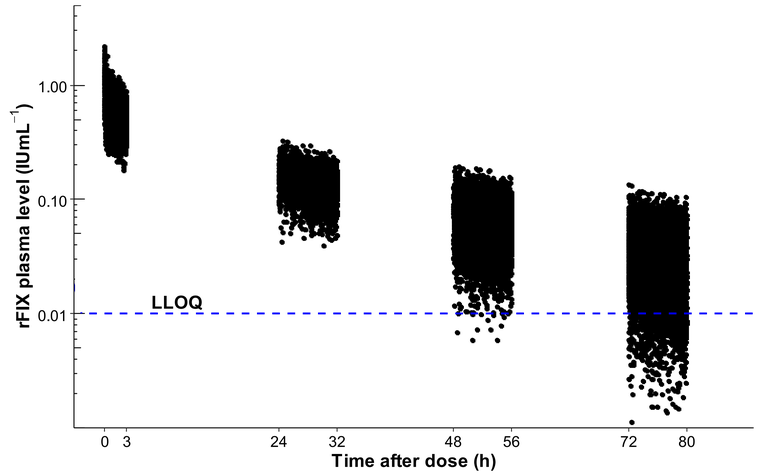


Table 1. Practical LSSs used for evaluation

Scheme	Post-infusion *0h – 3h*	Day 1 *24h - 32h*	Day 2 *48h – 56h*	Day 3 *72h - 80h*	Censoring (%)
1	x	x	x		1.1
2	x	x		x	17.4
3	x		x	x	17.5
4	x		x		1.1
5	x			x	17.4
6			x		1.1
7				x	17.4
8	x		xx		1.1
9	x			xx	17.4
10			xx		1.1
11				xx	17.4

Table 2. Predictive performance of trough concentration and calculated dose

Scheme	Trough concentration			Calculated dose		
	MPE (%)	*95%CI*	*RMSE (%)*	*MPE (%)*	*95%CI*	*RMSE (%)*
1	1.2	[0.59 - 1.87]	23	3.1	[2.52 - 3.66]	20.8
2	1.2	[0.51 - 1.79]	21	2.4	[1.8 - 2.93]	18.7
3	0.4	[-0.06 - 0.94]	16.4	1.8	[1.3 - 2.21]	15
4	1.8	[1.12 - 2.51]	25	3	[2.36 - 3.57]	21.9
5	4.1	[3.32 - 4.98]	27.5	0.8	[0.19 - 1.47]	21
6	-0.3	[-1 - 0.46]	26.1	5.5	[4.81 - 6.12]	24.2
7	3.5	[2.6 - 4.31]	28.2	1.5	[0.85 - 2.16]	21.5
8	0.8	[0.24 - 1.3]	19	2	[1.56 - 2.49]	16.6
9	4.2	[3.51 - 4.88]	22.9	-0.9	[-1.39 - -0.41]	16.2
10	-1	[-1.6 - -0.48]	20.1	4	[3.52 - 4.52]	18.3
11	3.8	[3.11 - 4.51]	23.3	-0.6	[-1.12 - -0.12]	16.4

Conclusions

1. Best overall predictive performance was established for the LSS with one sample taken post-infusion and two samples on day 2 (48h-56h) after dose administration.
2. Limited sampling strategies can be developed and evaluated for individualized dosing of rFIX in hemophilia B patients by *in silico* simulation.

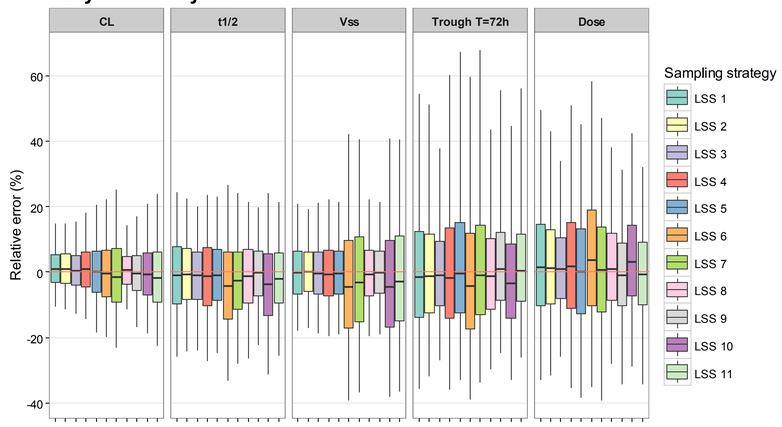
Results

For each LSS (*table 2*):

- Low bias (<5%) and precision (<25%) were observed for clearance (CL), elimination half-life (t1/2) and volume of distribution at steady-state (Vss).
- Imprecision of trough concentration on day 3 (72h-80h) was high (>25%) only for all LSSs with less than three observations.
- Bias of calculated dose was high (>5%) only for LSS6.
- Relative errors (*figure 2*) for individual estimates of trough concentrations and calculated dose were large, however 50% of the errors remained within +/-20% for all LSSs.

Predictive performance was best with one sample taken post-infusion and two samples on day 2 (LSS8).

Figure 2. Relative errors between values obtained by simulation and estimates from Bayesian analysis



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