

Impact of sampling times on the predictive performance of tobramycin population pharmacokinetic models

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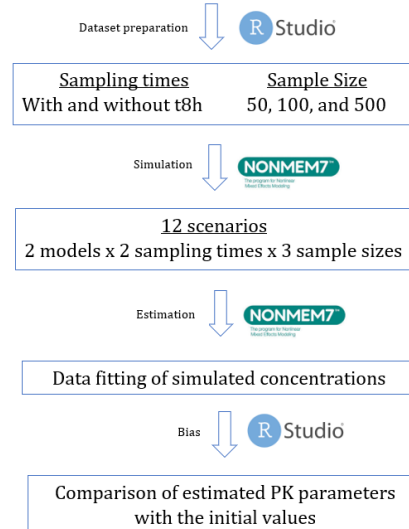
Introduction

- External evaluations are the most stringent methods for evaluating the predictive performance of population pharmacokinetic (PK) models.
- Our previous work has shown that we were unable to externally validate a previously published tobramycin population PK model due to large bias and imprecision.
- We hypothesize that this is due to the evaluated model not being developed using the same sampling times as in the validation dataset.
- The objective of this study is to investigate the effects of 8h post-dose sampling times on the performance of PK parameter estimation using models developed with (Crass *et al.*¹) and without (Koloskoff *et al.*²) 8h post-dose sampling times.

Methods

Model developed with 8h post-dose sampling times (Crass *et al.*)¹

Model developed without 8h post-dose sampling times (Koloskoff *et al.*)²



Results

Table 1. Characteristics of the evaluated models and final population pharmacokinetic parameter estimates

Author	No. of compartments	Software	CL (L/h) Formula	V ₁ (L) Formula
Crass <i>et al.</i> ¹	2	NONMEM VII	$TVCL = \text{MaxCL} \times (Ht/160)^{\text{Ht,CL}} \times (eGFR^{Ht,CL} / eGFR^{50^{Ht,CL}} + eGFR^{Ht,CL})$	$TVV_1 = \theta_{V1} \times (Ht/160)^{\text{Ht,V1}}$
Koloskoff <i>et al.</i> ²	2	NONMEM VII	$TVCL = \theta_{CL}$	$TVV_1 = \theta_{V1} \times (Ht/162.5)^{\text{Ht,V1}}$

CL, clearance; eGFR, estimated glomerular filtration rate; FOCE-I, first-order conditional estimation with η - ϵ interaction; Ht, height; TV, typical value; V₁, volume of central compartment

Table 2. Final population PK estimates

Author	CL (L/h)	IIV CL (%)	V ₁ (L)	IIV V ₁ (%)	Q (L/h)	IIV Q (%)	V ₂ (L)	IIV V ₂ (%)	Residual variability	
									Prop (%)	Add (mg/L)
Crass <i>et al.</i>	4.88	14.4	15.4	6.9	0.340	40.1	5.56	134.2	28.60	0.04
Koloskoff <i>et al.</i>	4.14	18.7	17.2	16.8	0.284	NA	6.77	NA	25.2	NA

CL, clearance; eGFR, estimated glomerular filtration rate; Ht, height; IIV, interindividual variability; NA, not applicable; Q, intercompartmental clearance; RV, residual variability; TV, typical value; V₁, central compartment volume; V₂, peripheral compartment volume

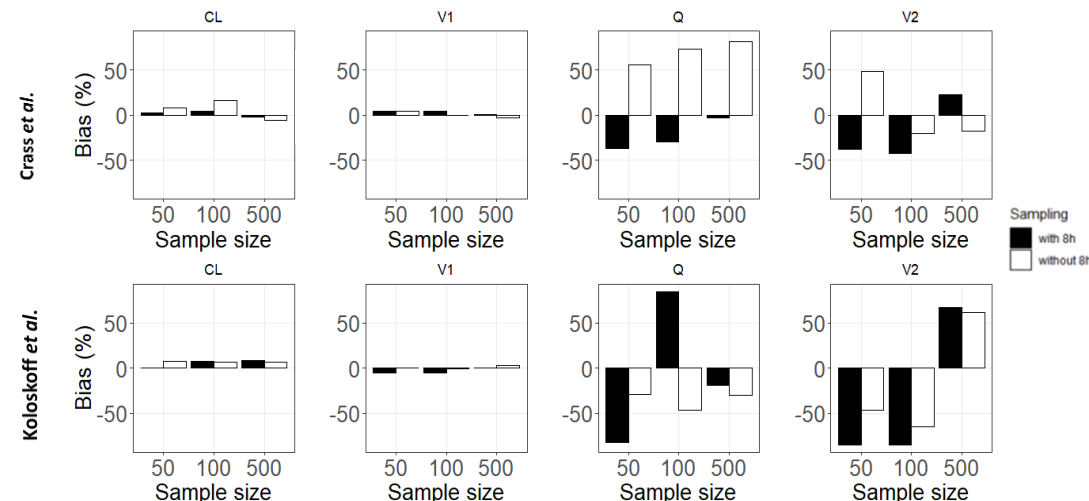


Figure 1. Bias of population PK parameters estimated with the model by Crass *et al.* and Koloskoff *et al.*

Key points

- Population PK parameters relating to the first compartment were not influenced when fitting data at divergent sampling times (i.e., t8h) as the original model
- Population PK parameters relating to the second compartment were biased when fitting simulated data at divergent sampling times (i.e., t8h) as the original model
- In general, increasing sample size was associated with lower bias values

References

- Crass, R. L., & Pai, M. P. (2019). Optimizing Estimated Glomerular Filtration Rate to Support Adult to Pediatric Pharmacokinetic Bridging Studies in Patients with Cystic Fibrosis. *Clin Pharmacokinet*, 58(10), 1323-1332. doi:10.1007/s40262-019-00761-5
- Koloskoff, K., et al., *Height is predictive of tobramycin pharmacokinetics in adult cystic fibrosis patients [abstract]*, in *Europe Congress of Clinical Microbiology and Infectious Diseases 2021*. Abstract nr 2257.

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