

SOFIE DHAESE¹, JAN DE WAELE¹ AND PIETER COLIN^{2,3}

¹Ghent University Hospital, Department of Critical Care Medicine, Ghent, Belgium

²University of Groningen, University Medical Center Groningen, Department of Anesthesiology, Groningen, The Netherlands

³Ghent University, Laboratory of Medical Biochemistry and Clinical Analysis, Ghent, Belgium

OPTIMAL EXPERIMENTAL DESIGN TO INFORM A CLINICAL TRIAL ON NON-LINEARITY OF PIPERACILLIN CLEARANCE IN CRITICALLY ILL PATIENTS

INTRODUCTION

Evidence on the non-linearity of piperacillin clearance at therapeutic plasma concentrations in critically ill patients is conflicting. Sparse research has demonstrated that up to 56-73% of the renally eliminated piperacillin is secreted *via* the renal tubuli which is a saturable process. Non linearity of piperacillin clearance impacts the optimal dosing regimen and this is particularly relevant given the recent introduction of continuous as opposed to intermittent infusion of beta-lactam antibiotics in several ICU's worldwide. As piperacillin concentrations during intermittent infusion are usually higher than concentrations achieved with the same dose *via* continuous infusion, saturation during intermittent infusion may occur while this may not be the case during continuous infusion.

PURPOSE

To revisit the evidence on the non-linearity of piperacillin clearance using clinical trial simulations. For this, the type I error rate and power for detecting non-linear piperacillin CL of published clinical trials on piperacillin PKs were evaluated. The difference between non-parametric (NPAG, non-parametric adaptive grid) and parametric (FOCE-I, first-order conditional estimation with interaction) parameter estimation in type I error rate and power was also investigated. Based on the same principles, an optimal experimental trial design was developed to inform a clinical trial on non-linearity of piperacillin clearance

METHODS

Piperacillin PK profiles were simulated according to the design of different published studies on piperacillin PK in patients (i.e. same number of patients, number of observations, mode of administration, doses, sampling times, etc., **figure 1**). For these simulations, the PopPK model by Landersdorfer, *et al.*, on piperacillin PKs in healthy volunteers, served as the true model. Cohorts of patients with non-linear piperacillin PKs were simulated according to the final parameter estimates by Landersdorfer (H_1). In parallel, cohorts with linear PKs were simulated by fixing the V_{max} estimate to zero (H_0). Two nested models, a two-compartment linear model and a two-compartment with parallel linear / non-linear elimination were fitted to the simulated datasets. The likelihood ratio test at the 5% level of significance was used to compare both models.

The type I error-rate and power were approximated by the frequency of significant LRT in the simulated datasets without non-linear (H_0) and with non-linear piperacillin clearance (H_1), respectively. In addition, a type I error calibration was implemented and the statistical power was calculated with this calibrated chi-square value in order to obtain the power of a specific study design corresponding to a type I error rate $\leq 5\%$.

The accuracy of K_m and V_{max} estimates was assessed by the percentage of times the estimated values for both K_m and V_{max} fell within a two-fold range (i.e. -50%; +100%) of the mean K_m and V_{max} estimations used for simulation

Parameter estimation was performed using the NPAG estimation routine as implemented in Pmetrics (Version 1.5.2; Laboratory of Applied Pharmacokinetics, Los Angeles, CA, USA) and the FOCE-I algorithm in NONMEM (Version 7.3; GloboMax LCC, Hanover, MD, USA).

RESULTS

Six published piperacillin PopPK models were selected from the literature of which three described linear clearance of piperacillin while the other three described non-linear clearance of piperacillin. Then number of patients per study ranged between 8 and 50 and the number of observations per patient ranged between 6 and 27 (**table 1**). The type-I error rate was between 0.8% and 26% with NPAG and between 1.9% and 75% with FOCE-I. The calibrated power of the study designs was between 4.3 and 97.1% with NPAG and between 0.2% and 47.9% with FOCE-I. None of the NPAG estimates for K_m and V_{max} fell within a two-fold range of the true K_m and V_{max} values used for simulation, not even in the study design with high calibrated power. For FOCE-I, accuracy was also low except for the study with high calibrated power where 16.4% of the estimates were within the 2-fold range. Our proposed study design (based on 10 patients) resulted in a type I error rate of 3%, a power of 100% with 47% of the parameter estimates within 2-fold of the values used for simulation. When NPAG was used instead of FOCE-I, the type I error rate increased to 12% without significantly affecting power. Remarkably, both for V_{max} and K_m parameter estimates were always higher than 2-fold the value used for simulations.

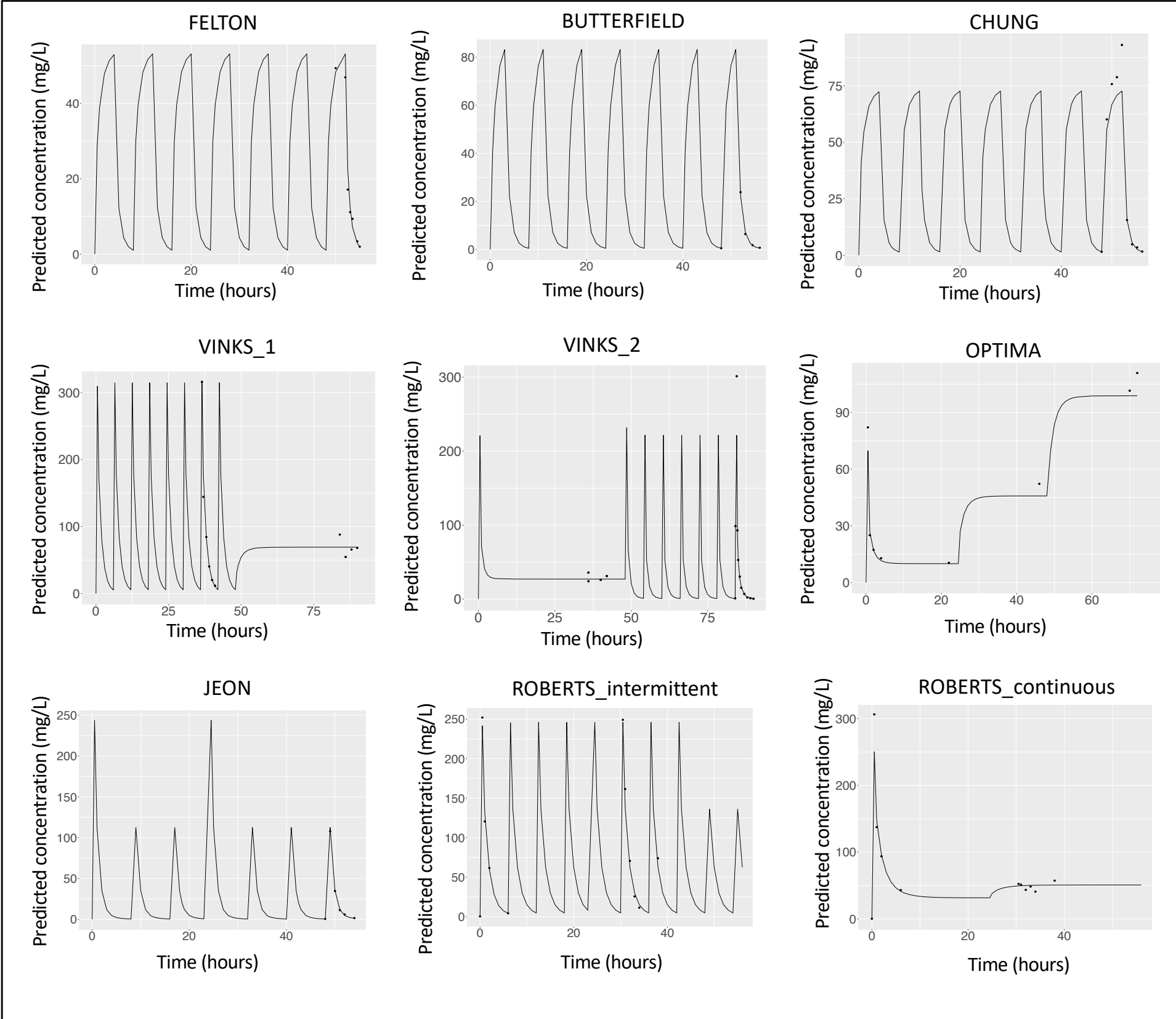


Figure 1: Simulated concentration-time curves and sampling times according to the design of the published PopPK models. Vinks, *et al.* used a cross-over design while Roberts, *et al.* included patients receiving both intermittent and continuous infusion.

Table 1: Type-I error rate, power and parameter accuracy for clinical trials reporting both linear and non-linear piperacillin PK's

Original design	Felton	Vinks	Butterfield	Roberts	Jeon	Chung*	OPTIMA
#patients	11	8	9	16	50	27	10
#observations	71	120	54	432	300	129	140
Type I error rate (%)	22.5/ 1.9	26 / 11	6.3 / 11	8.3 / 8.2	2.2/ 75	0.8	12 / 3
Power (%)	62.5 / 7.0	86.9 / 49	15.8 / 37	98.44 / 81	3.1 / 83	2.5	100 / 100
Power and accuracy (%)	0 / 6.4	0 / 7.1	0 / 0	0/ 16.4	0 / 3.1	0	0 / 47
Power after calibration	33.4 / 7.0	54.3 / 31.0	22.2 / 28.1	97.1 / 47.9	4.3/ 0.2	8.4	99.9 / 100
Estimate K_m (IQR)	362.4 (266.7;464.6) / 38.3 (15.5; 69.8)	405.6 (323;504.3) / 59.6 (15.4; 390)	449 (292.8;449.8) / 12.8 (3.85; 51.3)	396.1 (341.1;455.7) / 230 (44.4; 670)	1.13 (1.02;232.9)/ 108 (63.8; 171)	749.912 (749.8957;749.9238)	236.5 (200;270.7) / 41.6 (27.6;71)
Estimate V_{max} (IQR)	1451.4 (995.8;2000.9) / 889 (181; 1103)	1818.5 (1370.6;2299.5) / 360 (263; 3415)	1257.7 (759.9;2048.6) / 382 (187; 864)	1864.6 (1530.2;2186.6) / 1008 (217; 6495)	218.4 (96.9;1799) / 1406 (607; 2361)	1.64 (1.48;1.72)	2258.5 (1732.2;2735.3) / 251 (177;446)

Blue: NPAG, black FOCE-I, *we were unable to perform the simulations for Chung with NONMEM and we will look into this

CONCLUSION

Published studies evaluating the non-linear PK of piperacillin were **poorly powered** and likely resulted in **in-accurate estimations of K_m and V_{max}** . Further work is necessary to study the **influence on the estimation algorithm** on the statistical inference in the context of the differentiation between linear and non-linear PK's in clinical trials.

Contact

sofie.dhaese@ugent.be
Dept. Critical Care, Ghent University Hospital