Comparison of NONMEM and Pmetrics Analysis of Aminoglycoside Pharmacokinetics in Adult Patients with Cystic Fibrosis

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BACKGROUND

The most common cause of pulmonary infection exacerbations in patients with cystic fibrosis is *Pseudomonas aeruginosa,* which accounts for 37.5 % (1).

The treatment of choice for such infection is combination therapy of aminoglycosides, usually tobramycin, and a β-lactam, e.g. ceftazidime.

Aminoglycosides are narrow therapeutic index drugs and hence require routine therapeutic drug monitoring to ensure efficacy and safety.

There is a wide range of variability in aminoglycoside pharmacokinetics, and dosage individualisation is required.

AIMS

To compare the results of parametric and nonparametric analyses of the population PK of aminoglycosides in patients with cystic fibrosis.

METHODS

Aminoglycoside dosage histories and concentration measurements were available from patients with cystic fibrosis from Glasgow and The Hague.

The data were analysed using parametric population modelling approach with NONMEM (version 7, FOCE) (2) and a non-parametric approach with the software Pmetrics (version 0.3, NPAG) (3).

The parameter estimates, structural models and covariate models using both simple and mechanistic approaches, were compared between the parametric and non-parametric approaches.

RESULTS

Table 1: Summary of patient characteristics

Patient Characteristic	Glasgow data n = 166		The Hague data n = 165	
	Median	Range	Median	Range
Age (years)	23	14 - 66	32	14 – 88
Weight (kg)	50	30 - 86	60	35 – 108
Height (cm)	163	139 - 191	174	150 – 194
CLcr (ml/min)	92	35 - 181	104	26 – 174

Key: CrCL= Estimated creatinine clearance by Cockcroft and Gault equation (4) with serum creatinine concentration fixed to 60 µmol/L if less than 60 µmol/L

A two compartment model was superior to one compartment model with both approaches.

Table 2: Parameter estimates of the two compartment base model using NONMEM and Pmetrics

Parameter	Pmetrics Mean (CV %)	NONMEM Typical value (CV %)
CL (L/h)	5.24 (23 %)	4.85 (25 %)
V (L)	14.8 (21 %)	14.1 (15 %)
Q (L/h)	0.434 (21 %)	0.596 (79 %)
Vp (L)	7.08 (13.8 %)	7.18 (59 %)

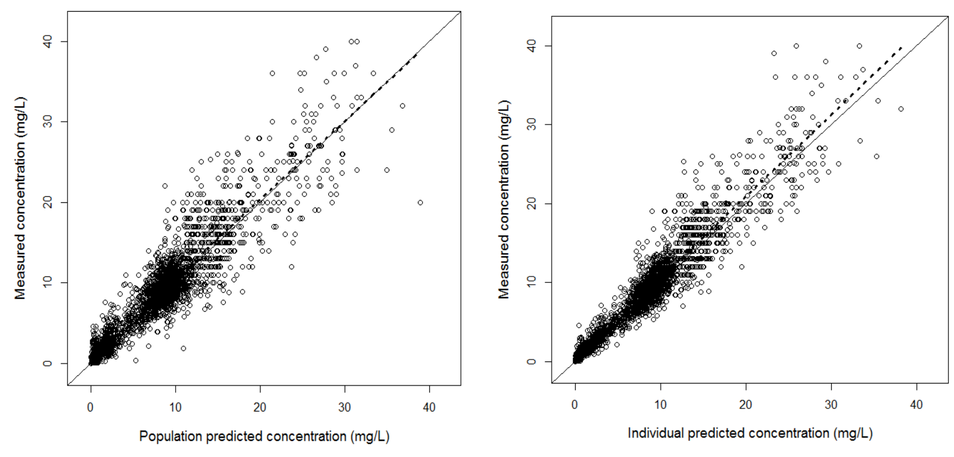
Table 3: Covariate development process

Model	Pmetrics Likelihood	NONMEM OFV
CL= CL V= V	9004	2866
$CL=CL_0$ x LBW + CLs (CrCL- 94) $V=V_0(1+Vs(LBW-40))$	9061	2916
$CL=CL_0$ x Weight + CLs (CrCL- 94) $V=V_0$ x (1 + Vs (Weight - 53))	8989	3037
$CL=CL_0(LBW/70)^{0.75}$ +CLs X RF $V=V_0X(1+Vs(LBW+(WT-LBW)/70))$	8789	3048
$CL=CL_0$ x BSA + CLs (CrCL- 94) $V=V_0$ (1+Vs (BSA - 1.6))	8675	2977
$CL=CL_0$ x Height + CLs (CrCL- 94) $V=V_0$ x (1 + Vs (Height - 166))	8568	2848

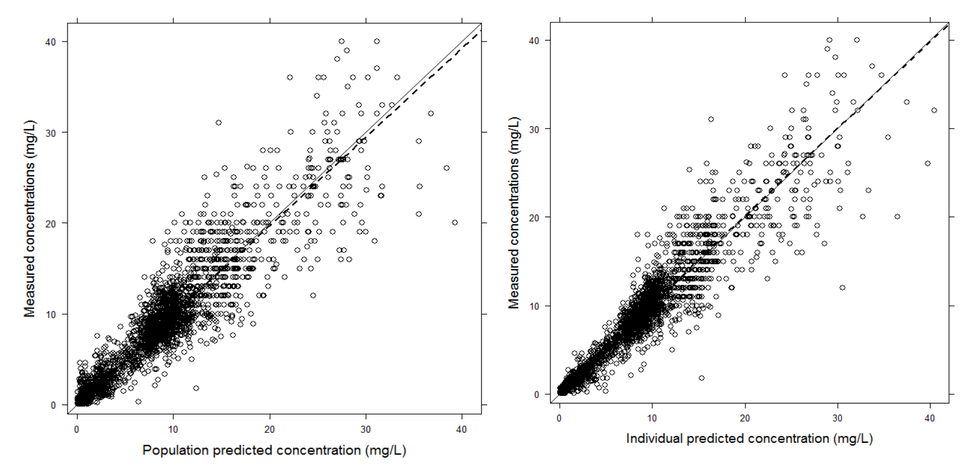
Key: CrCL= Estimated creatinine clearance by Cockcroft and Gault equation (4) with serum creatinine concentration fixed to 60 µmol/L if less than 60 µmol/L, LBW= Lean body weight (5), BSA= Body surface area (6), Renal function estimated by Anderson and Holford approach (7)

Figure 1: Measured versus predicted aminoglycoside concentrations using the final model.

Pmetrics



NONMEM



The dashed line is a smooth line

Table 4: Parameter estimates of final population models

Parameter	Pmetrics	NONMEM
CL (L/h)	0.03(L/h/cm) * HT(cm) + 0.02(L/h)* (CrCL(mL/min) - 94)	0.03(L/h/cm) * HT(cm) + 0.01(L/h)* (CrCL(mL/min) - 94)
V (L)	14.2 (L)*(1 + 0.013 *(HT - 166))	13.9 (L)*(1 + 0.011* (HT - 166))
Q (L/h)	0.6	0.6
Vp (L)	8.00	5.79

Key: HT= Height, CrCL= Estimated creatinine clearance by Cockcroft and Gault equation (4) with serum creatinine concentration fixed to 60 µmol/L if less than 60 µmol/L

CONCLUSION

Similar results were obtained when parametric and nonparametric approaches were used to analyse aminoglycoside data from patients with cystic fibrosis.

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References

1. Cystic Fibrosis Trust UK. UK Cystic Fibrosis Registry Annual Data Report 2010.
2. Beal S, Sheiner LB, Boeckman A et al. NONMEM User's Guides (1989-2009). Ellicott City, MD, USA: Icon Development Solutions, 2009.
3. Neely MN, van Guilder MG, Yamada WM, Schumitzky A, Jelliffe RW. Accurate Detection of Outliers and Subpopulations with Pmetrics, a Nonparametric and Parametric Pharmacometric Modelling and Simulation Package for R. Ther Drug Monit 2012; 34:467–476.
4. Cockcroft DW, MH G. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31-41.
5. Janmahasatian S, Duffull S, et al. Quantification of lean bodyweight. Clin Pharmacok. 2005;44:1051-65.
6. Mosteller R. Simplified calculation of body surface area. New Engl J Med. 1987;317:1098.
7. Anderson BJ, Holford NHG. Mechanistic basis of using body size and maturation to predict clearance in humans. Drug Metab Pharmacokinet 2009; 24: 25–36.