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INTRODUCTION

Physiologic changes due to disease status can lead to highly variable pharmacokinetics (PK) of amikacin in children. Therefore, considerations should be given when determining optimal amikacin dose for patients with specific diseases. Improved understanding of factors influencing PK can allow for the optimizing of dosage regimens to reduce adverse effects.

The aim of the study was to undertake a comparative pharmacometric analysis of amikacin use in pediatric patients with burn injuries verses those with oncology conditions.

METHODS

- Pediatric patients < 18 years of age with burn injuries (group 1) and with oncology conditions (group 2) who received > 1 dose of amikacin for the empirical treatment of gram-negative bacterial infections between Jan 2007 to Dec 2009 and Jan 2006 to Dec 2011 were included.
- Patients with burn injuries received amikacin at 10-20 mg/kg/day as part of early empiric treatment of presumed burn-related sepsis.
- Oncology patients received 20 mg/kg of amikacin intravenously for treatment of febrile neutropenia.
- Patients were treated once daily and concentrations were collected immediately before and 1 hour after the second dose.
- A population PK model was developed to describe the observed amikacin concentration over time in both subpopulations.
- Potential covariates examined included sex, body weight (WT), age (AGE), height, serum creatinine (SCR, measured by enzymatic method), C-reactive protein, and serum albumin levels.
- A binary covariate TYPE was created to denote the two different patient groups (burn 1, oncology 0).
- NONMEM 7.3 and R packages were used for model development, evaluation and diagnostic plotting.

DEMOGRAPHICS

Characteristics	Burn (N=72)	Onc (N=111)	Pooled (N=183)
Age (years)	5 (0.83 – 15)	6.2 (0.8 – 16.4)	5.6 (0.83 – 15.8)
Sex (Male)	49 (68.1%)	62 (55.9%)	111 (60.7%)
Weight (kg)	21 (10.5 – 68.5)	20 (8.3 – 63.1)	20 (9.5 – 64.1)
Height (cm)	114 (71.9 – 175.8)	115.5 (67 – 175)	114 (70.5 – 175)
Serum Creatinine (mg/dL)	0.4 (0.2 – 1)	0.32 (0.15 - 0.68)	0.35 (0.17 - 0.8)
Creatinine Clearance (mL/min/1.73m^2)	170.5 (81.1 – 327.5)	195.4 (127.0 – 338.7)	190 (105.4 – 336.9)

Table 1. Patient characteristics. Sex distribution is presented as male numbers (percentage). Other demographics are presented as median (5th – 95th percentiles).

RESULTS

Parameters	Descriptions	Base Model		Final Model		Bootstrap Results	
		Estimates	95% CI	Estimates	95% CI	Mean	95% CI
CL (L/h)	Clearance	2.63	2.47 - 3.11	2.26	1.93 - 2.59	2.28	1.84 - 2.68
V1 (L)	Central volume of distribution	1.62	1.26 - 2.2	6.03	4.99 - 7.07	5.75	4.62 - 7.44
Q (L/h)	Distribution clearance	1.29	1.05 - 1.55	0.8	0.46 - 1.14	0.81	0.32 - 1.29
V2 (L)	Peripheral volume of distribution	8.36	7.32 - 10.8	4.92	2.76 - 7.08	6.22	0.93 - 8.92
CL-AGE	Age influence on CL	-	-	0.17	0.05 - 0.29	0.16	0.03 - 0.31
CL-CRCL	Creatinine clearance on CL	-	-	0.10	- 0.002 - 0.20	0.23	-0.07 - 0.27
CL-WT	Weight influence on CL	-	-	0.47	0.31 - 0.62	0.50	0.30 - 0.63
V1-AGE	Age influence on V1	-	-	0.25	0.09 - 0.42	0.25	0.06 - 0.45
V1-WT	Weight influence on V1	-	-	0.54	0.32 - 0.77	0.58	0.29 - 0.79
V2-AGE	Age influence on V2	-	-	0.22	0.09 - 0.34	0.29	-0.05 - 0.48
CL-TYPE (L/h)	Subpopulation influence on CL	-	-	0.65	0.40 - 0.90	0.64	0.35 - 0.95
V1-TYPE (L)	Subpopulation influence on V1	-	-	0.27	0.07 - 0.47	0.31	-0.01 - 0.54
ω^2 - CL	Variance of CL BSV	0.19	0.14 - 0.25	0.046	0.032 - 0.060	0.074	0.018 - 0.075
ω^2 - V1	Variance of V1 BSV	-	-	0.058	0.022 - 0.094	0.043	0.013 - 0.103
ω^2 - Q	Variance of Q BSV	0.08	-0.02 - 0.18	-	-	-	-
σ^2	Variance of prop residual error	0.11	0.08 - 0.14	0.054	0.036 - 0.072	0.064	0.033 - 0.075

Table 2. Parameter estimates. All continuous covariates (AGE, CRCL, WT) were imposed assuming power relationship. The categorical covariate TYPE (0=oncology, 1=burn) was imposed assuming linear relationship. Bootstrap finished with 99% successful rate.

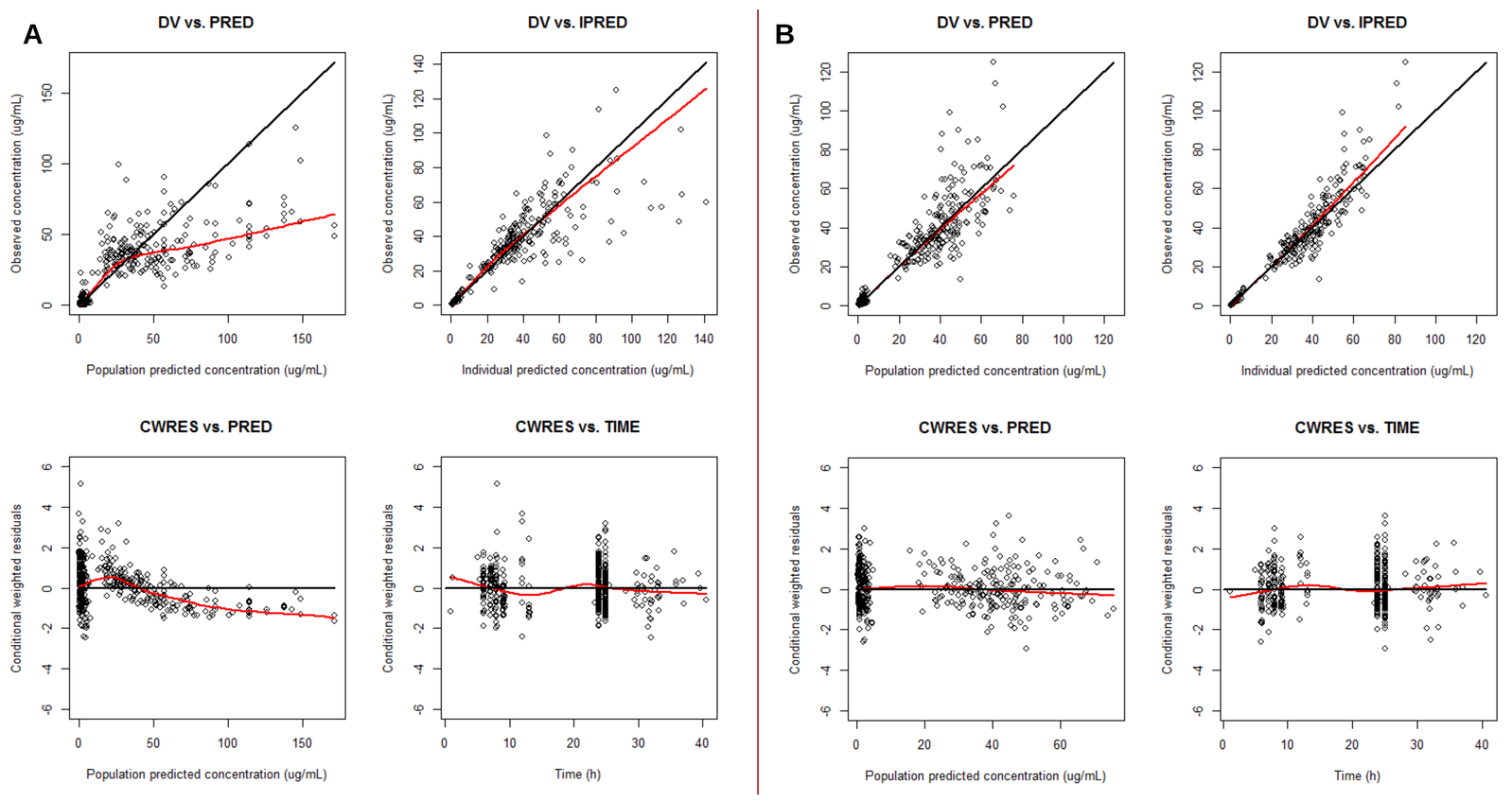

Figure 1. Diagnostic plots. A. base model. B. covariate model. Red line, loess smoothing curve with degree=1, span=2/3.

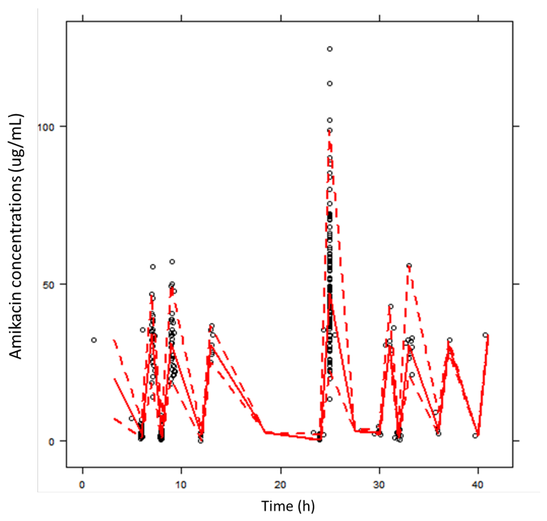

Figure 2. VPC plots. Solid line, model predicted median concentrations; dashed lines, model predicted 5th and 95th percentile concentrations.

CONCLUSION

The results of the current study suggest that besides patient-specific characteristics (current WT, AGE and CRCL) also disease-related characteristics should be considered when dosing amikacin in critically ill pediatric patients, in order to optimize therapeutic concentration targeting.

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REFERENCES

- Yu T et al., J Burn Care Res. 2015;36(4):e244-52
- Sherwin CM et al., Burns. 2014 Mar;40(2):311-8