Simultaneous pharmacokinetic modeling of gentamicin, tobramycin and vancomycin clearance from neonates to adults: towards a semi-physiological function for maturation in glomerular filtration. [1]

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Introduction

Glomerular filtration rate (GFR) is responsible for the elimination of a large number of water-soluble drugs. The aim of this analysis was to develop a **semi-physiological function** to describe **maturation in GFR-mediated clearance** from neonates to adults on the basis of simultaneous population pharmacokinetic modeling of **gentamicin, tobramycin** and **vancomycin**, drugs which are almost entirely eliminated through GFR.

To perform this analysis, a distinction was made between **drug-specific** and **system-specific** properties.

[1] Accepted Pharm Res, 2014

[2] Sherwin et al. J Pharm Pharmacol, 2009

[3] Lopez et al. Pediatr Crit Care Med, 2010

[4] de Hoog et al. Clin Pharmacol Ther,1997

[5] Anderson et al. Br J Clin Pharmacol, 2007

Methods

Table I: Overview of the patients characteristics (median (range))

Drug	Gentamicin [2,3]	Tobramycin [4]	Vancomycin [5]
Number of subjects	717	614	429
Number of blood samples	1705	1273	1168
Age	Median 2 days (1 day-15 yrs)	Median 3 days (2 days –18 yrs)	Median 16 days (1 day-17 yrs)
Subjects (n) per age group (range)			
1-28 days	682 (GA 23-43)	463 (GA 23-43)	283 (GA 23-34)
1-23 months	26	67	87
2-11 years	5	48	42
12-18 years	4	36	17
Bodyweight	2600g (440g – 80kg)	2010g (485g-85kg)	1800g (415g-85kg)
Serum creatinine (μmol/L)	72 (12-104)	72 (5-130)	51 (7-144.1)

A pharmacokinetic model was developed using NONMEM VI. The pediatric covariate model was considered to contain system-specific information on the developmental changes in GFR and therefore the same covariate model on clearance was implemented on all three drugs. The population values for clearance and volume of distribution were considered drug-specific values and estimated for each drug separately. Bodyweight, age, creatinine concentrations, co-administration of ibuprofen, indomethacin, diuretics, amoxicillin and type of aminoglycoside were tested as covariates.

Results: Model Building

A one compartment model was developed in which GFR mediated clearance from preterm neonates to adults was best described by a **bodyweight-dependent exponent (BDE) function** (Eq. 1), in which the BDE exponent varied from **1.4 in neonates to 1.0 in adults** (Table II)

Population clearance values for gentamicin, tobramycin and vancomycin were 0.21 L/h, 0.28 L/h and 0.39 L/h for a full term neonate of 4 kg, respectively (Table II).

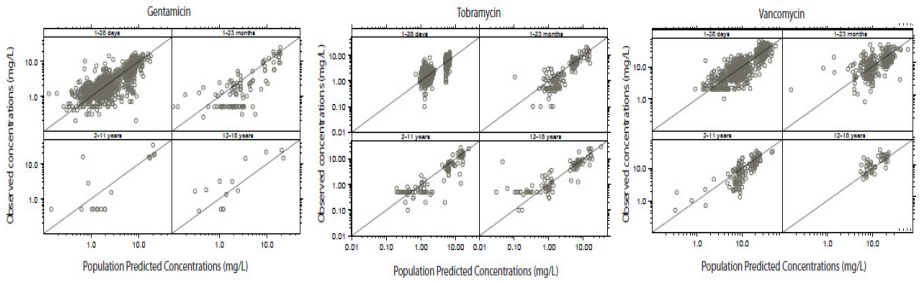
$$CL_{GFR} = CL_{Drug} \times \left(\frac{BW}{4kg}\right)^{BDE} \qquad BDE = L1 \times BW^{M}$$

Equation 1: Allometric equation with an exponent that varies with bodyweight. CL_{GFR} is clearance by glomerular filtration, *BW* is bodyweight, CL_{Drug} is the clearance of the drug (gentamicin, tobramycin, vancomycin); *L*1 is the intercept of the scaling exponent and *M* is the exponent which allows the scaling exponent to change with bodyweight.

Table II: Population parameter estimates of the final model

Parameter	Final pharmacokinetic covariate model (CV%)
L1	2.23 (6.23)
M	-0.065 (-12.1)
CLgenta $_{4kg}$ (L/h)	0.21 (2.01)
CLtobra $_{4kg}$ (L/h)	0.28 (2.47)
CL vanco $_{4kg}$ (L/h)	0.39 (2.72)
V1genta $_{4kg}$ (L)	1.45 (2.94)
V1tobra $_{4kg}$ (L)	1.90 (1.99)
V1vanco $_{4kg}$ (L)	2.22 (2.63)
k2 in V1genta =V_{4kg} x (BW/4kg)^{k2}	0.759 (4.35)
k3 in V1tobra = V_{4kg} x (BW/4kg)^{k3}	0.735 (2.56)
k4 in V1vanco = V_{4kg} x (BW/4kg)^{k4}	1 FIX
Qgenta = CLgenta, Qtobra = CLtobra, Qvanco = CLvanco, V2genta = V1genta, V2tobra = V1tobra, V2vanco = V1vanco	
ω^2 on CLgenta	0.143 (12.5)
ω^2 on CLtobra	0.158 (16.5)
ω^2 on CLvanco	0.171 (10)
σ^2 (proportional)	0.0886 (5.21)
σ^2 (additive) (mg/L)	0.0494 (22.7)

Figure 1: Observed versus population predicted concentrations of the final system-specific pharmacology model for gentamicin, tobramycin and vancomycin, split by four age categories.



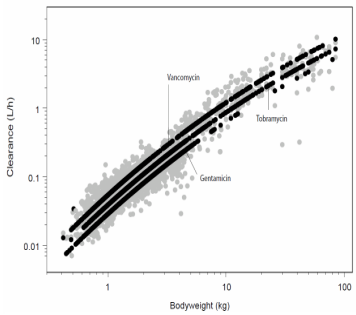
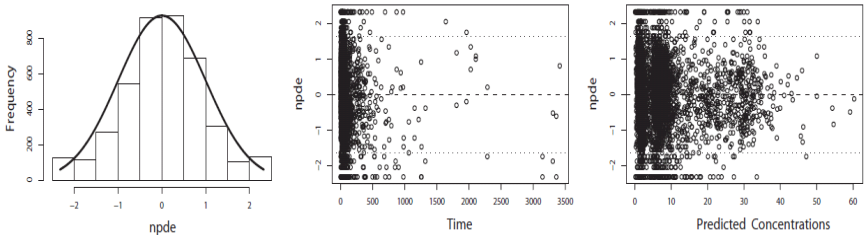


Figure 2: Individual (grey) and population predicted (black) clearance values for gentamicin, tobramycin and vancomycin versus bodyweight (kg) for the final system-specific pharmacology model.

Figure 3: NPDE results of the final system-specific pharmacology model for the three different drugs. Left panel: Histogram of the NPDE distribution with the solid line representing a normal distribution, middle panel: NPDE *versus* time, right panel: NPDE *versus* predicted concentrations.



Conclusions

Based on an integrated analysis of gentamicin, tobramycin and vancomycin data, a **semi-physiological function** for **GFR mediated clearance** was derived that can potentially be used to establish **evidence based dosing regimens** of renally excreted drugs in children.