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Population Pharmacokinetics and Relationship Between Demographic and Clinical Variables and Pharmacokinetics of Gentamicin in Neonates

L. M. L. Stolk,* P. L. J. Degraeuwe,† F. H. M. Nieman,‡ M. C. de Wolf,§ and A. de Boer§

*Departments of *Clinical Pharmacy, †Pediatrics, and ‡Clinical Epidemiology of the University Hospital of Maastricht; §Utrecht Institute for Pharmaceutical Sciences, Utrecht, The Netherlands.*

Summary: Population pharmacokinetic parameter estimates were calculated from 725 routine plasma gentamicin concentrations obtained in 177 neonates of 24 to 42 weeks' gestational age in their first week of life. K_{el} increases and V/W decreases with increasing gestational age. Almost identical results were obtained with iterative two-stage Bayesian fitting (MW\PHARM 3.30) as with a non-parametric maximization algorithm (NPEM2). The effect of various covariates on drug disposition was investigated retrospectively using multiple regression analysis. Predictive power for K_{el} increases with rising gestational age. For neonates ≤28.5 weeks and neonates >28.5 weeks and ≤30.9 weeks, the predictive power of the regression equation for K_{el} was relatively low (r^2 respectively 0.270 and 0.364). Better predictivity was found for K_{el} at gestational ages >30.9 weeks ($r^2 = 0.482$), with gestational age, postnatal age, and Apgar score at 5 minutes being predictors. A very strong correlation existed between volume of distribution and weight ($r^2 = 0.83$). Volume as a function of weight could be described with low predictivity by gestational age and to a lesser degree by Apgar score at 5 minutes ($r^2 = 0\ .298$)

The developed models need appropriate prospective clinical validation. **Key Words:** Newborn—Gentamicin pharmacology—Population pharmacokinetics—Predictors—Multiple regression analysis.

The aminoglycoside gentamicin is commonly used in combination with a β-lactam for prophylaxis or treatment of infections in preterm and term neonates (1). As a result of the narrow therapeutic range, the large interpatient variability of gentamicin disposition, and the heterogeneity of the neonatal population, dosage regimens should be individualized. Several recommendations for the initial gentamicin dosing, based on patients' demographic characteristics, have been proposed (2–5). Once plasma concentrations are available, the dosage regimen is often adjusted by pharmacokinetic modeling using maximum a posteriori Bayesian fitting. The Bayesian method uses measured drug concentrations, population-based parameters, and the expected variability associated with each measurement to determine individualized kinetic parameters of a patient. Bayesian fitting performs favorably for prediction of individual pharmacokinetic parameters in comparison with other methods like linear and non-linear least-squares regression (6). However to be able to successfully apply Bayesian forecasting, prior knowledge of the population parameters is needed (7). Several reasons caution against generalization and application of already published data: inhomogeneity of the population especially in respect to postnatal age, small number of patients and drug levels measured, incomplete

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Address correspondence and reprint requests to Dr L M L Stolk, Dept of Clinical Pharmacy and Toxicology, University Hospital of Maastricht, PO Box 5800, 6202 AZ Maastricht, The Netherlands; E-Mail LSTO@KFLS.AZM

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data, and differences or lack of information about demographic and clinical characteristics of the study populations. Therefore we have studied retrospectively the population pharmacokinetic parameters in a large sample of 177 preterm and term neonates during the first week of life with a nonparametric expectation maximization algorithm. In addition, we explored the impact of several demographic and clinical parameters on individual gentamicin pharmacokinetic parameters. In this study, the relationship between the individual gentamicin pharmacokinetic parameters and covariates was investigated using a three-step approach involving (1) Bayesian estimation of individual pharmacokinetic parameters for each patient, (2) selection of covariates, and (3) final model selection with multiple regression analysis.

MATERIALS AND METHODS

Study Design

Neonatal patients admitted from 1998 through 2000 to the Neonatal Intensive Care Unit at the University Hospital of Maastricht were eligible for this retrospective study. Infants were included if their postnatal age was ≤8 days, at least one peak and one trough gentamicin concentration were determined and patient data such as GA, PNA, W and dosing and sampling times, were available.

Parameters

The following patient characteristics were recorded: gestational age (wk) at birth (GA), postnatal age (PNA), weight (W), length (L) at the start of the therapy, gender (M/F), multiple pregnancy, Apgar score at 5 minutes (APGAR5), arterial cord pH (ApH), C-reactive protein (CRP), blood culture result, and co-medication of mother (indomethacin, corticosteroids, and β-mimetics). Body surface area (BSA) was calculated according to Haycock's formula (8). CRP >9 mg/L was considered positive. We have defined possible infection (POSINF) as CRP-positive or blood culture–positive and probable infection (PROBINF) as both CRP- and blood culture–positive. Since plasma creatinine in the first 2 weeks of life does not reflex the infant's glomerular filtration rate, this parameter was not included. The high plasma creatinine levels of the newborn represent maternal levels, and shortly thereafter tubular reabsorption seems to be responsible for the continued high plasma creatinine levels (9).

Administration and Dosage Regimen

Antibiotic therapy, including gentamicin, was given to infants presenting risk factors or signs of neonatal sepsis. A loading dose of 5 mg/kg (0.5 h infusion) was followed by maintenance doses of 2.5 mg/kg at 24-, 18-, and 12-hour intervals, according to GA: <30, 30–34, and >34 weeks, respectively. This dosing scheme was routinely used in our neonatology department. Blood samples were collected just before (trough) and 0.5 hours after the end of the second infusion (peak). Several peak/trough levels were measured on the days thereafter (maximum, 2 d) totalling a mean of 4.1 measurements per infant.

Co-medication

For prevention of peri-intraventricular hemorrhage, all neonates of GA <30 weeks and/or birth weight ≤1.25 kg were treated with indomethacin 0.1 mg/kg every 24 hours for 3 days. The influence of maternal prenatal co-medication of corticosteroids, indomethacin, and β-mimetics on the neonatal pharmacokinetic parameters was also studied. Influence of co-medication of the children was not included in this study because no significant interactions were found. However information about co-medication could not always be recovered.

Analytical Techniques

Concentrations of gentamicin were measured with fluorescence polarization immunoassay with the use of a TDxFLx (Abbott, Amstelveen, The Netherlands). The coefficient of variation for the gentamicin assay was less than 5% in the range 1 to 10 mg/L. The limit of detection was 0.27 mg/L (10). The error pattern of the assay was $SD = 0.02458 + 0.04948\ C + 0.0020318\ C^2$ (11).

Data Analysis

Population pharmacokinetic parameters for each dosage GA subgroup were calculated: group A (GA <30 wk;

TABLE 1. *General characteristics of the study population*

	Unit	N	Mean (SD)	Range
GA	weeks	177	32.4 (5.1)	24.0–42.4
PNA	days	177	1.96 (1.69)	0–8
Weight	kg	177	1.85 (1.04)	0.57–4.35
Length	cm	148	41.4 (6.1)	27.2–55
BSA	m^2	148	0.140 (0.049)	0.072–0.255
APGAR5	points	160	8.43 (1.58)	0–10
Arterial cord pH	pH	117	7.16 (0.13)	6.65–7.39

APGAR5, Apgar score at 5 minutes; BSA, body surface area; GA, gestational age; PNA, postnatal age.

TABLE 2. *Pharmacokinetic parameters according to gestational age group and mathematical approach*

		Group A (n = 73) GA < 30*	Group B (n = 50) 30 ≤ GA ≤ 34*	Group C (n = 54) GA > 34*
K_{el} (h^{-1})	NPEM2	0.0491 ± 0.0205	0.0688 ± 0.0196	0.1051 ± 0.0325
K_{el} (h^{-1})	MW\PHARM	0.054 ± 0.0170	0.0689 ± 0.0205	0.1018 ± 0.0281
V/W (L/kg)	NPEM2	0.7085 ± 0.2182	0.5641 ± 0.1017	0.5041 ± 0.1631
V/W (L/kg)	MW\PHARM	0.7006 ± 0.1242	0.5739 ± 0.0875	0.5279 ± 0.1145

* Values are expressed as median ± averages of DF50 and DF90.

GA, gestational age; K_{el}, first-order elimination constant; MW\PHARM, MW\PHARM computer program for MAP Bayesian fitting; NPEM2, nonparametric expectation maximization.

n = 73), Group B (30 ≤ GA ≤ 34 wk; n = 50), Group C (GA >34 wk; n = 54). Analysis took place according to a one-compartment open model with an iterative two-stage Bayesian fitting procedure (IT2B) (MW\PHARM 3.30, Mediware, The Netherlands) (12). MW\PHARM is the commonly used computer program for MAP Bayesian fitting of TDM results in the Netherlands. Recently an IT2B module has been added to the program. Population parameters were also calculated with a nonparametric expectation maximization algorithm (NPEM2, USCPACK 10.7, University of Southern California, USA) (13). We also analyzed the data with this program because a nonparametric method has the ability to discover subpopulations (13). The number of grid points used was 40,009. Individual pharmacokinetic parameters were calculated by maximum a posteriori Bayesian fitting (MW\PHARM 3.30).

Statistical analyses and multiple regression analyses were performed using SPSS 8.0 software (SPSS, Chicago, Illinois, USA). In cases of effect modification, subgroup analyses were performed (14). Discrete variables like POSINF and PROBINF were defined as dummy variables. Normal distribution of parameters was checked by residual analysis. Listwise deletion of missing cases was made for each regression equation. One-way ANOVA with Bonferroni multiple-comparison procedure was used to compare model parameter estimates.

RESULTS

Demographic and Clinical Characteristics

Table 1 summarizes the patient characteristics. The population consisted of 94 boys and 83 girls. Ninety-eight patients were products of singleton pregnancies, 50 were members of a twin pregnancy, and 8 were members of a triplet pregnancy (and 21 missing data). CRP and blood culture were both positive in 11 patients and CRP or blood culture was positive in 75 patients. Both CRP and blood culture were negative in 72 patients. There were 19 missing data. Gentamicin peak and trough concentrations around the second dose were respectively 5.95 ± 1.3 and 2.28 ± 0.82 mg/L (mean ± SD).

Population Pharmacokinetic Parameters

Population pharmacokinetic parameters were calculated for each dosage subgroup with MW\PHARM and with NPEM2. The results are given in Table 2. K_{el} increases and V/W decreases with increasing GA. No subpopulations or clinically important outliers have been detected. Log-likelihood values found for NPEM2 and MW/PHARM were respectively: group A—518.597 and 123.746; group B—246.133 and 71.840; group C—210.195 and 103.659. The mean (± SD) for K_{el} and V/W, calculated for each individual subject, were respectively: 0.0538 ± 0.0151 h^{-1} and 0.7244 ± 0.1561 L/kg (group A), 0.0736 ± 0.0198 h^{-1} and 0.5808 ± 0.0896 L/kg (group B), 0.1067 ± 0.0308 h^{-1} and 0.5504 ± 0.1101 L/kg. The differences in K_{el} and V/W between the three GA subgroups were highly significant ($P < 0.001$) except for V/W between subgroups B and C.

Predictors of Pharmacokinetic Parameters: K_{el}

GA, APGAR5, and PNA were statistically significant predictors for K_{el} in the total population (n = 160, 17 missing data). Results are given in Table 3. Next to these, there existed a significant interaction between GA and APGAR5 resulting in effect modification. Therefore, a subgroup analysis was performed with GA divided in quartiles. As the results for the two quartiles with the more advanced GA were similar, they were combined. The results of the subgroup analysis are given in Table 4.

Predictors of Pharmacokinetic Parameters: V

The results are given in Table 5. However, the correlation between volume and weight is very high (>90%)

TABLE 3. *K_{el} regression results**

Predictor	b	s.e.b.	β	t	p
GA	−0.00194	0.002	−0.311	−1.12	0.27
APGAR5	0.00454	0.006	−1.083	−3.32	0.001
PNA	−0.0213	0.001	0.252	5.19	<0.001
GA*APGAR5	0.000742	<0.001	1.736	3.71	<0.001
Constant	0.105	0.055		1.90	0.06

*Total group n = 160; $r^2 = 0.642$

APGAR5, Apgar score at 5 minutes; GA, gestational age; K_{el}, first-order elimination constant; PNA, postnatal age.

TABLE 4. *K_{el} regression results subgroups*

Predictor	b	s.e.b.	β	t	p
Subgroup GA < 28.5 weeks; N = 43; r^2 = 0.270:					
PNA	0.0058	0.001	0.520	3.90	<0.001
Constant	0.0416	0.004		11.65	<0.001
Subgroup 28.5 ≤ GA ≤ 30.9; N = 46; r^2 = 0.364:					
PNA	0.00546	0.001	0.630	5.02	<0.001
Constant	0.0489	0.003		14.55	<0.001
Subgroup GA > 30.9 weeks; N = 79; r^2 = 0.482:					
PNA	0.00440	0.002	0.213	2.52	0.014
GA	0.00461	0.001	0.550	6.53	<0.001
APGAR5	0.00476	0.002	0.235	2.77	0.007
Constant	−0.124	0.028		−4.40	<0.001

APGAR5, Apgar score at 5 minutes; GA, gestational age; K_{el}, first-order elimination constant; PNA, postnatal age.

(r^2 = 0.83; n = 177), making the model maybe unreliable because of collinearity.

Predictors of Pharmacokinetic Parameters: V/W

The results are given in Table 6. Because results of blood culture and possibly CRP also are usually not available at the start of the therapy, we have also calculated V/W expected without PROBINF AND POSINF: Table 7.

The standardized studentized residuals of all the models appeared to be normally distributed.

DISCUSSION

Population Pharmacokinetics

This study explored the population pharmacokinetics of gentamicin during the first week of life in a population comprising gestational ages from 24 to 42 weeks. Our data confirm that K_{el} increases and V/W decreases with increasing GA. These findings reflect a developmental increase in glomerular filtration rate and a decrease of total body water and extracellular water with gestational age (15–17). Comparison with published data is very difficult for reasons we outlined in the introduction. However in comparison with our data Dodge et al (18) found lower K_{el} and higher V/W for GA≤ 31 and 31< GA <34, respectively. We attribute the somewhat slower gentamicin elimination rate in the most immature patient group to the routine use of prophylactic indomethacin, which diminishes glomerular filtration rate. For clinical purposes the total population has been subdivided in three subgroups based on GA categories. These subpopulations were already used for dosing guidelines. The pharmacokinetic population parameters of the GA groups found with both NPEM and MW\PHARM were almost identical. Averages of DF50 and DF90 of the pharmacokinetic parameters found with NPEM were somewhat larger than those calculated with MW\PHARM, implicating larger interindividual variability.

The gentamicin disposition data have yielded a new initial dosing regimen (Table 8). Target trough level was below 1 mg/L (19). Target peak levels were set at a minimum of 5 mg/L and preferably 10 times the minimum inhibitory concentration (MIC) of the infecting microorganism because of the possibility of emergence of resistance. The MIC of the most important gram negative pathogen, *Escherichia coli*, is 1 mg/L, so target peak levels must lie in the upper part of the 5 to 10 mg/L range. This dosage regimen strongly resembles a recently proposed dosage regimen (20). In addition, the established population parameters are now being used in combination with gentamicin plasma concentrations for the calculation of the individual pharmacokinetic parameters.

TABLE 5. *Volume regression results**

Predictor	b	s.e.b.	β	t	p
Weight	0.666	0.050	1.212	13.21	<0.001
GA	−0.0372	0.010	−0.329	−3.58	<0.001
Constant	1.076	0.252		4.26	<0.001

GA, gestational age.
* Total group; N = 177; r^2 = 0.829.

TABLE 6. *Volume/weight regression equation results**

Predictor	b	s.e.b.	β	t	p
GA	−0.0314	0.002	−0.453	−6.38	<0.001
APGAR5	−0.0219	0.007	−0.234	−3.32	0.001
POSINF	0.0651	0.021	0.217	3.04	0.003
PROBINF	0.0186	0.047	0.028	0.40	0.692
Constant	1.220	0.080		15.19	<0.001

* Total group n = 144; r^2 = 0.336.
APGAR5, Apgar score at 5 minutes; GA, gestational age; POSINF, possible infection; PROBINF, probable infection.

Prediction of Individual Pharmacokinetics

The second aim of this study was to trace other demographic and clinical parameters influencing drug disposition. In newborns of less than 30.9 weeks GA, K_{el} was a fixed value only slightly influenced by PNA. The postnatal increase of GFR in the first week of life is known to be slow in infants with GA of 25 to 34 weeks when compared with full-term infants (15). In the current study, the use of prophylactic indomethacin may have accentuated this phenomenon. Better prediction of K_{el} is possible in neonates of greater than 30.9 weeks GA. In those babies, K_{el} is determined mainly by GA and to a lesser extent by APGAR5 and PNA. The correlation between V and W is a very strong, leading to the assumption that V is mainly determined by W. V/W for the total population can be predicted by GA and to a lesser extent by APGAR5 and PROBINF and POSINF. However predictive power is rather low. Because results of bacterial growth are nearly always unknown at the start of therapy, POSINF and PROBINF cannot be used as such. In other studies GA, PCA, PNA, urine output, and creatinine clearance were identified as predictors for the gentamicin clearance and W as predictor for V (2,4,5). Some of these co-variates were identified in our study as well. Our study compares favorably in several ways with other studies: extensive subdivision in GA categories, which was made possible by the large number and homogeneity of our study population; satisfactory number of plasma levels per patient (mean 4.1); the inclusion of AGPAR5, CRP, and blood culture as co-variables; and the predictive model for V/W.

CONCLUSION

During the first week of life, gentamicin K_{el} increases and V/W decreases with increasing GA. Regression analysis demonstrated an additional influence of PNA and APGAR5 on K_{el} in neonates of >30.9 weeks GA. In the whole population there is an added effect of APGAR5 and infection on V/W. The developed models need appropriate prospective clinical validation.

TABLE 7. *Volume/weight regression results (model without infection)**

Predictor	b	s.e.b.	β	t	p
GA	−0.0129	0.002	−0.436	−6.38	<0.001
APGAR5	−0.0232	0.006	−0.249	−3.64	<0.001
Constant	1.242	0.076		16.31	<0.001

* Total group: N = 160; r^2 = 0.298
APGAR5, Apgar score at 5 minutes; GA, gestational age.

TABLE 8. *Initial gentamicin dosing regimen based on population pharmacokinetic parameters and aiming at a peak level of 6–10 mg/L and a trough level of <1 mg/L*

Gestation age (wk)	Dose (mg/kg dose)	Interval (h)
≤30	5.0	48
30–34	4.5	36
>34	4.0	24

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