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Comparison of Four Renal Function Estimation Equations for Pharmacokinetic Modeling of Gentamicin in Geriatric Patients

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Most aminoglycoside pharmacokinetic models include an index of renal function, such as creatinine clearance, to describe drug clearance. However, the best clinical descriptor of renal function for the pharmacokinetic modeling of aminoglycosides has not been established. This analysis was based on 412 gentamicin concentrations from 92 geriatric patients who received intravenous gentamicin for various infectious diseases. Four two-compartment population models were fitted to gentamicin concentrations in a learning set of 64 patients using the nonparametric adaptive grid (NPAG) algorithm. Each model included an index of renal function, namely, the Cockcroft-Gault (CG), Jelliffe (JEL), modification of diet in renal disease (MDRD), or modified MDRD (MDRDm; adjusted to individual body surface area) equation as a covariate influencing gentamicin serum clearance. Goodness of fit and predictive performance of the four models were compared using standard criteria in both the learning set and in a validation set of 28 patients. A final analysis was performed to estimate the population pharmacokinetic parameter values of the entire 92-patient group. In the learning set, the CG-based model best fit the data, followed by JEL-, MDRD-, and MDRDm-based models, with relative reductions of the Akaike information criterion of 29.4, 20.2, 14.2, and 4.2, respectively. Bias and precision of population predictions were significantly different among the four models. In the validation set, individual predictions from the four models showed marginally different biases. The final estimation confirmed the previous results. Specifically, the CG-based model showed predictive performance that was comparable to or better than that of the MDRD-based model at each stage of the analysis. This study shows that methods used to estimate renal function should not be considered interchangeable for the model-based estimation of gentamicin concentrations.

The elimination kinetics and clinical dosing of aminoglycosides depends on renal function (2, 4). Many pharmacokinetic (PK) studies have reported a positive correlation between aminoglycoside serum clearance or elimination rate constant and estimated or measured creatinine clearance (CL_{CR}) (22, 23, 34, 41). Model-based, Bayesian estimation is considered to be the most efficient method to monitor and adjust dosage regimens of aminoglycosides in patients (2, 36). Such a procedure requires the prior identification and validation of the best structural and covariate models in a patient population (21). In the pharmacokinetic modeling of aminoglycosides, the incorporation of renal function as a covariate influencing aminoglycoside elimination usually improves the model fit and its predictive performance (20, 40).

While gold standards of renal function measurement are available, such as the clearance of inulin, iothalamate, or some radiolabeled molecules (e.g., EDTA), their application is limited to research. In clinical practice, renal function is most often estimated by the use of equations. For adults, the Cockcroft-Gault (CG) and the four-variable modification of diet in renal disease (MDRD) formulas are currently the most widely used equations for such a task in clinical practice. In the last decade, the MDRD equation has been extensively studied for the estimation of glomerular filtration rate (GFR) in various populations of patients. However, little is known about the use of this equation as a descriptor for the pharmacokinetic modeling and dose adjustment of renally excreted drugs (11). The equation that best predicts aminoglycoside clearance has not been established yet. The objective of the present study was to compare the performance of four renal function estimation equations for the population pharmacokinetic modeling of gentamicin.

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MATERIALS AND METHODS

Study population and renal function estimation. This was a retrospective study performed on patients hospitalized in various geriatric units from January 2001 to October 2009. Most patients were hospitalized in the University Hospitals of Lyon (Hospices Civils de Lyon). A few patients were hospitalized in Albigny and Villefranche hospitals, both located in the Lyon area. All patients benefited from routine therapeutic drug monitoring and the Bayesian adaptive control of their gentamicin dosage regimens using the MM-USC*PACK collection of programs (http://www.lapk.org; Laboratory of Applied Pharmacokinetics, USC School of Medicine, Los Angeles, CA). Patients who received gentamicin by the intramuscular route and those who had fewer than two serum level measurements were excluded.

For patients hospitalized in the University Hospitals of Lyon, the cre-

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atinine assay was based on an endpoint Jaffé reaction (colorimetric method) performed on an Olympus automated analyzer. Gentamicin concentrations were measured by turbidimetric assay on a Dimension Expand system (Siemens Healthcare Diagnostics, Deerfield, IL). The performance of the gentamicin assay, expressed as a coefficient of variation (CV), was 3.9, 2.65, and 2.38% for gentamicin levels of 3.0, 5.6, and 7.8 mg/liter, respectively.

For each patient, available data were age, sex, weight, height, serum creatinine levels, and gentamicin dosing history, including drug amounts, dosing times, infusion durations, and blood sampling times. Any changes in covariate levels during the therapy (e.g., body weight, serum creatinine) also were recorded precisely. Of note, 9 low serum creatinine values (4%) from 6 patients were rounded to 0.6 mg/dl (53 μmol/liter) because of the requirements of the MM-USC*PACK software.

For each patient, renal function was estimated and updated for any change of serum creatinine. Four equations were used to estimate renal function: the Jelliffe (JEL) (18), Cockcroft-Gault (8), MDRD (25), and modified MDRD (MDRDm; adjusted for individual body surface area) equations. The Jelliffe equation is implemented in the MM-USC*PACK software. The Cockcroft-Gault and MDRD equations were selected because they are currently the equations most widely used to estimate renal function in clinical practice. The MDRD equation adjusted to individual body surface area was selected because such an adjustment has been recommended for drug dosing in very small or large patients by the National Kidney Disease Education Program (http://nkdep.nih.gov/professionals/drug-dosing-information.htm#top).

The four equations are detailed below. The Jelliffe equation (18) is CL_{CR} (ml/min/1.73 m^2) = $[P - 0.4 \cdot W \cdot (C_2 - C_1)/T]/[(C_1 + C_2)/2 \cdot 1{,}440] \cdot (1.73/BSA)$, where P is the adjusted daily production of creatinine (in milligrams per day; estimated from previous works), W is total body weight (in hundreds of grams), C_1 and C_2 are the first and second serum creatinine values (in mg/dl), T is the time between the two serum creatinine samples (in days), and 1,440 is the number of minutes in 1 day. The estimate is adjusted to body surface area (BSA; in m^2) and expressed per 1.73 m^2 of surface area. Body surface area was estimated using the Gehan and George equation (13). The Cockcroft-Gault equation (8) is CL_{CR} (ml/min) = $[(140 - \text{age}) \cdot \text{weight} \cdot A]$/serum creatinine, where A is 1.23 if male, 1.04 if female. Age is measured in years, weight in kilograms, and serum creatinine in μmol/liter. The four-variable simplified MDRD equation (25) is GFR (in ml/min/1.73 m^2) = $186 \cdot (\text{serum creatinine} \cdot 0.0113)^{-1.154} \cdot \text{age}^{-0.203}$ (with the result multiplied by 0.742 if female and 1.21 if black). The four-variable simplified MDRD equation adjusted to BSA is GFR (ml/min) = GFR(MDRD) · (BSA/1.73 m^2), where BSA is the patients' individual body surface area estimated by the Du Bois formula (12).

Pharmacokinetic model building. The patient population was divided in two groups by random selection: a learning set of 64 patients and a validation set of 28 patients. The learning set was used for model selection and the initial estimation of pharmacokinetic parameters. The learning set then was used for the external validation of the predictive performance of the models selected in the first stage. The nonparametric adaptive grid (NPAG) algorithm (24) was used as the population approach for all analyses.

One-, two-, and three-compartment models without any covariates were fitted to gentamicin concentrations to determine the best structural model in the learning set. The influence of body weight on gentamicin volume of distribution (V_D) and estimated creatinine clearance (or estimated glomerular filtration rate) on gentamicin clearance then were assessed in the selected structural model.

The covariate models were described with the following linear functions.

$$V_D = V_S \cdot W \quad (1)$$

V_D is the gentamicin volume of distribution (liters), V_S is a slope parameter (liters/kg), and W is the total body weight (kg).

Gentamicin clearance was classically modeled as the addition of nonrenal and renal clearance, the latter being linearly correlated with renal function.

$$CL_{GEN} = CL_{NR} + CL_S \cdot E \quad (2)$$

CL_{GEN} is gentamicin total clearance (liters/h), CL_{NR} is gentamicin nonrenal clearance (liters/h), CL_S is the renal elimination coefficient, and E is the estimated creatinine clearance or estimated glomerular filtration rate calculated with the CG, JEL, MDRD, or MDRDm equation (in ml/min or ml/min/1.73 m^2).

The goodness of fit of candidate models was assessed using the likelihood-derived Akaike information criterion (AIC) (1). In comparing one model to another, a lower AIC value indicates a better fit. Bias and precision were used as measures of predictive performance for both population and individual predictions provided by the four models (35). Bias and precision were calculated as mean error (ME; in mg/liter) and mean squared error (MSE; in $mg^2/liter^2$) of prediction, respectively, according to the equations $ME = \Sigma (Cp_i - Co_i)/n$ and $MSE = \Sigma (Cp_i - Co_i)^2/n$, where Co_i and Cp_i represent the individual concentrations observed and predicted by the model (in mg/liter), respectively, and n is the total number of measured concentrations.

In addition, the graphical analysis of observed versus predicted concentrations was performed.

The model including body weight as a covariate on gentamicin volume of distribution did not provide a better fit than a simple two-compartment model (AIC values of 693 and 687.2, respectively). In contrast, the incorporation of renal function as a covariate for gentamicin clearance significantly improved the fit with each of the four estimation equations. The final model was a classical linear two-compartment model using renal function estimation as a covariate. The differential equations describing this model are the following:

$$dX_1/dt = R(1) - [(CL_{NR} + CL_S \cdot E)/V_D] \cdot X_1 - k_{CP} \cdot X_1 + k_{PC} \cdot X_2 \quad (3)$$

$$dX_2/dt = k_{CP} \cdot X_1 - k_{PC} \cdot X_2 \quad (4)$$

Where X_1 and X_2 are the amounts of gentamicin in the central and peripheral compartment (in mg), respectively, $R(1)$ is the infusion rate of gentamicin (in mg/h), CL_{NR}, CL_S, and E are the clearance parameters and covariate as described above, V_D is the volume of distribution of the central compartment (in liters), and k_{CP} and k_{PC} are the intercompartment transfer rate constants (h^{-1}). The output equation providing gentamicin serum concentration (Y_1, in mg/liter) is the following:

$$Y_1 = X_1/V_D \quad (5)$$

In the NPAG modeling procedure, each drug concentration was weighted by the reciprocal of the assay variance at that concentration. The overall assay error pattern was described by a second-order polynomial:

$$SD(Y_i) = 0.311 - 0.0918 \cdot Y_i + 0.0167 \cdot Y_i^2 \quad (6)$$

Where $SD(Y_i)$ is the predicted assay standard deviation for the measured concentration Y_i.

Validation of the PK model. The predictive abilities of the four final models were assessed in a subset of 28 patients who were not included in the previous analysis. The population nonparametric joint densities of pharmacokinetic parameters estimated by the NPAG algorithm in the learning set were used to calculate population predictions. Those predictions are important in clinical practice for guidance in initial dosing when no drug concentration is available from a patient. In addition, those densities were used as priors for the Bayesian estimation of individual parameters of the 28 patients and the subsequent calculation of individual predictions. Such an evaluation of Bayesian posterior estimates is important to assess the application of the models for the individual adaptive control of dosage regimens. Bias and precision of both population and individual predictions from the four models were compared.

Final analysis. Finally, the four models were fitted to gentamicin concentrations of all 92 patients to get final estimates of PK parameters. The nonparametric population joint densities estimated in the 64-patient

TABLE 1 Characteristics of the 92 patients treated by intravenous gentamicin

Characteristic	Result	
	Means ± SD	Median (min, max)
Gender (no. men/women)	37/55	
Age (yr)	82.7 ± 7.3	83.5 (63, 97)
Weight (kg)	65.0 ± 16.5	62.0 (41, 120)
Height (cm)	164 ± 8.4	165 (147, 186)
Body surface area (m^2)	1.70 ± 0.2	1.67 (1.35, 2.25)
Body mass index (kg/m^2)	24.2 ± 6.1	22.9 (15.4, 49.9)
Serum creatinine[a] (mg/dl)	1.24 ± 0.56	1.11 (0.6, 3.26)
Serum creatinine[a] (μmol/liter)	109.8 ± 49.5	97.7 (53.0, 288.2)
Initial dose of gentamicin (mg/kg)	3.8 ± 1.9	3.4 (0.9, 13.6)
Initial dose of gentamicin (mg)	243 ± 147	200 (80, 1,200)
CL_{CR} JEL[a] (ml/min/1.73 m^2)	43.2 ± 18.1[b]	40.6 (12.9, 99.3)
CL_{CR} CG[a] (ml/min)	44.2 ± 20.2[b]	42.2 (9.5, 101.4)
GFR MDRD[a] (ml/min/1.73 m^2)	62.4 ± 28.2[b]	58.5 (14.8, 142.4)
GFR MDRDm[a] (ml/min)	60.5 ± 27.8[b]	58.5 (12.0, 144.0)

[a] $n = 224$.
[b] The estimates of renal function from the four equations were significantly different ($P < 0.001$ by global comparison).

learning set were used as initial prior distributions for this population analysis. The goodness of fit and predictive performance were assessed as described above for the learning set.

Statistical comparison. The nonparametric Kruskal-Wallis test was used to compare the bias and precision of the four models at each stage of the analysis. A specific comparison of the CG-based model and the MDRD-based model was also performed using the Mann-Whitney test. Statistical significance was set at 0.05 for all comparisons. The Kruskal-Wallis test was also used to compare the estimation of renal function provided by the four formulas.

RESULTS

The characteristics of the whole study population are shown in Table 1. The mean initial dose of gentamicin was 3.8 mg/kg (243 mg). About two-thirds of patients (63%) were administered gentamicin once daily as the initial dose interval. Twenty-nine percent of patients received gentamicin under traditional dosing (2 to 3 doses per day) and 8% under an extended interval (>24 h) as the initial dosing. Both gentamicin dose and dosing interval could have been adjusted during subsequent therapeutic drug monitoring and the Bayesian adaptive control of gentamicin therapy.

Estimations of renal function from the four equations were significantly different ($P < 0.001$), with the CG and JEL formulas providing lower estimates than the MDRD and MDRDm formulas. The patients' characteristics, such as age, weight, height, and BSA, were comparable in the learning and validation groups (data not shown).

Goodness of fit and predictive performance observed in the learning set are presented in Table 2. The CG-based model best fit the data, followed by the JEL-, MDRD-, and MDRDm-based models, with AIC values of 657.8, 667.0, 673.0, and 683.0, respectively (Table 2). The bias and precision of population predictions from the four models were significantly different ($P < 0.001$ and $P = 0.027$, respectively). The CG-based model showed the greatest precision, while the MDRD-based model provided the worst precision. In accordance with these results, the specific comparison between CG and MDRD models showed that the CG model was marginally more precise but significantly more biased than the MDRD-based model (MSE of 3.69 versus 4.59 $mg^2/liter^2$ [$P = 0.04$] and ME of −0.54 versus −0.19 mg/liter [$P = 0.002$], respectively).

Performances of both population and individual predictions in the 28-patient validation set are shown in Table 3. Plots of observed gentamicin concentrations versus individual predictions from the four models are depicted in Fig. 1. Population predictions from the MDRDm model showed the lowest bias and the best precision. However, the bias and precision of population predictions were not significantly different between the four models ($P = 0.44$ for both measures). Individual predictions (Bayesian posterior estimates) from the four models showed marginally different biases ($P = 0.04$), with the CG-model being the least biased. Precision levels were not significantly different among the four models ($P = 0.73$). Compared to the MDRD-based model, individual predictions from the CG-based model were significantly less biased (−0.471 versus −0.009 mg/liter, respectively; $P = 0.007$). Precision levels were not significantly different (1.78 versus 2.10 $mg^2/liter^2$, respectively; $P = 0.52$).

In the final analysis of the entire patient data set ($n = 92$), the JEL- and CG-based models provided better fits than the MDRD and MDRDm models, with AIC values of 993.8, 995.4, 1,010 and 1,006.4, respectively. The predictive performance from the four models is shown in Table 4. The MDRD-based model provided the largest bias and imprecision in population predictions. Overall, these results confirmed that the MDRD equation was less suited than the CG and Jelliffe equations for the model-based prediction of gentamicin concentrations.

The final estimates of population pharmacokinetic parameters are presented in Table 5. Of note, the MDRD-based model showed approximately 2-fold slower median transfers between the central and the peripheral compartments than the three other models. The examination of the nonparametric joint distribution of clear-

TABLE 2 Goodness of fit and predictive performance (population predictions) of the four models in the learning set ($n = 64$ patients, 281 gentamicin concentrations)

Model	AIC	Relative reduction of the AIC[a]	Bias[b] (in mg/liter) (95% CI)	Precision[c] (in $mg^2/liter^2$) (95% CI)	Regression equation of observed vs predicted concn
JEL	667.0	20.2	−0.58 (−0.79, −0.36)	3.74 (2.12, 5.36)	$y = 0.96x + 0.74$; $R^2 = 0.78$
CG	657.8	29.4	−0.54 (−0.76, −0.33)	3.69 (2.13, 5.26)	$y = 0.95x + 0.76$; $R^2 = 0.78$
MDRD	673.0	14.2	−0.19 (−0.44, 0.06)	4.59 (2.95, 6.24)	$y = 0.95x + 0.40$; $R^2 = 0.71$
MDRDm	683.0	4.2	−0.12 (−0.35, 0.12)	4.10 (2.63, 5.58)	$y = 0.92x + 0.47$; $R^2 = 0.74$

[a] Calculated as the AIC of the reference two-compartment model without covariate (687.2) minus the AIC of the selected model.
[b] $P < 0.001$.
[c] $P = 0.027$.

TABLE 3 Predictive performance of the four models in the validation set ($n = 28$ patients, 131 gentamicin concentrations)

Model	Prediction			
	Population		Individual	
	Bias (in mg/liter) (95% CI)	Precision (in mg^2/$liter^2$) (95% CI)	Bias[a] (in mg/liter) (95% CI)	Precision (in mg^2/$liter^2$) (95% CI)
JEL	−0.55 (−0.89, −0.22)	4.17 (2.85, 5.49)	−0.39 (−0.64, −0.13)	2.35 (1.20, 3.51)
CG	−0.71 (−1.07, −0.35)	4.86 (3.29, 6.43)	−0.009 (−0.26, 0.24)	2.10 (1.06, 3.14)
MDRD	−0.46 (−0.82, −0.11)	4.46 (3.09, 5.83)	−0.47 (−0.68, −0.26)	1.78 (1.07, 2.49)
MDRDm	−0.28 (−0.61, 0.06)	3.84 (2.67, 5.01)	−0.38 (−0.60, −0.17)	1.73 (0.79, 2.66)

[a] $P = 0.04$. The other measures were not significantly different between the four models.

ance parameters showed other interesting differences (Fig. 2). This figure displays all of the support points that form the discrete distribution of population parameters. Each support point represents a pair of CL_S and CL_{NR} values and its specific probability. The CG and JEL models were characterized by a subset of support points of high CL_S values (ranging from approximately $4 \cdot 10^{-2}$ to $5.5 \cdot 10^{-2}$), while the MDRD and MDRDm models had more support points of low CL_S and high nonrenal clearance (more than 1.5 liters/h). This can be interpreted as CG and JEL being clearance models more dependent on renal function estimation than the MDRD equation-based model. These differences in parameter distributions also accommodate for the difference in the estimation of renal function observed in the study population (Table 1).

DISCUSSION

The most appropriate estimator of renal function for the estimation of aminoglycoside concentrations has not been established yet. Two recent studies compared the CG and the MDRD equations for the prediction of aminoglycoside concentrations, yielding conflicting results. Bookstaver et al. (5) stated that the MDRD equation provided better predictions than the CG equation, while Ryzner et al. (32) reported the opposite result. However, both studies had methodological insufficiencies that undermine their conclusions (15). Most recently, Pai and colleagues studied the linear correlation between various estimators of renal function and serum clearances of tobramycin and gentamicin (29). They

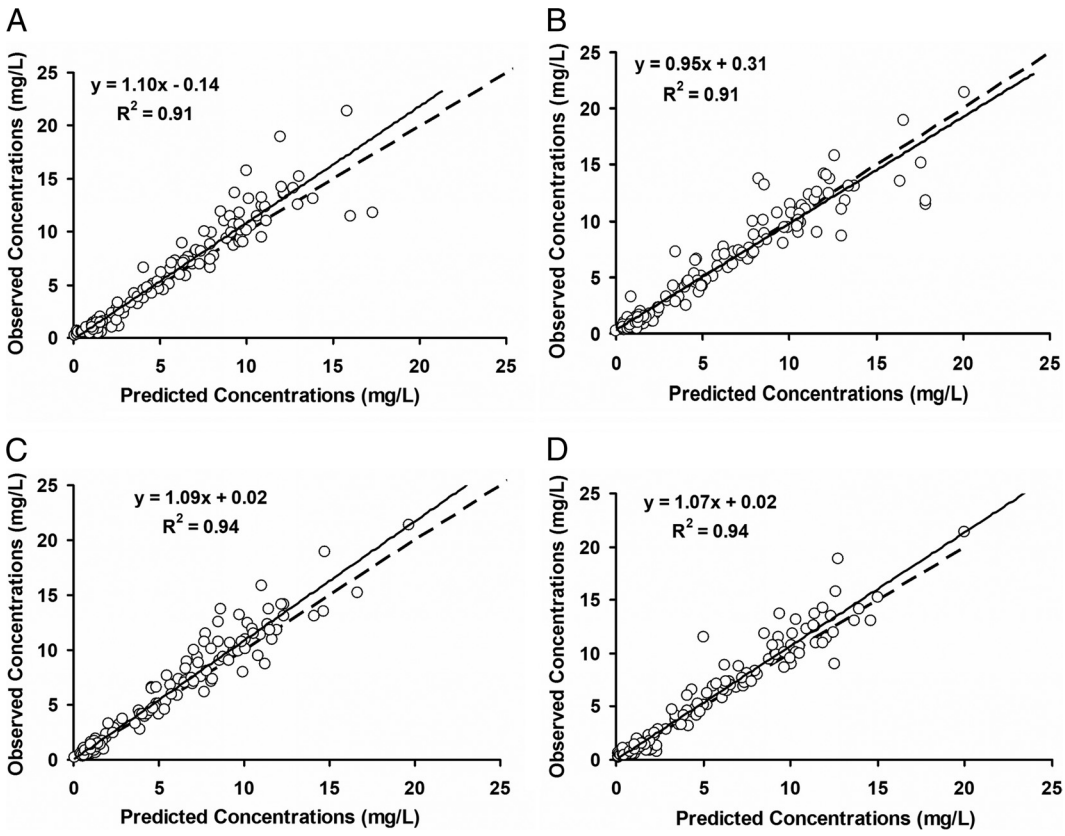

FIG 1 Observed concentrations of gentamicin versus individual predictions from the Jelliffe (A)-, Cockcroft-Gault (B)-, MDRD (C)-, and MDRDm (D)-based models in the 28-patient validation set. The solid line is the best regression line, the dashed line is the identity line ($y = x$).

TABLE 4 Goodness of fit and predictive performance (population predictions) of the four models in the final analysis ($n = 92$ patients, 412 gentamicin concentrations)

Model	AIC	Bias (mg/liter)	Precision ($mg^2/liter^2$)
JEL	993.8	0.015	3.72
CG	995.4	0.18	3.84
MDRD	1010	0.85	4.25
MDRDm	1006.4	−0.49	3.86

found that GFR estimated by the chronic kidney disease epidemiology collaboration (CKD-EPI) equation best correlated with aminoglycoside clearance. However, the authors did not investigate the performance of each clearance model for the prediction of aminoglycoside concentrations.

To our knowledge, this is the first study comparing different estimators of renal function for the prediction of gentamicin concentrations by the population approach. The population approach is considered the reference methodology to study the relationship between clinical descriptors and the pharmacokinetic behavior of a drug (38). In this study, we used a nonparametric population algorithm (NPAG), which estimates the joint distribution of parameters and covariates without parametric assumptions (27). Also, this study provides population pharmacokinetic models of gentamicin in elderly patients, a patient population for which there has been a dearth of PK data.

In this study, a two-compartment model incorporating renal function estimation, but not body weight, was selected. This was surprising, because previous studies have reported a linear correlation between aminoglycoside volume of distribution and body weight (40). Also, drug doses of aminoglycosides are calculated per kilogram of body weight in routine clinical practice. However, this finding confirms the results of our previous study on amikacin in a large population of 580 adult patients (6). In this study, population analysis of amikacin pharmacokinetics was performed in five groups of patients (groups were created by data partitioning). In four groups, the use of body weight as a covariate influencing amikacin volume of distribution did not improve the model fit.

Our estimates of parameter values are consistent with those from other studies. The mean population volume of distribution from the four models ranged from approximately 14 to 16 liters. When divided by the mean body weight observed in the population (65 kg, which leads to 0.22 to 0.25 liters/kg), those values are comparable to standard values (9). Significant nonrenal clearance has been found in this study, with median values ranging from 7.8 ml/min (0.47 liters/h) to 11.5 ml/min (0.69 liters/h) for the four models. High variability was observed for this parameter. Hickling and colleagues reported a lower value of nonrenal clearance when using estimated CL_{CR} (6.0 ml/min) but a higher value when using measured CL_{CR} (29.4 ml/min) as the independent variable in their regression equations (17). The median slope parameter of gentamicin clearance found in the present study (0.45 for clearance expressed in ml/min; one has to multiply the CL values [in liters/h] shown in Table 5 by 16.67 for conversion to ml/min) was much less than that found by Debord et al. (0.91), who used a similar nonparametric population approach to study amikacin pharmacokinetics in geriatric patients (10). However, in their study, the nonrenal clearance was a fixed parameter, which could partly explain such a difference. The parameter values estimated in our study are in agreement with those from Keller et al., who reviewed the renal function dependence of the pharmacokinetic parameters of netilmicin. They reported a meta-analytical equation for netilmicin clearance versus CL_{CR} with an intercept parameter of 5.04 and a slope parameter of 0.578 ml/min (22). Our results indicate that gentamicin body clearance is, on average, lower than estimated creatinine clearance or GFR (data not shown), which is consistent with results from Keller and other scientists who studied aminoglycoside drugs (22, 31, 34).

While the tubular reabsorption of aminoglycosides has been

TABLE 5 Summary of population pharmacokinetic parameter values of gentamicin estimated by NPAG in the entire patient set[a] ($n = 92$ patients, 412 gentamicin concentrations)

Model and result type	CL_{NR} (liter/h)	CL_S	k_{CP} (h^{-1})	k_{PC} (h^{-1})	V_D (liter)
JEL					
Mean	0.68	0.025	0.68	2.01	15.7
Median (IQR)	0.49 (0.28–0.69)	0.027 (0.014–0.041)	0.12 (0.049–0.69)	0.21 (0.046–1.23)	17.2 (12.4–19.6)
%CV	97.1	56.9	151.1	166.9	39.0
CG					
Mean	0.79	0.023	0.61	1.19	15.3
Median (IQR)	0.47 (0.26–0.90)	0.027 (0.014–0.041)	0.13 (0.056–0.44)	0.23 (0.038–0.89)	16.0 (10.6–20.1)
%CV	97.6	54.3	223.3	222.4	39.5
MDRD					
Mean	0.93	0.015	0.34	0.72	16.3
Median (IQR)	0.69 (0.35–1.04)	0.027 (0.014–0.041)	0.084 (0.051–0.17)	0.12 (0.036–0.29)	18.3 (12.7–21.0)
%CV	84.7	60.6	186.3	255.6	38.8
MDRDm					
Mean	0.86	0.017	0.65	1.55	14.5
Median (IQR)	0.65 (0.32–0.95)	0.027 (0.014–0.041)	0.15 (0.068–1.01)	0.29 (0.10–1.32)	14.9 (9.25–20.0)
%CV	97.0	58.8	133.7	180.4	41.9

[a] IQR, interquartile range. CL_S multiplied by 100 provides an estimate of gentamicin renal clearance in a patient with creatinine clearance equal to 100 ml/min.

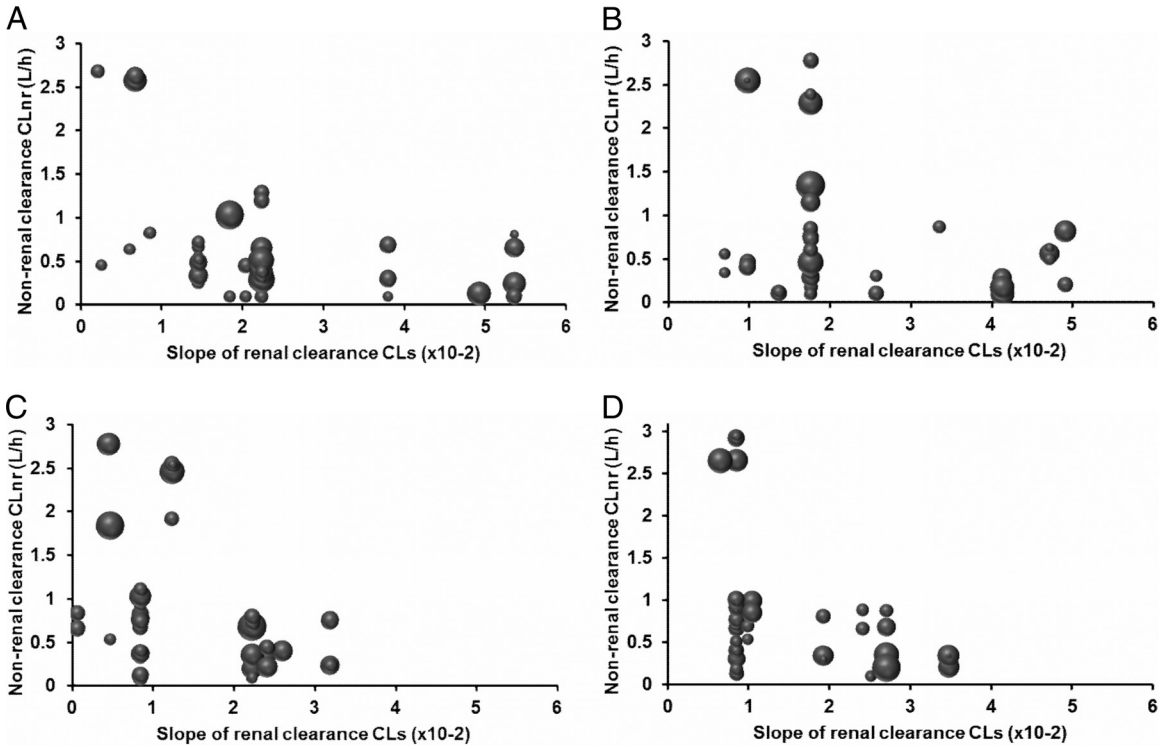

FIG 2 Nonparametric joint distribution of clearance parameters from the Jelliffe (A)-, Cockcroft-Gault G (B)-, MDRD (C)-, and MDRDm (D)-based models in the entire patient set ($n = 92$). Each circle represents a discrete support point from the nonparametric population distribution; the surface is proportional to the probability of the point.

well documented (28, 30), little is known about the possible mechanisms of nonrenal clearance of aminoglycosides. However, evidence of such nonrenal clearance has been provided by PK studies in anephric patients (26). The seminal studies from Schentag et al. in the late 1970s clearly showed important aminoglycoside tissue accumulation in humans (33), and pharmacokinetic studies with prolonged serum and urine collections have shown a very prolonged terminal elimination phase and suggested that a three-compartment model better describes aminoglycoside elimination (39). As a consequence, the significant nonrenal clearance of aminoglycosides estimated with two-compartment models might only be a surrogate for prolonged tissue distribution and accumulation.

Overall, the JEL- and CG-based models provided better fits (lowest AIC values) than the MDRD- and MDRDm-based models in the analysis of the learning ($n = 64$) and whole ($n = 92$) data sets. Specifically, the CG-based model performed better than the MDRD-based model in terms of goodness of fit (AIC value) in the learning set and in the final analysis. This model was also significantly less biased than the MDRD-based model for individual predictions of gentamicin concentrations in the validation set. While these results need to be confirmed in other populations, this suggests that the CG- and JEL-based models would be more efficient than the MDRD model for the Bayesian fitting of gentamicin concentrations in clinical practice, as one can perform with the MM-USC*PACK software (19).

The Jelliffe and Cockcroft-Gault equations both incorporate body weight in the estimation of renal function. In contrast, body weight is not directly included in the MDRD and MDRDm equations. Some studies, mostly performed with obese patients, have reported that body weight influences aminoglycoside clearance (3). As a consequence, the Jelliffe- and CG-based pharmacokinetic models may be more flexible, since they allow gentamicin clearance to change when body weight changes. We assume that this characteristic explains the difference observed in clearance parameter distributions (Fig. 2) and the overall better performance of the CG- and JEL-based models compared to that of the MDRD- and MDRDm-based models. However, as the distribution of weights in this geriatric population was relatively small, it would be interesting to explore this question in a population with more variability in body weights.

This study has several limitations that should be considered. First, we only assessed four renal function estimation equations, while many others have been presented in the literature. We focused on the CG and MDRD formulas because they are the two most widely used equations in clinical practice. In addition, they have shown the best evidence for the estimation of renal function in elderly patients (37). The Jelliffe and MDRDm equations were also studied for methodological reasons (see Materials and Methods). In addition, the Jelliffe equation is the only equation that uses a pair of serum creatinine levels, thus accommodating unstable renal function (18). We did not evaluate the various corrections or modifications of the Cockcroft-Gault equation that have been proposed, such as using lean or ideal body weight instead of total body weight, or fixing very low values of serum creatinine to an arbitrary minimum value. Kirkpatrick and coworkers reported a better correlation between gentamicin clearance and creatinine clearance estimated by a modified CG equation including these

kinds of corrections (23). While these modifications are not recommended to estimate GFR (http://nkdep.nih.gov/professionals/drug-dosing-information.htm#top), it would be interesting to evaluate their value for pharmacokinetic modeling in a specific study.

The estimation of renal function by the Jelliffe and MDRDm equations requires individual BSA and height to be measured. The height of geriatric patients may be difficult to determine accurately. Many elderly people have spinal curvature or osteoporosis-related vertebral fractures. Others just cannot stand properly because of their medical condition. In such cases, height may be estimated by use of the Chumlea equation, for example (7). Data related to the height of patients were recorded at the time of the gentamicin therapeutic drug monitoring. While all heights were recorded, it is likely that some heights were only estimated. This was a potential source of imprecision for the estimation of renal function with the Jelliffe and MDRDm equations.

The analytical issues associated with serum creatinine assays should also be discussed. In this study, all serum creatinine levels were measured by nonstandardized colorimetric methods. Since then, IDMS (isotope dilution mass spectrometry)-traceable methods, mostly enzymatic, have been developed, and such methods are currently used in our institution. It has been shown that various serum creatinine assay methods may provide significantly different estimates of creatinine clearance. For example, in the study by Hanser et al., the mean creatinine clearance calculated with the CG equation with serum creatinine measured by eight different assays ranged from 69 to 102 ml/min in men more than 60 years old and without kidney disease (16). As a consequence, the performance of the four models might be different in patients for whom serum creatinine would be measured by other methods. While the high precision and specificity of modern enzymatic assays for serum creatinine measurement are desirable, the generalization of such methods could raise some problems for the drug dose adjustment. On the one hand, the estimation of CL_{CR} with the Cockcroft-Gault equation is theoretically invalid with those modern methods. On the other hand, the MDRD equation has not been formally evaluated for drug dosing (11, 14).

Finally, we did not evaluate the dose requirements predicted by the four pharmacokinetic models. It is possible that the differences observed in data fitting and predictive performance, although statistically significant, are associated with negligible differences in the doses required to reach some predefined target serum levels in patients. Further research is necessary to explore this question.

Conclusions. This study has shown that the method used to estimate renal function may significantly influence the model-based prediction of aminoglycoside concentrations. Thus, renal function estimation equations should not be considered interchangeable for aminoglycoside pharmacokinetic modeling and dose adjustment. In this study, two-compartment models based on the CG and Jelliffe equations better fitted gentamicin concentrations than models based on the MDRD equations in geriatric patients. This is also one of the first population pharmacokinetic studies of aminoglycosides in geriatric patients. The presented models thus can serve as benchmarks for further studies with other drugs, in other populations, and for the Bayesian adaptive control of gentamicin dosage regimens in such a population.

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REFERENCES

1. **Akaike H.** 1974. A new look at the statistical model identification. IEEE Trans. Automatic Control. **19**:716–723.
2. **Avent ML, Rogers BA, Cheng AC, Paterson DL.** 2011. Current use of aminoglycosides: indications, pharmacokinetics and monitoring for toxicity. Intern. Med. J. **41**:441–449.
3. **Bauer LA, Edwards WA, Dellinger EP, Simonowitz DA.** 1983. Influence of weight on aminoglycoside pharmacokinetics in normal weight and morbidly obese patients. Eur. J. Clin. Pharmacol. **24**:643–647.
4. **Begg EJ, Barclay ML.** 1995. Aminoglycosides–50 years on. Br. J. Clin. Pharmacol. **39**:597–603.
5. **Bookstaver PB, Johnson JW, McCoy TP, Stewart D, Williamson JC.** 2008. Modification of diet in renal disease and modified Cockcroft-Gault formulas in predicting aminoglycoside elimination. Ann. Pharmacother. **42**:1758–1765.
6. **Bourguignon L, et al.** 2009. Amikacin pharmacokinetics in adults: a variability that question the dose calculation based on weight. Therapie **64**:47–53.
7. **Chumlea WC, et al.** 1998. Stature prediction equations for elderly non-Hispanic white, non-Hispanic black, and Mexican-American persons developed from NHANES III data. J. Am. Diet Assoc. **98**:137–142.
8. **Cockcroft DW, Gault MH.** 1976. Prediction of creatinine clearance from serum creatinine. Nephron **16**:31–41.
9. **Dager WE.** 1994. Aminoglycoside pharmacokinetics: volume of distribution in specific adult patient subgroups. Ann. Pharmacother. **28**:944–951.
10. **Debord J, Charmes JP, Marquet P, Merle L, Lachatre G.** 1997. Population pharmacokinetics of amikacin in geriatric patients studied with the NPEM-2 algorithm. Int. J. Clin. Pharmacol. Ther. **35**:24–27.
11. **Dowling TC, Matzke GR, Murphy JE, Burckart GJ.** 2010. Evaluation of renal drug dosing: prescribing information and clinical pharmacist approaches. Pharmacotherapy **30**:776–786.
12. **Du Bois D, Du Bois EF.** 1916. A formula to estimate the approximate surface area if height and weight be known. Nutrition **5**:303–313.
13. **Gehan EA, George SL.** 1970. Estimation of human body surface area from height and weight. Cancer Chemother. Rep. **54**:225–235.
14. **Gill J, Malyuk R, Djurdjev O, Levin A.** 2007. Use of GFR equations to adjust drug doses in an elderly multi-ethnic group–a cautionary tale. Nephrol. Dial. Transplant. **22**:2894–2899.
15. **Goutelle, S, Bourguignon. L, Ducher M, Maire P.** 2009. Comment: modification of diet in renal disease and modified Cockcroft-Gault formulas in predicting aminoglycoside elimination. Ann. Pharmacother. **43**: 1145–1146.
16. **Hanser AM, et al.** 2001. Comparison of methods for the determination of blood creatinine. Ann. Biol. Clin. (Paris) **59**:737–742.
17. **Hickling KG, Begg EJ, Perry RE, Atkinson HC, Sharman JR.** 1991. Serum aminoglycoside clearance is predicted as poorly by renal aminoglycoside clearance as by creatinine clearance in critically ill patients. Crit. Care Med. **19**:1041–1047.
18. **Jelliffe R.** 2002. Estimation of creatinine clearance in patients with unstable renal function, without a urine specimen. Am. J. Nephrol. **22**:320–324.
19. **Jelliffe R, Bayard D, Milman M, Van Guilder M, Schumitzky A.** 2000. Achieving target goals most precisely using nonparametric compartmental models and "multiple model" design of dosage regimens. Ther. Drug Monit. **22**:346–353.
20. **Jelliffe RW, Iglesias T, Hurst AK, Foo KA, Rodriguez J.** 1991. Individualising gentamicin dosage regimens. A comparative review of selected models, data fitting methods and monitoring strategies. Clin. Pharmacokinet. **21**:461–478.
21. **Jelliffe RW, et al.** 1998. Model-based, goal-oriented, individualised drug therapy. Linkage of population modelling, new "multiple model" dosage design, Bayesian feedback and individualised target goals. Clin. Pharmacokinet. **34**:57–77.

22. **Keller F, Erdmann K, Giehl M, Buettner P.** 1993. Nonparametric meta-analysis of published data on kidney-function dependence of pharmacokinetic parameters for the aminoglycoside netilmicin. Clin. Pharmacokinet. **25**:71–79.
23. **Kirkpatrick CM, Duffull SB, Begg EJ.** 1999. Pharmacokinetics of gentamicin in 957 patients with varying renal function dosed once daily. Br. J. Clin. Pharmacol. **47**:637–643.
24. **Leary R, Jelliffe R, Schumitzky A, Van Guilder M.** 2001. An adaptive grid nonparametric approach to pharmacokinetic and dynamic (PK/PD) population models, p. 389–394. Proceedings of the 14th IEEE Symposium on Computer-Based Medical Systems. CBMS, Bethesda, MD.
25. **Levey AS, Greene T, Kusek JW, Beck GJ.** 2000. A simplified equation to predict glomerular filtration rate from serum creatinine. J. Am. Soc. Nephrol. **11**:155A.
26. **Luft FC, et al.** 1978. Pharmacokinetics of netilmicin in patients with renal impairment and in patients on dialysis. Antimicrob. Agents Chemother. **14**:403–407.
27. **Mallet A, et al.** 1988. Handling covariates in population pharmacokinetics, with an application to gentamicin. Biomed. Meas. Infect. Control **2**:138–146.
28. **Nagai J, Tanaka H, Nakanishi N, Murakami T, Takano M.** 2001. Role of megalin in renal handling of aminoglycosides. Am. J. Physiol. Renal Physiol. **281**:F337–F344.
29. **Pai MP, Nafziger AN, Bertino JS, Jr.** 2011. Simplified estimation of aminoglycoside pharmacokinetics in underweight and obese adult patients. Antimicrob. Agents Chemother. **55**:4006–4011.
30. **Pastoriza-Munoz E, Bowman RL, Kaloyanides GJ.** 1979. Renal tubular transport of gentamicin in the rat. Kidney Int. **16**:440–450.
31. **Roberts GW, Ibsen PM, Schioler CT.** 2009. Modified diet in renal disease method overestimates renal function in selected elderly patients. Age Ageing **38**:698–703.
32. **Ryzner KL.** 2010. Evaluation of aminoglycoside clearance using the modification of diet in renal disease equation versus the Cockcroft-Gault equation as a marker of glomerular filtration rate. Ann. Pharmacother. **44**:1030–1037.
33. **Schentag JJ, et al.** 1977. Gentamicin disposition and tissue accumulation on multiple dosing. J. Pharmacokinet. Biopharm. **5**:559–577.
34. **Schentag JJ, Lasezkay G, Cumbo TJ, Plaut ME, Jusko WJ.** 1978. Accumulation pharmacokinetics of tobramycin. Antimicrob. Agents Chemother. **13**:649–656.
35. **Sheiner LB, Beal SL.** 1981. Some suggestions for measuring predictive performance. J. Pharmacokinet. Biopharm. **9**:503–512.
36. **Tod M.** 2001. Individualising aminoglycoside dosage regimens after therapeutic drug monitoring. Simple or complex pharmacokinetic methods? Clin. Pharmacokinet. **40**:803–814.
37. **Van Pottelbergh G, Van Heden L, Mathei C, Degryse J.** 2010. Methods to evaluate renal function in elderly patients: a systematic literature review. Age Ageing **39**:542–548.
38. **Wakefield J, Bennett J.** 1996. The Bayesian modeling of covariates for population pharmacokinetic models. J. Am. Stat. Assoc. **91**:917–927.
39. **Wenk M, Spring P, Vozeh S, Follath F.** 1979. Multicompartment pharmacokinetics of netilmicin. Eur. J. Clin. Pharmacol. **16**:331–334.
40. **Xuan D, Nicolau DP, Nightingale CH.** 2004. Population pharmacokinetics of gentamicin in hospitalized patients receiving once-daily dosing. Int. J. Antimicrob. Agents **23**:291–295.
41. **Zaske DE, et al.** 1982. Gentamicin pharmacokinetics in 1,640 patients: method for control of serum concentrations. Antimicrob. Agents Chemother. **21**:407–411.