



# Comparison of Four Renal Function Estimator-Based Models for the Prediction of Gentamicin Concentrations in Geriatric Patients by Use of Nonparametric Population Approach



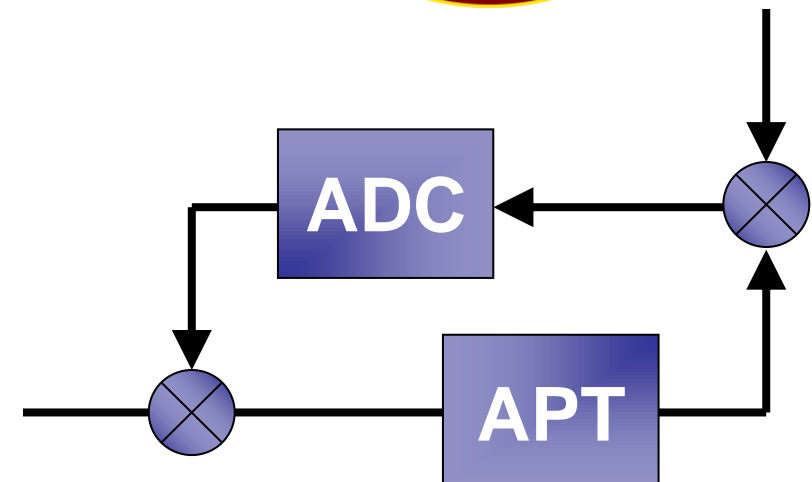
N. Charhon<sup>1</sup>, L. Bourguignon<sup>1,2</sup>, P. Maire<sup>1,2</sup>, R.W. Jelliffe<sup>4</sup>, M. Neely<sup>4</sup>, S. Goutelle<sup>1,2,3</sup>

<sup>1</sup>Hospices Civils de Lyon, Groupement Hospitalier de Gériatrie, Service pharmaceutique – ADCAPT, Francheville, France ;

<sup>2</sup>Université de Lyon 1, F-69000, Lyon ; CNRS, UMR5558, Laboratoire de Biométrie et Biologie Evolutive, F-69622, Villeurbanne, France ;

<sup>3</sup>ISPB - Faculté de Pharmacie de Lyon, Université Lyon 1, Lyon, France ;

<sup>4</sup>Laboratory of Applied Pharmacokinetics, USC Keck School of Medicine, Los Angeles CA, USA



## OBJECTIVES

Most aminoglycoside pharmacokinetic models include an index of renal function, such as creatinine clearance to describe elimination [1]. However, the best clinical descriptor of renal function for PK modeling of aminoglycosides has not been established. The objective of this study was to compare four gentamicin (GENT) PK models based on the Cockcroft-Gault (CG), Jelliffe (JEL), MDRD, and modified MDRD (MDRDm, adjusted to individual body surface area) formulae.

## METHODS

This analysis was based on **427 gentamicin concentrations** from **92 geriatric patients** who received intravenous GENT for various infectious diseases. Monitoring of gentamicin concentrations was part of routine patient care. Four **bicompartmental models** were fitted to GENT concentrations in a learning set of 64 patients using the **NPAG algorithm** [2]. Each model included an index of renal function (CG, JEL, MDRD, or MDRDm) as a covariate influencing GENT serum clearance. The Akaike information criterion (AIC) was used to assess the goodness-of-fit of candidate models. Mean prediction error (ME) and mean squared prediction error (MSE) were used to evaluate bias and precision, respectively. In a validation set of 28 patients, population and individual predictions were made from each of the four model nonparametric population PK parameter joint densities. Bias and precision of the four models were compared with the Kruskal-Wallis test in both the learning and validation sets.

## RESULTS

Demographic and biological data of the entire set of 92 patients are shown in table 1. The four equations provided significantly different estimations of renal function. Patient characteristics were not significantly different between the two sets (data not shown). Inclusion of creatinine clearance as covariate on clearance improved the fit for all four models.

In the **learning set**, the **CG-based model best fitted the data** (lowest AIC value), followed by JEL, MDRD, and MDRDm-based models (table 2 and 3). Bias and precision of population predictions were significantly different ( $p < 0.001$  and  $p = 0.027$ , respectively) (table 3). Compared with the MDRD model, the CG model had **extra support points** of high  $K_s$  value which make GENT clearance more sensitive to renal function variation (fig. 2).

In the **validation set**, bias and precision of population predictions were not significantly different between the models. However individual predictions (Bayesian posterior) from the four models showed marginally different bias ( $p = 0.04$ ) (table 4 and fig. 1). Overall, the CG-based model provided the best fit and predictive performance.

**Table 3.** Goodness-of-fit and predictive performance (population predictions) of the four models in the learning set (N = 64).

Model	AIC	BIC	Bias (mg/L) <sup>a</sup>	Precision (mg <sup>2</sup> /L <sup>2</sup> ) <sup>b</sup>	Nb of grid points
CG	<b>657.8</b>	676.0	-0.35	<b>3.69</b>	31
JEL	667.0	685.2	-0.14	4.19	35
MDRD	673.0	691.1	-0.19	4.59	28
MDRDm	683.0	701.2	<b>-0.12</b>	4.10	32

<sup>a</sup>  $p < 0.001$ ; <sup>b</sup>  $p = 0.027$ , Kruskal-Wallis test

**Table 4.** Predictive performance of the four models in the validation set (N=28)

	Population predictions		Individual predictions	
	Bias (mg/L)	Precision (mg <sup>2</sup> /L <sup>2</sup> )	Bias (mg/L) <sup>a</sup>	Precision (mg <sup>2</sup> /L <sup>2</sup> )
CG Model	-0.711	4.862	<b>-0.009</b>	2.100
JEL Model	-0.554	4.167	-0.388	2.354
MDRD Model	-0.463	4.458	-0.471	1.777
MDRDm Model	-0.277	3.842	-0.383	1.730

<sup>a</sup>  $p = 0.04$ , Kruskal-Wallis test

## CONCLUSIONS

PK models of gentamicin based on various estimators of renal function may provide significantly different results. In this study, **the model based on the CG equation predicted GENT concentrations slightly better than the JEL, MDRD, and MDRDm equations in geriatric patients.** In clinical practice, one should continue to use the CG equation for model-based adaptive control of GENT dosage regimens in geriatric patients.

References:

[1] Jelliffe RW, et al, Clin Pharmacokinet 1991;21(6):461-78

[2] Leary R, Jelliffe R, Schumitzky A, Van Guilder M. 14th IEEE Symposium on Computer-Based Medical Systems (CMBS'01), 2001

**Table 1.** Demographic and biological data of the 92 patients treated by intravenous gentamicin. (data are given as mean +/- SD)

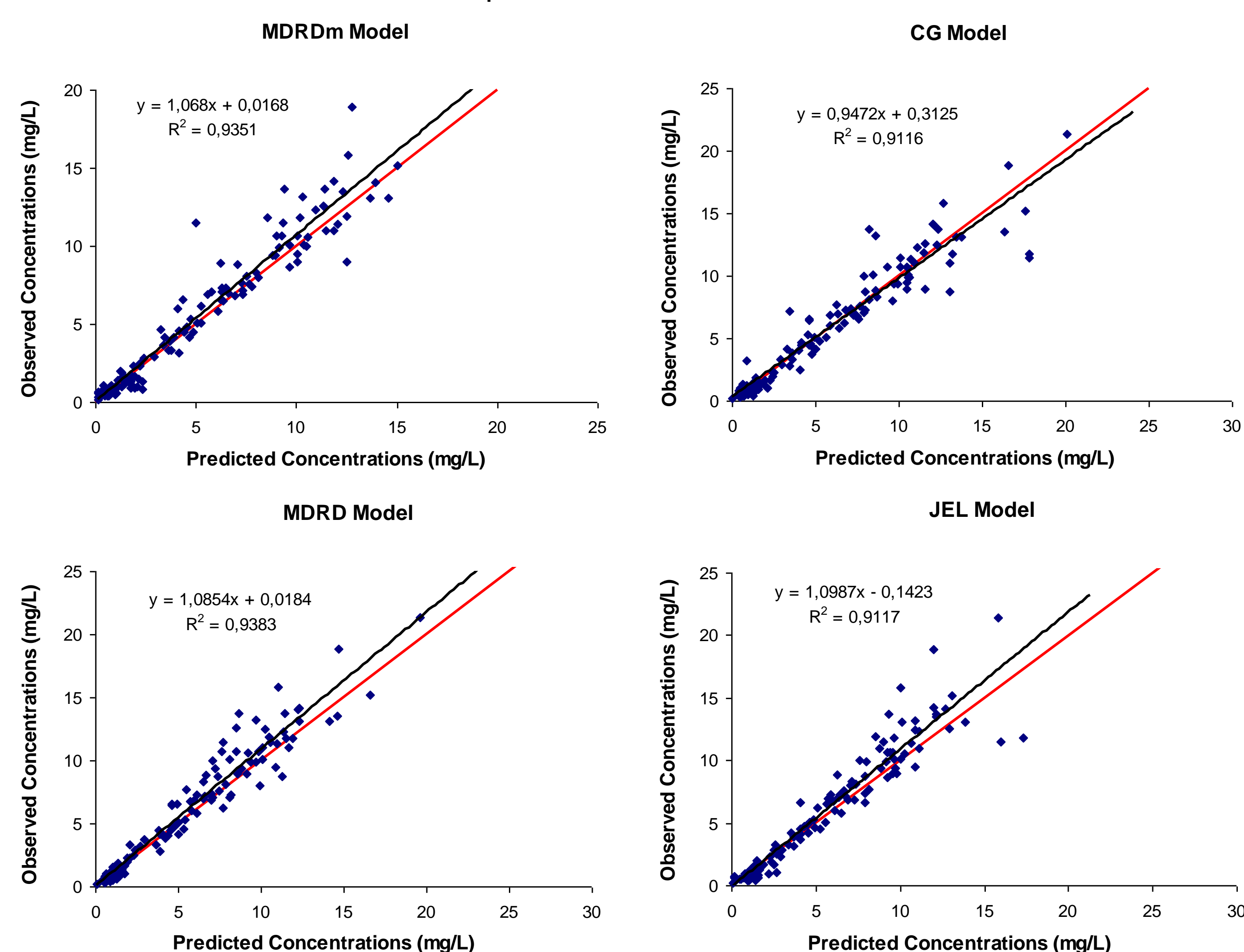
Men/Women	37/55
Age (years)	82.7 +/- 7.3
Weight (kg)	65.0 +/- 16.5
Serum creatinine (mg/dL) N = 224	1.24 +/- 0.56
CCr CG (mL/min)	44.19 +/- 20.24 *
CCr JEL (mL/min/1.73m <sup>2</sup> )	43.23 +/- 18.12 *
GFR MDRD (mL/min/1.73m <sup>2</sup> )	62.37 +/- 28.22 *
GFR MDRDm (mL/min)	60.53 +/- 27.79 *

\*  $p < 0.001$ , Kruskal-Wallis test

**Table 2.** Population pharmacokinetic parameter values estimated by NPAG in the learning set (N=64)

		Cl <sub>NR</sub> (L/h)	K <sub>s</sub>	K <sub>CP</sub> (h <sup>-1</sup> )	K <sub>PC</sub> (h <sup>-1</sup> )	V <sub>D</sub> (L)
MDRD Model	mean	0.912	0.0134	0.512	1.117	16.024
	CV %	83.9	62.9	152.2	210.2	44.5
MDRDm Model	mean	0.718	0.0170	0.600	2.006	15.272
	CV %	75.7	61.4	150.8	168.4	41.4
CG Model	mean	0.769	<b>0.0232</b>	0.707	1.389	15.328
	CV %	96.7	58.3	227.3	210.0	42.4
JEL Model	mean	0.739	0.0227	0.853	2.292	14.999
	CV %	88.2	55.9	163.9	159.4	42.7

**Fig. 1.** Observed concentrations of gentamicin versus individual predictions from the 4 models in the 28-patient validation set.



**Fig. 2.** Nonparametric joint distribution of clearance parameters for the CG and MDRD models estimated in the learning set.

