

Differences among six prevalent creatinine clearance calculation methods by covariate modeling of CL for Netilmicin using NONMEM for inference



I. Oteo[1], N. Jauregizar[1], A. Astobieta[2], J.M Rodriguez Sasiain[3], J.C Lukas[3], R. Calvo[1]

[1] Department of Pharmacology, University of the Basque Country, Leioa, Bizkaia, Spain. tel: +94 601 55 60

[2] Clínica Virgen Blanca, Galdakao, Bilbao, Bizkaia, Spain.

[3] Drug Modelling and Consulting. DynaKin S.L., PTB, Suite 801-B, 48160 Derio, Bizkaia. Spain



In many clinical situations the evaluation of renal function is required, particularly common in antibiotic therapy. The direct metric is glomerular filtration rate (GFR) but its measurement is complicated, so a variety of formulae and nomograms have been derived to obtain a surrogate of GFR, the creatinine clearance (CrCL). CrCL is then calculated based on empirical functions of varying complexity that include serum creatinine concentration and patient demographics. The MDRD (Modification of Diet in Renal Disease) method of CrCL calculation is increasingly used but the appropriateness of its use has not been demonstrated for all applications.¹

The aim of the present study was to compare the ability of 6 different methods, including MDRD, in calculating creatinine clearance (CrCL) as predictor of clearance (CL) within a mixed effects pharmacokinetic (PK) model for netilmicin, a potentially nephrotoxic aminoglycoside drug.

Methods

Plasma levels (n= 310) and serum creatinine levels, from 62 adult patients treated with netilmicin (a single dose of 100 mg) for short-term prophylaxis after minor urological surgery as previously analyzed in Jauregizar et al (2003)² were used. Patients were in good general health, and had normal renal function (serum creatinine ≤ 1.9 mg/dL).

First, CrCL was calculated by 6 alternative methods: Cockcroft & Gault (1976)³; Mawer et al. (1972)⁴; MDRD formulae⁵; DAF method (2010)⁶; Jelliffe et al. (1973)¹ in addition to the method used in Jauregizar et al (2003)² (Mawer method corrected by ideal weight, calculated from Peck's formula⁷ (MM)).

Then, the NONMEM[®] objective function (OFV) was used to compare the predictive ability for the CL of netilmicin in this population of the 6 methods for CrCL. The base model was a monocompartmental PK model. As starting point, the same covariate model ($CL = \theta_{slope} * CrCL$), developed by Jauregizar et al. (2003)² was used in all cases. The FOCE method with INTERACTION (proportional residual error) were used throughout. The OFV is approximately chi-square distributed and a change of 3.8 is significant at $p < 0.05$.

Additionally, a third order GAM (equation 1) was also applied in covariate fits for all methods with CrCL as the sole variable in order to describe the best relationship between Bayesian estimated CL and covariates. Then, a population PK model was developed for each CrCL calculation method.

$$\theta_i = \alpha + \theta_1(X_{i1}) + \theta_2(X_{i2}) + \dots + \theta_n(X_{in}) + \eta \quad eq.1$$

Where α is the "intercept"; θ_i Bayesian estimated parameters; $X_{i1}, X_{i2}, \dots, X_{in}$ are the covariate values 1, 2, ..., n centered around the median covariate value, for each of the individuals; $\theta_1, \theta_2, \dots, \theta_n$ functions that express the relationship between each of covariate and Bayesian PK parameters. And η is the random interindividual variation $\eta \sim N(0, \omega^2)$.

Results

Preliminary ANOVA analysis showed that CrCL estimation using the MM method resulted statistically different when compared with DAF and MDRD methods. In the same way, the Jelliffe method was different compared with Mawer, DAF and MDRD methods.

Using NONMEM and the same covariate model in all cases, the MDRD had OFV= 173.342 (vs. 141.858 for MM) with other methods lying in between but also significantly less predictive than MM (Table 1). Similarly, the interindividual variability was higher for MDRD compared with MM (38.60% vs 29.22% respectively). The parameter θ_{slope} varied from 0.051 – 0.066 among methods. That situation could affect variability if CrCL calculated by one specific method is introduced in a PK model developed for another one.

Method	OFV
MM	141.858
Cockcroft & Gault	145.889
Mawer	146.931
Jelliffe	159.487
DAF	171.388
MDRD	173.342

Table 1. Objective Function Values (OFV) sorted from lowest to highest obtained for each method when the same Population Pharmacokinetic model was applied.
Model parameters: $TVCL = \theta_{CL} * CrCL$; $TVV1 = \theta_{V1} + \theta_{GEND} * GEND$; $TVV2 = \theta_{V2}$ and $TVQ = \theta_Q$.
Inter-subject variability in CL and V1.

In fact, using GAM methodology, the relationship between CL and covariates changed for each particular method (Table 2).

Applying the GAM derived equation for CL in each method and the same model for the rest of PK parameters, the lower OFV was obtained with the MDRD method (137.080). However, this equation showed higher imprecision in the estimation of all parameters of netilmicin in patients with normal renal function ($Scr \leq 1.9$ mg/dL), therefore this method not seem appropriate in this situation.

MM (OFV = 141.858)			Jelliffe (OFV = 145.710)		
$TVCL = \theta_{CL} * CrCL$			$TVCL = \alpha + \theta_{BW} * BW + \theta_{CrCL} * CrCL$		
Parameter	Value	SEE(%)	Parameter	Value	SEE(%)
θ_{CrCL}	0.06	3.93	α	-1.63	17.24
			θ_{BW}	0.04	27.78
			θ_{CrCL}	0.04	23.94

Cockcroft & Gault (OFV = 139.621)			Mawer (OFV = 139.654)		
$TVCL = \alpha + \theta_{HGT} * HGT + \theta_{CrCL} * CrCL$			$TVCL = \alpha + \theta_{HGT} * HGT + \theta_{CrCL} * CrCL$		
Parameter	Value	SEE(%)	Parameter	Value	SEE(%)
α	-6.46	37.93	α	-7.07	35.36
θ_{HGT}	0.04	34.45	θ_{HGT}	0.05	34.98
θ_{CrCL}	0.04	18.33	θ_{CrCL}	0.04	19.73

MDRD (OFV = 137.080)			DAF (OFV = 139.713)		
$TVCL = \alpha + \theta_{HGT} * HGT + \theta_{BW} * BW + \theta_{CrCL} * CrCL$			$TVCL = \alpha + \theta_{HGT} * HGT + \theta_{BW} * BW + \theta_{CrCL} * CrCL$		
Parameter	Value	SEE(%)	Parameter	Value	SEE(%)
α	-13.00	108.46	α	-14.90	33.62
θ_{HGT}	0.06	147.81	θ_{HGT}	0.08	45.25
θ_{BW}	0.04	50.86	θ_{BW}	0.04	48.54
θ_{CrCL}	0.04	17.48	θ_{CrCL}	0.04	17.78

"TVCL" Equations obtained by GAM methodology

Table 2. Population pharmacokinetic model parameter estimates of netilmicin after intravenous administration of 100 mg infusions. (SEE%: % standard error of estimate. Table only shows the most relevant parameters for comparison. Model parameters: $TVV1 = \theta_{V1} + \theta_{GEND} * GEND$; $TVV2 = \theta_{V2}$ and $TVQ = \theta_Q$.
Inter-subject variability in CL and V1: $CL = TVCL * EXP(ETA(2))$; $V1 = TVV1 * EXP(ETA(1))$).

Inter-subject variability in CL was reduced by 70% with the six formulae. The intra-subject variability was about 25% with all methods, with a SEE% varied from 21.59 to 28.79%.

Although, all methods, except the Jelliffe, had lower OFV than MM, the precision for the CL intercept estimation was better with MM (SEE%=3.93%) and Jelliffe (SEE%=17.24%) in this population.

Conclusion

The change from one method to another for CrCL calculation in a specific drug and patient population, appears not justified without model development, particularly in several well defined clinical situations, such as obesity, cancer patients, HIV-infected population or chronic renal disease, among others.

The approach employed here has helped identify as clinically important those covariates that are not included in the CrCL calculation and that should be considered. Therefore, to dose renally excreted drugs "body weight", "height", "age", "gender" and "serum creatinine" should be considered either during CrCL calculation or during Bayesian parameters estimation.

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