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

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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)7 in addition to the method used in Jauregizar et al (2003)2 (Mawer method corrected by ideal weight, calculated from Peck’s formula8 (MM)).

Then, the NONMEM® objective function (OFV) was used to compare the predictive ability of the Cl for 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 = \( \Theta V1 \times \alpha \))+ \( \Theta HGT \times \beta HGT \times \gamma \)) + \( \Theta BW \times \beta BW \times \gamma \)) was used in all cases. The FOCE method with INTERACTION (proportional residual error) was 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.

\[ \theta = \alpha + \beta X_1 + \beta X_2 + \ldots + \beta X_n + \eta \]

Where \( \alpha \) is the “intercept”; \( \beta \) Bayesian estimated parameters; \( X_1, X_2, \ldots, X_n \) are the covariate values 1, 2, \ldots, \( n \) centered around the median covariate value, \( \eta \) 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 \( \beta_{HGT} \) 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.

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 ≤ 1.9 mg/dL), therefore this method not seem appropriate in this situation.

**References**

3. Cockcroft & Gault (OFV = 139.621) TVCL = a + b0*HGT + b0*CrCL Parameter Value SEE(%) a 0.06 1.93
4. Mawer (OFV = 139.654) TVCL = a + b0*HGT + b0*CrCL Parameter Value SEE(%) a 0.04 1.93
5. MDRD (OFV = 137.080) TVCL = a + b0*HGT + b0*BW + b0*CrCL Parameter Value SEE(%) a -6.46 37.93
6. DAF (OFV = 139.713) TVCL = a + b0*HGT + b0*BW + b0*CrCL Parameter Value SEE(%) a 0.04 18.33

Inter-subject variability in CrCL 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.

**Table 1. Objective Function Values (OFV) sorted from lowest to highest for each method when the same Population Pharmacokinetic model was applied.**

<table>
<thead>
<tr>
<th>Method</th>
<th>OFV</th>
</tr>
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<tbody>
<tr>
<td>MM</td>
<td>141.858</td>
</tr>
<tr>
<td>Cockcroft &amp; Gault</td>
<td>145.889</td>
</tr>
<tr>
<td>Mawer</td>
<td>146.931</td>
</tr>
<tr>
<td>Jelliffe</td>
<td>155.487</td>
</tr>
<tr>
<td>DAF</td>
<td>171.388</td>
</tr>
<tr>
<td>MDRD</td>
<td>173.342</td>
</tr>
</tbody>
</table>

**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.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>SEE(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \alpha )</td>
<td>-13.00</td>
<td>108.46</td>
</tr>
<tr>
<td>( \beta_{HGT} )</td>
<td>0.06</td>
<td>147.81</td>
</tr>
<tr>
<td>( \beta_{BW} )</td>
<td>0.04</td>
<td>50.86</td>
</tr>
<tr>
<td>( \beta_{CrCL} )</td>
<td>0.004</td>
<td>17.48</td>
</tr>
</tbody>
</table>

Inter-subject variability in CL and V1. - CL = TVCL - EXP(ETA(1)); V1 = TVV1 - EXP(ETA(1)).