Creatinine-based GFR predicting equations in renal transplantation: reassessing the tubular secretion effect

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Abstract

Background. The real utility of blocking the tubular secretion of creatinine with cimetidine in order to ameliorate the prediction of renal graft function is questionable, particularly in the context of an increasing diffusion of the Modification of Diet in Renal Disease (MDRD) study equation. We have compared the impact of cimetidine on the performances of the Cockcroft–Gault (C–G) and MDRD equations in 56 renal transplant patients with an estimated glomerular filter rate (GFR) >30 mL/min/1.73 m² for whom true GFR was directly measured by inulin clearance.

Methods. Serum creatinine concentration (SCr) was measured [isotope dilution mass spectrometry (IDMS) traceable enzymatic assay] at the beginning of the inulin clearance procedure and 2 days later, after three oral cimetidine doses of 800 mg every 12 h. Predictive and diagnostic performances of the re-expressed MDRD and C–G formulas were compared before and after cimetidine intake.

Results. Mean SCr (±SD) increased from 120 μmol/L (±34) before to 154 μmol/L (±47) after cimetidine. The beneficial effect of cimetidine was significant only on the accuracy of the C–G formula (accuracy 30% post-cimetidine of 93 and 79% for the C–G and MDRD equations, respectively). Likewise, while a higher proportion of patients were correctly staged using the chronic kidney disease classification after cimetidine with the C–G equation (59% before and 68% after), no improvement was seen with the MDRD formula (59 vs 57%). For both equations, receiver operating characteristic curves analysis showed only a marginal gain in GFR prediction.

Conclusion. Our data do not support the use of a cimetidine-based strategy for the evaluation of renal graft function in the clinic, particularly when the GFR is estimated by the MDRD equation.
The tubular secretion of creatinine directly accounts for the overestimation of GFR systematically seen with the measurement of creatinine clearance. Thus, the predictive performance of the C–G formula that was originally derived to estimate the creatinine clearance is expected to largely benefit from the blockade of creatinine tubular secretion. On the contrary, the MDRD equation that was developed to directly predict an iothalmate-measured GFR already integrates and corrects the error related to the non-glomerular excretion of creatinine. Consequently, the predictive performance of this equation is expected to be less affected, if affected at all, by the blockade of creatinine tubular secretion. Nevertheless, several studies have reported that, similarly to the C–G formula, the MDRD equation tends to overestimate the GFR in renal transplant patients [1,3,16,17], raising the possibility that, in this specific population, the tubular secretion of creatinine is more prominent than in the MDRD study population, i.e. in a chronic kidney disease (CKD) population with native kidneys. The predictive performance of the MDRD equation when this equation is applied to a renal transplant population might be thus substantially affected by the creatinine tubular secretion factor. In line with this possibility, Schiff and colleagues have suggested that the performance of the MDRD equation was indeed ameliorated in renal transplant patients after cimetidine [11]. However, this study, along with the few studies [10,18] that have specifically looked at the effect of cimetidine in transplant patients, relied on small effectives and on a methodology different from what is currently recommended [19].

Overall, the real utility to block the tubular creatinine secretion is still questionable in renal transplantation, particularly in the context of an increasing diffusion of the MDRD equation.

In the present study, we aimed to re-evaluate the clinical gain expected from blocking creatinine secretion with cimetidine on the predictive and diagnostic performances of the C–G formula in kidney transplant patients and to determine whether the MDRD equation might also benefit from this pharmacological blockade.

Materials and methods

Study design

In this 12-month, single-centre prospective study, each screened renal transplant recipient who met the inclusion criteria and returned the written consent received a total dose of 2400 mg of cimetidine. This study compares the predictive performances of the MDRD equation and C–G formula before and after the treatment in reference to the inulin clearance measure. The study was conducted in full compliance with the amended Declaration of Helsinki following approval from the local ethical committee and was declared to www.clinicaltrial.gov (NCT00475059). The promoter of the study was CHU de Saint-Etienne, France.

Inclusion procedure

Patients aged >18 years old, single kidney transplanted for at least 1 year, receiving a tacrolimus (Tac)-based immunosuppressive regimen, with a MDRD-based estimated GFR ≥30 mL/min/1.73 m², and admitted for a routine inulin clearance were eligible. Key exclusion criteria were an unstable renal function defined by a variation of >25% of Scr (realized within the last 3 months before inclusion), an intake of creatinine secretion blockers (trimethoprim, pyremethamine, cimetidine) in the week preceding inclusion, serious hepatic deficiency, trough level of Tac >12 ng/mL and carvedilol or phenytoin co-administration.

Scr measurement and trough Tac level were performed at the beginning of the inulin clearance and after three oral cimetidine doses of 800 mg every 12 h (Cimetidine Arrow®).

Laboratory tests, GFR estimates and inulin clearance

Scr assay was an enzymatic method Crea Vitros® (Ortho-Clinical Diagnostics, Issy-les-Moulineaux, France), calibrated to be IDMS traceable according to the manufacturer's instructions. The Tac residual concentrations were determined with a Dade Behring®Expand® antibody-conjugated magnetic immunoassay until 1 April 2007 followed by the MassTrak™ LC/MS/MS ( Waters®) method.

The studied GFR estimates were as follows:

- Re-expressed four-variable MDRD equation
  \[
  \text{GFR}_{\text{MDRD}} = 175 \times \left( \frac{\text{serum creatinine}}{88.4} \right)^{-1.154} \times \frac{\text{age}^{-0.203}}{0.742 \times \left( \frac{\text{if female}}{1.210} \times \left( \frac{\text{if African-American}}{1} \right) \right)}
  \]

- Normalized C–G formula
  \[
  \text{GFR}_{\text{C–G}} = \left( 140 - \text{age} \right) \times \frac{\text{weight}}{\text{BSA}} \times \frac{1.73}{\text{BSA}} \times 1.04
  \]

- Age in years, Scr in micromoles per litre

- Normalized body surface area (BSA) in square metres

The clearance of inulin (INUTEST™ 25%, Fresenius, Linz, Austria) was performed using the continuous intravenous infusion technique. After an equilibration period of 45 min, two clearance periods of 30 min each were analysed. Blood samples, drawn from the arm opposite to the infusion site, were obtained at the midpoint of each clearance period. Urine was collected by spontaneous voiding. In case of urine flow rate differing by >1 mL/min between the two periods, a third period was performed. Inulin concentrations were quantitated according to standard colorimetric assay (resorcinol method) on a UV 1205 spectrophotometer (BIOCHROM, Cambridge, UK). The GFR was measured as the mean of at least two urinary clearances of inulin with the formula U/V, where U and P are inulin concentrations in urine and plasma and F is urine flow rate (mL/min). GFR were expressed per 1.73 m² of BSA by multiplying measured values by 1.73/BSA.

Study end points

The primary efficacy variable was the 30% accuracy (Acc30) defined as the proportion of estimates falling within 30% of the true GFR. The predictive performance was also assessed by the calculation of the bias (absolute and relative) and the precision (absolute bias standard deviation and limits of agreement represented by the Bland and Altman analysis).

The diagnostic performances were evaluated by the receiver operating characteristic (ROC) curve, the sensitivity to detect a 60 mL/min/1.73 m² GFR threshold and the capacity of the estimate to correctly classify a renal transplant patient into his/her corresponding CKD stage.

The interaction between the Tac metabolism and cimetidine was analysed by comparing mean Tac trough level before and after treatment.

Statistical analysis

We have reported in a previous study an Acc30 of 70% for the C–G and MDRD equations in renal transplant recipients [16]. The MDRD equation has been originally qualified based on an Acc30 of 90% in non-transplant patients [19]. The sample size necessary to show an improvement of Acc30 from 70 to 90% was 59 patients with a power of 80% and an alpha risk of 0.05. Sixty patients were finally expected to be included.

The comparison between the Acc30 before and after cimetidine was performed by the McNemar test with a significance level of 0.05. Acc30, sensitivity and area under the ROC curve (AUC) are given with their respective 95% confidence interval. Agreement between estimated GFR and inulin clearance were assessed according to the Bland and Altman analysis [20].

Mean Tac residual concentrations were compared using a paired t-test. All calculations were made by programming the different GFR predicting equations into Microsoft Excel Viewer® 2003 (Microsoft Corporation, Irvine, CA, USA). Statistical analysis was performed using SPSS®.
Cockcroft–Gault

Table 1. Descriptive statistics for inulin clearance and estimates before and after cimetidine oral intake

<table>
<thead>
<tr>
<th>GFR (mL/min/1.73 m²)</th>
<th>Mean ± SD</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference method</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inulin clearance</td>
<td>53.0 ± 17.9</td>
<td>50.5</td>
<td>18–105</td>
</tr>
<tr>
<td>MDRD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>56.4 ± 17.1</td>
<td>52.8</td>
<td>30–100</td>
</tr>
<tr>
<td>After</td>
<td>43.2 ± 14.3</td>
<td>42.3</td>
<td>19–82</td>
</tr>
<tr>
<td>Cockcroft–Gault</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>61.9 ± 16.8</td>
<td>60.7</td>
<td>25–108</td>
</tr>
<tr>
<td>After</td>
<td>49.3 ± 15.4</td>
<td>48.4</td>
<td>21–92</td>
</tr>
</tbody>
</table>

Table 2. Predictive performances of GFR estimates before and after cimetidine treatment

<table>
<thead>
<tr>
<th>GFR estimates</th>
<th>R²</th>
<th>Bias Absolute (mL/min/1.73 m²)</th>
<th>Relative (%)</th>
<th>Precision Absolute bias SD (mL/min/1.73 m²)</th>
<th>Relative bias SD (%)</th>
<th>Accuracy 30% [±95% confidence interval]</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDRD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>0.551</td>
<td>+3.4</td>
<td>+11.3</td>
<td>12.6</td>
<td>27.6</td>
<td>71 [60–83]</td>
</tr>
<tr>
<td>After</td>
<td>0.666</td>
<td>−9.8</td>
<td>−16.4</td>
<td>10.3</td>
<td>18*</td>
<td>79 [68–89]</td>
</tr>
<tr>
<td>Cockcroft–Gault</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>0.598</td>
<td>+8.8</td>
<td>+22.6</td>
<td>11.8</td>
<td>27.2</td>
<td>64 [52–77]</td>
</tr>
<tr>
<td>After</td>
<td>0.642</td>
<td>−3.8</td>
<td>−4.2</td>
<td>10.8</td>
<td>16.2*</td>
<td>93 [86–99]</td>
</tr>
</tbody>
</table>

*P < 0.01, F-statistics for the comparison of precision, McNemar test for the comparison of accuracy.

Results

Patient population

Among the 230 kidney transplant recipients who underwent an inulin clearance between March 2007 and March 2008, 114 were eligible to participate. Sixty consecutive patients were finally included and 56 patients completed the study with the following baseline characteristics: all were Caucasians except one African, mainly male (sex ratio = 2.75), with a mean age of 52 years (range 25–73) at the time of the inulin clearance measurement. All of them received a graft from a deceased donor except one. The transplantation duration at inclusion ranged from 12 to 240 months. The body mass index averaged 25 kg/m² (range 16–35), and the mean body surface area was 1.80 m² (range 1.3–2.3). The causes of end-stage chronic renal disease were mostly non-diabetic glomerular diseases (53%), inherited kidney disease (12%), congenital uropathy (12%), diabetic nephropathy (10%) and other or unknown nephropathy (13%). All patients received Tac with a mean dose of 10 mg/day (range 5–15). The mean inulin-measured GFR (±SD) was 53 mL/min/1.73 m² (±11.8). After treatment, the bias reversed with both estimates [MDRD: −9.8 mL/min/1.73 m² (±10.3), C–G: −3.8 mL/min/1.73 m² (±10.8)]. Cimetidine improved the correlation with inulin clearance and the precision of both MDRD and C–G formulas (Table 2). Likewise, the interval of agreement given by the Bland and Altman representation reduced after the treatment for both estimates (Figure 1).

Predictive performances

Before cimetidine treatment, MDRD and C–G formulas overestimated the GFR with an absolute bias (±SD) respectively of 3.4 mL/min/1.73 m² (±12.6) and 8.8 mL/min/1.73 m² (±11.8). After treatment, the bias reversed with both estimates [MDRD: −9.8 mL/min/1.73 m² (±10.3), C–G: −3.8 mL/min/1.73 m² (±10.8)]. Cimetidine improved the correlation with inulin clearance and the precision of both MDRD and C–G formulas (Table 2). For both equations, the gain in accuracy was particularly pronounced in the subgroup of patients characterized by a high SCr increase (>25%) after cimetidine intake (high responders patients, n = 30; Figure 2A). This subgroup had a higher basal GFR overestimation (11.3 and 8.2 mL/min/1.73 m² for C–G and MDRD, respectively). On the contrary, patients for whom SCr was only moder-
ately increased (<25%; low responders patients, n = 26) exhibited a better initial Acc30 that remained stable after cimetidine (Figure 2B). Comparison of the main characteristics between high and low responders is presented in Table 3. High responders exhibited a significantly lower GFR.

Diagnostic performances

While a higher proportion of patients were correctly staged after cimetidine with the C–G equation (59% before and 68% after), no improvement was seen with the MDRD formula (59 vs 57%).

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Fig. 1. Modified Bland and Altman analysis of the MDRD formula before (A) and after cimetidine (B) and C–G equation before (C) and after treatment (D). The mean difference is indicated by the drawn line and limits of agreement (mean difference ± 2 SD) are represented by the dashed lines.

Fig. 2. Accuracy 30% of both GFR estimates before and after cimetidine in the high creatinine increase (>25%) patient subset (A) and in the moderate creatinine increase (<25%) group (B).
Although the sensitivity to detect a 60 mL/min/1.73 m² threshold was increased by creatinine tubular secretion blockade, specificity dramatically deteriorated for both estimates (Table 4). Accordingly, ROC curves analysis showed only a marginal, non-significant increase in AUC after cimetidine (Figure 3).

Safety and tacrolimus interaction

One patient suffered from a side effect (nausea), leading to treatment discontinuation, with a rapid and complete recovery.

Mean Tac trough concentration before cimetidine was 7.1 ng/mL and remained stable after (6.9 ng/mL, $P = 0.66$).

Table 3. Comparison of patients according to their response to cimetidine

<table>
<thead>
<tr>
<th></th>
<th>High responders (mean ± SD) $n = 30$</th>
<th>Low responders (mean ± SD) $n = 26$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56 ± 12</td>
<td>48 ± 14</td>
</tr>
<tr>
<td>Sex ratio</td>
<td>2.4</td>
<td>3.3</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25 ± 4</td>
<td>25 ± 3</td>
</tr>
<tr>
<td>Inulin clearance (mL/min/1.73 m²)</td>
<td>47 ± 16</td>
<td>60 ± 17.3</td>
</tr>
<tr>
<td>Transplantation duration (months)</td>
<td>50 ± 57</td>
<td>50 ± 50</td>
</tr>
<tr>
<td>Tacrolimus trough level (ng/mL)</td>
<td>7.1 ± 2.5</td>
<td>7.0 ± 1.8</td>
</tr>
</tbody>
</table>

High responders are defined as patients exhibiting an increase in serum creatinine after cimetidine, >25%. Low responders are defined as patients exhibiting an increase in serum creatinine after cimetidine, >25%. SD, standard deviation; n.s., not significant.

Table 4. Diagnostic performances of GFR estimates before and after cimetidine treatment to detect a 60 mL/min/1.73 m² GFR threshold

<table>
<thead>
<tr>
<th>GFR estimates</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>ROC AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDRD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>0.74 [0.60–0.89]</td>
<td>0.62 [0.41–0.83]</td>
<td>0.83 [0.72–0.93]</td>
</tr>
<tr>
<td>After</td>
<td>0.97 [0.92–1]</td>
<td>0.24 [0.06–0.42]</td>
<td>0.89 [0.80–0.97]</td>
</tr>
<tr>
<td>Cockcroft–Gault</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>0.66 [0.5–0.81]</td>
<td>0.81 [0.64–0.98]</td>
<td>0.85 [0.75–0.95]</td>
</tr>
<tr>
<td>After</td>
<td>0.91 [0.82–1]</td>
<td>0.48 [0.26–0.69]</td>
<td>0.90 [0.82–0.98]</td>
</tr>
</tbody>
</table>

ROC AUC, area under the receiver operating characteristic curve.

Discussion

In this study, we deliberately did not analyse the performances of the Nankivell formula, as this equation has never demonstrated its superiority in transplant patients [1,3,16]. It was also important to restrict our analysis to the two most commonly used estimates in order to limit multiple statistical analyses. Patients with a GFR <30 mL/min/1.73 m² were not included since the optimal blocking dose of cimetidine is unknown at this level of GFR (a much higher dose of cimetidine might be necessary in this situation, which raises legitimate safety concerns).

The main results of our study are that blocking creatinine tubular secretion with cimetidine in kidney transplant patients (i) significantly improves the accuracy of prediction of the C–G formula, but (ii) has only a marginal positive effect on the MDRD equation’s performance, and (iii) does not permit a substantial gain for the diagnostic of CKD in kidney transplantation.

Our results regarding the beneficial effect of cimetidine on the performance of C–G formula in terms of accuracy, a parameter that includes both the bias and the precision of the estimate, are consistent with those of the few studies that have looked into the effect of the creatinine tubular secretion blockade in transplant patients. Kemperman et al. evaluated the effect of the cimetidine intake on the C–G formula in a smaller cohort of kidney transplant reci-

Fig. 3. ROC curve analysis of the MDRD formula (left chart) and of the C–G equation (right chart) before and after cimetidine intake.
patients (n = 24) [10]. A strong improvement of the bias and the precision (given by the limits of agreement) was noticed after treatment. Examining the correlation with a diethylenetriamine pentaacetae (DTPA) clearance, Schiff et al. also reported a good GFR prediction by the MDRD and the C−G formulas after cimetidine in 15 kidney−pancreas transplanted recipients [11]. More recently, Tangri et al. evaluated the effect of cimetidine in 43 heart transplant recipients and showed a beneficial effect with the C−G formula in reference to a 99mDTPA plasma clearance [18].

Although we also found that the accuracy of the MDRD equation tends to improve after cimetidine, this amelioration was only modest and not significant. This is particularly important since the MDRD equation is currently becoming the first-choice GFR estimate [21]. At present, the potential interest of cimetidine should thus preferentially be evaluated for the MDRD equation. In this context, our data do not support any pertinent benefit from the integration of a cimetidine corrected creatinine value into the MDRD equation. This result is not totally surprising given the modalities of development of this equation, which is supposed to take the creatinine tubular secretion into account. Accordingly, the MDRD equation largely underestimated the true GFR after cimetidine intake.

Beyond its effect upon the accuracy of prediction, the blockade of creatinine tubular secretion does not translate into a better diagnostic performance for the MDRD equation and the C−G formula. While after cimetidine the two equations logically have a better sensitivity for the diagnosis of CKD, they both experience an even more pronounced degradation of their specificity.

Even though blocking creatinine tubular secretion with cimetidine has no clear clinical utility in kidney transplantation, our data do, however, suggest that the high level of creatinine tubular secretion participates in the poor predictive performances of the creatinine-based equations in renal transplant recipients. The level of tubular creatinine secretion was quite heterogeneous in our population and allowed us to specifically look at a subgroup of high responder patients. We observed that the predicting equations had a particularly bad performance before cimetidine in this subgroup of patients as compared to their low responder counterparts (Acc30 for the MDRD equation of 63 vs 81%, respectively). Importantly, cimetidine has a beneficial effect only for the high responders and did not alter the already acceptable performances of the equations for the low responder patients. Those high responder patients appeared to present a wider positive basal bias, reinforcing the idea that creatinine tubular secretion plays a crucial role in the overestimation of GFR in kidney transplant population.

Taken together, these data suggest that the improvement of GFR prediction after cimetidine is due to the selective correction of a particularly high level of creatinine tubular secretion, which is present in a large number of transplant patients (>50% of the patients in our cohort). The amelioration of GFR estimation after cimetidine is, however, not significant either because cimetidine fails to completely block the secretion of creatinine or more certainly because the tubular secretion process is only one factor among many others, explaining the inability of SCr to fairly reflect GFR.

Interestingly, the subgroup of high responders also had a lower GFR, supporting the notion that creatinine tubular secretion increases with the progression of renal dysfunction.

As previously reported [10,11,18,22], the cimetidine intake was particularly well tolerated by our patients. Of note, we did not find any significant interaction with tacrolimus metabolism. Despite this excellent tolerance, one has to mention the possibility of exceptional cases of acute interstitial nephritis associated with cimetidine hypersensitivity [23,24], certainly making a non-therapeutic prescription of cimetidine even more questionable.

In conclusion, the tubular secretion of creatinine is one of the many factors explaining the difficulty of predicting GFR from SCr in kidney transplant patients. By inhibiting this secretion, cimetidine ameliorates the accuracy of creatinine-based GFR estimates. However, this amelioration is at best partial and does not help in the diagnosis of CKD in transplant patients. Overall, our data do not support the use of a cimetidine-based strategy for the evaluation of renal graft function in the clinic, particularly when the GFR is estimated by the MDRD equation.

Conflict of interest statement. None declared.

References

Donor–recipient age matching improves years of graft function in deceased-donor kidney transplantation

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Abstract

Background. Donor and recipient age in kidney transplantation are known to affect graft and patient survival. In deceased-donor (DD) transplantation, donor and recipient age matching are being increasingly accepted as part of the kidney allocation programme. The aims of this study are to evaluate the effect of donor and recipient age on transplant outcomes and to determine the effect of changing existing allocation criteria to allocation based on age matching of donors and recipients on total graft years of function.

Methods. Using the Australia and New Zealand Dialysis and Transplant Registry, all DD kidney transplant recipients in Australia and New Zealand between 1991 and 2006 were analysed (n = 4616). Outcomes analysed were overall graft failure, death with functioning graft and serum creatinine. We calculated the mean time to graft loss as 60 and 55 years, respectively, over up to 16 years follow-up. We then examined the gain in graft years if all older kidneys were allocated to older recipients.

Results. Older donors were associated with higher risk of overall graft failure (adjusted hazard ratio (HR) = 1.79, 95% confidence interval (95% CI) = 1.45, 2.21 and HR = 1.29, 95% CI = 1.09, 1.53, respectively) at 1–8 years post-transplant and higher serum creatinine at 1 and 5 years post-transplant (mean differences 32.74 μmol/L, 95% CI 27.60, 37.89 and 38.17 μmol/L, 95% CI 27.58, 48.77, respectively). Overall, young and old recipients with young donor