Evaluating cimetidine for GFR estimation in liver transplant recipients

Navdeep Tangri¹, Ahsan Alam¹, Michael D. Edwards², Ashley Davidson¹, Marc Deschênes¹,³ and Marcelo Cantarovich¹,³

¹Department of Medicine, McGill University Health Center, Montreal, Quebec, Canada, ²Everest Clinical Research Services, Markham, Ontario, Canada and ³Multi-Organ Transplant Program, Department of Medicine, McGill University, Montreal, Quebec, Canada

Correspondence and offprint requests to: Marcelo Cantarovich; E-mail: marcelo.cantarovich@muhc.mcgill.ca

Abstract

Background. Serum creatinine (Scr)-based equations lack accuracy in predicting glomerular filtration rate (GFR) in patients with liver disease. Cimetidine has been shown to improve the performance of Scr-based GFR formulae.

Methods. We evaluated the use of cimetidine on the performance of GFR-estimating equations in 39 liver transplant recipients. The patients received oral cimetidine (800 mg tid) during a 24-h urine collection. The next day, the patients underwent radionucleotide GFR (rGFR) determination and Scr was measured for creatinine clearance (CrCl) and GFR estimation using the Cockcroft–Gault, Nankivell and modified diet in renal disease (MDRD) equations. Data were analysed using the Pearson correlation statistic and Bland–Altman plots.

Results. The mean rGFR was 65 ± 26.4 mL/min. The use of cimetidine increased the bias between rGFR and the Nankivell and MDRD equations. The combined root mean square error for the CrCl, Cockcroft–Gault, Nankivell and MDRD equations without cimetidine were 20.2, 15.6, 17.0 and 15.5 and cimetidine-aided were 28.2, 23.2, 23.7 and 24.3, respectively.

Conclusions. All the tested equations without using cimetidine predicted GFR with modest accuracy. The addition of cimetidine decreased the precision and increased the bias of all the GFR-estimating equations. In the absence of accurate GFR-estimating equations, rGFR should be used to monitor kidney function in liver transplant recipients.

Keywords: cimetidine; creatinine clearance; GFR; liver disease; liver transplantation; tubular secretion

Introduction

Chronic kidney disease (CKD) is a well-recognized complication of orthotopic liver transplantation and is associated with increased morbidity and mortality [1–5]. The early detection of CKD is important to implement renal protection strategies to prevent the development of end-stage renal disease. The diagnosis of CKD relies on the estimation of the glomerular filtration rate (GFR). Radionucleotide GFR (rGFR), the gold standard for GFR estimation, remains costly and cumbersome. GFR-estimating equations and timed urine collections perform poorly in patients with liver disease and liver transplantation and tend to overestimate the true GFR [6–9]. This systematic bias can lead to under-diagnosis of CKD and may prevent the institution of treatment strategies that reduce the progression of kidney disease. Identifying a method to improve the accuracy of GFR estimation would facilitate the diagnosis and long-term monitoring of liver transplant patients with CKD.

Cimetidine, an H2-receptor antagonist, inhibits the tubular secretion of creatinine. Cimetidine-aided creatinine clearance (CrCl) correlates well with rGFR in patients with CKD, lupus nephritis and kidney transplant [10–13]. Our group has previously demonstrated an improvement in the accuracy of prediction equations using cimetidine in kidney–pancreas transplant recipients [13].

The purpose of the present study was to examine the degree of accuracy between cimetidine-aided CrCl and the cimetidine-aided estimated GFR with rGFR in long-term liver transplant patients.

Materials and methods

Thirty-nine prevalent liver transplant patients were recruited from an outpatient transplant clinic at a single transplant centre. Patients who had received a liver transplant, were on a calcineurin inhibitor and with stable renal function >1 year post-transplant were eligible for this study. Patients were prescribed three doses of oral cimetidine 800 mg, to be taken every 8 h, beginning 24 h before the rGFR test. During that period, patients also completed a 24-h urine collection to measure the cimetidine-aided CrCl. On the day of the rGFR test, serum creatinine (Scr), urea, albumin and body weight were measured. All creatinine measurements were performed in the same laboratory. Blood samples were obtained simultaneously with the GFR measurement. A modified kinetic Jaffé colorimetric method was used to measure Scr.

In order to compare changes in predictive accuracy with the addition of cimetidine, we obtained 24-h CrCl (n = 35), Scr and rGFR studies (n = 39) performed 1 year prior to the initiation of the cimetidine-aided study. These studies were completed as part of our routine annual post-transplant follow-up.
The CrCl was calculated in millilitres per minute as follows:

1. 24-h CrCl = (urine creatinine [in millimoles per litre] × urine volume [in millilitres]/Scr [in millimoles per litre]) × (1.23 for men, 1.04 for women) [14].
2. Cockcroft–Gault = (140 – age) × weight [in kilogrammes]/Scr [in millimoles per litre] × (1.23 for men, 1.04 for women) [14].
3. Modified diet in renal disease (MDRD) = (170 × Scr [in milligrammes per decilitre] – 0.995) × age [0.178] × weight [in milligrammes per decilitre] × 0.173 × albumin [in milligrammes per decilitre] × 0.762 for women] [15].

GFR was measured by ⁹⁹mTc-DTPA plasma clearance at 1 and 3 h [17]. Results were adjusted to a body surface area (BSA) of 1.73 m², except for the Nankivell and MDRD equations, which are already adjusted.

The Pearson correlation test was used to compare the different relationships of estimated or measured kidney function with rGFR as the reference. A paired t-test statistic was used to compare differences in the mean estimated level of kidney function with the rGFR. A P-value <0.05 was considered significant.

We also analysed the data using the method of Bland and Altman [18]. This relates the mean of the rGFR and the estimated result to the difference between estimated and measured GFR values directly estimates the global bias. The width of the standard deviation (SD) of the mean difference is an estimation of test precision; a large width means a low precision.

The combined root mean square error (CRMSE) was examined for GFR estimates with and without cimetidine. CRMSE is calculated as the square root of the [(mean difference between estimated and measured GFR)² (SD of the difference)]². It measures both bias and precision.

Statistical analysis was performed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

This study was approved by the Institutional Review Board at the McGill University Health Center and all patients provided informed consent.

## Results

The average age of the study sample was 61 ± 11 years, the majority (64%) was male and the mean BMI was 28.5 ± 7.1 kg/m². The mean Scr at the time of cimetidine treatment was 142 ± 36 μmol/L with a mean rGFR of 62.9 ± 24.3 mL/min/1.73m². There were no African Americans in this cohort. The median time from transplantation to study enrolment was 5.1 years (interquartile range 2.4 to 7.5 years).

The results of the rGFR test, 24-h urine cimetidine-aided CrCl and calculated results from the Cockcroft–Gault, Nankivell and MDRD equations are shown in Table 1.

All the Scr-based formulae had a moderate degree of correlation with the rGFR (Pearson correlation coefficient 0.41 to 0.68). Pre-treatment with cimetidine improved the degree of correlation between rGFR and the Cockcroft–Gault formula. Cimetidine had no effect on the degree of correlation between rGFR and either the MDRD or Nankivell formula or the calculated CrCl from the 24-h urine collection (Table 2).

Bland and Altman analyses for cimetidine-aided and non-cimetidine-aided rGFRs are shown in Figure 1. The

| Table 1. Assessments of kidney function with and without cimetidine |
|-------------------------|-------------------------|
|                         | No cimetidine (n = 39)  | Cimetidine (n = 39) |
|                         | ml/min/1.73 m² | P-value | ml/min/1.73 m² | P-value |
|-------------------------|-------------------------|
| rGFR                    | 61.6 ± 19.6 | –       | 62.9 ± 24.3 | –       |
| 24-h                    | 58.6 ± 19.5 | 0.94    | 45.1 ± 19.1 | <0.001  |
| CrCl                    | Cimetidine (24-h)  |
| C-G                     | 63.5 ± 19.1 | 0.45    | 49.2 ± 13.8 | <0.001  |
| MDRD                    | 61.7 ± 19.3 | 0.98    | 46.0 ± 13.7 | <0.001  |
| Nankivell               | 60.1 ± 16.2 | 0.54    | 48.1 ± 13.4 | <0.001  |

All values are reported as mean ± SD. rGFR, ⁹⁹mTc-DTPA radionuclide glomerular filtration rate; 24-h CrCl, 24-h creatinine clearance; C-G, Cockcroft–Gault formula; MDRD, modification of diet in renal disease study equation; Nankivell, Nankivell equation. P-value represents paired t-test with reference to rGFR.

| Table 2. Correlation and measures of agreement with ⁹⁹mTc-DTPA radionuclide GFR |
|-------------------------|-------------------------|
|                         | No cimetidine (n = 39)  | Cimetidine (n = 39) |
|                         | Bias | Precision | CRMSE | Bias | Precision | CRMSE |
|-------------------------|-------------------------|
| 24-h                    | –0.30| 20.2 | 0.51| –17.8 | 21.9 | 28.2 |
| CrCl                    | Cimetidine (24-h)  |
| C-G                     | 0.68* | 1.9 | 15.5 | 0.76* | –13.7 | 18.7 | 23.2 |
| MDRD                    | 0.62* | 0.1 | 17.0 | 0.64* | –17.0 | 16.6 | 23.7 |
| Nankivell               | 0.64* | –1.5 | 15.5 | 0.61* | –14.8 | 19.3 | 24.3 |

rGFR, ⁹⁹mTc-DTPA radionuclide glomerular filtration rate; 24-h CrCl, 24-h creatinine clearance; C-G, Cockcroft–Gault formula; MDRD, modification of diet in renal disease study equation; Nankivell, Nankivell equation; CRMSE, combined root mean square error = square root of [(mean difference between estimated and measured GFR)² (SD of the difference)]². *P < 0.05.

MDRD formula without cimetidine was the least biased and the Nankivell and Cockcroft–Gault formulae without cimetidine had the best precision. The addition of cimetidine reduced the accuracy of all the estimating equations, but improved the correlation for the Cockcroft–Gault formula. The CRMSE, an overall evaluation of the bias and precision, did not improve with cimetidine for any of the GFR estimation equations. The Nankivell and the Cockcroft–Gault formulae had the best CRMSE values without cimetidine.

## Discussion

The most important finding of this study was that the addition of cimetidine does not improve the performance of creatinine-based equations in estimating GFR in liver transplant recipients. We also found that the Nankivell and Cockcroft–Gault formulae, without cimetidine, had the best estimate of accuracy and precision in this population.

The adverse effects of CKD on survival in patients with liver transplant are well described [1,3]. Previous investi-
Difference 24-hr CrCl and rGFR (ml/min/1.73m²)

Mean of adjusted 24-hr CrCl and rGFR (ml/min/1.73m²)

A 24-hour Creatinine Clearance

B 24-hour Creatinine Clearance + Cimetidine

C Cockcroft-Gault

D Cockcroft-Gault + Cimetidine

Difference C-G GFR and rGFR (ml/min/1.73m²)

Mean of adjusted C-G GFR and rGFR (ml/min/1.73m²)

E MDRD

F MDRD + Cimetidine

Difference MDRD GFR and rGFR (ml/min/1.73m²)

Mean of adjusted MDRD GFR and rGFR (ml/min/1.73m²)

G Nankivell

H Nankivell + Cimetidine

Difference Nankivell GFR and rGFR (ml/min/1.73m²)

Mean of adjusted Nankivell GFR and rGFR (ml/min/1.73m²)
gators have found a decrease in patient and graft survival in patients who develop CKD after non-renal transplant. The ascertainment of CKD status, through GFR measurement, is complicated in these patients due to reduced muscle mass, reduced hepatic creatinine generation and calcineurin inhibitor use, leading to increased tubular creatinine excretion. In fact, the poor performance of GFR-estimating equations and overestimation of GFR by measured CrCl in patients with liver disease is well known [7–9]. While progress has been made in estimating equations in patients with kidney transplants, novel methods to estimate GFR in patients with liver transplants remains understudied [16,19]. Given the additional factors of reduced muscle mass and hepatic creatinine generation, equations developed in kidney and heart transplant cohorts may not be applicable to liver transplant recipients. We, therefore, studied the use of cimetidine, an inhibitor of tubular creatinine secretion, in order to reduce urinary creatinine excretion independent of GFR and, therefore, improve the overestimation bias in GFR-estimating formulas.

Our findings contrast with the previous literature that suggests a benefit of cimetidine in other CKD populations. Cimetidine has been shown to improve the predictive ability of timed CrCl estimates in patients with kidney transplants and patients with lupus nephritis [11,12]. Similarly, we have previously demonstrated the efficacy of cimetidine in improving GFR estimation in patients with kidney–pancreas transplantation [13]. In the current study, however, we found no improvement in GFR estimation using cimetidine, and we suggest that the lack of effect is related to two notable differences in the study population. Firstly, our study population consisted of patients with liver transplant who had relatively preserved muscle mass and stable liver function. As a result, the lower muscle mass and hepatic creatinine generation in patients with advanced liver disease was likely not present and, therefore, led to a relatively unbiased non-cimetidine GFR estimate. The addition of cimetidine, as expected, further lowered estimated GFR and significantly worsened the bias in GFR estimation. Secondly, the prior studies demonstrating the benefit of cimetidine have had small numbers of patients with severe renal disease. Given that the tubular secretion of creatinine is increased at lower GFRs, this could have led to an increased benefit with the addition of cimetidine. Our current study population had relatively preserved renal function with a mean GFR of 65 mL/min. Since the proportion of creatinine excretion from tubular secretion increases as GFR declines, we hypothesized that the lack of more severe CKD (GFR <60 mL/min) in our liver transplant patients may have contributed to the lack of benefit from cimetidine. In fact, a lack of improvement of GFR estimation with cimetidine was also noted in our previous report of heart transplant patients with relatively preserved kidney function [20].

We found the Nankivell and Cockcroft–Gault formulae to have the best estimate of precision and accuracy in our population. Our results could be explained by the fact that the Nankivell formula was developed in patients with renal transplants and, therefore, may be more generalizable to a liver transplant cohort. This may be due to the use of similar medication regimens, namely, calcineurin inhibitors, in patients with liver and kidney transplant. Our findings contrast with the results of a prior study by Gonwa et al. that found the MDRD formula to be superior to the Nankivell and Cockcroft–Gault formulae [7]. However, the differences in performance between the equations were small in both studies, and Nankivell estimates were not available for the majority of patients in their study population at 5 years post-transplant.

Investigators have also studied the use of cystatin C as an estimate of GFR in patients with liver transplant and found superior performance to creatinine-based equations [9,21]. Since we were interested in the effect of cimetidine on the performance of creatinine-based equations, we did not obtain cystatin C values in our population.

The strengths of our approach are that we included 39 patients with 78 rGFR values in our analysis. To the best of our knowledge, this is the largest study examining the effect of cimetidine on the performance of creatinine-based GFR-estimating equations in liver transplant recipients. In addition, we were able to test the predictive ability of several creatinine-based equations in our population.

Our study has limitations, however, that must be kept in mind when interpreting the study results. We acquired data retrospectively on our study subjects for all non-cimetidine timed urine collections, GFR estimates and rGFR measurements. However, since our analysis examined the correlation between the estimated GFR and rGFR within the same period in time, this should not significantly bias our results. Secondly, we used 99mTc-DTPA as our gold standard for GFR estimation. If the relationship between 99mTc-DTPA rGFR and true GFR is different in liver transplant recipients, this would have affected our results.

We were also unable to verify the adherence of the oral cimetidine dosing. Although we do not suspect non-compliance with the intervention, improved compliance with cimetidine would have only further improved the accuracy of the 24-h CrCl and Cockcroft–Gault calculated CrCl. Again, in clinical practice, cimetidine would be given as an outpatient medication and our conditions would mimic real-life settings and enhance the generalizability of our study results. Finally, the majority of our patients were non-African American and had relatively preserved kidney function.

Conclusion

In conclusion, our findings do not support the use of cimetidine to improve the accuracy of GFR prediction. The Nankivell and the Cockcroft–Gault formulae provided the most precise and accurate measures of GFR in our liver transplant population, but the degree of correlation with the rGFR was moderate. In the absence of more accurate equations to estimate the GFR, rGFR should be used to assess kidney function in liver transplant patients. If routine GFR measurement is not possible, our results suggest that creatinine-based equations could be used, with an understanding that accuracy may be diminished. Further research focusing on estimating GFR in liver transplant patients is needed.
Impaired glucose homeostasis in renal transplant recipients receiving basiliximab

Willy Aasebo1, Karsten Midtvedt1, Tone Greitland Valderhaug2, Torbjørn Leivestad3, Anders Hartmann1,4, Anna Varberg Reisæter1, Trond Jenssen1,5 and Hallvard Holdaas1

1Section of Nephrology, Rikshospitalet University Hospital, Oslo University Hospital, 0027 Oslo, Norway, 2Thoracic surgical department, Rikshospitalet University Hospital, Oslo University Hospital, 0027 Oslo Norway, 3Institute of Immunology, Rikshospitalet University Hospital, Oslo, Norway, 4Faculty of Medicine, University of Oslo, Oslo, Norway and 5Institute of Clinical Medicine, University of Tromso, NO-9037 Tromso, Norway

Correspondence and offprint requests to: Willy Aasebo; E-mail: willy.aasebo@rikshospitalet.no, waasebo@online.no

Abstract

Background. The pathogenesis of new onset diabetes after transplantation (NODAT) is multifactorial. Suppression of regulatory T lymphocytes may have a negative impact on pancreatic β-cells. Induction with basiliximab affects regulatory T-cell function and may therefore, theoretically, also affect glucose homeostasis in renal transplant recipients.

Methods. All kidney recipients ≥50 years of age without diabetes mellitus transplanted from 1 January 2005 to 31 December 2007 were included in a single-centre retrospec-