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Chapter 4

Cimetidine improves prediction of the glomerular filtration rate by the Cockcroft-Gault formula in renal transplant recipients

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Abstract

**Background:** The glomerular filtration rate (GFR) can be predicted from plasma creatinine, age, gender and body weight, using the formula of Cockcroft and Gault. Cimetidine improved the accuracy of GFR-prediction in renal disease and also in diabetes mellitus type 2, due to inhibition of tubular creatinine secretion. We investigated the accuracy and precision of GFR-prediction from the Cockcroft-Gault formula after cimetidine (CG\text{cim}) in renal transplant recipients and compared the results to the endogenous creatinine clearance without cimetidine.

**Methods:** The endogenous creatinine clearance was measured in 24 outpatients from a 24-hour urine collection (C\text{c}24). CG\text{cim} was calculated from plasma creatinine after oral cimetidine 2400 mg during 24 hours preceding the GFR-measurement. GFR was measured as the urinary clearance of continuously infused $^{125}$I-iothalamate. Creatinine was determined with an automated enzymatic assay in plasma and with an alkaline picrate assay in urine.

**Results:** GFR was 47.8 ± 16.8 ml/min/1.73m$^2$ (mean ± SD), C\text{c}24 was 71.8 ± 23.1 ml/min/1.73m$^2$ and CG\text{cim} was 52.8 ± 14.9 ml/min/1.73m$^2$. C\text{c}24 overestimated GFR in every patient by an average of 23.8 ml/min/1.73m$^2$ and up to 57 ml/min/1.73m$^2$, whereas CG\text{cim} overestimated GFR significantly less by an average 4.9 ml/min/1.73m$^2$ ($P < 0.001$) with a maximum of 20 ml/min/1.73m$^2$. Also the precision of CG\text{cim} was significantly better than that of C\text{c}24: the SD of the difference from GFR was 9.0 ml/min/1.73m$^2$ for CG\text{cim} and 14.5 ml/min/1.73m$^2$ for C\text{c}24 ($P < 0.05$).

**Conclusion:** CG\text{cim} is useful for GFR-prediction in outpatient renal transplant recipients and has a far better accuracy and precision than C\text{c}24. We propose a strategy after kidney transplantation of one GFR-measurement at baseline and follow-up with CG\text{cim}.
GFR-prediction after kidney transplantation

Introduction

In renal transplant patients accurate information on the glomerular filtration rate (GFR) is useful both for clinical management and for analysis of the long term results of kidney transplantation. Assessment of renal function in patients with a kidney transplant is usually done by plasma creatinine. This is not an accurate reflection of GFR in patients with renal disease [1-3] and also not in renal allograft recipients [4], because creatinine is not only filtered by the glomeruli but also secreted in the proximal tubules [5]. Similarly, the endogenous creatinine clearance is of limited value and has been reported to overestimate GFR by 38-60 % in patients with a kidney transplant [4,6,7]. Not surprisingly, a comparable but slightly lower overestimation is found when an assessment of the creatinine clearance is made by the formula of Cockcroft and Gault: 33-38 % [6-8]. Furthermore, the endogenous creatinine clearance and Cockcroft-Gault formula are not only inaccurate but also not suitable for follow-up, because the relative contribution of tubular secretion often changes with time [9,10].

The H₂-receptor antagonist cimetidine, a weak organic base, inhibits tubular creatinine secretion competitively in the proximal tubular organic ion transporter system [11,12] and has been shown to improve GFR-estimation by the endogenous creatinine clearance [13-16]. However, intravenous or prolonged oral dosing schedules have been used in these studies. A one-day course of oral cimetidine was sufficient for accurate GFR-estimation by the Cockcroft-Gault formula in patients with renal disease and in type 2 diabetic patients with plasma creatinine concentrations below 180 μmol/l [17,18].

The aim of the present study was to investigate the accuracy and precision of the Cockcroft-Gault formula with cimetidine administration, compared to the endogenous creatinine clearance without cimetidine, for GFR-estimation in outpatient renal allograft recipients.

Materials and Methods

Study population

Between November 1998 and June 2000 twenty-four adult renal transplant patients participated in the study. The following exclusion criteria were applied. 1. Plasma creatinine concentration above 180 μmol/l. The reason for this is, that during inhibition of tubular creatinine secretion a new steady state of plasma creatinine will be reached at a higher level. In a previous study we have shown that it takes less then 24 hours to reach this new steady state in patients with a...
plasma creatinine less than 180 μmol/l [17]. Therefore one day of cimetidine administration was sufficient. 2. Body mass index below 15 or above 30 kg/m², as muscle mass is not reflected well by body weight in these patients. 3. Regular use of cimetidine, trimethoprim or high dose salicylates, as these drugs inhibit tubular secretion. Plasma creatinine concentration had to be stable during the preceding outpatient controls.

Fourteen patients were male, median age was 50 years (range 29 - 58), median duration after transplantation was 32 months (range 2.5 - 240). Twenty patients received a cadaveric donor kidney, the other four a living related donor kidney. Systolic blood pressure was 133 ± 14 mm Hg (mean ± SD), diastolic blood pressure was 84 ± 6 mm Hg and body mass index was 24.5 ± 2.1 kg/m². Eighteen patients were treated with a combination of prednisone and calcineurin blockers; three with a combination of prednisone and purine antagonists, two with triple therapy and one patient received no immunosuppression, because of an identical donor. It has been shown before that cimetidine does not influence ciclosporine levels [19]. No adverse effects related to cimetidine were observed in these patients.

**Study procedures**

The patients delivered a 24-hour urine collection during a regular outpatient visit. A plasma creatinine sample was taken at the same time for measurement of the endogenous creatinine clearance (C\textsubscript{cr} 24). An appointment was made for the GFR-measurement within 6 weeks. Patients were instructed to take 800 mg of cimetidine at 8 A.M. and 8 P.M. the day before and at 8 A.M. the day of the GFR-measurement. A second plasma creatinine sample was drawn at 10.30 A.M. during the GFR-measurement. This plasma sample was used for prediction of GFR from the Cockcroft-Gault formula (CG\textsubscript{cim}):

\[
\frac{(140-\text{age}) \times \text{body weight}}{0.815 \times \text{plasma creatinine}}
\]

[for women correction factor 0.85; age in years, weight in kg, plasma creatinine in μmol/l]

The GFR-procedure started a 8.30 A.M. Patients were seated and drank at least 200 ml of tap water every hour to maintain sufficient urine flow. After a blank urine sample was voided and a blood sample drawn a loading dose of \( ^{125} \text{I-ithalamate} \) and \( ^{131} \text{I-hippuran} \) was given and continuous infusion of both tracers was started for measurement of GFR and effective renal plasma flow (ERPF). After an equilibration period of two hours, two clearance periods of two hours each were analyzed. Urine samples were collected at least every 2 hours by spontaneous
voiding. After the blank sample, plasma samples were taken at 1, 2, 4 and 6 hours. GFR was measured as the mean of two urinary clearances of $^{125}$I-iothalamate with the formula $UdV/P$, where $U$ and $P$ are tracer concentrations in urine and plasma and $V$ is the urine flow rate (ml/min). The $^{125}$I-iothalamate clearances were corrected for inaccurate urine collections with a correction factor obtained from the $^{131}$I-hippuran clearance, as described by Donker et al. and Apperloo et al. [20,21]. During continuous infusion the plasma tracer concentrations will not be stable, due to the circadian rhythm of GFR and ERPF and sometimes also because of an incorrect estimate of the infusion rate [22,23]. For instance, in case of a falling $^{125}$I-iothalamate concentration the GFR is higher than the measured $^{125}$I-iothalamate clearance. Therefore, a second correction was made for a systematic increase or decrease of plasma tracer concentrations [23,24].

Activities of radio-isotopes in plasma and urine were determined in duplicate with a gamma counter. Creatinine concentration was measured in urine with the kinetic alkaline picrate (or Jaffé) reaction (Roche Diagnostics, Mannheim, Germany), in plasma with an enzymatic PAP+ (Phenol/4-Aminoantipyrine)-assay (Roche Diagnostics, Mannheim, Germany). The alkaline picrate assay is known for its falsely elevated plasma creatinine values due to non-creatinine chromogens [25]. For accurate GFR-prediction an enzymatic creatinine assay that lacks this interference is obligatory, as we have shown previously in patients with type 2 diabetes mellitus [26].

**Statistical analysis**

Data are expressed as means ± SD, unless stated otherwise. Statistical analysis was performed using SPSS for Windows, release 7.5. A $P$-value less then 0.05 was considered to be significant. Clearances were corrected for body surface area according to the formula of DuBois and DuBois and expressed as ml/min/1.73m² [27]. GFR-estimates from the endogenous creatinine clearance without cimetidine or the Cockcroft-Gault formula with cimetidine were compared to the measured GFR both in correlation plots and in an analysis modified from Bland and Altman [28]. The accuracy and precision are determined in this type of analysis by relating the difference between the estimated and measured GFR in each patient to the measured GFR in the same patient. Whether a systematic increase or decrease of the difference is present for an increasing GFR can also be analyzed. The limits of agreement can be expressed as mean difference ± 2 SD and mean - 2 SD, in which 95% of the values are located. The mean difference is a measure of
accuracy, while the SD of the difference is a measure of precision. The coefficient of variation is calculated as the SD divided by the mean GFR. The variances of the agreements were compared with the method described by Armitage and Berry [29]. The paired t-test was used to compare the differences. For comparison of the ratio estimated/measured GFR a division was made for GFR-values below and equal to or above 40 ml/min/1.73m², as an earlier study had shown that tubular secretion could not be inhibited completely by usual dosages of cimetidine in the low GFR-range [17].

![Figure 1](image)

**Figure 1** The plasma creatinine concentration of 24 renal transplant patients before and after the administration of cimetidine. The mean values are 122 μmol/l without and 147 μmol/l with cimetidine, indicated by horizontal lines.

### Results

The plasma creatinine concentration increased in all patients after cimetidine administration, from 122 ± 28 to 147 ± 41 μmol/l (Figure 1). A large variation of the increase was present. The relation between estimated and measured GFR is shown in Figure 2. GFR was 47.8 ± 16.8 ml/min/1.73m², the endogenous creatinine clearance without cimetidine administration ($C_e$24) was 71.6 ± 23.1 ml/min/1.73m² and GFR-prediction from the Cockcroft-Gault formula with cimetidine ($CG_{cin}$) was 52.8 ± 14.9 ml/min/1.73m². $C_e$24 overestimated GFR in every patient.
The agreement between the estimated and measured GFR is given in Figure 3. $C_{\text{cr},24}$ overestimated GFR by an average of 23.8 ml/min/1.73m$^2$ and up to 57 ml/min/1.73m$^2$. $CG_{\text{cim}}$ overestimated GFR significantly less than $C_{\text{cr},24}$ by an average of 4.9 ml/min/1.73m$^2$ ($P < 0.001$), indicating a better accuracy, with a maximum of 20 ml/min/1.73m$^2$. The precision of $CG_{\text{cim}}$ was also significantly better than that of $C_{\text{cr},24}$, as shown by a smaller SD of the difference from GFR: 9.0 ml/min/1.73m$^2$ for $CG_{\text{cim}}$ and 14.5 ml/min/1.73m$^2$ for $C_{\text{cr},24}$ ($P < 0.05$). The coefficient of variation was 19% for $CG_{\text{cim}}$ and 30% for $C_{\text{cr},24}$. $CG_{\text{cim}}$ overestimated GFR in all cases where GFR was below 40 ml/min/1.73m$^2$. Therefore, the ratio estimated/measured GFR was compared for a GFR above and below 40 ml/min/1.73m$^2$. The mean ratio $CG_{\text{cim}}$/GFR was 1.05 in the seventeen patients with a GFR ≥ 40 ml/min/1.73m$^2$ and 1.46 in the seven patients with a lower GFR. The ratio $C_{\text{cr},24}$/GFR was 1.41 in the high and 1.99 in the low GFR-range.
Figure 3 Analysis modified from Bland and Altman of 24 patients. In this analysis the difference between two methods is plotted against the reference method for each individual patient. This was done for the endogenous creatinine clearance without cimetidine administration (C\textsubscript{e,24}) and GFR (left panel) and for the Cockcroft-Gault formula with cimetidine administration (CG\textsubscript{cin}) and GFR (right panel). The mean difference is indicated by the drawn line, the limits of agreement (mean - 2 SD and mean + 2 SD) are indicated by the dashed lines.

Discussion

The present study has shown that prediction of the GFR in renal transplant recipients can be markedly improved by administration of cimetidine, using the Cockcroft-Gault formula. The accuracy and precision of CG\textsubscript{cin} was significantly better than that of C\textsubscript{e,24}, as shown by a far smaller and less variable difference from the measured GFR. The ratio estimated/measured GFR was larger, when GFR was below 40 ml/min/1.73m\textsuperscript{2}, but the absolute differences between estimated and measured GFR remained within the limits of agreement. It is speculative why tubular secretion was not inhibited completely in every patient by the applied dose of cimetidine. This has also been observed before in patients with renal disease [17]. Van Acker et al. found that patients with incomplete inhibition had a higher cimetidine clearance and that a higher degree of inhibition could be obtained by a higher dose of cimetidine [16]. It can be hypothesized that cimetidine administered above the maximum daily dose of 2000 mg or in combination with trimethoprim, which inhibits the same tubular transporter [30], will inhibit tubular secretion completely.
Only one comparable study has been done in renal allograft recipients [6]. Marceen et al. studied 32 patients with a varying degree of renal dysfunction. They found that GFR-estimation by the Cockcroft-Gault formula was superior to the endogenous creatinine clearance. Without cimetidine the overestimation was 38 % instead of 60 % and with cimetidine 10 % instead of 18 %. However, no absolute differences were given in that study and no analysis according to Bland and Altman was performed. The coefficient of variation for the Cockcroft-Gault formula in that study was 35 %. In the present study this was 19 %. The explanation for this is unclear. A difference between the two studies is a more accurate plasma creatinine assay used in the present study. Although not mentioned by the authors, they most likely used an alkaline picrate or Jaffé assay, known for its falsely elevated plasma creatinine values due to non-creatinine chromogens [25].

Two other studies have been published on the accuracy and precision of the endogenous creatinine clearance with cimetidine administration for GFR-estimation in renal transplant patients [31,32]. Hirata-Dulas et al. reported an improvement of the accuracy and precision of the creatinine clearance with cimetidine, measured simultaneously with the renal inulin clearance, but the mean overestimation was still 23 % [31]. In patients with a reduced allograft function the overestimation was relatively more pronounced. This was probably due to the dose reduction of cimetidine applied in that study. In a second study a finding of van Acker et al. was used, that a single high cimetidine dose of 1200 mg caused complete inhibition of tubular creatinine secretion from 3 to 6 hours after administration [16]. Zaltzman et al. applied this finding in renal allograft recipients with a GFR ranging from 7 to 47 ml/min/1.73m² [32]. The 3-hour creatinine clearance starting one hour after 800 mg of cimetidine overestimated GFR by 12 %. The reproducibility of this test was good with a day-to-day variability of 7.1 %.

We did not investigate the value of the Cockcroft-Gault formula for follow-up of GFR. Follow-up of predicted GFR from this formula, but without cimetidine administration, was studied by Schuck et al. [7]. A significant discrepancy was found between the change in GFR and the change in predicted GFR in 14 of 22 patients. It can be speculated that this was caused by a change in the relative contribution of tubular creatinine secretion in individual patients. If so, cimetidine is a useful tool to abolish or at least reduce this discrepancy. In a previous follow-up study in type 2 diabetic patients, using cimetidine, we found no discrepancy between the change in GFR and the change in predicted GFR by the Cockcroft-Gault formula in 18 of 21 patients, which supports this contention [33]. A similar study should be done in renal transplant recipients.
If this also appears satisfactory, then a strategy can be advocated to determine GFR once after transplantation with a reference method, such as inulin or radiotracers, in order to analyze the difference between GFR and the Cockcroft-Gault formula after cimetidine (CG_{cim}). Further follow-up of renal function can then be done with CG_{cim}.

In conclusion, after kidney transplantation GFR can be predicted from plasma creatinine, determined with an enzymatic assay after 2400 mg of cimetidine in three divided doses during 24 hours and applied in the Cockcroft-Gault formula. The accuracy and precision of CG_{cim} were significantly better than those of the endogenous creatinine clearance without cimetidine (C_{c,24}). The ratio predicted/measured GFR was higher in a small number of patients with a GFR <40 ml/min/1.73m² than in the others. We suggest that GFR is measured once in renal allograft recipients, after which follow-up of GFR can be done with CG_{cim}.

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References


