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ORIGINAL ARTICLE

Creatinine clearance after cimetidine administration in a new short procedure: comparison with plasma and renal clearances of iohexol

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ABSTRACT

Background. Creatinine clearance after cimetidine administration (Cim-CreatClr) was once proposed as a method of glomerular filtration rate (GFR) measurement, but has been largely abandoned. We investigated whether a new short procedure for Cim-CreatClr determination could be considered an appropriate method for GFR measurement.

Methods. A 150-min protocol involving oral cimetidine administration was developed to determine Cim-CreatClr. In total, 168 patients underwent simultaneous assessments of creatinine clearance before and after cimetidine administration [basal creatinine clearance (Basal-CreatClr) and Cim-CreatClr, respectively], renal iohexol clearance and plasma iohexol clearance (R-iohexClr and P-iohexClr, respectively). We compared the agreement between the various methods of GFR measurement, using Bland–Altman plots to determine biases, precisions (standard deviation of the biases) and accuracy (proportions of GFR values falling within 10, 15 and 30% of the mean: P10, P15 and P30, respectively).

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Results. After cimetidine administration, Basal-CreatClr decreased by 19.8% [95% reference limits of agreement (95% LoA): −2.2 to 41.7%]. The bias between Cim-CreatClr and P-iohexClr was −0.6% (95% LoA −26.8 to 28%); the precision was 14.0%; P10, P15 and P30 were 57.1% [95% confidence interval (95% CI) 49.3 to 64.7%], 73.2% (95% CI 65.8 to 79.7%) and 97.0% (95% CI 93.2 to 99.0%), respectively. Due to the positive bias (16.7%; 95% LoA −3.6 to 36.9%) of Cim-CreatClr relative to R-iohexClr, accuracy of Cim-CreatClr relative to R-iohexClr was poor despite a good precision (10.3%).

Conclusions. Our study shows a high level of agreement between Cim-CreatClr and P-iohexClr. These results suggest that this short Cim-CreatClr procedure is a valid method for GFR measurement, which might be useful, in particular, in situations in which P-iohexClr is not suitable or not available.

Keywords: cimetidine, creatinine clearance, GFR measurement, iohexol plasma clearance, iohexol renal clearance

INTRODUCTION

Glomerular filtration rate (GFR) is the best indicator of kidney function, but the true GFR cannot be measured directly. It is, therefore, either estimated from serum concentrations of endogenous filtration markers (estimated GFR, eGFR) or measured by determining the clearance of exogenous filtration markers (measured GFR, mGFR) [1]. GFR measurements are particularly useful in clinical situations in which the imprecision of eGFR may lead to inappropriate decisions [2]. The renal clearance of inulin is the gold standard for GFR measurement, but its use remains complex and has been associated with severe adverse events. Furthermore, inulin is not currently available in several countries [3].

Iohexol plasma clearance (P-iohexClr), one of the most widely used methods for GFR measurement, is sufficiently accurate relative to inulin clearance [1, 4, 5]. It is widely used because it is relatively simple and does not require timed urine collections. Nevertheless, P-iohexClr is not suitable for all patients, particularly those with oedematous conditions, for which it can overestimate GFR [6]. Furthermore, although anaphylactic reactions during iohexol GFR measurement are uncommon [7, 8], iohexol cannot be administered to patients with a history of allergic reaction to iodinated contrast media. Moreover, late blood samples (up to 24 h) are required for patients with low GFR values, and this is not always feasible [9]. Previous studies including small numbers of patients suggested that creatinine clearance after cimetidine administration (Cim-CreatClr) could be used for GFR measurement [10–12], but this method has since been largely abandoned. As creatinine is both freely filtered and secreted in the proximal tubule, creatinine clearance overestimates GFR [1]. Cimetidine absorption blocks the tubular secretion of creatinine, resulting in a creatinine clearance close or identical to the true GFR [10, 11, 13]. A more recent study on a cohort of kidney transplant recipients investigated whether the inhibition of creatinine tubular secretion on cimetidine treatment (administered over several consecutive days) could improve the performance of creatinine-based equations for estimating GFR. This strategy was not useful for the Modification of Diet in Renal Disease formula, which already includes tubular creatinine secretion [14].

Since September 2016, we have systematically determined Cim-CreatClr in our protocol for GFR measurement, alongside P-iohexClr and renal iohexol clearance (R-iohexClr). By adding Cim-CreatClr to our standard protocol, we aimed to determine an upper limit beyond which the true GFR cannot theoretically lie, thereby identifying possible outliers of mGFR. Indeed, in the absence of tubular creatinine reabsorption, creatinine clearance cannot be lower than the true GFR. We avoided increasing the analysis time beyond that routinely required for iohexol clearance determinations, by implementing a short Cim-CreatClr procedure including three measurements of creatinine clearance over 30-min periods, beginning 60 min after cimetidine intake.

In this study, we retrospectively analysed the concordance between Cim-CreatClr and P-iohexClr and R-iohexClr, to assess the suitability of this procedure for measuring GFR.

MATERIALS AND METHODS

The ethics committee/Institutional Review Board Mondor approved this single-centre study (IRB00011558), which was conducted in the Nephrology department of Henri Mondor Hospital. Informed consent has been obtained from all the patients.

We retrospectively analysed all GFR measurements performed by P-iohexClr, R-iohexClr and Cim-CreatClr between September 2016 and November 2018. We excluded patients with oedematous conditions, such as cirrhosis, nephrotic syndrome or oedema of cardiac origin, for which P-iohexClr could be inaccurate.

Determination of the R-iohexClr and P-iohexClr

The concentrations of iohexol in plasma and urine were determined by high-performance liquid chromatography (HPLC), as previously described [15]. External quality control was performed for plasma and urine iohexol determinations, through regular exchanges with an external laboratory. A 5 mL bolus of iohexol (300 mg/L Omnipaque; GE Healthcare, France) was injected intravenously. After equilibration for 90 min (distribution time of iohexol in the extracellular compartment), blood (from the contralateral arm) and urinary samples were collected over six consecutive 30-min clearance periods (Figure 1). Diuresis levels were kept sufficiently high by the oral administration of 250 mL water initially and 125 mL every 30 min thereafter. R-iohexClr was determined as the mean of the six clearance-period values.

Blood samples were analysed for iohexol determinations 120, 150, 180, 210, 240 and 270 min after iohexol injection.

We used the Brochner-Mortensen equation to calculate P-iohexClr from the plasma disappearance curve [16]. R-iohexClr and P-iohexClr were adjusted for body surface area (BSA) calculated by the Mosteller formula [17].

Determination of Cim-CreatClr

Plasma and urinary creatinine levels were determined with a traceable, compensated-kinetics Jaffe colorimetric (Roche Diagnostics) isotope dilution mass spectrometry method on a

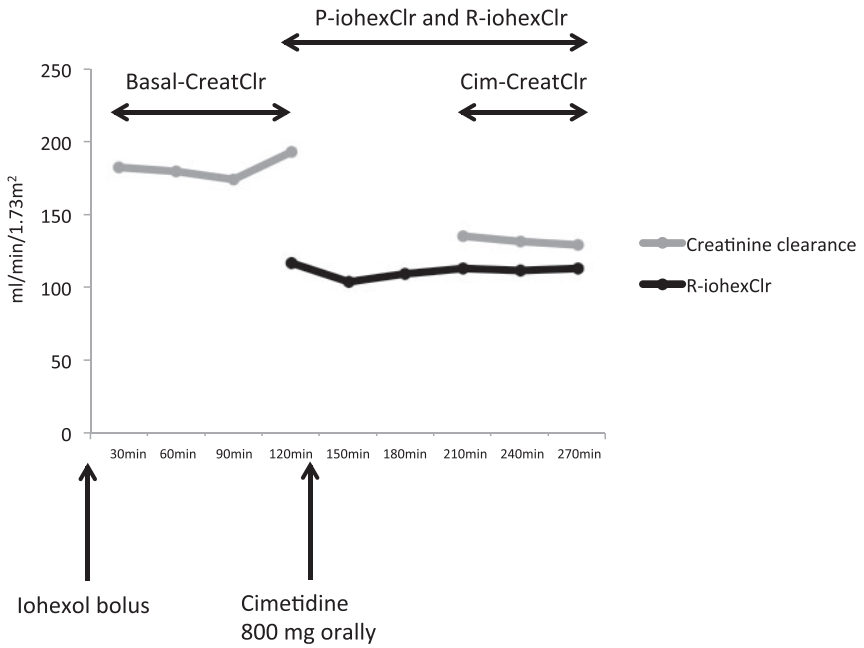

FIGURE 1: Protocol for determining R-iohexClr, P-iohexClr and creatinine clearances. The values provided are from one patient for whom mGFR determination was performed before living kidney donation.

Cobas601 analyzer. Basal creatinine clearance (Basal-CreatClr) was measured as the mean of four consecutive 30-min periods before cimetidine administration. A single dose of 800 mg cimetidine was then administered orally. After 60 min (time for gastrointestinal absorption and significant cimetidine elimination through urinary excretion), Cim-CreatClr was calculated as the mean of three consecutive 30-min periods (Figure 1). We did not determine plasma creatinine for all clearance periods, to avoid the collection of excessive amounts of blood. For Basal-CreatClr, we used plasma creatinine determined at the beginning of the four clearance periods. For Cim-CreatClr, we used plasma creatinine determined at the beginning of Cim-CreatClr for the first two periods, and, as we hypothesized that plasma creatinine levels would be modified by the decrease in creatinine clearance on cimetidine, we determined plasma creatinine at the end of Cim-CreatClr and used this value to calculate clearance for the third period of Cim-CreatClr. Basal-CreatClr and Cim-CreatClr were adjusted for BSA [17].

Calculation of eGFR

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to calculate eGFR [18]. We did not apply the correction factor for African-American ethnicity to patients of Caribbean or African ancestry. Indeed eGFR values corrected in this manner have been shown to overestimate true GFR in African Europeans [19] and in sub-Saharan Africans [20].

Statistical analysis

Continuous variables are expressed as the mean ± SD. We analysed the relationships between Basal-CreatClr and Cim-CreatClr, and between Cim-CreatClr P-iohexClr and R-iohexClr, in pairwise comparisons, by Passing–Bablok regression, calculating the slope, intercept and their 95% confidence intervals (95% CI) [21]. We then plotted Bland–Altman plots [22] of the relative differences, defined as the differences divided by the mean (except for the two clearances of creatinine quantifying intrinsically different variables, and for which the differences were divided by Basal-CreatClr). Relative biases were calculated as the mean relative difference [expressed as a percentage with 95% reference limits of agreement (95% LoA)]. Absolute biases were calculated as the means of absolute differences (expressed in mL/min/1.73 m^2 with 95% LoA). We calculated the precisions (standard deviation of the biases), and accuracies, that is, the proportions of GFR values falling within 10, 15 and 30% of the mean value for the measurements (P10, P15 and P30, respectively), with their 95% CI according to binomial distribution. The biases, precisions and the accuracies were determined for both the overall population, and for GFR subgroups (P-iohexClr <45, 45–59, 60–89, >90 mL/min/1.73 m^2). Accuracies (P10, P15 and P30) were compared, when necessary, in McNemar's test. Values of $P < 0.05$ were considered statistically significant. Agreement between the methods was also assessed with Lin's concordance correlation coefficient (CCC) [23]. Means of continuous variables were compared in paired or unpaired two-tailed *t*-tests. Values of $P < 0.05$ were considered statistically significant. The intra-period coefficients of variation (CV) for the three renal clearances were calculated as the ratio of the standard deviation to the mean of the different clearance periods. Analyses were performed with Microsoft Excel and MedCalc®, version 18.11.3 (Medcalc Software bvba, Ostend, Belgium).

RESULTS

Between September 2016 and November 2018, 179 patients were referred to our institution for GFR determinations and were evaluated concomitantly with P-iohexClr, R-iohexClr and Cim-CreatClr. Eleven patients were excluded from the analysis because of oedematous conditions (cirrhosis = 9, nephrotic syndrome = 2). The two main indications for GFR measurement were the assessment of eligibility for kidney donation in 63 cases (38%) and confirmation of CKD in patients with slightly low eGFR values but without other markers of kidney damage in 33 cases (20%). GFR was also measured in 72 CKD patients (43%)

Table 1. Characteristics of the study population

Parameters	Values
Age (years)	51.5 ± 14.5
Sex: M:F	91:77
Ethnicity	
White	117 (70)
African or Caribbean ancestry	51 (30)
Body weight (kg)	72.2 ± 13.7
Height (m)	1.70 ± 0.11
BMI (kg/m^2)	24.9 ± 3.7
Indication for GFR measurement	
Eligibility for kidney donation	63 (38)
Confirmatory testing of CKD	33 (20)
GFR measurement in CKD patients	72 (43)
HIV-seropositive subjects	12 (7)
Sickle-cell disease nephropathy	9 (5)
Vascular kidney disease	8 (5)
Kidney transplant recipients	7 (4)
Polycystic kidney disease	6 (4)
Tubulointerstitial kidney diseases	5 (3)
Multiple myelomas	4 (2)
Solitary kidney	4 (2)
IgA nephropathy	3 (2)
Liver transplant recipients	3 (2)
Diabetic nephropathy	2 (1)
Others	9 (5)
P-iohexClr	87.2 (25.7; 126.1)
R-iohexClr	72.9 (16.2; 115.3)
Basal-CreatClr	104.6 (26.8; 172.0)
Cim-CreatClr	86.0 (20.9; 133.9)

Apart from the GFR and creatinine clearance values, which are expressed as medians (2.5th; 97.5th percentiles), continuous variables are expressed as mean ± SD. Categorial variables are expressed as absolute numbers (percentages). M, male; F, female; BMI, body mass index; IgA, immunoglobulin A.

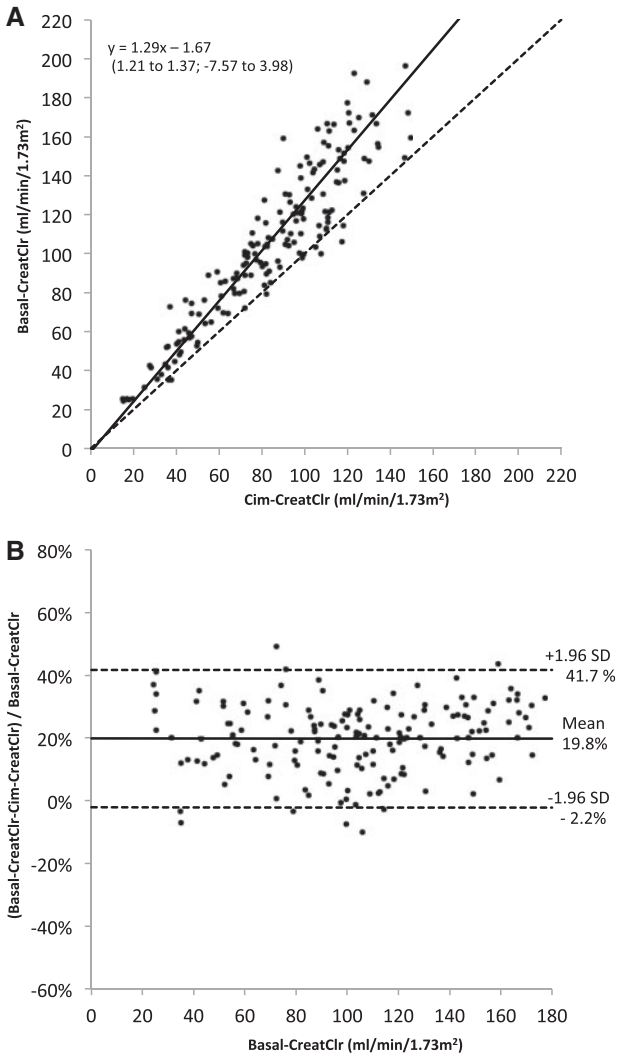

FIGURE 2: Comparison of Basal-CreatClr and Cim-CreatClr. The relationship between these two clearances was analysed by Passing–Bablok regression (**A**). The equation for the regression line is indicated in the figure. The dashed line is the line of identity. The thick line is the regression line. Bland–Altman plots comparing Basal-CreatClr and Cim-CreatClr (**B**). The solid lines indicate the bias (the mean relative difference) and the dashed lines indicate the lower and upper limits of the interval of agreement (−1.96 SD and +1.96 SD).

for whom it was assumed that eGFR might be inaccurate (Table 1). No significant adverse events were observed in these patients after cimetidine administration.

Modification of creatinine clearance after cimetidine administration

Mean Basal-CreatClr and mean Cim-CreatClr were 104.8 ± 39.8 and 83.5 ± 31.1 mL/min/1.73 m^2, respectively ($P < 0.05$). Plasma creatinine levels were 97.4 ± 48.0 µmol/L and 97.0 ± 47.3 µmol/L ($P = 0.52$) at the first and the second determinations (before and 60 min after cimetidine administration), respectively. The last plasma creatinine determination (150 min after cimetidine administration) was slightly higher than the second determination, at 100.1 ± 48.1 ($P < 0.05$). The intra-period CV for Basal-CreatClr and Cim-CreatClr was 9.4 ± 7.8% and 10.4 ± 9.0%, respectively. The relationship between the two clearances according to Passing–Bablok regression is illustrated in Figure 2A. Cim-CreatClr was consistently lower than or equal to Basal-CreatClr (only eight patients had Cim-CreatClr values slightly higher than Basal-CreatClr, and in these cases, the difference was <10%). The mean relative bias between Basal-CreatClr and Cim-CreatClr, corresponding to creatinine tubular secretion inhibition, was 19.8% (95% LoA −2.2 to 41.7%) (Figure 2B and Table 2). In contrast to previous reports [24], we found no association between body mass index and tubular creatinine secretion (Supplementary data, Table S1). We identified 31 patients (18.4%) for whom Basal-CreatClr was only slightly modified after cimetidine administration (Cim-CreatClr >0.9 × Basal-CreatClr). Seven of these 31 patients were infected with HIV and on treatments known to inhibit tubular creatinine secretion (cobicistat, $n = 5$; dolutegravir, $n = 2$).

Comparison of P-iohexClr and R-iohexClr

Mean P-iohexClr and R-iohexClr were 81.7 ± 28.3 and 71.0 ± 27.1 mL/min/1.73 m^2, respectively ($P < 0.05$). The intra-period CV for R-iohexClr was 11.1 ± 8.7%. The relationship obtained by Passing–Bablok regression is illustrated in Figure 3A. For the overall population, the relative bias was 16.0% (−8.7 to 40.8%). The values of relative and absolute biases according GFR ranges are summarized in Figure 3B and Table 3.

Table 2. Relationship between Basal-CreatClr and Cim-CreatClr in the overall population and in subgroups based on GFR ranges (defined according to P-iohexClr values)

	Overall population ($n = 168$)	GFR <45 ($n = 21$)	GFR 45–59 ($n = 19$)	GFR 60–89 ($n = 55$)	GFR ≥90 ($n = 73$)
Basal-CreatClr versus Cim-CreatClr					
Relative bias	19.8 (−2.2 to 41.7)	23.8 (−3.7 to 51.3)	21.2 (0.4 to 42.0)	19.0 (−2.8 to 40.8)	18.6 (−2.8 to 40.1)
Absolute bias	21.4 (−9.9 to 52.6)	10.6 (−6.6 to 27.8)	14.3 (−4.3 to 32.9)	20.2 (−8.7 to 49.1)	27.0 (−7.7 to 61.8)
Precision (%)	11.2	14.0	10.6	11.1	10.9

Relative bias is expressed as a percentage (95% LoA). Absolute bias is expressed in mL/min/1.73 m^2 (95% LoA). *n*, number of patients.

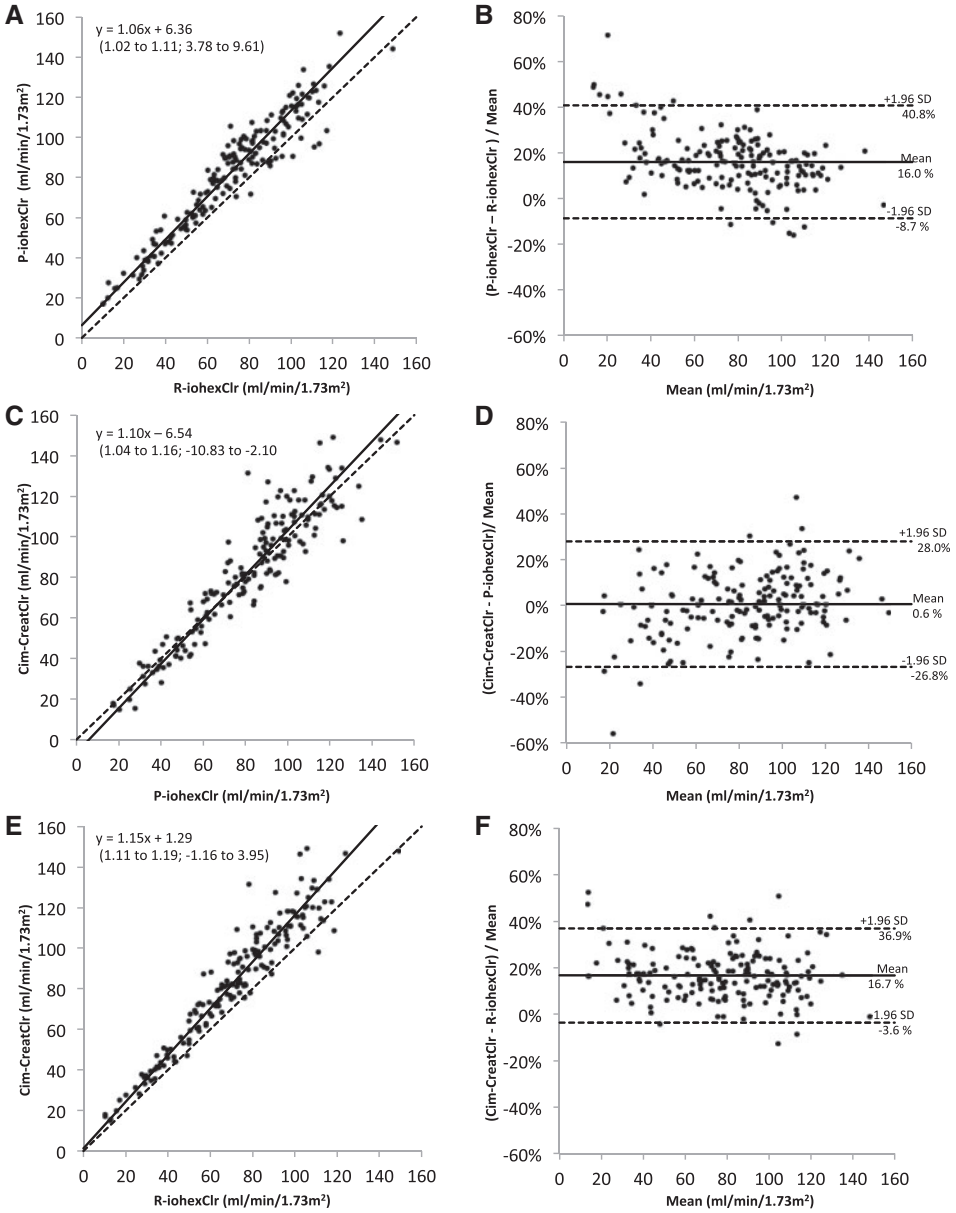

FIGURE 3: Pairwise comparisons of the three GFR measurement methods (Passing–Bablok regression on the left and Bland–Altman plot on the right). Relationship between the three GFR measurement methods analysed, as assessed by Passing–Bablok regression: P-iohexClr versus R-iohexClr (**A**), Cim-CreatClr versus P-iohexClr (**C**) and Cim-CreatClr versus R-iohexClr (**E**). The equations for the regression lines are indicated in each figure. Dashed lines are lines of identity. The thick lines are the regression lines. Bland–Altman plots comparing P-iohexClr and R-iohexClr (**B**), Cim-CreatClr and P-iohexClr (**D**) and Cim-CreatClr and R-iohexClr (**F**). The mean of the results obtained with the two GFR measurement methods is plotted on the x-axis. The solid lines indicate the bias (the mean relative difference) and the dashed lines indicate the lower and upper limits of the interval of agreement (−1.96 SD and +1.96 SD).

Table 3. Concordance of P-iohexClr, R-iohexClr and Cim-CreatClr in the overall population and in the subgroups based on GFR ranges (defined according to P-iohexClr values)

	Overall population ($n = 168$)	GFR <45 ($n = 21$)	GFR 45–59 ($n = 19$)	GFR 60–89 ($n = 55$)	GFR ≥90 ($n = 73$)
P-iohexClr versus R-iohexClr					
Relative bias	16.0 (−8.7 to 40.8)	28.9 (−6.2 to 63.9)	19.1 (−1.4 to 39.5)	13.7 (−6.6 to 34.1)	13.3 (−7.3 to 34.0)
Absolute bias	10.6 (−5.5 to 26.8)	7.4 (0.1 to 14.7)	8.8 (0.3 to 17.4)	9.5 (−4.6 to 23.7)	12.9 (−6.7 to 32.4)
Precision (%)	12.6	17.9	10.4	10.4	10.5
P30	89.9 (84.3, 94.0)	57.1 (34.0, 78.2)	84.2 (60.4, 96.6)	94.5 (84.9, 98.9)	97.3 (90.5, 99.7)
P15	47.6 (39.9, 55.5)	23.8 (8.2, 47.2)	42.1 (20.3, 66.5)	52.7 (38.8, 66.4)	52.1 (40.0, 63.9)
P10	26.2 (19.7, 33.5)	14.3 (3.1, 36.3)	21.1 (5.1, 45.6)	34.5 (22.2, 48.6)	24.7 (15.3, 36.1)
Cim-CreatClr versus P-iohexClr					
Relative bias	0.6 (−26.8 to 28.0)	−5.8 (−43.9 to 32.3)	−6.1 (−30.9 to 18.6)	3.9 (−22.6 to 30.4)	1.7 (−21.2 to 24.6)
Absolute bias	1.8 (−20.4 to 24.0)	−1.2 (−12.6 to 10.3)	−2.7 (−15.7 to 10.3)	3.8 (−19.1 to 26.8)	2.3 (−22.7 to 27.3)
Precision (%)	14.0	19.4	12.6	13.5	11.7
P30	97.0 (93.2, 99.0)	90.5 (69.6, 98.8)	100 (82.4, 100)	96.4 (87.5, 99.6)	98.6 (92.6, 100)
P15	73.2 (65.8, 79.7)	57.1 (34.0, 78.2)	63.2 (38.4, 83.7)	74.5 (61.0, 85.3)	79.5 (68.4, 88.0)
P10	57.1 (49.3, 64.7)	42.9 (21.8, 66.0)	47.4 (24.4, 71.1)	58.2 (44.1, 71.3)	63.0 (50.9, 74.0)
R-iohexClr versus Cim-CreatClr					
Relative bias	16.7 (−3.6 to 36.9)	23.2 (−0.5 to 46.9)	13.0 (−3.3 to 29.3)	17.6 (−3.0 to 38.2)	15.0 (−3.4 to 33.5)
Absolute bias	12.4 (−6.1 to 30.9)	6.3 (0.1 to 12.4)	6.1 (−2.6 to 14.9)	13.3 (−5.3 to 31.9)	15.1 (−4.6 to 34.8)
Precision (%)	10.3	12.1	8.3	10.5	9.4
P30	90.5 (85.0, 94.5)	76.2 (52.8, 91.8)	100 (82.4, 100)	89.1 (77.8, 95.9)	93.2 (84.7, 97.7)
P15	47 (39.3, 54.9)	19.0 (5.4, 4.2)	57.9 (33.5, 79.7)	47.3 (33.7, 61.2)	52.1 (40.0, 63.9)
P10	23.8 (17.6, 31.0)	14.3 (3.0, 36.3)	36.8 (16.3, 61.6)	21.8 (11.8, 35.0)	24.7 (15.3, 36.1)

Relative bias is expressed as a percentage (95% LoA). Absolute bias is expressed in mL/min/1.73 m^2 (95% LoA). P10, P15 and P30 are expressed as percentage (95% CI). *n*, number of patients.

Relative bias was higher for patients with a low GFR, whereas absolute bias was similar for all GFR levels.

Comparison of Cim-CreatClr with P-iohexClr and R-iohexClr

The relative bias between Cim-CreatClr and P-iohexClr was close to zero in the overall population (−0.6%, 95% LoA −26.8 to 28.0%). This bias was greater in absolute values in patients with a GFR <60 mL/min/1.73 m^2 (Figure 3C and Table 3). P10, P15 and P30 were 57.1% (49.3 to 64.7%), 73.2% (65.8 to 79.7%) and 97.0% (93.2 to 99.0%), respectively (Table 3). Thirty patients (17.9%) had P-iohexClr values at least 10% higher than Cim-CreatClr. These patients accounted for 33.3, 42.1, 10.9 and 12.3 of the subgroups of patients with GFR levels of <45, 45–59, 60–89 and ≥90 mL/min/1.73 m^2, respectively.

The relative bias between Cim-CreatClr and R-iohexClr was 16.7% (95% LoA −3.6 to 36.9%). The precision of Cim-CreatClr relative to R-iohexClr was high (10.3%), but its accuracy was poor: P10, P15 and P30 were 23.8% (95% CI 17.6 to 31.0%), 47.0% (95% CI 39.3 to 54.9%) and 89.9% (95% CI 85.0 to 94.5%), respectively (Table 3).

In the 24 patients who were not taking any regular treatment known to interfere with tubular creatinine secretion, and in whom cimetidine did not modify creatinine clearance, mean Cim-CreatClr and mean P-iohexClr were 98.1 ± 24.5 and 88.3 ± 21.8 mL/min/1.73 m^2, respectively, the relative bias was 10.4% (LoA −9.1 to 30.0%) and the precision was 10.0%.

Comparison of eGFR and Basal-CreatClr with P-iohexClr

We assessed the added value of Cim-CreatClr, by comparing creatinine-based eGFR with P-iohexClr, and Basal-CreatClr with P-iohexClr (Table 4 and Figure 4).

For the overall population, the relative bias between eGFR and P-iohexClr was −6.4% (95% LoA −42.3 to 29.6%), and P30, P15 and P10 were 88.1% (95% CI 82.2 to 92.6%), 60.7% (95% CI 52.9 to 68.1%) and 41.1% (95% CI 33.6 to 48.9%), respectively. These results are significantly lower than those for Cim-CreatClr and P-iohexClr ($P < 0.05$). These results, stratified by ethnicity, are detailed in Supplementary data, Table S2. The performance of eGFR was better for the Caucasian subpopulation, but P10 remained lower than that between Cim-CreatClr and P-iohexClr in these patients [45.3% (36.1 to 54.8%) versus 58.1% (48.6 to 67.2%); $P < 0.05$].

Basal-CreatClr is highly biased relative to P-iohexClr, resulting in poor accuracy, despite good precision (Table 4 and Figure 4). We also evaluated Basal-CreatClr, after correction for the mean relative bias between Basal-CreatClr and Cim-CreatClr: corrected basal-CreatClr = (1 − 0.198) × Basal-CreatClr. Corrected basal-CreatClr had a good P15 and P30 relative to P-iohexClr, but P10 was lower than that between Cim-CreatClr and P-iohexClr [47.0% (39.3 to 54.9%) versus 57.1% (49.3 to 64.7%); $P < 0.05$] (Table 4 and Figure 4).

The CCCs between the different methods of GFR assessment are reported in Table 5. P-iohexClr and Cim-CreatClr displayed the best agreement and excellent accuracy.

DISCUSSION

Comparisons to assess the accuracy of GFR measurement method should theoretically be performed with the reference method, that is, the renal clearance of inulin. Due to unavailability of inulin in France, as in many other countries [3], a comparison of Cim-CreatClr to P-iohexClr, one of the most widely used methods of GFR measurement [25], seemed pertinent. In a systematic review of the accuracy of GFR measurement methods using renal inulin clearance as reference, Soveri *et al.* [1]

Table 4. Concordance of eGFR (CKD-EPI), Basal-CreatClr and P-iohexClr in the overall population and in the subgroups based on GFR ranges (defined according to P-iohexClr values)

	Overall population ($n = 168$)	GFR <45 ($n = 21$)	GFR 45–59 ($n = 19$)	GFR 60–89 ($n = 55$)	GFR ≥90 ($n = 73$)
eGFR (CKD-EPI) versus P-iohexClr					
Relative bias	−6.4 (−42.3 to 29.6)	−8.1 (−49.8 to 33.6)	−5.6 (−38.0 to 26.7)	−2.0 (−38.9 to 35)	−9.4 (−43.0 to 24.3)
Absolute bias	−4.4 (−32.9 to 24.0)	−1.8 (−14.6 to 11.0	−2.0 (−18.6 to 14.5)	−0.4 (−28.8 to 28.0	−8.9 (−40.8 to 23.1)
Precision (%)	18.3	21.3	16.5	18.9	17.2
P30	88.1 (82.2, 92.6)	85.7 (65.4, 95.0)	94.7 (74.0, 99.9)	87.3 (75.5, 94.7)	87.7 (77.9, 94.2)
P15	60.7 (52.9, 68.1)	57.1 (34.0, 78.2)	52.6 (28.9, 75.6)	56.4 (42.3, 69.7)	67.1 (55.1, 77.7)
P10	41.1 (33.6, 48.9)	47.6 (25.7, 70.2)	31.6 (12.6, 56.6)	43.6 (30.3, 57.7)	39.7 (28.5, 51.9)
Basal-CreatClr versus P-iohexClr					
Relative bias	23.3 (−7.2 to 53.9)	22.5 (−12.6 to 57.7)	18.4 (−12.3 to 49.1)	25.6 (−6.3 to 57.5)	23.1 (−4.9 to 51.2)
Absolute bias	23.2 (−14.3 to 60.6)	9.5 (−9.5 to 28.4)	11.6 (−10.0 to 33.2)	24.0 (−12.6 to 60.6)	29.5 (−9.6 to 68.5)
Precision (%)	15.6	17.9	15.7	16.3	14.3
P30	70.8 (63.3, 77.6)	71.4 (47.8, 88.7)	78.9 (54.4, 93.9)	65.5 (51.4, 77.8)	72.6 (60.9, 82.4)
P15	32.1 (25.2, 39.8)	38.1 (18.1, 61.6)	52.6 (28.9, 75.6)	25.5 (14.7, 39.0)	30.1 (19.9, 42.0)
P10	16.7 (11.4, 23.2)	19 (5.4, 41.9)	31.6 (12.6, 56.6)	9.1 (3.0, 20.0)	17.8 (9.8, 28.5)
Corrected basal-CreatClr versus P-iohexClr					
Relative bias	1.5 (−29.6 to 32.6)	−0.7 (−34.9 to 36.4)	−3.5 (−34.6 to 27.6)	3.8 (−28.7 to 35.4)	1.3 (−27.2 to 29.9)
Absolute bias	2.4 (−25.2 to 30.1)	1.1 (−12.9 to 15.0)	−1.0 (−18.0 to 15.9)	4.0 (−25.3 to 33.4)	2.5 (−28.8 to 33.76)
Precision (%)	15.9	18.2	15.9	16.6	14.6
P30	94.0 (89.3, 97.1)	90.5 (69.6, 98.8)	94.7 (74.0, 99.9)	92.7 (82.4, 98.0)	95.6 (88.5, 99.1)
P15	68.5 (60.9, 75.4)	47.6 (25.7, 70.2)	63.2 (38.4, 83.7)	65.5 (51.4, 77.8)	78.1 (66.9, 86.9)
P10	47.0 (39.3, 54.9)	38.1 (18.1, 61.6)	31.6 (12.6, 56.6)	50.9 (37.1, 64.7)	50.7 (38.7, 62.6)

Relative bias is expressed as a percentage (95% LoA). Absolute bias is expressed in mL/min/1.73 m^2 (95% LoA). P10, P15 and P30 are expressed as percentages (95% CI). *n*, number of patients.

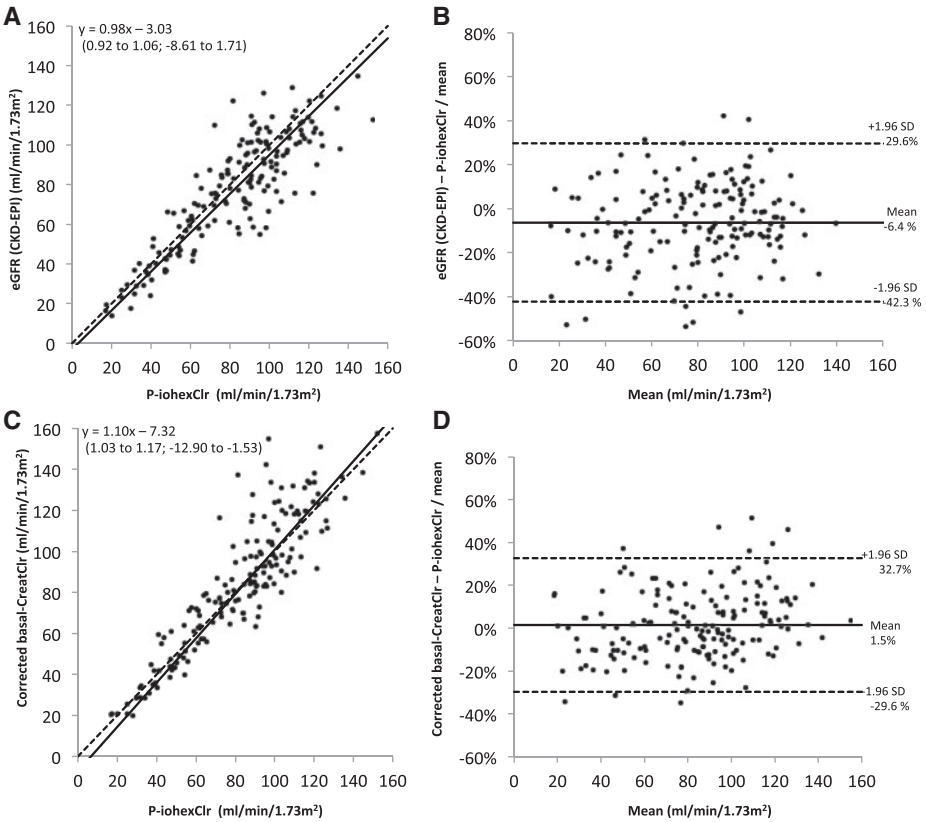

FIGURE 4: Comparisons of eGFR (CKD-EPI) and corrected basal-CreatClr with P-iohexClr (Passing–Bablok regression on the left and Bland–Altman plot on the right). Relationship between eGFR and corrected basal-CreatClr was analysed, as assessed by Passing–Bablok regression: eGFR versus P-iohexClr (**A**) and corrected basal-CreatClr versus P-iohexClr (**C**). The equations for the regression lines are indicated in each figure. Dashed lines are lines of identity. The thick lines are the regression lines. Bland–Altman plots comparing eGFR and P-iohexClr (**B**) and corrected basal-CreatClr and P-iohexClr (**D**). The mean of the results obtained with the two GFR assessment methods is plotted on the *x*-axis. The solid lines indicate the bias (the mean relative difference), and the dashed lines indicate the lower and upper limits of the interval of agreement (−1.96 SD and +1.96 SD).

Table 5. Agreement between the different methods of GFR assessment evaluated with Lin's CCC

	P-iohexClr versus R-iohexClr	Cim-CreatClr versus P-iohexClr	Cim-CreatClr versus R-iohexClr	eGFR versus P-iohexClr	Basal-CreatClr versus P-iohexClr	Corrected basal-CreatClr versus P-iohexClr
CCC (95% CI)	0.89 (0.86 to 0.91)	0.93 (0.90 to 0.94)	0.87 (0.84 to 0.90)	0.85 (0.80 to 0.89)	0.69 (0.63 to 0.74)	0.89 (0.85 to 0.92)
ρ (precision)	0.96	0.93	0.96	0.87	0.90	0.90
C_b (accuracy)	0.93	0.99	0.90	0.99	0.77	0.99

CCC evaluates the degree to which pairs of observations fall on the line at an angle of 45° passing through the origin. ρ is the Pearson correlation coefficient, which measures how far each observation deviates from the best-fit line (precision). C_b is a bias correction factor, which measures the extent to which the best-fit line deviates from the 45° line through the origin (accuracy).

found a median bias of P-iohexClr of 3% (95% CI 0 to 6%) with P10 and P30 of 50% (95% CI 43 to 58%) and 86% (95% CI 81 to 91%), respectively. These results are similar to those reported here for the comparison of Cim-CreatClr and P-Iohexol (median bias: −0.6%, P10: 57.1%, P30: 97%). Moreover, we found that the degree of agreement between P-iohexClr and Cim-CreatClr, as assessed with the CCC, was moderate, but displayed an excellent accuracy. In addition, the performance of Cim-CreatClr relative to P-iohexClr was significantly better than that of eGFR. The results of our study, therefore, suggest that Cim-CreatClr may be an accurate method of GFR measurement.

Given the bias between Basal-CreatClr and Cim-CreatClr, and the high degree of precision between Basal-CreatClr and P-iohexClr, we also evaluated the performance of Basal-CreatClr corrected for this bias. The accuracy of corrected basal-CreatClr was almost identical to that of Cim-CreatClr for P15 and P30, but it remained significantly inferior for P10. By blocking the tubular secretion of creatinine, cimetidine not only corrects the bias between Basal-CreatClr and GFR, but also improves the precision of creatinine clearance.

Interestingly, we identified 17.9% patients for whom P-iohexClr was at least 10% higher than Cim-CreatClr (more than a third of the patients with a GFR <60 mL/min/1.73 m^2). Assuming that creatinine is freely filtered and secreted in the proximal tubule but not reabsorbed, Cim-CreatClr cannot be below the true GFR value. Thus, in patients with P-iohexClr values higher than Cim-CreatClr, Cim-CreatClr may be closer to the true GFR than P-iohexClr. However, this observation may reflect the absence of late iohexol blood samples for the patients with the lowest GFR values [4, 5, 7, 26].

The systematic bias between Cim-CreatClr and R-iohexClr reduced accuracy of Cim-CreatClr relative to R-iohexClr, whereas precision was very good. One of the reasons for this good precision may be that the variability of urine collection interferes with both renal clearances. The scientific evidence validating R-iohexClr as an accurate method for measuring GFR relative to inulin is weak, with only two studies including a total of 47 patients performed [1]. R-iohexClr has been more widely compared with P-iohexClr [9] and with the renal clearance of iothalamate [27]. R-iohexClr was under-biased relative to P-iohexClr [9]. This bias was particularly important for low GFR values in the absence of late blood samples, but even for patients with GFR >60 mL/min/1.73 m^2, the bias exceeded 10% [9]. These data are similar to our data comparing P-iohexClr and R-iohexClr. R-iohexClr was also under-biased (−15%) relative to the renal clearance of iothalamate [27]. This bias was consistent over the entire GFR range, and was equivalent to that between Cim-CreatClr and R-iohexClr in our study. Renal iothalamate clearance is known to overstate inulin renal clearance slightly [1, 28, 29], but the magnitude of this bias suggests that R-iohexClr would under-evaluate true GFR [3, 27]. If R-iohexClr under-evaluates GFR by 10–15%, this systematic error could lead to inappropriate clinical decisions for patients with normal or near-normal GFR.

Cim-CreatClr seems to be an accurate method of GFR measurement, but the preferential indications for its optimal use remain to be determined. Given the low availability of non-iodinated exogenous tracers (^{51}Cr-EDTA and ^{99m}Tc-DTPA must be used in regulated radiation protection conditions, inulin is no longer available in many countries, etc.), Cim-CreatClr may be a particularly interesting option in patients with a history of allergy to iodinated contrast agents. Cim-CreatClr may also be appropriate for patients with oedematous conditions, for which P-iohexClr is not suitable. Similarly, Cim-CreatClr may be a relevant method of GFR measurement method in patients with low predicted GFR values for whom it is not possible to collect a late blood sample for logistical reasons. Finally, in patients with poor vascular access, the repeated blood sampling required to determine the plasma clearance of exogenous tracer may be difficult to perform. In this situation, a single-sample method is a useful alternative [30]. Our study suggests that Cim-CreatClr may also be used in these patients. Indeed, as plasma creatinine level was only slightly higher at the end of the procedure (150 min after cimetidine ingestion), Cim-CreatClr could probably be performed with a single plasma creatinine determination without the loss of much precision.

van Acker *et al.* [10] considered the question of the optimal dose and timing of cimetidine administration. They observed that the maximum effect after cimetidine administration was not achieved during the first 3-h clearance period, but they did not study creatinine clearance for shorter periods within these 3 h. They proposed a procedure involving urine collection for a period of 3–6 h after the administration of a single dose of cimetidine (1200 mg). We did not apply this procedure for two reasons. Firstly, we felt it was preferable not to exceed the recommended dosage for usual indications. Secondly, we sought to integrate Cim-CreatClr into our usual GFR measurement procedure, which ruled out waiting 3 h after cimetidine ingestion. In addition, to reduce the imprecision of urinary clearance (incomplete bladder emptying in particular), it is advisable to average repeated clearance periods [31].

One important concern about Cim-CreatClr determination is the inability of cimetidine to prevent tubular creatinine completely in a significant proportion of patients [10].

In addition to seven HIV patients receiving drugs known to block tubular creatinine secretion, we identified 24 patients (14.3%) for whom Basal-CreatClr was unchanged or only slightly modified after cimetidine administration. We hypothesize that the intermediate bias between Cim-CreatClr and P-iohexClr in this subpopulation (smaller than the bias between Basal-CreatClr and P-iohexClr, but greater than that between Cim-CreatClr and P-iohexClr in the overall population) may indicate

that some patients constitutionally have an absence of tubular creatinine secretion and that cimetidine is not effective in others. Previous data suggesting that tubular reabsorption of creatinine may occur provide an argument against the extensive use of Cim-CreatClr [32, 33]. However, this phenomenon has never been clearly demonstrated [34]: for example, van Acker *et al.* found no cases in which Cim-CreatClr was significantly lower than inulin clearance [10]. Finally, the extra-renal clearance of creatinine (losses in sweat and faeces) may limit the accuracy of Cim-CreatClr, but this phenomenon seems to be relevant only in the pre-dialysis stage of CKD [35, 36]. Our study was also subject to methodological limitations. It was retrospective and, therefore, subject to the limitations inherent to this type of approach. The limited sample sizes of the subgroups with GFR values <60 mL/min/1.73 m^2 weakens our conclusions for these patients, particularly for patients with GFR <45 mL/min/1.73 m^2. There is also the intrinsic limitation common to all renal clearance measurement methods, which are dependent on the quality of bladder emptying. Increasing the number of clearance periods can lessen this inaccuracy, but this methodology is cumbersome. Taken together, these limitations of Cim-CreatClr (e.g. failure to block the tubular secretion of creatinine in some patients, bladder emptying error) may explain the variability of Cim-CreatClr relative to P-iohexClr. This variability may also be explained by factors specific to P-iohexClr, such as the variability in the volume of distribution between patients, and inaccuracies occurring during tracer injection or timed collection of blood samples.

In conclusion, there was good concordance between Cim-CreatClr and P-iohexClr, indicating that this short protocol of Cim-CreatClr would be an appropriate method for measuring GFR. Cim-CreatClr may be an interesting alternative for patients for whom determinations of the plasma clearance of iohexol are not appropriate. Our Cim-CreatClr protocol also has the advantage of a short duration (2.5 h versus at least 4–5 h for plasma clearance of exogenous tracer), low cost and potentially wide availability (no restriction of use due to the availability of an HPLC chain, gamma counter, etc.). Further prospective studies comparing Cim-CreatClr with other reference methods are required for the definitive validation of this method.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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