ABSTRACT
Renal function contributes markedly to the adequacy of continuous ambulatory peritoneal dialysis (CAPD). The best way to measure it in clinical practice has not been established. Ten stable CAPD patients with residual renal function were investigated to compare the GFR measured as inulin clearance (Clᵢ) with the creatinine clearance (Clᵣ), the urea clearance (Clᵤ), and with 0.5(Clᵢ + Clᵤ). Thereafter, an analysis of whether the administration of cimetidine could improve the accuracy of these clearances was performed. Two clearance periods (CP) of 24 h were investigated. During CP-2, patients received 400 mg cimetidine twice daily, for a total dose of 1200 mg. Two h before the urine and dialysate collection period, inulin was administered iv. Calculations were done for each CP for Clᵢ, Clᵣ, Clᵤ, Clᵢ - Clᵣ, the Clᵢ/Clᵣ ratio, and the tubular secretion of creatinine (TS). No differences between CP-1 and CP-2 were present for urinary excretion of volume and solutes, and clearance rates of inulin and urea. The median Tₛ decreased from 0.71 μmol/min (range, −0.24 to 5.90) in CP-1 to 0.30 μmol/min (range, −0.18 to 0.64) in CP-2 (P < 0.05). Therefore, the median ratio of Clᵢ/Clᵣ decreased from 1.23 (range, 0.87 to 2.20) in CP-1 to 1.11 (range, 0.95 to 1.51) in CP-2 (P < 0.05). The median overestimation of the Clᵢ in CP-1 by the Clᵢ was 0.90 ml/min (range, −0.28 to 3.80) and by the 0.5(Clᵢ + Clᵤ) was 0.30 (range, −0.67 to 1.52). The median overestimation of Clᵢ during cimetidine treatment in CP-2 was 0.43 ml/min (range, −0.21 to 1.20). The range, in differences between Clᵢ and Clᵣ in CP-2 was smaller that than between Clᵣ and 0.5(Clᵢ + Clᵤ) in CP-1. The difference between the clearance rate of inulin and creatinine or the combined clearance rate of urea and creatinine was not influenced by the magnitude of the average GFR. It can be concluded that the administration of cimetidine improved the accuracy of measuring the GFR with the Clᵢ in CAPD patients.

Key Words: GFR, urea clearance, creatinine clearance, CAPD, cimetidine

A correct measurement of residual GFR in dialysis patients is important because the prescribed dialysis dose should take residual renal function into account (1). The endogenous creatinine clearance is an inaccurate determinant of the GFR in healthy individuals and in nondiabetic patients with renal failure, because tubular secretion of creatinine may contribute considerably to the urine excretion of this solute (2–4). This leads to an unpredictable overestimation of GFR. Cimetidine has been used to inhibit the secretion of creatinine in the proximal tubules without altering the GFR (5). During administration of this drug, the creatinine clearance rate was found to approach the inulin clearance rate in healthy individuals and in patients with moderate renal insufficiency (6–8). We recently found that this approach was not useful in hemodialysis patients, presumably because of competitive inhibition of the secretion of cimetidine by other organic compounds (9). It appeared that the best approximation of GFR in these patients was the creatinine clearance rate obtained 24 h before the next hemodialysis session because the tubular secretion of creatinine was minimal in that period. The mean of endogenous creatinine and urea clearance rates has been found to underestimate the GFR in hemodialysis patients about 0.5 ml/min for an inulin clearance rate of 3 ml/min (10). This approach has also been advocated in continuous ambulatory peritoneal dialysis (CAPD) patients, but without a comparison with inulin clearance (11).

The aim of the study presented here was to establish the best method that can be used in clinical practice to measure residual GFR in CAPD patients. Therefore, inulin clearance rates, as a reference standard, were compared with endogenous creatinine clearance rates, the mean of urea and creatinine clearance rates, and creatinine clearance rates after the administration of cimetidine. In addition, fractional clearance rates of sodium, osmoles, and water were determined.

SUBJECTS AND METHODS

Ten chronic peritoneal dialysis patients (two of whom were women), with a median age of 59 yr (range, 25 to 78) and a
urine output of at least 100 mL per day, participated in the study. The patients were in a stable condition, and none of them had peritonitis at the time of the study or in the 4 preceding wk. The median time on peritoneal dialysis was 17 months (range, 5 to 41). The underlying renal diseases were chronic glomerulonephritis (6), tubulointerstitial nephritis (2), and adult polycystic kidney disease (2). No diuretics were permitted during the study and in the 2 preceding wk. The patients had no dietary restrictions. Body weight at the start and end of each dialysis exchange was recorded. All patients gave informed consent and the protocol was approved by the Medical Ethics Committee of the University Hospital of Amsterdam.

Two clearance periods of 24 h were investigated, with an interval of 1 week between them. Patients voided by spontaneously emptying their bladders. The first clearance period (CP-1) was used to obtain baseline levels. During the second clearance period (CP-2), patients received 400 mg of cimetidine (Tagamet®; SmithKline Beecham Farma B.V., Rijswijk, The Netherlands) twice daily; the first dose was taken 12 h before the start of the clearance period. The total dose of cimetidine during the study was 1200 mg. Two h before each collection period, 2.5 g intramuscularly and 2.5 g intravenously (Intest; Laesovas Gesellschaft, Linz, Austria) was administered iv. Before the collection period, the peritoneal cavity was drained and the bladder was emptied by the patient’s spontaneous voiding. Urine and dialysate samples were taken for the determination of inulin. Urine and dialysate were collected during the study period of 24 h for the clearance determinations. The patients were able to carry out urine collections and peritoneal dialysate exchanges accurately.

Plasma sodium, chloride, potassium, urea, creatinine, osmolality, and inulin values were measured just before and after the collection period. Volume, sodium, chloride, potassium, urea, creatinine, osmolality, and inulin values were measured in the 24-h urine collection, and volume, urea, creatinine, and inulin values were measured in the 24-h dialysate collections. Cimetidine was also measured in the plasma, urine, and dialysate samples in CP-2.

Plasma, urine, and dialysate concentrations of inulin were measured by a modification of Walser’s method with the color reaction diphenylamine (12). The concentrations of creatinine were assayed by an enzymatic method (Boehringer Mannheim, Mannheim, Germany). The other solutes were measured by standard autoanalyzer methods (SMAC: Technicon, Tarrytown, NY; Hitachi H747; Boehringer Mannheim). Osmolality was determined with an osmometer (Advanced Instruments, Inc., Needham Heights, MA). Urine, dialysate, and plasma concentrations of cimetidine were measured by HPLC (13).

Calculations and Statistics

All clearance measurements were performed on the same blood and urine or dialysate samples. The following equation was used to calculate the daily renal clearance rates of creatinine (ClC), inulin (ClI), urea (ClU), and osmoles (Clom):

\[ \text{Cl} (\text{mL/min}) = \frac{(U \times V)}{(P \times \Delta t)} \]  

(1)

In this equation, \( U \) is the urinary concentration, \( V \) is the urine volume, \( P \) is the geometric mean of plasma concentrations before and after the 24-h urine and dialysate collection period, and \( \Delta t \) is the duration of the collection period. With the same equation, but using dialysate volume and concentrations instead of urine, the peritoneal clearance rates were calculated for inulin, creatinine, and urea. The renal electrolyte free water clearance was calculated as follows (13,14):

\[ \text{Cl}_{\text{H}_{2}\text{O}} (\text{mL/min}) = \left(\frac{V}{t}\right) \times \left[1 - \left(\frac{U_{\text{Na}+K}}{P_{\text{Na}+K}}\right)\right] \]  

(2)

where \( V/t \) is urine volume rate (mL/min) and \( U_{\text{Na}+K} \) is the sum of the urinary concentration of sodium and potassium. The electrolyte free water clearance was used instead of the standard free water clearance to assess the effect of the urine output on osmoregulation more accurately (14,15).

The ratio of creatinine and inulin clearance rates (ClC/ClI) was calculated, and the tubular secretion rate of creatinine (TSr, in \( \mu \text{mol/min} \)) was determined by subtracting the filtered creatinine load from the urinary creatinine excretion rate. The filtered load was calculated as the product of ClI and plasma creatinine concentration. The fractional excretion rate of sodium was calculated by the following equation.

\[ \text{FE}_{\text{Na}}(\%) = \left(\frac{\text{sodium clearance}}{\text{inulin clearance}}\right) \times 100 \]  

(3)

Similar equations were used for urea and osmoles. The fractional water excretion rate was calculated as:

\[ \text{FE}_{\text{H}_{2}\text{O}} = \frac{\text{Cl}_{\text{H}_{2}\text{O}}}{\text{Cl}_{\text{inulin}}} \]  

(4)

The fractional volume excretion rate was calculated similarly:

\[ \text{FE}_{\text{volume}} = \left(\frac{V}{t}\right)/\text{inulin clearance} \]  

(5)

To determine the extrarenal clearance rate of inulin, the same method as previously described for hemodialysis patients was used (9). The following equations were used:

\[ V_d = M_1/P_1 \]  

(6)

\[ M_1 = (M_{\text{inulin-ftr}} - M_{\text{inulin-eq}}) \]  

(7)

\[ M_2 = V_d \times P_3 \]  

(8)

\[ \text{Cl}_{\text{TOT}} = (M_1 - M_2)/(\sqrt{P_1} \times \sqrt{P_2} \times \Delta t) \]  

(9)

\[ \text{Cl}_I = \text{Cl}_{\text{TOT}} - \text{Cl}_U - \text{Cl}_D \]  

(10)

In these equations, \( V_d \) is the volume of distribution of inulin at the start of the CP, \( M_1 \) is the mass of inulin at the start of the CP, and \( M_2 \) is the mass of inulin at the end of the CP. \( M_1 \) was calculated as the difference between the quantity of inulin administered \( M_{\text{inulin-ftr}} \) and the quantity of inulin removed by urine and dialysate after the 2-h equilibration period \( M_{\text{inulin-eq}} \). \( P_1 \) is the plasma concentration of inulin at start of CP and \( P_2 \) is the plasma concentration of inulin at the end of CP. \( \text{Cl}_{\text{TOT}} \) is the total clearance amount of inulin, \( \text{Cl}_I \) is the extrarenal clearance amount of inulin, \( \text{Cl}_U \) is the renal clearance amount of inulin, and \( \text{Cl}_D \) is the peritoneal clearance amount of inulin.

Wilcoxon’s nonparametric two-sided test and Spearman’s test were used for the urine solute and volume excretion amounts and urine clearance rates because these data were not distributed normally. Differences between the plasma parameters were tested by t test. Plasma values are given as mean values ± SD. For comparison between the GFR (ClI) and ClI or the mean of ClI and ClU, linear regression and the method of Bland and Altman were used (16). In the last type of analysis, the differences between the two methods are plotted versus their means. Linear regression was also used to study the relation between the urinary excretion rate and peritoneal net ultrafiltration rate.
RESULTS

The two clearance periods were not different with regard to urine production, the clearances rates of inulin, urea, osmoles, H₂O, and sodium, or for the fractional clearances rates of these substances (Table 1). The plasma concentrations of inulin were similar before CP-1 (203 ± 53 mg/L) and CP-2 (201 ± 48), and after CP-1 (91 ± 27) and CP-2 (96 ± 26). The other plasma concentrations were also similar (data not shown). One patient had a Clᵢ of 11.8 mL/min; after this study, CAPD treatment was discontinued with this patient.

Cimetidine decreased the tubular secretion rate of creatinine from 0.71 μmol/min to 0.30 μmol/min (Table 2). As a result, the endogenous creatinine clearance rate was lower during CP-2 (P < 0.05). It overestimated the inulin clearance rate with 0.90 mL/min in CP-1 and with 0.43 mL/min in CP-2. No significant effect on the mean urea and creatinine clearance rates was found (Table 2). Correlations between the inulin clearance rate and the various approximations of GFR are shown in Figure 1. Bland and Altman analysis of these approximations is shown in Figure 2. The mean overestimation of GFR was similar for the mean of the combined urea and creatinine clearance rates, and for the creatinine clearance rate during cimetidine treatment, but the 95% confidence interval was lowest for the creatinine clearance rate measured during cimetidine treatment. The data did not suggest that the difference between inulin clearance and the other approximations was influenced by the magnitude of the GFR.

The plasma cimetidine concentration was 3.1 ± 1.2 mg/L at the start of CP-2 and 2.2 ± 1.8 mg/L at the end of CP-2. The mean plasma cimetidine/creatinine ratio was 0.016 ± 0.011. No relation was found between the plasma cimetidine/creatinine ratio and the differences in clearance rates between Clᵢ and the Clᵢ. The amount of cimetidine excretion in the urine during the 24 h of CP-2 was 26.5 mg (range, 11.1 to 124.8), and that in the dialysate was 7.3 mg (range, 3.5 to 17.5, P < 0.005). A positive correlation was found between the total urinary cimetidine excretion amount and the clearance rate of inulin and creatinine (P < 0.005).

The amount of inulin removed in the equilibration period of 2 h was 65 mg (range, 41 to 231) in the urine for CP-1 and 56 mg (range, 18 to 194) for CP-2, and 111 mg (range, 58 to 161) in the dialysate for CP-1 and 103 mg (range, 78 to 136) for CP-2. Therefore, the estimated amount of inulin present in the body was similar during CP-1 and CP-2, both at the beginning and the end of the clearance period. This enabled us to calculate the volume of distribution of inulin, which was 15.5% (range, 12.6 to 32.4) of body weight in CP-1 and 14.7% (range, 12.6 to 28.3) in CP-2. No relation was found between body weight, which was 71 kg (range, 57.5 to 100) and the volume of distribution of inulin. The total body clearance rate during CP-1 was 6.4 mL/min (range, 4.6 to 16.3) in CP-1 and 6.2 mL/min (range, 4.8 to 18.6) in CP-2. The calculated extrarenal clearance rate of inulin was 0.5 mL/min (range, 0.1 to 2.8) in CP-1 and 0.6 mL/min (range, 0.0 to 2.2) in CP-2.

A negative correlation was found between the urinary excretion rate and peritoneal net ultrafiltration rate for CP-1 (r = −0.80, P < 0.01) and CP-2 (r = −0.76, P < 0.02) (Figure 3A). No relation was found between the urinary excretion rate and the mean initial glucose concentration of the dialysate (Figure 3B), or between the peritoneal net ultrafiltration rate and the initial dialysate glucose concentration (Figure 3C).

DISCUSSION

This study shows that administration of cimetidine significantly improves the accuracy of estimation of the GFR with the creatinine clearance in CAPD patients. Comparison of the two clearance periods in our

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CP-1 median (range)</th>
<th>CP-2 median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>V/V (mL/min)</td>
<td>0.65 (0.21 to 1.21)</td>
<td>0.70 (0.22 to 1.08)</td>
</tr>
<tr>
<td>Clᵢ (mL/min)</td>
<td>3.21 (1.63 to 11.2)</td>
<td>2.68 (1.31 to 13.6)</td>
</tr>
<tr>
<td>Clᵢ(mL/min)</td>
<td>0.30 (0.01 to 0.81)</td>
<td>0.32 (0.02 to 0.78)</td>
</tr>
<tr>
<td>Clᵢ(mL/min)</td>
<td>2.50 (0.83 to 8.80)</td>
<td>2.11 (1.07 to 10.8)</td>
</tr>
<tr>
<td>Clᵢ(mL/min)</td>
<td>0.60 (0.21 to 1.01)</td>
<td>0.52 (0.23 to 0.91)</td>
</tr>
<tr>
<td>Clᵢ(mL/min)</td>
<td>0.25 (0.10 to 0.75)</td>
<td>0.26 (0.10 to 0.68)</td>
</tr>
<tr>
<td>FE_volume (%)</td>
<td>18.4 (5.9 to 74.2)</td>
<td>17.0 (6.3 to 82.4)</td>
</tr>
<tr>
<td>FE_U (%)</td>
<td>8.1 (1.4 to 49.9)</td>
<td>7.7 (1.1 to 59.3)</td>
</tr>
<tr>
<td>FE_S (%)</td>
<td>77.0 (46.4 to 107.0)</td>
<td>82.4 (51.7 to 101.3)</td>
</tr>
<tr>
<td>FE_U (%)</td>
<td>16.5 (6.4 to 62.0)</td>
<td>15.8 (6.7 to 44.3)</td>
</tr>
<tr>
<td>FE_U (%)</td>
<td>7.4 (1.8 to 22.4)</td>
<td>8.1 (2.5 to 19.2)</td>
</tr>
</tbody>
</table>

*V/V, urine volume; Clᵢ, inulin clearance; Clᵢ, urea clearance; Clᵢ(mL/min), osmole clearance; Clᵢ(mL/min), electrolyte free water clearance; FE_volume, fractional excretion of volume; FE_U, fractional sodium excretion; FE_U, fractional urea excretion; FE_U, fractional osmole excretion; FE_U, fractional free water excretion.
TABLE 2. The effect of cimetidine on the creatinine clearance rate, the Cl\textsubscript{C}/Cl\textsubscript{1} ratio, the tubular creatinine clearance rate (Cl\textsubscript{C} - Cl\textsubscript{1}), and rate of tubular secretion of creatinine (T\textsubscript{S}) during Clearance Periods 1 (CP-1) and 2 (CP-2)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CP-1 median (range)</th>
<th>CP-2 median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl\textsubscript{C} (mL/min)</td>
<td>4.00 (1.67 to 15.0)</td>
<td>3.22 (1.27 to 14.8)</td>
</tr>
<tr>
<td>(Cl\textsubscript{C} + Cl\textsubscript{U})/2 (mL/min)</td>
<td>2.98 (1.63 to 11.9)</td>
<td>2.58 (1.63 to 11.5)</td>
</tr>
<tr>
<td>Ratio Cl\textsubscript{C}/Cl\textsubscript{1}</td>
<td>1.23 (0.87 to 2.20)</td>
<td>1.11 (0.95 to 1.51)</td>
</tr>
<tr>
<td>Cl\textsubscript{C} - Cl\textsubscript{1} (mL/min)</td>
<td>0.90 (−0.28 to 3.80)</td>
<td>0.43 (−0.21 to 1.20)</td>
</tr>
<tr>
<td>T\textsubscript{S} (µmol/min)</td>
<td>0.71 (−0.24 to 5.90)</td>
<td>0.30 (−0.18 to 0.64)</td>
</tr>
</tbody>
</table>

\( ^{a} P < 0.05. \)

Figure 1. The relationship between Cl\textsubscript{1} and Cl\textsubscript{C}, between Cl\textsubscript{1} and the mean of Cl\textsubscript{C} and Cl\textsubscript{u}, and between Cl\textsubscript{1} and Cl\textsubscript{C} after the administration of cimetidine. The left and middle panels show data from CP-1, and the right panel shows data from CP-2.

Figure 2. Bland and Altman analysis of the differences between Cl\textsubscript{1} and Cl\textsubscript{u}, between Cl\textsubscript{1} and the mean of Cl\textsubscript{C} and Cl\textsubscript{u}, and between Cl\textsubscript{1} and Cl\textsubscript{C} after the administration of cimetidine.

A study shows that the Cl\textsubscript{1} with single-shot inulin and urine collections is an appropriate method for the measurement of residual renal function in CAPD patients. A continuous or repeated administration of inulin is not necessary because the decrease of plasma concentrations of inulin during 24 h averaged only 55%. Also, single-shot inulin with urine collec-
tions has been used for the measurement of GFR in hemodialysis patients (9,10).

The Cl\textsubscript{u}/Cl\textsubscript{c} ratio is relatively high when GFR is low, because the contribution of the tubular secretion of creatinine to total clearance amount increases in patients with impaired renal function (4). However, this ratio was found to decrease again for GFR values lower than 18 mL/min, caused by competitive inhibition of tubular creatinine secretion by uremic toxins (17). The Cl\textsubscript{u}/Cl\textsubscript{c} ratio has been reported to reach a value of 1.25 ± 0.05 when the inulin clearance was about 2 mL/min (17). These data are supported by our observations, which showed an average ratio of 1.23 with an average GFR of 3.2 mL/min.

The effectiveness of cimetidine in the inhibition of the tubular secretion of creatinine is assumed to be dependent on the magnitude of the cimetidine/creatinine ratio. The mean ratio obtained in our CAPD patients was 0.016. This is markedly lower than previous findings of our group, which showed that a cimetidine/creatinine ratio of at least 0.064 was necessary to obtain the inhibition of tubular creatinine secretion in patients with moderate renal insufficiency (8). In addition, in a similar study in hemodialysis patients, the cimetidine/creatinine ratio ranged between 0.012 and 0.017 without significant reduction of the Cl\textsubscript{u}/Cl\textsubscript{c} ratio during the interdialytic interval (9).

With CAPD and hemodialysis patients, differences in metabolic acidosis or in the accumulation of uremic waste products in the middle-molecular range, which suppress the tubular secretion of creatinine, may be an explanation for the increased susceptibility of CAPD patients to the effect of cimetidine (18). The 800 mg daily dose of cimetidine used in this study was two times the dose recommended for patients with minimal renal function (19). This resulted in plasma concentrations of cimetidine of between 2 and 3 mg/L. These concentrations were more than two times higher than those found in healthy patients using the same dose of cimetidine. Plasma levels below 1 mg/L are generally found in subjects with normal renal function (19). No central nervous system side effects were seen during this short administration of the high dose of cimetidine.

The Cl\textsubscript{u} is lower than the GFR because of the reabsorption of urea by the proximal tubules. The overestimation of the GFR by the Cl\textsubscript{u} could be corrected mathematically after the combination of Cl\textsubscript{u} and Cl\textsubscript{c}. The use of the Cl\textsubscript{u} is questionable because of the large variability in fractional excretion rate caused by hydration state and by the differences in tubular reabsorption. However, the method has been advocated as an estimation of the GFR in CAPD patients (11). The study presented here shows that this approach can be used for the comparison of mean values, but that a wide range exists in the difference between the combined clearance rates of urea and creatinine and the Cl\textsubscript{u}. The range, in the difference between the clearances, was smallest for creatinine clearance during cimetidine treatment. Therefore, this method should be used for the establishment of residual GFR in individual CAPD patients.

The extrarenal clearance rate of inulin in our patients was 0.6 mL/min. This value is in accordance with earlier studies, in which the difference between the total and the renal clearance rates of inulin was only a few mL/min (20,21). A similar extrarenal clearance rate of inulin was found in our study in chronic hemodialysis patients (9). The fractional excretion rate of volume and solutes in CAPD patients was also in the same range, as in hemodialysis patients (9).

An unexpected strong inverse relationship was
found between the peritoneal net ultrafiltration rate and the residual urine production rate: the higher the rate of urine production, the lower the ultrafiltration rate. This was not caused by an artefact, namely, that patients with a low urine volume would have more hypertonic exchanges. One explanation could be that a greater peritoneal ultrafiltration rate could influence residual GFR by hypoperfusion of the kidney. An alternative explanation might be that a low residual renal function easily leads to some overhydration with a decrease in colloidal osmotic pressure. This would decrease the peritoneal backfiltration of dialysis fluid and therefore increase net ultrafiltration. Further studies are necessary to confirm this observation and investigate the possible causes.

It can be concluded that the Clc with 800 mg of cimetidine daily approximates the GFR in CAPD patients. Also, the mean of Clc and Clm without cimetidine approximates the GFR, but the range of the difference with Clc was larger than that for the Clc with cimetidine. Therefore, the creatinine clearance rate during the administration of cimetidine is an appropriate method in research studies on residual renal function in CAPD patients, and the mean of Clc and Clm is appropriate for routine clinical practice to establish residual GFR in individual patients.

REFERENCES