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Preliminary Report

Three consecutive day collection of dialysate and urine to identify non-compliance in CAPD patients

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Abstract

Background. Compliance with dialysis prescription is an important determinant of adequacy of CAPD. Several reports have suggested that non-compliance may be detected by a high creatinine excretion ratio (CrEx ratio = measured creatinine excretion in a 24-h collection of urine and dialysate/predicted creatinine excretion) and that it occurs in a substantial proportion of patients. However the validity of this screening method to identify non-compliant patients has been questioned, mostly because of the interindividual variation of creatinine excretion in a CAPD population.

Methods. Whenever possible we performed a 3-day collection of dialysate and urine in all patients on our CAPD programme, and calculated the daily CrEx ratio. Non-compliance was defined as a progressive and greater than 7.5% decrease of the CrEx ratio associated with a more than 7.5% decrease of serum creatinine during the test.

Results. Among 19 patients only one (5%) fullfilled both criteria for non-compliance and the subsequent interview revealed that he was truly non-compliant. The other patient admitting non-compliance had a significant decrease of CrEx ratio but showed only a slight decrease of serum creatinine.

Conclusions. Our preliminary results suggest that this 3-day collection test, unlike previous procedures, identifies non-compliance with a good specificity. However, it may not be sensitive enough to detect a low level of non-compliance and has the disadvantage of being quite cumbersome. It may require further refinements to be clinically useful.

Key words: CAPD; creatinine excretion; compliance

Introduction

Adequacy of CAPD has received a great deal of attention in recent years. The relationship between dialytic dose (as assessed by urea and creatinine kinetics) and clinical outcome has been a subject of controversy, with some authors [1–3] showing a positive correlation between dialytic dose and clinical outcome, and others [4,5] questioning this relationship. Recent data from the CANUSA study [6] seem to confirm that estimates of adequacy correlate with survival of CAPD patients.

One important determinant of the actual dialytic dose is each individual patient's compliance with dialysis prescription. Several reports suggested that non-compliance occurs in a substantial proportion of patients [7–9], who can be identified by comparing the measured creatinine excretion over a 24-h period (mCrEx) to the predicted creatinine excretion based on the formulae of Cockroft and Gault (pCrEx) [13]. A non-compliant patient performing chronically fewer exchanges than prescribed will reach a steady state with a high serum creatinine. On the test day, when compliance is guaranteed by supervised collection of urine and dialysate, there will be a wash-out of accumulated creatinine, resulting in an unusually high mCrEx and thus an abnormally high creatinine excretion ratio (CrEx ratio = mCrEx/pCrEx) [7]. However, the validity of this CrEx ratio in predicting non-compliance has been questioned by Blake *et al.* [10], who reported that some of their patients with a high CrEx ratio continued to excrete a constant daily amount of creatinine over a 4 consecutive day period, which strongly argues against the wash-out phenomenon being the explanation for an elevated CrEx ratio. Furthermore a theoretical analysis by Tsamaloukas [11] showed that, based on first-order pharmacokinetics and on the wide distribution of creatinine production in a CAPD patient population, the CrEx ratio with a cut-off value of 1.24 was neither a sensitive nor a specific marker of non-compliance.

We reasoned that the determination of CrEx during 3 consecutive days and analysing its variation in the individual patient, rather than the single measurement method used so far, would allow a more precise identification of non-compliant patients. This study was thus undertaken to assess the use of this approach in detecting non-compliance.

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Patients and methods

During a 9-month period and whenever technically feasible we performed a 3-day urine and dialysate collection in stable patients who had been on CAPD for at least 3 months. On day 1 the patients came to the hospital and a sample of blood was drawn and analysed for concentration of urea and creatinine. Patients were instructed to perform their exchanges as prescribed and to collect the outflowing dialysate as well as their urine. On the morning of days 2 and 3 one of the investigators collected dialysate and urine of the last 24-h at the patient's home. On day 4 the patients came again to the centre, bringing the last 24-h collection, and another sample of blood was drawn. Creatinine concentrations were simultaneously measured in all samples of blood, dialysate, and urine using an enzymatic method on the central hospital laboratory autoanalyser (Hitachi multichannel, sensitivity 10 mmol/l). Glucose interference with this method is negligible. Urea concentrations were determined by the same autoanalyser method.

Measured creatinine excretion was calculated by adding the measured creatinine content in urine and dialysate to an estimate of extrarenal creatinine degradation, according to the formula of Mitch and Walser [12]. Predicted creatinine excretion was calculated using the formulae of Cockroft and Gault [13]. Weekly Kt/V was calculated from the urea generation over the 3-day period, using the Watson formulae [14] to estimate V. Weekly creatinine clearance was calculated as the sum of peritoneal clearance and of 60% of residual renal creatinine clearance [15]. Normalized protein catabolic rate (nPCR) was calculated according to the formula of Bergström *et al.* [16] and normalized to g/kg standard weight (V/0.58).

We estimated that a patient omitting one exchange every other day (one of 8 exchanges) would have approximately a 12.5% reduction of peritoneal clearance. Given that peritoneal creatinine excretion on average represents 60% of total creatinine excretion (data not shown) the resulting decrease in total clearance would be approximately 7.5%. If one assumes that a new steady-state is reached after the 3-day collection (in reality it would take a bit longer) the expected reduction of serum creatinine should be in the same proportion, that is 7.5% for this level of non-compliance. Similarly the amount of creatinine excreted on the first day of guaranteed compliance would exceed the baseline value by some 7.5%. We thus defined non-compliance as a progressive and greater than 7.5% reduction of CrEx ratio during the 3 days of the study, associated with a more than 7.5% decrease of serum creatinine.

Standard descriptive statistical methods (mean, standard deviation) were used.

Results

Nineteen of the 29 patients of our CAPD programme were included in the study. Reasons for non-inclusion were intercurrent illness or transplantation in four, lack of collaboration or willingness to participate in four, and distance from the study centre in two.

Table 1 summarizes the clinical characteristics of the 19 patients studied.

Table 2 shows the daily CrEx ratio, as well as the serum creatinine concentration at the beginning and at the end of the 3-day period. The mean CrEx ratio on day 1 was 1.13 ± 0.15 and five (26%) had a CrEx ratio above the suggested cut-off for non-compliance of 1.24 [8]. In three patients (DA, MG, SE) there was a more than 7.5% decrease in the CrEx ratio but only one (DA) showed a simultaneous decrease of serum creatinine exceeding 7.5%. This patient admitted non-compliance and the test result was the first clue to an underlying depression which had to be treated thereafter.

Table 1. Clinical characteristics

Patients (male/female)		19	(12/7)
Age (years)	61 ± 13	(32–76)	
Weight (kg)	67 ± 11	(48–88)	
Height (cm)	167 ± 9	(150–183)	
Primary renal disease			
Glomerulonephritis		4	
Polycystic kidney disease		3	
Hypertensive nephrosclerosis		2	
Chronic interstitial nephritis		4	
Diabetic nephropathy		2	
Other		4	
Months on CAPD	15 ± 9	(4–40)	
Daily regimen			
4×2 l	17		
4×2.5 l	1		
3×1.5 l + 1×2 l	1		
Creatinine and urea kinetics			
Residual renal Cr clearance (ml/min)		3.1 ± 3.2	(0–12.5)
Weekly Cr clearance (l/week/1.73 m^2)		67 ± 17	(45–122)
Weekly Kt/V		2.18 ± 0.42	(1.48–3.27)
Normalized PCR (g/kg per day)		1.16 ± 0.37	(0.59–2.05)

Data are given as mean $\pm$ SD and (range).

The two other patients (MG, SE) with a significant decrease of CrEx ratio had a small decrease of plasma creatinine during the study period (3.2 and 3.9%). The first of them had an initial CrEx ratio of 1.28 and admitted occasional non-compliance related to excessive alcohol intake. The second patient reliably denied any CAPD exchange omission and had above average net ultrafiltration on day 1 which explained the higher initial CrEx ratio of 0.93.

All other 16 patients denied non-compliance. Among these the initial CrEx ratio was greater than 1.24 in three (19%). The measured creatinine excretion of those three patients remained fairly constant and there was no significant decrease of the serum creatinine. Interestingly the only patient who was initially suspected by the CAPD nurses to be non-compliant (FT), belonged to this high CrEx ratio group with a remarkably constant amount of creatinine excretion over the 3 days.

One patient (JM) had a 7.6% decrease in serum creatinine, but his measured creatinine excretion profile was not suggestive of non-compliance and his CAPD treatment was tightly supervised by his wife, who could hardly be suspected of non-compliance!

Discussion

Among the 19 patients studied, three (16%) had a progressive and greater than 7.5% decrease of the CrEx

Table 2. Three-day collection test

Patient	Serum creatinine (mmol/l)			Creatinine excretion ratio (net ultrafiltration litres per day)			
	Initial	Final	Change %	Day 1	Day 2	Day 3	Change %
DA	719	624	−13.2	1.23 (0.30)	1.16 (1.10)	1.11 (0.95)	−9.8
MG	776	751	−3.2	1.28 (0.90)	1.22 (0.0)	1.17 (0.0)	−8.6
SE	465	447	−3.9	0.93 (2.50)	0.89 (1.40)	0.85 (1.10)	−8.6
JH	704	688	−2.3	1.27 (0.40)	1.12 (0.05)	1.18 (0.25)	−7.1
HA	924	868	−6.1	1.25 (1.20)	1.29 (1.90)	1.21 (0.70)	−3.2
SA	585	672	14.9	1.32 (0.55)	1.26 (0.55)	1.28 (0.75)	−3.0
CM	483	497	2.9	0.75 (1.00)	0.77 (0.90)	0.75 (0.85)	0.0
KM	821	826	0.6	1.21 (0.60)	1.25 (0.60)	1.22 (0.55)	0.8
GH	354	393	11.0	1.21 (1.10)	1.27 (1.20)	1.22 (1.15)	0.8
JM	580	536	−7.6	1.02 (0.50)	1.13 (0.45)	1.03 (0.60)	1.0
PM	736	877	19.2	1.09 (1.10)	1.02 (1.00)	1.11 (1.50)	1.8
BK	675	655	−3.0	1.07 (0.50)	1.10 (0.30)	1.10 (0.45)	2.8
FT	1754	1671	−4.7	1.32 (2.55)	1.32 (3.00)	1.36 (3.25)	3.0
GE	885	922	4.2	1.15 (0.70)	1.24 (1.55)	1.19 (1.45)	3.5
KE	557	550	−1.3	1.17 (1.10)	1.19 (0.40)	1.24 (0.55)	6.0
SR	801	834	4.1	1.08 (0.50)	1.21 (1.65)	1.17 (1.45)	8.3
MR	1053	1221	16.0	1.02 (0.60)	1.10 (1.55)	1.12 (1.45)	9.8
RA	764	727	−4.8	1.12 (−0.40)	1.19 (−0.35)	1.24 (0.75)	10.7
TR	1016	964	−5.1	0.95 (1.10)	1.05 (1.90)	1.08 (2.10)	13.7
Mean	771	775	0.9	1.13	1.15	1.14	1.2
SD	301	296	8.7	0.15	0.14	0.14	6.8

Serum creatinine change (%) = (final serum Cr − initial serum Cr) × 100/initial serum Cr.
Creatinine excretion ratio change (%) = (CrEx ratio day 3/CrEx ratio day 1) × 100/CrEx ratio day 1.

ratio between days 1 and 3. Of these only one had a simultaneous more than 7.5% decrease of the serum creatinine during the test period. Interestingly this patient had an initial CrEx ratio of 1.23, and would therefore not have been considered non-compliant using the cut-off value of 1.24 suggested by Warren *et al.* [8]. The one patient fulfilling both criteria of non-compliance was truly non-compliant (omission of 1 or 2 exchanges a day) as the subsequent interview revealed. Another patient with a significant CrEx ratio decrease admitted to a low degree of non-compliance (approximately one exchange omitted every other day). Her serum creatinine decreased only about 3% during the test days, despite an initial CrEx ratio of 1.28. The third patient with decreasing CrEx ratio had also a slight decrease in serum creatinine, but convincingly denied non-compliance.

Compliance with the dialysis prescription is difficult to investigate, because there is no gold standard for validating different screening methods. By comparing measured to predicted creatinine excretion, non-compliance was strongly suspected in a substantial proportion of patients [7–9]. Keen *et al.* [7] suggested that overall compliance with prescribed exchanges was only 78%. Warren and Brandes [8] defined non-compliance as a CrEx ratio greater than 1.24 and reported that 26% of their 64 patients were non-compliant. Applying the same cut-off value of 1.24 Nolph *et al.* [9] concluded that 11.5% of their 121 patients were non-compliant. They observed a decrease in serum albumin in patients with a CrEx ratio greater than 1.24 which was interpreted as inadequate dialysis because of non-compliance. Blake *et al.* [10] found the CrEx ratio to be greater than 1.24 in 40% of their patients. However, as demonstrated theoretically by Tsamaloukas [11], this test is neither sensitive nor specific to identify non-compliance mostly because of the wide distribution of creatinine production in a CAPD population. The experimental data of Blake *et al.* [10] strengthen this opinion by showing that the measured creatinine excretion remained fairly constant over a 4 day period in 7 patients with a high CrEx ratio, indicating that in most cases the high value for this ratio was not due to the wash-out of creatinine accumulated because of non-compliance, but to constitutive high creatinine production. Moreover in that study the only patient who admitted non-compliance had a CrEx ratio of 1.09. These investigators were the first who tried to distinguish between non-compliance and high creatinine production as the cause for the increased CrEx ratio by collecting dialysate and urine over successive days. We used a similar approach to screen our patients for non-compliance. With this method each patient serves as his own control and rather than the absolute value for the CrEx ratio it is the variation of this ratio in the individual patient that defines non-compliance.

In a non-compliant patient the CrEx ratio is expected to decrease progressively during the test because of the wash-out of extra creatinine accumulated during the period of non-compliance. What cut-off value of CrEx ratio decrease between day 1 and day 3 should be used to suggest non-compliance? Burkhart *et al.* [17] have shown in six stable CAPD patients that after a 3-day period during which one of four exchanges per day was omitted, the CrEx ratio increased on average by

11.5% during the first day when the usual four exchanges were performed again. Goel *et al.* [18] observed a 6% increase in the CrEx ratio when a fifth exchange (resulting in a 26% increase in drain volume) was added to the usual four exchanges regimen in nine CAPD patients. As expected the observed increase correlated inversely with the residual renal creatinine clearance. We chose somewhat arbitrarily a cut-off of 7.5% decrease of CrEx ratio between days 1 and 3 to suggest non-compliance and we requested the CrEx ratio of day 2 to be below the CrEx of day 1 and above the one of day 3. One may argue that a variation of this magnitude may occur just by chance, given the intraindividual variations of the CrEx ratio even in compliant patients (Table 2 and Lo *et al.* [19]). This is the reason we chose to require additionally a more than 7.5% decrease in serum creatinine to define non-compliance. This should increase the specificity of the test but is likely to decrease its sensitivity. Given the delicate situation created by erroneously suspecting non-compliance, it seems preferable to favour specificity.

In summary, in our small group of 19 CAPD patients two (11%) were found to be non-compliant. The true non-compliance rate in a typical Swiss CAPD population may be somewhat higher because several non-collaborative patients could not be studied. One of the two non-compliant patients was correctly identified by our screening test, while the other had some characteristics suggestive of non-compliance but failed to fulfil all criteria. Thus, unlike the 1-day CrEx method, this 3-day collection test seems to detect non-compliance with a good specificity, which is rather important in such a delicate area as compliance testing. It may, however, not be sensitive enough to detect a low level of non-compliance and has the disadvantage of being quite cumbersome. Confirmation of these preliminary results will require further study. Other complementary approaches to identify non-compliance should be developed, for example book-keeping of all CAPD bags used in comparison to the number prescribed.

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