Relationship of Serum Cystatin C to Peritoneal and Renal Clearance Measures in Peritoneal Dialysis: A Cross-sectional Study

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Background: Clinical management of peritoneal dialysis patients includes assessments of peritoneal and renal clearances of the low-molecular-weight endogenous solutes creatinine and urea. Cystatin C is a low-molecular-weight protein used as a glomerular filtration rate marker. We investigated whether serum cystatin C concentration is related to peritoneal and renal clearances of creatinine and urea.

Study Design: Cross-sectional study.

Setting & Participants: 119 patients undergoing peritoneal dialysis in a single dialysis unit.

Predictor: Peritoneal, renal, and total clearance of urea as Kt/V_{urea} and creatinine as weekly creatinine clearance (C_{Cr}). Residual renal function (RRF) as the average of renal clearances of urea and creatinine.

Outcomes & Measurements: Serum concentrations of cystatin C measured by using a particle-enhanced nephelometric immunoassay.

Results: Serum cystatin C concentration was related inversely to RRF (Spearman rank correlation coefficient [r_s] = −0.65; $P < 0.001$), total weekly C_{Cr} ($r_s = -0.52$; $P < 0.001$), and total Kt/V_{urea} ($r_s = -0.23$; $P = 0.01$). In a multiple regression model, weight, normalized protein catabolic rate, and RRF had independent effects on serum cystatin C concentrations. Additional multiple regression models showed that only the renal components of Kt/V_{urea} and weekly C_{Cr} contributed to serum cystatin C concentrations.

Limitations: Absence of reference GFR method.

Conclusions: Serum cystatin C concentrations reflect predominantly renal, not peritoneal, clearance. Serum cystatin C measurement may be a simple and practical alternative to measurement of RRF.

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INDEX WORDS: Cystatin C; dialysis adequacy; peritoneal dialysis; residual renal function.

Quantification of the effective delivered dose of dialysis that an individual patient receives typically is derived from an estimation of the clearance of the small solutes urea (molecular weight, 60 d) and creatinine (molecular weight, 113 d) from blood into spent dialysate and urine. Prospective studies from the early 1990s identified total small-solute clearance as an independent risk factor for death in patients with end-stage renal disease treated with peritoneal dialysis (PD).[1,2] The Canada-USA (CANUSA) Study[1] concluded that a decrease in urea clearance (Kt/V_{urea}) of 0.1 units was associated independently with a 5% increase in relative risk of death. Later analyses modified the paradigm of small-solute clearance by showing that the relative contributions of renal and peritoneal clearances to overall clearance were nonequivalent, with residual renal function (RRF) assuming primary importance and independently associated with survival.[3,4] Furthermore, a prospective randomized controlled study of dialysis adequacy from Mexico[5] did not show a survival advantage of increasing the contribution from PD above a standard regimen.

Current assessments of dialysis adequacy and RRF are confounded by the numerous measurements necessary to calculate small-solute clearances. For example, measurements of volume of spent dialysate, urine volume collected over 24 to 48 hours, and sampling for urea and creatinine in blood, urine, and dialysate contribute to random errors. Additionally, although formulaic determinations of volume of distribution of urea or total body water (V) are used because they are close to isotopic body water measurements,[6] they may be erroneous in PD patients who are overhydrated.[7] Tests of adequacy and RRF typically are performed routinely at 6- to 12-month intervals.[8] These assessments are time consum-

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ing and cumbersome and day-to-day reproducibility of such measurements may be poor.[9] It therefore is desirable to explore whether a more simple and convenient marker of clearance could be used in patients treated with PD.

Uremic syndrome is characterized by the retention and accumulation of many toxins, including small solutes and such low-molecular-weight proteins as β_2-microglobulin, retinol-binding protein, and cystatin C.[10] Cystatin C is a 13.2-kd cysteine protease inhibitor that is favored over other low-molecular-weight proteins as a marker of glomerular filtration rate (GFR) because its production rate appears to be constant and its elimination route is predominantly renal.[11-13] Cystatin C is readily measured from a single blood sample by using reliable and reproducible assays.

The present study investigates relationships between serum cystatin C concentrations and the currently used markers of PD adequacy (peritoneal weekly creatinine clearance [C_{Cr}] and peritoneal Kt/V_{urea}) and renal elimination (renal weekly C_{Cr}, renal Kt/V_{urea}, and RRF) in a large cohort of patients treated with PD.

METHODS

This is a cross-sectional study of adult dialysis patients receiving PD in the Kent Renal Unit. In line with national recommendations,[8] our unit's policy is that all patients undergoing PD as long-term renal replacement therapy undergo a peritoneal adequacy test when they are established on dialysis therapy, repeated at varying intervals to guide therapy. Between February 2003 and June 2005, all (n = 131) patients who underwent peritoneal adequacy tests were invited to participate in the study. No patient refused to participate in the study. Twelve patients consented to participate in the study, but did not have samples stored for cystatin C measurement. All patients gave informed consent, and the study had full approval from the local research ethics committee (no. EK214/11/02). A full clinical history was recorded, including primary renal disease, known presence of diabetes mellitus, PD modality, and PD therapy duration.

During the study period, an additional 109 patients entered the PD program, but did not have an adequacy assessment undertaken for a variety of reasons, including early switch to hemodialysis therapy (n = 19) or transplantation (n = 13), death (n = 22), severe cognitive impairment (n = 8), and other reasons (n = 47; including recovery of renal function, poor compliance, loss from area, terminal cancer, and age < 18 years). The 121 patients not entered into the study consisted of 74 men and 47 women with a mean age of 62 years; 21% had diabetes.

Patients underwent assessment of RRF, normalized protein catabolic rate (nPCR), Kt/V_{urea}, and weekly C_{Cr}. These parameters were calculated using Adequest (Baxter Healthcare Ltd, Newbury, UK), with V calculated using the Watson method.[6] RRF was calculated from the mean of urea clearance and C_{Cr}. Both RRF and C_{Cr} were adjusted to a standardized body surface area of 1.73 m^2. Serum was collected simultaneously and stored at −80°C for up to 6 months for subsequent cystatin C measurement: the stability of cystatin C under these conditions is well established.[11] Cystatin C was measured by using a particle-enhanced nephelometric immunoassay on a BN Prospec analyzer (Dade Behring Ltd, Milton Keynes, UK). Laboratory reference range was 0.54 to 1.06 mg/L,[14] and between-day imprecision was 3.5% at a concentration of 2.3 mg/L. Urea and creatinine in dialysis fluid and urine were measured by using enzymatic methods that avoid problems of interference in creatinine measurement caused by the high glucose concentrations.

Relationships between cystatin C concentrations and components of adequacy (peritoneal Kt/V_{urea} and peritoneal weekly C_{Cr}), RRF, renal Kt/V_{urea}, renal weekly C_{Cr}, and other clinical variables were studied using Analyse-It (Analyse-it Software Ltd, Yorkshire, UK) and InStat (GraphPad.com) statistical packages. P less than 0.05 is considered significant. Most variables did not follow a Gaussian distribution, and appropriate nonparametric tests (Spearman rank correlation coefficient [r_s] and Mann-Whitney U test) were used.

Multiple linear regression analysis was used to assess which clinical variables had an independent effect on serum cystatin C concentration. Log serum cystatin C concentration was the dependent outcome and other clinical variables (age, sex, weight, diabetes mellitus, time on dialysis therapy, hemoglobin level, nPCR, RRF, total Kt/V_{urea}, and total weekly C_{Cr}) were included as either continuous or dichotomous data. Residuals were normally distributed when the dependent outcome, serum cystatin C concentration, was $\log_{10}$ transformed. Manual backward elimination was performed, and clinical variables that were not significant ($P \geq 0.05$) were excluded from analysis. Separate multiple regression analyses were undertaken to elucidate the relative importance of the renal and peritoneal components of both Kt/V_{urea} and weekly C_{Cr} to serum cystatin C concentration. Multicollinearity was not detected in any of the final models used.

RESULTS

Patient clinical and biochemical characteristics are listed in Table 1. There were no significant unadjusted associations between serum cystatin C concentrations and age, weight, hemoglobin level, or nPCR (Table 2). Cystatin C concentration was related inversely to RRF (and urine volume), with higher levels observed in anuric patients than patients with residual kidney function ($P < 0.01$; Fig 1); inversely related to total weekly C_{Cr}; and also weakly inversely related to total Kt/V_{urea}. There was a weak relationship between time on PD therapy and serum cystatin C concentration. Serum creatinine levels also showed negative associations with total weekly C_{Cr}, total Kt/V_{urea}, and RRF, whereas