Time Profiles of Peritoneal and Renal Clearances of Different Uremic Solutes in Incident Peritoneal Dialysis Patients

Bert Bammens, MD, Pieter Evenepoel, MD, PhD, Kristin Verbeke, Pharm, PhD, and Yves Vanrenterghem, MD, PhD

• ***Background:*** **Residual renal function (RRF) contributes substantially to the adequacy of peritoneal dialysis (PD). In the presence of RRF, maintenance of an adequate fluid balance is facilitated, level of systemic inflammation is lower, and renal endocrine functions are preserved. The beneficial impact of RRF also may be related to the preservation of specific renal elimination mechanisms, such as tubular metabolism or secretion, which are crucial for the removal of some uremic retention solutes.** ***Methods:*** **Time profiles of peritoneal and renal clearances of urea nitrogen (60 d), creatinine (113 d), phosphate (96 d), the middle molecule β_2-microglobulin (β_2M; 11.8 kd), and the protein-bound solute *p*-cresol (108 d) were investigated prospectively in 24 incident PD patients. Data were analyzed by using the linear mixed models procedure.** ***Results:*** **During a median follow-up of 7.2 months (range, 5.6 to 8.6 months), RRF ($P = 0.001$) and 24-hour urine volume ($P = 0.004$) declined significantly. Twenty-four–hour peritoneal drainage volume increased ($P < 0.0001$). Renal clearances of urea nitrogen ($P = 0.0002$), creatinine ($P = 0.001$), and phosphate ($P = 0.001$) decreased. Peritoneal clearances of these solutes increased ($P = 0.002$, $P < 0.0001$, and $P < 0.0001$, respectively). There was a decline in renal clearances of β_2M ($P = 0.0004$) and *p*-cresol ($P < 0.0001$). No change in peritoneal clearances of these solutes was noted ($P = 0.188$ and $P = 0.559$, respectively).** ***Conclusion:*** **Increasing PD dose may compensate for deteriorating RRF with respect to the elimination of water-soluble solutes. This is not the case for the middle molecule β_2M and the protein-bound solute *p*-cresol.** ***Am J Kidney Dis*** **46:512-519.**

INDEX WORDS: *p*-Cresol; protein-bound solutes; peritoneal dialysis (PD); clearances; residual renal function.

DURING THE PAST decade, it has been recognized that residual renal function (RRF) contributes substantially to the adequacy of peritoneal dialysis (PD). A reanalysis of the Canada USA study was first to describe a 12% survival advantage for every 5-L/wk/1.73 m^2 increase in RRF.[1] Several well-controlled studies have confirmed this finding.[2-7]

The importance of RRF as a predictor of survival has been attributed to its role in the maintenance of an adequate fluid balance.[8-10] This is emphasized by the Canada USA reanalysis, in which urinary volume per se had a stronger predictive power than the mean of renal urea nitrogen and creatinine clearances.[1] On the other hand, several observations showed that patients with lower RRF have greater circulating proinflammatory cytokine levels, making them more vulnerable to wasting and atherosclerosis.[3,11,12] Furthermore, preservation of endocrine functions of the kidney also may contribute to the beneficial impact of RRF on survival. The production of erythropoietin and 1-α-hydroxylation of vitamin D have been suggested to be better preserved in dialysis patients with than without substantial RRF.[13-16]

However, the importance of renal clearance also might be explained by the finding that the elimination of some uremic retention solutes depends largely on renal metabolism and/or secretion at the tubular level, which cannot be equaled by peritoneal transport. This is the case for the middle molecule β_2-microglobulin (β_2M), as well as for the group of protein-bound solutes.[17] β_2M is filtered in glomeruli and reabsorbed and degraded in proximal tubular cells. Its renal catabolism in a healthy subject was

From the Department of Medicine, Division of Nephrology, and Laboratory of Digestion and Absorption, University Hospital Gasthuisberg, Leuven, Belgium.

Received March 22, 2005; accepted in revised form May 18, 2005.

Originally published online as doi:10.1053/j.ajkd.2005.05.016 on July 15, 2005.

Supported in part by governmental grant no. 1127602N from the Fonds voor Wetenschappelijk Onderzoek.

Presented in part at the 24th Annual Dialysis Conference, San Antonio, TX, February 9-11, 2004, and the First Joint Congress of the International Society for Peritoneal Dialysis and the European Peritoneal Dialysis Meeting, Amsterdam, The Netherlands, August 28-31, 2004.

Address reprint requests to Pieter Evenepoel, MD, PhD, Department of Medicine, Division of Nephrology, University Hospital Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium. E-mail: pieter.evenepoel@uz.kuleuven.ac.be

0272-6386/05/4603-0016$30.00/0

doi:10.1053/j.ajkd.2005.05.016

found to be 150 to 220 mg/d.[18] Protein-bound solutes are excreted mainly by tubular secretion through the organic anion transport system of proximal tubular cells.[19] In a recent observational study including 30 prevalent PD patients, total clearances of β_2M and the protein-bound solute *p*-cresol were not unexpectedly less than those of the small water-soluble solutes urea nitrogen, creatinine, and phosphate. However, the contribution of renal to total clearances was considerably greater for β_2M and *p*-cresol than for the water-soluble molecules.[20] Moreover, peritoneal clearance values of urea nitrogen, creatinine, and phosphate correlated inversely with their respective renal clearances, which was not the case for β_2M and *p*-cresol. The findings generated the hypothesis that the well-accepted practice of adapting PD prescription to compensate for the gradual loss of renal function may succeed in increasing peritoneal clearances of small water-soluble solutes, but not middle molecules and protein-bound solutes. However, the cross-sectional design of the study precluded firm conclusions on this issue.

The present study aims to confirm the hypothesis by prospectively investigating the time profiles of peritoneal, renal, and total clearances of different types of uremic retention solutes in incident patients treated with PD.

METHODS

Patients

We performed a single-center, longitudinal, observational study. All patients with end-stage renal disease starting PD treatment at the Leuven University Hospital (Belgium) between July 1, 2002, and December 1, 2003 (N = 30), were informed about the study and asked for their consent. Four of these patients refused to participate. Two of the remaining 26 patients were excluded from the final analysis because PD-related complications urged early transfer to hemodialysis therapy, which resulted in an insufficient number of study visits to enable proper evaluation. The present report describes data for the 24 remaining patients.

Causes of end-stage renal disease were diabetic nephropathy (n = 1), polycystic kidney disease (n = 1), glomerular disease (n = 8), tubulointerstitial disease (n = 7), vascular disease (n = 4), and unknown (n = 3). Demographic (age at start of PD therapy, sex, length) and clinical data (medication and comorbidity at start of PD therapy) were collected by reviewing medical records. Comorbidity at the start of PD therapy was scored according to Davies et al[21] and reported as low, medium, or high grade.

Treatment

According to usual clinical practice, all patients were started on a continuous ambulatory PD regimen with 4 exchanges of conventional lactate-buffered glucose solutions (Dianeal 1.36%; Baxter, Lessines, Belgium). Automated PD using an electronic cycler was started later, depending on patient preference. After an initial inhospital training period of approximately 1 week, patients were seen at the outpatient clinic at 6- to 8-week intervals. At each visit, clinical parameters and clearance data for urea nitrogen and creatinine were taken into account for therapy adjustments (adjustment of dry weight, medication, and dialysis prescription). Fluid balance was maintained by the use of high glucose concentrated solutions (Dianeal 3.86%; Baxter) and/or the polyglucose icodextrin during 1 long dwell per day (Extraneal; Baxter), as judged appropriate by the treating physician.

Study Design

At outpatient visits 1 to 5, sampling was performed for the calculation of urea nitrogen, creatinine, phosphate, β_2M, and *p*-cresol clearances, as well as for the calculation of weight-normalized protein nitrogen appearance (nPNA). A midday blood sample was obtained, and total amounts of urine and peritoneal drainage were collected during the preceding 24-hour period, weighed, and sampled. All samples were stored at –80°C until analysis. Blood pressure and dry body weight were measured at each occasion. The study was approved by the Ethical Committee of the University Hospital Leuven.

Analytical Methods

Urea nitrogen, creatinine, and phosphate were measured by means of standard laboratory techniques. β_2M was quantitated by means of rate nephelometry using an Immage Instrument (Beckman Coulter, Brea, CA). Total *p*-cresol (ie, combined free and protein-bound fraction) was analyzed by means of gas chromatography-mass spectrometry (GC-MS) technology, as described earlier.[20] In summary, after deproteinization (acid and heat), addition of the internal standard (2,6-dimethylphenol), and extraction (ethyl acetate), samples were transferred to the GC-MS (Trace GC-MS; Thermofinnigan, San José, CA) for injection and separation on a column, followed by identification of *p*-cresol by means of mass spectrometry. Quantitative results were obtained by means of the internal standard method and calculated as concentrations. R^2 of the calibration line was 0.998. The method has low intra-assay and interassay variabilities (coefficients of variation, 3.33% and 5.30%, respectively). The detection limit for measurement of *p*-cresol is 0.15 mg/L. Extraction efficiency is 91.5%.

Calculations

Peritoneal, renal, and total clearances normalized to 1.73 m^2 of body surface area (liters per week per 1.73 m^2) were calculated for all solutes by means of direct determination from dialysis fluids, urine, and midday serum solute concentrations. According to National Kidney Foundation–Kidney Disease Outcomes Quality Initiative guidelines,[22]