Effect of the Peritoneal Dialysis Prescription on Pentosidine in Children

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Introduction

Peritoneal dialysis (PD) is used extensively in the treatment of end stage renal disease in children (1). Because there may be a long-term need for PD in pediatric patients, viability of the peritoneal membrane is a major focus in this field. High dextrose concentration in commercially available PD solutions can cause diabetiform vascular changes in the peritoneum and is toxic to peritoneal mesothelial cells (2,3). High dextrose and glucose degradation products present in commonly prescribed peritoneal dialysate solutions have been demonstrated in vitro and in vivo to cause formation of advanced glycation end products (AGEs) on peritoneal proteins (4-7). In addition, ESRD is itself a condition associated with increased formation and accumulation of AGEs on proteins throughout the body (5, 8-10). AGEs are inadequately and incompletely removed by dialysis (6,11). The pentosidine content of peritoneal proteins reflects both formation in the peritoneum and clearance of AGE-modified proteins from the circulation (5,6).

The goal of this project was to elucidate the relationship between the peritoneal and plasma accumulation of pentosidine and peritoneal membrane function, as well as to identify clinical factors leading to alterations in these parameters in children.

Patients and methods

Twenty-seven patients (13 boys and 14 girls) treated with PD in two centers (Rainbow Babies and Children's Hospital/University Hospitals of Cleveland, Case Western Reserve University (CWRU), US, and Cukurova University, School of Medicine, Turkey, participated in this study. The study was approved by the ethical committees of the participant universities. Inclusion criteria were age >2 and <21 years at study entry visit and treatment with PD for at least one month prior to study entry. Patients with diabetes mellitus or an episode of peritonitis within two months of study entry were excluded from the study.

All patients received an exchange volume of 900-1100 ml/m^2 BSA. CCPD patients received 6 to 13 exchanges over 8-13 hours per night, followed by a last fill. CAPD patients received 4-5 exchanges per day. For the study, all but two patients used 1.5% dextrose dialysate for their last fill, while two patients used a mixture of 1.5% and 2.5% dextrose dialysate. The PD nurse, using routine sterile technique and gravity drainage from the indwelling PD catheter, collected a peritoneal fluid sample for measurement of pentosidine. In addition, blood was sampled for pentosidine levels.

Charts were reviewed to document the frequency of peritonitis over the period of treatment with PD. Results of routine dialysis adequacy performed within three months of study entry were collected. $Kt/V_{Urea,}$ total creatinine clearance (CCr), and residual creatinine clearance were calculated using PD Adequest 2.0 software (Baxter). A single 4-h peritoneal equilibration test (PET) was conducted on 16 patients during the current study according to standard procedure (12). In the remaining patients, the most recent PET evaluation, performed within 1 year of the study, was abstracted from the charts. The volume of dialysate, and the percentage dextrose used in the patient's routine dialysis prescription was abstracted from monthly logs.

Pentosidine

Pentosidine measurements were performed at CWRU using high-performance liquid chromatography in a well characterized, previously described assay (4).

Calculations and statistical analysis

Total daily dialysate volume was standardized to 1.73 m^2 body surface area (BSA) to determine volume by patient size (L/day/1.73 m^2). To determine the average peritoneal exposure to dextrose in the dialysate, we calculated a "Dextrose score" based on the number of liters of 1.5, 2.5 and 4.25% dextrose (1.36, 2.27, and 3.86% glucose) used per week (L/week *dextrose concentration/BSA, arbitrary units). Peritonitis rate was determined by dividing the total number of peritonitis episodes by the total number of months of treatment with PD.

The relationship of plasma and peritoneal pentosidine content with clinical parameters was modeled using multivariate regression analysis. Additional between-group analyses were performed using analysis of variance (ANOVA). Linear regression analyses demonstrate clear-cut relationships between parameters. Results are expressed as mean ± SD, with $p<0.05$ accepted as being statistically significant.

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Results

A comparison of the clinical characteristics of the patients is shown in Table 1.

Table 1. Clinical and laboratory characteristics of the patients

Parameter	CAPD (n=14)	CCPD (n=13)	p	Adana, Turkey (n=17)	Cleveland, Ohio USA (n=10)	p
Age (years) *Range*	12.3±5.9 *(10.4-18.9)*	14.3±2.1 *(2.4-20.0)*	NS	14.5±2.1 *(10.4-18.9)*	11.5±6.51 *(2.4-20.0)*	NS
Weight (kg) *Range*	34.4±6.4 *(22.7-42.7)*	43.7±29.7 *(12.2-123.0)*	NS	34.4±7.8 *(22.7-54)*	44.3±33.9 *(12.2-123.0)*	NS
BSA (m^2)	1.1±0.2	1.3±0.5	NS	1.1±0.2	1.2±0.6	NS
PD duration (months)	40.7±26.6 *(6-66)*	33.5±18.8 *(1-102)*	NS	33.2±17.0 *(6-66)*	43.4±30.1 *(1-102)*	NS
Kt/V_{Urea}	2.3±0.7	3.0±0.9	.03	2.3±0.7	3.2±0.9	0.01
Total CCr ($L/week/1.73m^2$)	79.8±39.2	79.3±48.5	NS	91.6±48.3	61.5±27.8	NS
Residual CCr ($L/week/1.73m^2$)	24.8±382	25.8±43.2	NS	34.1±45.8	12.3±26.3	NS
D/P Urea (4 hours)	0.89±0.09	0.92±0.06	NS	0.90±0.09	0.93±0.06	NS
D/P Creat (4 hours)	0.72±0.04	0.66±0.04	NS	0.70±0.13	0.67±0.16	NS
D/D0 glucose	0.38±0.17	0.38±0.11	NS	0.38±0.16	0.38±0.14	NS
Peritonitis rate (peritonitis/month of Rx with PD)	0.073 ± 0.074	0.046±0.055	NS	0.06±0.07	0.053±0.058	NS
Volume dialysate (L/day)	17.5±3.8	5.2±3.7	<0.04	5.5±1.8	13.8±5.6	<0.0001
Volume by patient size ($L/day/1.73m^2$)	7.9±1.2	17.8±6.4	<0.0001	8.2±2.4	20.2±4.9	<0.0001
Dextrose exposure score (l/wk*conc dextrose/BSA, arbitrary units)	66.6±12.7	153.5±13.1	0.0004	71.3±50.4	171.6±13.3	<0.0001
Plasma Pentosidine (pmol/mg protein)	18.1±11.2	18.8±19.3	0.92	20.4±17.3	14.2±6.9	0.35
Peritoneal Pentosidine (pmol/mg protein)	24.1±14.1	24.9±19.6	0.91	26.2±19.7	21.7±9.5	0.50

CAPD= Continuous ambulatory peritoneal dialysis, CCPD=Continuous cyclic peritoneal dialysis, PD=Peritoneal dialysis, D/P=Dialysate to plasma ratio, BSA=Body surface area, NS=Not significant

Table 2. Multivariate stepwise analysis modeling factors that influence plasma/peritoneal pentosidine levels

	Plasma pentosidine (pmol/mg protein)		Peritoneal pentosidine (pmol/mg protein)	
	p	R square	P	R square
4-h D/P Urea	0.014	0.255	0.015	0.229
4-h D/Do Glucose	0.071	0.502	0.031	0.575
Residual CCr ($L/week/1.73m^2$)	0.201	0.315	0.075	0.334
Total CCr ($L/week/1.73m^2$)	0.116	0.400	0.037	0.461

D/P=Dialysate to plasma ratio, CCr=Creatinine clearance

No statistically significant differences were found in age, gender, height, weight, BSA, PD duration, frequency of peritonitis, and total CCr ($L/week/1.73\ m^2$) between the CAPD and CCPD patients. Also, there was no significant difference in the 4-h D/P Urea, 4-h D/D_0 glucose or 4-h D/P creatinine in the CCPD group when compared with CAPD

group. Mean Kt/V_{Urea} was higher in CCPD patients than in CAPD patients (p=0.03), although there was no statistically significant difference in total or residual CCr. Daily volumes of peritoneal dialysate by patient size were found to be significantly higher in the CCPD patients than in the CAPD patients. Despite these differences, there was no effect of treatment modality (CAPD vs CCPD) or differences in medical management between the two countries on plasma or peritoneal pentosidine content (Table 1). The pentosidine contents of plasma and peritoneal proteins were significantly lower in patients with residual renal function than in patients who were anuric (plasma pentosidine, 11.2 ± 8.8 vs 24.1 ± 16.6, p=0.02, respectively, peritoneal pentosidine 14.9 ± 11.9 vs 31.1 ± 3.7, p=0.01, respectively). There were a total of 32 episodes of peritonitis in the children treated with CCPD, and 40 episodes of peritonitis in the children treated with CAPD. Six children in the CCPD group (46.2%) and 3 children in the CAPD group (21.4%) had no peritonitis episodes. There was no statistically significant difference in plasma and peritoneal pentosidine levels and peritoneal transport kinetic characteristics between patients without peritonitis and patients with one or more episodes of peritonitis.

Multiple regression analysis using a probability to enter cut-off of 0.25 in a stepwise analysis showed that 4-h D/P Urea, 4-h D/D_0 glucose, residual CCr (L/week/1.73m^2) and total CCr (L/week/1.73m^2) were factors with influence on plasma and peritoneal pentosidine levels (p=0.01 and p=0.001 respectively). PD duration, and peritonitis rate did not enter the model. The pentosidine content of plasma proteins was significantly lower than the peritoneal proteins in both groups. Of interest is the highly significant positive linear correlation between the pentosidine content of proteins in the two compartments (plasma and peritoneum).

Discussion

To date, there are limited data available regarding the peritoneal/plasma accumulation of AGEs in children treated with different PD modalities. The frequent, short exchanges used in CCPD may increase the time that the peritoneum is exposed to dialysate at a low pH and at peak glucose concentrations (1,2).

Pentosidine is an AGE derivative which has been well characterized as a marker of glycoxidation reactions in the body. In an earlier study, patients on PD had lower pentosidine levels in the plasma than those on HD, but the pentosidine content of peritoneal proteins was markedly higher in PD compared to HD (6). The results of our current study indicate that concentrations of plasma and peritoneal pentosidine, are not affected by different PD modalities or by the quantity of dextrose to which children are exposed.

In the whole study group, multiple linear regression analysis showed that plasma and peritoneal pentosidine levels were most influenced by residual CCr. In addition, total CCr, 4-h D/P urea, 4-h D/D_0 glucose were significant components of the model, independent of dialysis modality (Table 2). These observations emphasize the importance of renal clearance of AGEs, even at very low levels of residual renal function. As previously demonstrated in adults (13), we found that the concentration of pentosidine was significantly higher in dialysate than in plasma and demonstrated a highly significant positive linear correlation. Two possible explanations have been suggested for the lower pentosidine content of plasma proteins than peritoneal proteins in patients on PD—including a preferential increase in transport of AGE-rich proteins across the peritoneal membrane and the shedding of pentosidine-rich cellular proteins from the highly glycosylated peritoneal tissue into the dialysate (8,14). In addition these observations suggest that there is little peritoneal toxicity, as measured by pentosidine accumulation in pediatric patients treated with PD.

AGEs have been proposed to play an important role in the diabetiform vascular changes seen in the peritoneum in patients treated with PD. Increased AGE deposition has been associated with increased peritoneal permeability (15). In addition, peritonitis changes the peritoneum's ability to transport fluid and solutes, altering the efficiency of dialysis (16-18). These two factors might be expected to have an additive effect to diminish effective peritoneal transport. In this study, however, we found no association between the pentosidine content of plasma and peritoneal proteins, the incidence of peritonitis, and peritoneal membrane transport kinetics.

In summary, these data demonstrate that residual renal function, and overall parameters of dialysis clearance have the greatest impact on protein pentosidine content in children treated with PD. There is no evidence that increased levels of pentosidine on peritoneal proteins reflect or affect peritoneal membrane function in children. Finally, peritonitis appears to have no effect on peritoneal pentosidine levels, or function as measured by PET test. In conclusion, these data suggest that PD is a well-tolerated therapy in children with no evidence that current practice causes changes in peritoneal membrane function, or in the peritoneal clearance of plasma or peritoneal proteins rich in pentosidine.

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