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Original article

Longitudinal changes in peritoneal equilibration test with or without peritonitis in children

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Abstract. This study was conducted to evaluate longitudinal changes in the peritoneal equilibration test (PET) in children treated with continuous peritoneal dialysis (CPD). The effects of prolonged CPD and episodes of peritonitis on the PET were examined. PET was repeated up to five times in 12 paediatric patients who were subdivided into groups with and without peritonitis. In the peritonitis group ($n = 6$), the dialysate/plasma (D/P) creatinine ratio at a 4-h dwell time decreased progressively with time on CPD in five of six patients. In a comparison of the initial and final PETs performed at a mean interval of 22.8 ± 11.6 months, the D/P creatinine ratio in the final PET was significantly lower than in the initial PET ($P < 0.01$). In contrast, in the non-peritonitis group ($n = 6$), the D/P creatinine ratio in the final PET was unchanged for 28.2 ± 12.3 months from the initial PET. The D/Do glucose ratio at a 4-h dwell time was unchanged over time in each group. Thus, repeated PET measurements revealed that membrane permeability for creatinine was not affected by prolonged CPD itself, but decreased with time after episodes of peritonitis. Although the protocol for PET is not standardised in children, PET was useful for determining the sequential changes in peritoneal function in such patients on CPD.

Key words: Peritoneal dialysis – Continuous ambulatory peritoneal dialysis – Peritoneal function – Creatinine clearance – Ultrafiltration – Dialysis failure

Introduction

Continuous peritoneal dialysis (CPD) is an effective means of administering chronic dialysis to children with end-stage renal disease, primarily because of its simplicity together with other medical and social advantages. However, there is concern that the prolonged administration of CPD or episodes of peritonitis may affect the peritoneal function of children as well as adults [1, 2].

The peritoneal equilibration test (PET) was developed by Twardowski et al. [3] to characterise the peritoneal permeability for solutes in adults. Although PET has not been standardised in children [4–6], it is useful for making an adequate prescription for dialysis and also for determining the cause of inadequate dialysis during prolonged treatment. We evaluated retrospectively the effect of long-term CPD and episodes of peritonitis on the peritoneal function of paediatric patients by performing PET at least twice at the initiation of CPD and after long-term CPD.

Patients and methods

Twelve children with end-stage renal disease were maintained on CPD, either as continuous ambulatory peritoneal dialysis, nocturnal intermittent peritoneal dialysis or continuous cycling peritoneal dialysis. Patients were divided into two groups of 6 patients each: (1) non-peritonitis, with no history of any episode of peritonitis and (2) peritonitis group, with a history of at least one episode of peritonitis. Their mean ages were similar (12.4 ± 4.4 and 11.1 ± 8.5 years, respectively).

The incidence of peritonitis was: one episode in 4 patients, two episodes in 1 patient and six episodes in 1 patient. The causal organisms isolated were: *Staphylococcus aureus* in two episodes, *Staphylococcus epidermidis* in two episodes, α-*Streptococcus* in one episode and *Pseudomonas aeruginosa* in two episodes. PET was performed at least 1 month after any episode of peritonitis had resolved.

Each child received a modified version of the PET as described by Twardowski et al. [3], consisting of an infusion of Dianeal 2.5% dextrose (Baxter Healthcare, Deerfield, Ill., USA). The patients' usual infusion volume of dialysate, which was similar in the initial and final PET (35.0 ± 6.7 vs. 36.4 ± 7.4 ml/kg), was used in this study. A single serum sample was obtained during the procedure. Dialysate and plasma glucose and creatinine were analysed on standard automated laboratory equipment (Glucose Auto and Stat GA-1140, Kyoto Daiichi Kagaku; JCA-RX30 using the Jaffe reaction, Nihon Densi). The creatinine concentration was corrected by a factor determined in our laboratory: corrected creatinine (mg/dl) = creatinine (mg/dl) – glucose (mg/dl) ×0.00018.

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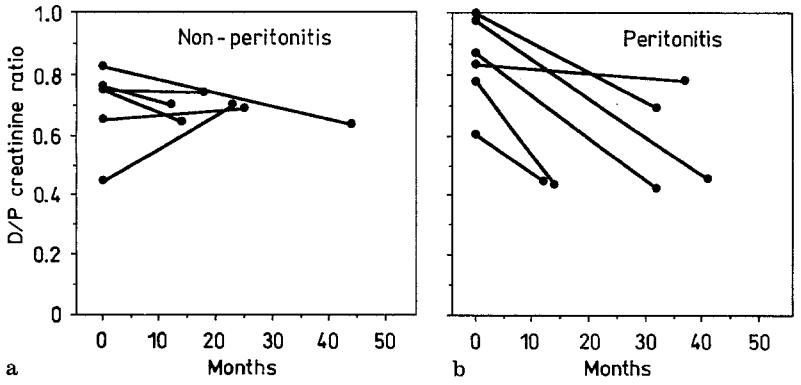

Fig. 1. Dialysate/plasma (*D/P*) creatinine ratio at a 4-h dwell time in the initial and final peritoneal equilibration test (PET) in **a** the non-peritonitis and **b** the peritonitis groups. The interval between the initial PET and the final PET is expressed as number of months

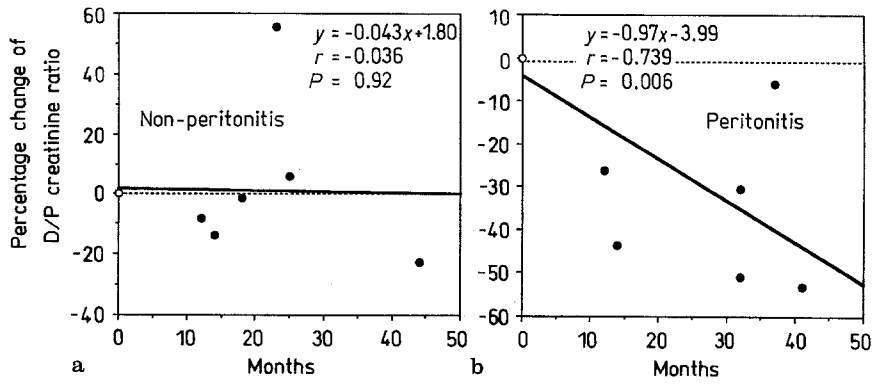

Fig. 2. Percentage change in D/P creatinine ratio at a 4-h dwell time from the initial PET to the final PET in: **a** the non-peritonitis and **b** the peritonitis groups. A significant negative correlation between percentage change in D/P creatinine ratio in the final PET and the number of months on CPD was found in the peritonitis group, but not in the non-peritonitis group

Peritoneal transport was estimated from the dialysate (D) to plasma (P) ratio of creatinine (D/P) calculated at 4 h. Similarly, the ratio of dialysate glucose at 4 h to dialysate glucose at time 0 (D/Do) was used to estimate the transport of glucose across the peritoneum. When the change in D/P creatinine ratio and D/Do glucose ratio exceeded 1 SD of the initial ratio (SD values calculated from all patients), it was regarded as significant.

Results are expressed as the mean plus or minus SD. Statistical analysis utilised unpaired and paired Student's *t*-tests and least-squares linear regression analysis. A level of $P < 0.05$ was considered statistically significant.

Results

The initial PET was performed at 7.2±7.0 months in the non-peritonitis group and at 7.0±6.1 months in the peritonitis group following initiation of CPD. The total number of PETs performed on each patient ranged from 2 to 5 (mean 3.33) in the non-peritonitis group and from 2 to 4 (mean 3.00) in the peritonitis group. The final PET was performed at 29.8±14.8 months in the non-peritonitis group and at 35.0±14.4 months in the peritonitis group following initiation of CPD. The mean interval between the initial and final PET was 28.2±12.3 months in the non-peritonitis group and 22.8±11.6 months in the peritonitis group (minimum 12 months).

The mean D/P creatinine ratios at a 4-h dwell time were compared for the initial and final PETs (Fig. 1). The mean D/P creatinine ratio in the initial PET did not differ significantly between the non-peritonitis and peritonitis groups (0.700±0.134 vs. 0.845±0.144). In the final PET, the mean D/P creatinine ratio was significantly decreased in the peritonitis group (from 0.845±0.144 to 0.541±0.157; $P = 0.008$, paired *t*-test), but not in the non-peritonitis group (from 0.700±0.134 to 0.687±0.039). When we analysed the individual cases, the D/P creatinine ratio in the non-peritonitis group was decreased in 1 patient and increased in another. In contrast, the D/P creatinine ratio in the peritonitis group decreased progressively in 5 of 6 patients following the episodes of peritonitis.

When the D/P creatinine ratio at 4 h in the final PET was expressed as a percentage change from the D/P creatinine ratio in the initial PET, the percentage change in D/P creatinine ratio showed a significant negative correlation with the number of months on CPD in the peritonitis group ($r = -0.739$, $P = 0.006$), but not in the non-peritonitis group ($r = -0.036$, $P = 0.92$) (Fig. 2). To examine the effect of ageing on the change in the D/P creatinine ratio, patients were divided according to Geary et al. [4] as ≦8 years ($n = 4$) and >8 years ($n = 8$). The percentage change in D/P creatinine ratio did not correlate significantly with the number of months on CPD in either age group (≦8 years, $r = -0.646$, $P = 0.084$ or >8 years, $r = -0.262$, $P = 0.33$).

The D/Do glucose ratio at a 4-h dwell time in the initial PET did not differ significantly in the non-peritonitis and peritonitis groups (0.400±0.105 vs. 0.285±0.134). In the final PET, the mean D/Do glucose ratio did not differ from that in the initial PET in either the non-peritonitis (0.409±0.078) or the peritonitis group (0.281±0.161). For the 5 patients in the peritonitis group with a decrease in the D/P creatinine ratios, the D/Do glucose ratio was increased in 1, unchanged in 2 and decreased in 2 others. The percentage change in D/Do glucose ratio in the final versus the initial PET was not correlated with the number of months

on CPD in either the non-peritonitis ($r = 0.295$; $P = 0.35$) or the peritonitis group ($r = 0.201$, $P = 0.53$).

Discussion

The PET was developed by Twardowski et al. [3] to characterise the function of the peritoneum in adults. Based on the results of this test, the transport rate of the peritoneum was classified as high, high-average, low-average or low. PET is presently recommended for use in adults to help determine the optimal schedule for peritoneal dialysis, especially when initiating CPD.

Although standardisation of PET and characterisation of the peritoneum in children would also be of great importance in helping to determine the optimal dialysis schedule, there is only limited information about PET in children. PETs carried out in children have variously involved a small number of patients, differing time intervals after the initiation of CPD and volumes of dialysate that were adjusted for body weight or for body surface area. The PET categories determined in adults can not simply be applied to children, since membrane permeability for solutes is generally considered to be higher in children than in adults. If the PET results in children were evaluated by adult standards, at least 70% would fall into the high or high-average permeability categories [4].

In this study, PET was performed to determine the longitudinal change in peritoneal function in children during long-term CPD. We found that membrane permeability for creatinine decreased progressively following episodes of peritonitis. In contrast to the peritonitis group, peritoneal function in the non-peritonitis group did not change with time over a 30-month period. Such factors as ageing, initiation of CPD [7] and the acute phase of peritonitis, which can transiently affect membrane permeability, did not alter peritoneal permeability in the peritonitis group, since age distribution and the time of the initial PET were similar in the two groups and PET was performed 1 month after completing antibiotic treatment. These results clearly indicate that peritonitis is a risk factor for deterioration of peritoneal function. Three patients in the peritonitis group have developed dialysis failure. Two required a change in the CPD prescription and 1 was switched to haemodialysis.

Consistent with our results, Rubin et al. [8] reported that membrane function may be impaired by frequent episodes of peritonitis. There are also reports of deterioration in peritoneal function associated with sclerosing peritonitis [9, 10]. Several investigators, however, have failed to show changes in creatinine transport in paediatric and adult patients who experienced episodes of peritonitis [1, 11]. There are two possible reasons for the observed decrease in creatinine transport in our peritonitis group: (1) a 4-h PET was used to determine the kinetics of creatinine instead of a 24-h creatinine clearance and (2) we studied membrane function over a longer period than previous investigators. Recently, Lo et al. [7] reported that the change in peritoneal function in adults determined by PET was unrelated to the number of episodes of peritonitis. In their study, the final PET was performed at a mean of 27.3 ± 28.1 (SD) months after the induction of CPD, similar to the duration of follow-up in the present study. It is unclear why we observed a change in peritoneal function following episodes of peritonitis and they did not. Differences in the age of the patients, the pathogens involved and the severity of peritonitis are possible factors. Longitudinal studies of peritoneal function with PET conducted in children by several groups of investigators should help to improve our understanding of this important parameter.

The functional deterioration in the peritonitis group may be due to fibrotic changes in the peritoneum. Fibrosis of the peritoneal membrane has been variously ascribed to the detachment of mesothelial cell junctions, chronic inflammation with destruction of the mesotheliums and, perhaps, the process of sclerosing peritonitis [12]. In the early stages of sclerosing peritonitis, the peritoneal membrane is hyperpermeable due to an increase in peritoneal blood flow. In contrast, after the development of sclerosing peritonitis, the membrane becomes hypopermeable and is associated with an irreversible loss of ultrafiltration [13]. Another cause of the functional deterioration is the adhesion of the peritoneal membrane. Although the exact reason for the decrease in membrane permeability in our paediatric patients is not known, fibrosis and adhesion of the peritoneum induced by an inflammatory process during peritonitis may have been involved.

A risk of ultrafiltration failure has been associated with prolonged CPD and episodes of peritonitis [9, 14]. However, in our paediatric patients the D/Do glucose ratio did not change in proportion to the duration of CPD or following episodes of peritonitis, and no patient developed ultrafiltration failure. The reason for the discrepancy between the change in D/P creatinine ratio and D/Do glucose ratio is not clear. These results suggest that adhesion of the peritoneum may not be severe, even if present, since one would expect both creatinine transport and ultrafiltration to be disturbed in a case of severe peritoneal adhesions. It is possible that ultrafiltration failure develops only after longer periods on CPD.

In conclusion, the membrane permeability for creatinine decreased progressively with time following episodes of peritonitis in our paediatric patients. Although PET is not standardised for use in children, it was useful for determining longitudinal changes in membrane function. Measurement of peritoneal function with PET annually would help to detect peritoneal dysfunction at an early stage, even before the appearance of the clinical manifestations of membrane failure and of sclerosing peritonitis. The prevention of peritonitis in paediatric patients being treated with CPD is essential to preserving the peritoneal function and thus improving their quality of life.

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Literature abstracts

Nephrol Dial Transplant (1994) 9: 1778–1785

Muscle and plasma amino acids and nutritional status in kidney-transplanted children

F. Perfumo, A. Canepa, J. C. Divino Filho, E. Nilsson, A. Carrea, E. Verrina, R. Gusmano, and J. Bergström

Nutritional status, assessed by anthropometric and biochemical methods, protein and amino-acid (AA) composition and muscle water were evaluated in 11 kidney transplanted children and in a control group of 10 children with normal renal function who were undergoing elective surgery. Samples of the rectus abdominis muscle were taken when surgery was performed in the control children and when the peritoneal catheter was removed in the transplanted children. The mean time from the transplantation to the study time was 97 ± 14 days (range 72–114 days).

Height was reduced in the transplanted children compared to the controls but skinfold thickness, arm muscle circumference and serum proteins (total protein, albumin, transferrin, pseudocholinesterase) were normal. The body mass index was over the 50° percentile in nine of the eleven children.

The muscle contents of total, extracellular, and intracellular water, alkali-soluble protein (ASP), DNA and the ASP/DNA ratio were not significantly different in transplanted children from those in the controls. Plasma leucine and taurine levels were significantly decreased, whereas plasma citrulline and alanine levels and the glycine/serine ratio were increased. Muscle threonine, alanine + taurine, glycine and aspartic acid levels as well as the glycine/serine ratio were increased in the transplanted children.

Transplanted children show an almost normal muscle AA profile and a plasma AA pattern that seems to be related to the prednisone therapy.

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Mutations in the type IV collagen α3 (COL4A3) gene in autosomal recessive Alport syndrome

Henny H. Lemmink, Toshio Mochizuki, Lambertus P. W. J. van den Heuvel, Cornelis H. Schröder, Alberto Barrientos, Leo A. H. Monnens, Bernard A. van Oost, Han G. Brunner, Stephen T. Reeders, and Hubert J. M. Smeets

A group of 22 unrelated patients with sporadic or non-X-linked Alport syndrome were screened for mutations in the non-collagenous domain of the type IV collagen α3 (COL4A3) chain gene. The five 3′-exons of this gene, located on chromosome 2qter, were tested by single strand conformation polymorphism analysis and direct sequencing. One patient was heterozygous and another homozygous (Mochizuki et al., Nature Genetics, in press) for a deletion of five nucleotides. A third patient appeared to be a compound heterozygote for two different nonsense mutations. In two patients and the father of a decreased patient we found a heterozygous substitution of an evolutionary conserved leucine by proline. However, segregation data of the mutation and a COL4A3/COL4A4 CA-repeat marker in their families argued against a causative role of the missense mutation. Even drastic changes of strongly conserved amino acids, as in the Leu36Pro case, may not be significant. Autosomal recessive inheritance due to pathogenic COL4A3 mutations accounts for at least 13% of Alport syndrome cases in this sample. It is concluded that COL4A3 is a major gene in the genetically and clinically heterogeneous Alport syndrome.