

Original Article

Peritoneal equilibration test with conventional ‘low pH/high glucose degradation product’ or with biocompatible ‘normal pH/low glucose degradation product’ dialysates: does it matter?

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Abstract

Background. The evaluation of the peritoneal transport characteristics is mandatory in peritoneal dialysis (PD) patients. This is usually performed in routine clinical practice with a peritoneal equilibration test (PET) using conventional dialysates, with low pH and high glucose degradation product (GDP) concentrations. An increasing proportion of patients are now treated with biocompatible dialysates, i.e. with physiological pH and lower GDP concentrations. This questions the appropriateness to perform a PET with conventional solutions in those patients. The aim of our study is to compare the results of the PET using biocompatible and conventional dialysates, respectively.

Methods. Nineteen stable PD patients (13 males, 6 females; mean age: 67.95 ± 2.36 years, mean body surface area: 1.83 ± 0.04 m², dialysis vintage: 2.95 ± 0.19 years) were included, among which 10 were usually treated with biocompatible and 9 with conventional solutions. Two PETs were performed, within a 2-week interval, in each patient. PET sequence (conventional solution first or biocompatible solution first) was randomized in order to avoid ‘time bias’. Small (urea, creatinine and glucose), middle (beta-2-microglobulin) and large molecules’ (albumin and alpha-2-macroglobulin) dialysate/plasma (D/P) concentration ratios and clearances were measured during each PET. Ultrafiltration (UF) and sodium filtration were also recorded. Results of both tests were compared by the Wilcoxon paired test.

Results. No statistical difference was found between both dialysates for small molecule transport rates or for sodium filtration and UF. However, a few patients were not similarly classified for small-solute transport characteristics within the PET categories. Beta-2-microglobulin and albumin D/P ratios at different time points of the PET were significantly higher with the biocompatible, when compared with the conventional, solutions: 0.10 ± 0.03 versus 0.08 ± 0.02 ($P < 0.01$) and 0.008 ± 0.003 versus 0.007 ± 0.003 ($P = 0.01$), respectively. A similar difference

was also observed for beta-2-microglobulin that was higher with biocompatible dialysates (1.04 ± 0.32 versus 0.93 ± 0.32 mL/min, respectively).

Conclusion. Peritoneal transport of water and small solutes is independent of the type of dialysate which is used. This is not the case for the transport of beta-2-microglobulin and albumin that is higher under biocompatible dialysates. Vascular tonus modification could potentially explain such differences. The PET should therefore always be carried out with the same dialysate to make longitudinal comparisons possible.

Keywords: albumin; beta-2-microglobulin; biocompatible solutions; peritoneal dialysis; peritoneal equilibration test

Introduction

The evaluation of the peritoneal transport characteristics is of major clinical importance in peritoneal dialysis (PD) patients [1–3]. This is usually performed in routine clinical practice with a peritoneal equilibration test (PET) [4]. The original procedure, performed with a single 4-h dwell, classically uses conventional solutions with a 2.27% glucose concentration. Also, Parikova *et al.* [18] documented an absence of difference between both types of dialysates for the peritoneal transport rates of middle and large molecules. Dialysate/plasma (D/P) ratios are then calculated to evaluate the peritoneal solute transport rate and patients are thereafter categorized, according to D/P creatinine ratios, into four different transport patterns: slow, slow average, fast average and fast. Several studies have shown the interest of performing PET with hypertonic 3.86% glucose solutions to improve information on ultrafiltration (UF) and mainly on aquaporin-mediated free water transport [5–11].

Conventional dialysates are hypertonic glucose solutions ranging between 1.36 and 3.86% with an acidic pH

(5.5) and lactate, as buffer agent. Despite the low pH of conventional solutions, high levels of glucose degradation products (GDPs) are produced. Several studies have shown that high GDP concentrations, mainly 3-deoxyglucose, methylglyoxal and glyoxal, increase angiogenesis, submesothelial fibrosis, which may eventually lead to dialysis failure. The introduction of new dialysates with bicompartimented bags has decreased the concentration of GDPs as glucose is conserved in a highly acidic solution. The neutral pH (7.4) and the mix of bicarbonate and lactate as buffer agents decrease abdominal pain and discomfort during dialysis. A benefit of the new solutions has also been demonstrated in terms of better protection of the peritoneal membrane integrity reflected by the CA125 level [12–14], but not for the preservation of the residual renal function [15], when compared with conventional dialysates.

A number of recent controlled observational follow-up studies comparing the effect of biocompatible and conventional dialysates on small solute and water transport (reviewed in ref. [16]) also showed discordant results. As a matter of debate, La Milia *et al.* [17] postulated that biocompatible solutions could influence UF as dissociation of sodium chloride is incomplete at normal pH, with a subsequent negative effect of lower concentration of ionized sodium on water transport induced by crystalloid osmosis. Also, Parikova *et al.* [18] documented an absence of difference between both types of dialysates for the transport rates of peritoneal middle and large molecules.

An increasing number of patients are now treated with new biocompatible solutions, because of the above-mentioned theoretic advantages, while PET might still be performed using conventional dialysates. It is not known whether this approach has a detrimental effect on the interpretation of the PET results.

The aim of our study was to compare, in the same patients, the results of two consecutive PETs using a 3.86% conventional low pH/high GDP glucose dialysate and a 3.86% normal pH/low GDP glucose dialysate, or vice-versa.

Materials and methods

Nineteen stable PD patients (13 males, 6 females; mean age: 67.95 ± 2.36 years, mean body surface area (BSA): 1.83 ± 0.04 m², dialysis vintage: 2.95 ± 0.19 years) were included, among which 10 were usually treated with biocompatible and 9 with conventional solutions. They had all been on regular automated PD (APD) for at least 3 months. Their medical condition was stable without active inflammation (C-reactive protein <10 mg/L) and they had been free of acute abdominal pathology (including peritonitis) for at least 3 months. The recommended 3.86% glucose modified PET was used according to the International Society for Peritoneal Dialysis (ISPD) recommendations [19].

Two PETs were performed in each group within a 2-week interval. One test was performed with the conventional dialysate (Dianeal[®] Baxter) and the other with the new biocompatible dialysate (Physioneal[®] Baxter). PET sequence (conventional solution first or biocompatible solution first) was randomized in order to avoid 'time bias'. The same solution of the PET was used the night before the test to exclude putative solute transport changes related to the dialysate itself. Blood samples were drawn after 120 min, as recommended [4]. A dialysate sample (10 mL) was taken at the start of the test and after 60, 120 and 240 min, as previously described. Net UF, i.e. the net difference between dialysate volume effluent and volume infused, was recorded.

Small, middle and large molecule measurements

Serum measurements of urea, creatinine, glucose, sodium and phosphate were performed using the routine laboratory technique on a Modular analyser (Roche Diagnostic). The Jaffé method was used for creatinine determination, and the results were corrected for the interference with high glucose levels. Sodium measurements have been made by indirect ion-selective electrode. Albumin, alpha-2-macroglobulin and beta-2-microglobulin in both serum and dialysate were measured by immunonephelometry on the BN II analyser (Siemens).

Calculations

The D/P ratios of small, middle and large molecules (urea, creatinine, phosphate, albumin, beta-2-microglobulin and alpha-2-macroglobulin) were calculated at specific times (60, 120 and 240 min, respectively). The ratio of dialysate glucose concentrations at specific 't' (60, 120 and 240 min) times, when compared with the glucose concentration of the instilled dialysate (D/D0), was also calculated.

D/P sodium was measured at the beginning of the PET and at 1 h. Sodium filtration was defined as the difference between D/P sodium [corrected for sodium diffusion using mass transfer area coefficient (MTAC) creatinine] at 1 h when compared with its value at the initiation of the test [20].

The dialysate clearances of different molecules (urea, creatinine, phosphate, albumin, beta-2-microglobulin and alpha-2-macroglobulin) were calculated using the following formula:

$$\text{Clearance [solute]} = \frac{[\text{Solute}] \text{ dialysate at Hour 4} \times \text{Effluent volume}}{[\text{Solute}] \text{ serum} \times 240}$$

where [solute] represents the solute concentration.

Sodium removal (NaR) was calculated as follows:

$$\begin{aligned} \text{NaR (mmol)} &= [\text{volume dialysate out (L)} \\ &\times [\text{Na}] \text{ dialysate out (mmol/L)}] - [\text{volume dialysate in (L)} \\ &\times [\text{Na}] \text{ dialysate in (mmol/L)}] \end{aligned}$$

The MTAC of creatinine and urea was calculated according to Waniewski *et al.* [21, 22].

Statistical analysis

This is a multicentre prospective study where results are expressed as mean values ± 1 standard deviation (SD) and also as median values with 25–75 confidence intervals (CIs). PET results have been compared by the Wilcoxon paired test. Graphics error bars are expressed in standard error of the mean (SEM). The statistical significance level was set to 0.05.

Ethical considerations

PET is a part of the normal procedure of care for PD patients. All patients gave written informed consent for the supplementary PET and the additional sample collection of blood and dialysate. The study design was approved by the local ethics committee.

Results

The PET results using both dialysates are presented independently of patient usual treatment.

Ultrafiltration, sodium removal and small solutes removal

There was no statistical difference between both solutions in terms of net UF at the end of the test (240 min): 340 ± 258 versus 386 ± 233 mL with biocompatible and conventional dialysates, respectively (Table 1). Sodium filtration and sodium removal at 240 min are identical between solutions.

D/P ratios for urea and creatinine at 240 min and for D_{240}/D_0 glucose were not statistically different between PETs. The respective MTACs and clearances were also virtually similar.

However, the categorization of the peritoneal transport rate was slightly different in a few patients, as illustrated in Figure 1 according to the type of dialysate which was used for the test.

Middle molecule transport [*beta*-2-microglobulin—molecular weight: 11 800 Da]

The D/P ratio for beta-2-microglobulin at 240 min was significantly greater with biocompatible solutions: 0.109 ± 0.037 versus 0.094 ± 0.032 with biocompatible and conventional dialysates, respectively ($P < 0.01$; Table 2). A statistical difference was already observed for the 120-min ratios (Figure 2). A similar difference was observed for beta-2-microglobulin clearance (1.04 ± 0.32 for biocompatible versus 0.93 ± 0.32 mL/min for conventional dialysates; $P < 0.05$).

Large molecule transport (albumin—molecular weight: 69 kDa, alpha-2-macroglobulin—molecular weight: 725 kDa)

The D/P albumin ratio was statistically higher with biocompatible solutions PET 0.008 ± 0.003 in biocompatible dialysates versus 0.007 ± 0.003 in conventional dialysates ($P = 0.01$; Figure 3 and Table 2). There was also a same trend for D/P alpha-2-macroglobulin and for both molecules clearances, although it did not reach statistical significance.

Discussion

The evaluation of water and solute peritoneal transport rates is of major clinical importance in PD patients. The objective of our study was to compare the results of peritoneal transport rates consecutively assessed, in the same patients, with conventional and biocompatible dialysates.

A significantly greater transport rate for beta-2-microglobulin and albumin, but not for alpha-2-macroglobulin, was observed when biocompatible solutions were used. The observation for the latter molecule could probably be accounted for by its large molecular size and the relatively 'short' PET duration that does not allow significant differences to appear. By contrast, there was no statistical difference between both dialysates for small molecule transport rates, sodium filtration, sodium removal and UF.

Similar results, although less significant than those of the D/P ratios, were also obtained for middle and large molecule clearances. The finding that D/P albumin reached significance, but not albumin clearance, could potentially be explained by the PET duration: longer exchange time, i.e. over 4 h, might have led to significant results.

The analysis of the various transport categories, based on the initial description of Twardowski *et al.* [4], also showed some differences according to the type of dialysate which is used: there was a higher proportion of 'fast average' and no case of 'small' transport categories when

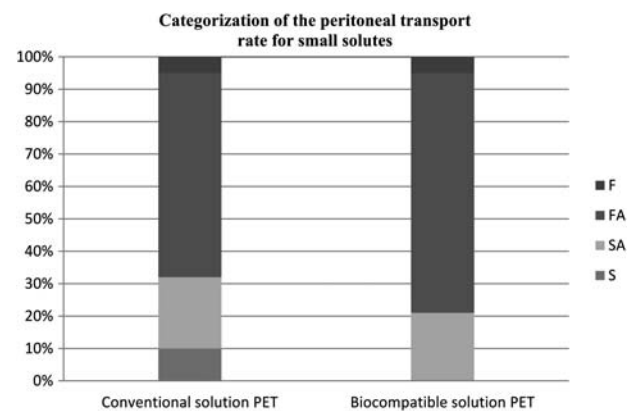


Fig. 1. Categorization of the peritoneal transport rate for small solutes according to the type of dialysate which was used for the test. F, fast; FA, fast average; SA, slow average; S, slow; transport rate status. Two and four patients with an S and an SA transport rate status with conventional dialysates are now categorized as SA and FA transporters, respectively, with biocompatible dialysates.

Table 1. Results of UF, sodium filtration, sodium removal and small molecule D/P ratios, MTAC and clearances according to both types of dialysates

	Biocompatible PET		Conventional PET		P-value
	Mean [\pm SD]	Median [CI 25–75]	Mean [\pm SD]	Median [CI 25–75]	
UF ₂₄₀ (mL)	340 [\pm 258]	340 [200–500]	386 [\pm 233]	417 [250–507]	NS
Sodium sieving	−0.06 [\pm 0.04]	−0.051 [−0.079–0.034]	−0.05 [\pm 0.02]	−0.043 [−0.063–0.031]	NS
NaR ₂₄₀ (mmol)	32.9 [\pm 31.3]	31.9 [7.2–58.6]	38.9 [\pm 28.6]	35.7 [27.5–55.4]	NS
D/P ₂₄₀ urea	0.92 [\pm 0.05]	0.93 [0.87–0.95]	0.91 [\pm 0.05]	0.92 [0.86–0.95]	NS
D/P ₂₄₀ creatinine	0.691 [\pm 0.089]	0.68 [0.65–0.74]	0.677 [\pm 0.094]	0.68 [0.62–0.73]	NS
D_{240}/D_0 glucose	0.33 [\pm 0.08]	0.33 [0.27–0.39]	0.31 [\pm 0.07]	0.29 [0.25–0.34]	NS
MTAC creatinine (mL/min)	8.9 [\pm 3.0]	8.5 [6.8–11.1]	8.7 [\pm 2.7]	8.7 [6.8–10.7]	NS
MTAC creatinine/BSA (mL/min/m ²)	4.9 [\pm 1.6]	4.8 [3.7–6.2]	4.8 [\pm 1.5]	4.9 [3.5–5.9]	NS
MTAC urea (mL/min)	23.5 [\pm 7.1]	23.1 [17.3–28.1]	22.5 [\pm 6.1]	23.4 [16.8–26.8]	NS
MTAC urea/BSA (mL/min/m ²)	12.8 [\pm 3.8]	12.9 [10.3–14.6]	12.5 [\pm 3.9]	12.8 [9.2–14.1]	NS
Clearances (mL/min)					
Urea	9.0 [\pm 0.99]	9.0 [8.4–9.8]	9.0 [\pm 1.01]	8.9 [8.5–9.7]	NS
Creatinine	6.7 [\pm 0.88]	7.0 [5.8–7.4]	6.7 [\pm 1.01]	6.7 [6.2–7.3]	NS

Results are expressed as mean values \pm 1 SD and median values with 25–75 CIs. NS, not significant.

Table 2. Results of beta-2-microglobulin, albumin and alpha-2-macroglobulin D/P ratios and clearances according to both types of dialysate

	'Biocompatible' PET		'Conventional' PET		P-value
	Mean [\pm SD]	Median [CI 25–75]	Mean [\pm SD]	Median [CI 25–75]	
D/P ₂₄₀ beta-2-microglobulin	0.109 [\pm 0.037]	0.099 [0.088–0.138]	0.094 [\pm 0.032]	0.087 [0.072–0.118]	<0.01
D/P ₂₄₀ albumin	0.0078 [\pm 0.0029]	6.8 [5.8–10.7]	0.0066 [\pm 0.0026]	6.4 [4.6–8.9]	0.01
D/P ₂₄₀ alpha-2-macroglobulin	0.0009 [\pm 0.0013]	0.00 [0.00–1.46]	0.0007 [\pm 0.0013]	0.00 [0.00–1.22]	NS
Clearances (mL/min)					
Beta-2-macroglobulin	1.04 [\pm 0.32]	0.97 [0.90–1.22]	0.93 [\pm 0.32]	0.82 [0.75–1.11]	<0.05
Albumin	0.075 [\pm 0.026]	0.073 [0.054–0.099]	0.066 [\pm 0.027]	0.065 [0.045–0.083]	NS
Alpha-2-macroglobulin	0.011 [\pm 0.010]	0.007 [0.005–0.014]	0.010 [\pm 0.011]	0.005 [0.004–0.009]	NS

Results are expressed as mean values \pm 1 SD and median values with 25–75 CIs. NS, not significant.

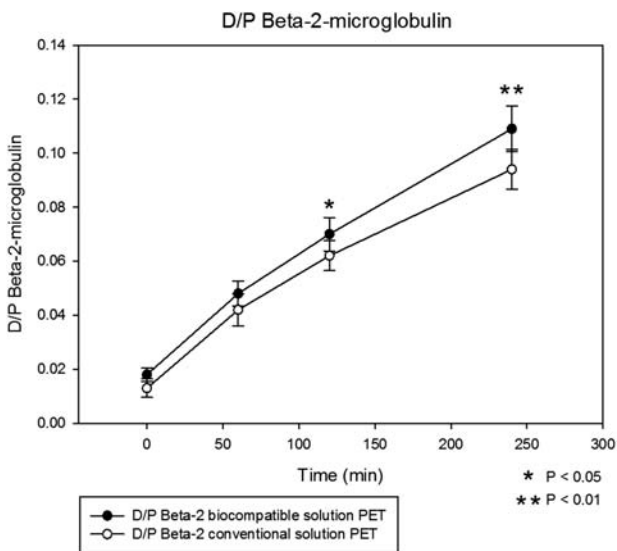


Fig. 2. D/P beta-2-microglobulin comparison between biocompatible (black circle) and conventional (open circle) solution PET. Results are expressed as mean values \pm 1 SEM. * P < 0.05; ** P < 0.01.

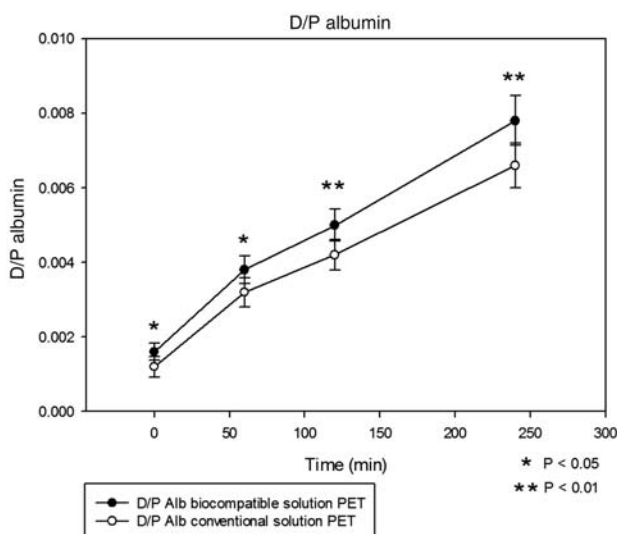


Fig. 3. D/P albumin comparison between biocompatible (black circle) and conventional (open circle) solution PET. Results are expressed as mean values \pm 1 SEM. * P < 0.05; ** P < 0.01.

biocompatible solutions were used. These differences could have a significant impact on PD prescription in routine clinical practice as, for instance, APD prescription is based on those transport categories [23].

In summary, our results suggest that biocompatible solutions seem to increase the peritoneal transport rates of beta-2-microglobulin and albumin, at least, during an acute exposition, as is the case during a PET, an observation which is different, as mentioned above, from that previously reported by Parikova *et al.* Indeed, those authors failed to find any influence of the type of solutions on transperitoneal solute transport for small solutes, as in our study, and also for middle and large molecule clearances, as evaluated by a standard peritoneal analyses with an intraperitoneal injection of dextran 70 [18]. Given the absence of deleterious effect of dextran 70 on peritoneal transport rate assessment [24], we cannot explain those discordant results. Since both our studies rely on a small number of patients and because D/P ratios are not available in the study by Parikova *et al.*, our findings need to be re-evaluated and verified in a larger cohort of patients.

We have to acknowledge several limitations for the interpretation of the results obtained in the present study: the small sample size, the usual well-known PET limitations (interference of high glucose concentration with creatinine determination, difficulty in sodium measurement, interference of residual volume etc.), the higher D/P albumin ratio at time 0 for the biocompatible solutions and the absence of randomization of the type of dialysate which was routinely used.

The results we have observed might have been obtained 'by chance'. Now, is there a rationale for a higher transport rate for beta-2-microglobulin and albumin during the PET using biocompatible dialysates? Although physiological mechanisms involved in the peritoneal transport rate of macromolecules still remain ill-defined, the main hypothesis leads to some peritoneal vascular tonus variations with specific acute vasodilatory action of the biocompatible dialysate within the peritoneal vasculature. A lower content in GDPs in the biocompatible dialysates might paradoxically induce a higher local exposition to nitric oxide [25–27], leading to an increased vascular flow rate, as recently documented for albumin transport in mice lacking endothelial caveolae [28]. Although this would be an attractive hypothesis, it still has to be reconciled with

some preclinical findings reported by Mortier *et al.* [29], in animals. Those authors showed that conventional, but not biocompatible, solutions had important vasoactive effect on peritoneal microcirculation that had been attributed to their GDP and lactate content. Finally, as our patients were not randomized to be routinely given conventional or biocompatible dialysates, individual reduced selectivity of the endothelial glycocalyx to larger solute transport or differences in the peritoneal interstitial tissue might also explain the differences observed between both types of dialysates.

More clinical studies, including a larger number of naïve and prevalent PD patients, are therefore necessary to better differentiate the intraperitoneal haemodynamic changes related to the use of both types of dialysates.

Conclusion

The evaluation of the peritoneal transport rate of beta-2-microglobulin and albumin is dependent on the type of dialysate which is used. Higher peritoneal transport rates are observed under biocompatible, when compared with conventional dialysates. Vascular tonus modification could potentially explain such differences. The PET should therefore always be carried out with the same dialysate to allow longitudinal comparisons.

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