Icodextrin with nitroprusside increases ultrafiltration and peritoneal transport during long CAPD dwells

CAROLINE E. DOUMA, JOHAN K. HIRALALL, DIRK R. DE WAART, DIRK G. STRUIJK, and RAYMOND T. KREDIET

Renal Unit, Department of Medicine and Department of Clinical Chemistry, Academic Medical Center University of Amsterdam, Amsterdam, and the Foundation of Home Dialysis Midden-West Nederland, Utrecht, The Netherlands

Icodextrin with nitroprusside increases ultrafiltration and peritoneal transport during long CAPD dwells. Addition of the nitric oxide (NO) donor nitroprusside to 1.36% glucose dialysate enlarges the effective peritoneal surface area during four-hour dwells. The theoretical positive effect on ultrafiltration is, however, counteracted by an increase in glucose absorption. The absorption of the glucose polymer icodextrin is much lower in comparison with glucose-based dialysis solutions, due to its high molecular weight. In the present study 7.5% icodextrin dialysate solution with and without the addition of 4.5 mg/liter nitroprusside was studied during eight-hour CAPD dwells. Two Standard Peritoneal permeability Analyses, adapted for eight-hour dwells, were performed in 10 stable CAPD patients. Nitrate and cGMP were measured as parameters of NO synthesis. The transcapillary ultrafiltration increased in a linear way with icodextrin (ICO) and was even higher after the addition of nitroprusside (NP): 666 (ICO) versus 834 (NP) ml/8 hr, \(P = 0.03\). The effective lymphatic absorption rate was not different. The resulting net ultrafiltration increased with nitroprusside: 344 (ICO) versus 540 (NP) ml/8 hr, \(P < 0.01\). The mass transfer area coefficient of urea increased 15% and that of creatinine 26% with nitroprusside, consistent with the expected enlargement of the vascular peritoneal surface area. The increase in protein clearances was more pronounced the larger the protein: \(\alpha\)-2-microglobulin 19%, albumin 47%, IgG 63% and \(\alpha\)-2-macroglobulin 95%. Dialysate/plasma (D/P) ratios of nitrate were not higher than the expected values on the basis of its molecular weight (\(P < 0.001\)). They increased 19% with nitroprusside. Also, the D/P ratio cyclic guanosine monophosphate (cGMP) after four hours increased with nitroprusside (0.39, range 0.13 to 0.55 ICO, and 0.82, range 0.36 to 1.39 NP, \(P = 0.01\)). With nitroprusside the D/P ratio cGMP was higher than expected after four and eight hours (\(P < 0.001\)). This points to local generation of NO after addition of nitroprusside. The nitroprusside induced increase in the mass transfer area coefficients (MTAC) of creatinine and in the ultrafiltration caused an increase in the creatinine clearance from 4.2 ml/min to 5.0 ml/min during the eight-hour dwell. This means that nitroprusside adds 3 liters/week to the peritoneal clearance of creatinine. The adequacy of peritoneal dialysis can therefore be improved by the addition of nitroprusside to 7.5% icodextrin, used for the long exchange.

Impaired ultrafiltration in continuous ambulatory peritoneal dialysis (CAPD) patients is often associated with high transport rates of low molecular weight solutes [1–4]. This reflects the presence of a large vascular surface area, which in theory would allow high water transport rates. However, when a low molecular weight osmotic agent, such as glucose, is used, this mechanism is counteracted by a rapid decline of the osmotic gradient, because of the high absorption rate of glucose [5]. Using a high molecular weight osmotic agent, like the glucose polymer icodextrin, the situation is different. Icodextrin has an average molecular weight of 16,800 Da and the absorption is 16 to 20% during 6- to 12-hour dwells [6, 7]. This absorption will mainly be by uptake into the lymphatic system due to its high molecular weight. Therefore, icodextrin can be expected to increase ultrafiltration in the presence of a large peritoneal vascular surface area. This has indeed been found in stable CAPD patients [5, 8] and also during peritonitis [9].

The nitric oxide donor nitroprusside causes vasodilation, which is mediated by the synthesis of cyclic guanosine monophosphate (cGMP) [10]. Nitric oxide has a half-life time of a few seconds and is oxidized to nitrite and nitrate [11]. Nitrite in the circulation reacts rapidly with oxyhemoglobin, resulting in a stoichiometric formation of methemoglobin and nitrate [12]. Exposure of animal peritoneal tissues to nitroprusside causes opening of previously not perfused capillaries and enlarges the capillary pore area [13, 14]. Intraperitoneal administration of nitroprusside during four-hour dwells with 1.36% glucose increased the effective peritoneal surface area, leading to an increase in the glucose absorption. The resulting rapid decrease in osmotic gradient counteracted the initial positive effect on the ultrafiltration by the enlarged surface area [15]. These results suggested that the addition of nitroprusside to icodextrin based dialysis solutions might lead to a marked increase in ultrafiltration, even during long dwells.

The aim of the present study was to analyze peritoneal fluid and solute kinetics using a 7.5% icodextrin dialysis solution during an eight-hour exchange and to investigate the effects of intraperitoneally administered nitroprusside on these parameters. The contribution of nitric oxide was investigated by analysis of nitrate and cGMP.

METHODS

Patients

Ten stable CAPD patients were studied twice within one week with a modified Standard Peritoneal permeability Analysis (SPA),
during eight-hour dwells [16]. The patients had a mean age of 59 years (range 44 to 68 years). The median body wt was 76.4 kg (range 66.2 to 86.5 kg) and the median body surface area was 1.95 m² (range 1.71 to 2.06 m²). They were treated with CAPD for 11 to 48 months, median 20 months. The causes for renal replacement therapy were chronic glomerulonephritis (N = 3), diabetic nephropathy (2), hypertensive nephropathy (2), polycystic kidney disease (1), amyloidosis (1) and analgesic nephropathy (1). All patients used commercially available glucose dialysate (Dianeal®; Baxter B.V., Utrecht, The Netherlands) and were free of peritonitis at the time of the study and in the four preceding weeks. At the time of the test two patients used 1.5 liter exchanges and eight patients used 2.0 liter exchanges of dialysate. The protocol was approved by the Committee of Medical Ethics of the University Hospital of Amsterdam, and informed consent was obtained from all patients after an explanation of the purpose and methods of the study.

Study design

Two modified SPAs were performed with 7.5% icodextrin (Icodial®; ML Laboratories PLC, Liverpool, UK), one day with and the other day without the addition of 4.5 mg/liter sodium nitroprusside (nitroprusside sodium 1%). The bag was wrapped in tin foil and nitroprusside was added just before the experiment, because nitroprusside is not stable in light. The sequence of both tests was randomized. The SPAs were modified for eight-hour dwell periods with 7.5% icodextrin. In brief, the peritoneal cavity was rinsed with 7.5% icodextrin solution before instillation of the dialysate into the abdomen. On the nitroprusside day, 4.5 mg/liter nitroprusside was also added to the first rinsing bag. Dextran 70 (Macrodex®; NPBI, Emmer-Compascuum, The Netherlands; or Hyskon®; Medisan Pharmaceuticals AB, Uppsala, Sweden) was added to the test solution for measurements of peritoneal fluid kinetics [17]. Dialysate samples were taken before inflow and 10, 20, 30, 60, 120, 180, 240, 300, 360, 420 and 480 minutes after inflow of the test solution. These samples were collected after a temporal drainage of 100 to 200 ml to avoid the effect of dead space. After drainage of the test solution at 480 minutes, the peritoneal cavity was rinsed with 1.36% glucose. Samples were taken from this rinsing bag for the calculation of the residual volume. Blood samples were drawn before and after the test. Dextran 1 (20 ml, Promitren®; NPBI) was injected intravenously before the test to prevent possible anaphylaxis to dextran 70 [18].

Measurements

Total dextran 70 was determined by means of high-performance liquid chromatography as described previously [19], with the following modifications. Interference of dextrin with the determination of dextran was suppressed by conversion of dextrin to oligosaccharides using α-amylase incubation during 60 minutes at 37°C. This was followed by deproteinization with ZnSO₄ and K₃Fe(CN)₆. The column used was a Bio-Sil SEC 250 Guard 80×7.8 (Biorad). Alpha-amylase is especially able to break the α₁ to α₄ linkages, resulting in conversion of dextrin to maltose, maltotriose and other glucose oligomers [20].

Urea, creatinine and urate were determined by enzymatic methods (Boehringer Mannheim, Mannheim, Germany). Beta-2-microglobulin was measured with an IMx system using a Micro particle Enzyme Immunoassay (Abbott Laboratories, North Chicago, IL, USA). Albumin, IgG and α₂-macro globulin were determined by nephelometry (BN100; Behring, Marburg, Germany).

Blood and dialysate samples for nitrate and cGMP were centrifuged at 1530 g for ten minutes and immediately stored at −20°C. Nitrate was measured by ion-pair high performance liquid chromatography. The lower detection limit was 2.5 μmol/liter. cGMP was measured by an Enzyme Immunoassay (Cayman Chemical Company, Ann Arbor, MI, USA).

Calculations

The peritoneal fluid parameters were calculated as described previously [21]. Briefly, fluid transport across the peritoneum during CAPD is influenced by opposing mechanisms. The transcapillary ultrafiltration (TCUF) increases the intraperitoneal volume; it was calculated as the dilution of the volume marker dextran 70. The TCUF rate was obtained by dividing the transcapillary ultrafiltration by the dwell time. The loss of the volume marker from the peritoneal cavity was used to calculate the effective lymphatic absorption rate. This convective loss includes all pathways of uptake into the lymphatic system, both subdiaphragmatic and interstitial. The change in intraperitoneal volume can be obtained by the dilution of the volume marker after correction for incomplete recovery. The net ultrafiltration rate is the change in intraperitoneal volume divided by the dwell time and is equal to the total difference between the TCUF rate and the lymphatic absorption rate.

The data of the TCUF during the eight-hour dwell were fitted with linear regression and also with a Lineweaver-Burke plot. A Lineweaver-Burke plot is the linear regression between the reciprocal values of the TCUF and the reciprocal of time [17]. The correlation coefficients of the individual regression lines were compared to define which method gave the best fit. Using the Lineweaver-Burke plot, it is possible to calculate the maximum theoretical intraperitoneal volume in the absence of lymphatic flow (TCUF_{max}) and the transcapillary ultrafiltration in the first minute (TCUF_{0,1min}) [17].

The transport of low molecular weight solutes was expressed as mass transfer area coefficients (MTAC). This is the maximum theoretical clearance of a solute by diffusion at time zero, before solute transport has started. The MTACs of urea, creatinine and urate were calculated according to the model of Waniewski, Werynski, Heimbürger and Lindholm [22], with a correction factor for plasma water [23]. For nitrate and cGMP, dialysate/plasma (D/P) ratios were calculated, because in some patients the cGMP concentrations in dialysate were greater than in plasma after the addition of nitroprusside. Therefore, it was not possible to calculate MTACs. The D/P ratios of nitrate and cGMP were calculated after four and after eight hours, and were corrected for plasma water by multiplication with 1.05 [24].

Peritoneal clearances of urea, creatinine, β₂-microglobulin, albumin, IgG and α₂-macro globulin were calculated after eight hours using the equation: Cl (μl/min) = (D*V)/(P*I), where Cl is the clearance, D is the dialysate concentration, V is the dialysate volume, P is the plasma concentration and I is the dwell time. The clearances of the four proteins and their free diffusion coefficients in water were used to calculate the restriction coefficient for macromolecules. The restriction coefficient (RC) provides a functional characterization of the intrinsic peritoneal permeability [21, 25, 26]. This parameter is the slope of the power relationship between the clearances of the four above-mentioned proteins (Cl)
and their free diffusion coefficient in water ($D_{20,W}$) when plotted on a double logarithmic scale: $Cl = constant \times D_{20,W}^{RC}$.

Based on the power relationship between the D/P ratios of urea, creatinine, urate and β2-microglobulin, and their molecular weights, a regression line was calculated. By interpolation of the molecular weights of nitrate and cGMP on this line, the expected D/P ratios were calculated, assuming that their dialysate concentrations would only be determined by diffusion from the circulation. The differences between observed and expected D/P ratios of nitrate and cGMP were tested by a modified t-test to analyze whether the deviation from the regression line was significant. This test takes the variability of the regression line between molecular weights and D/P ratios into account [27].

The results are given as median values and ranges, because most of the data were not normally distributed. Wilcoxon matched-pairs rank sum tests and Spearman-rank correlation tests were used for distribution free testing.

RESULTS

Fluid kinetics

The 7.5% icodextrin dialysis solution with and without nitroprusside was well tolerated without side effects. The TCUF rate during the eight-hour dwell was higher after the addition of nitroprusside: 1.38 ml/min, range 0.86 to 4.49 ml/min (icodextrin) and 1.75 ml/min, range 1.27 to 4.34 ml/min (icodextrin with nitroprusside), $P = 0.03$. The difference in TCUF was significant after three hours and at every time point thereafter (Fig. 1). The effective lymphatic absorption rate with icodextrin was 0.81 ml/min (0.21 to 3.10 ml/min) and did not change with nitroprusside: 0.74 ml/min (0.19 to 2.16 ml/min), $P = 0.5$. The resulting net ultrafiltration rate increased 49% during the eight-hour dwell from 0.72 ml/min, range 0.14 to 1.42 ml/min (icodextrin) to 1.14 ml/min, range 0.48 to 2.50 ml/min (icodextrin with nitroprusside), $P < 0.01$. The difference in net ultrafiltration became significant after two hours (Fig. 1). After eight hours the net ultrafiltration without nitroprusside was 344 ml (range −65 to 673 ml) and with nitroprusside 540 ml (225 to 1192 ml), $P < 0.01$.

Both linear regression and the Lineweaver-Burke plots fitted well for the TCUF during the dwell. The r-values with icodextrin were 0.986 (range 0.953 to 0.998) using linear regression and 0.979 (0.924 to 0.990) obtained with Lineweaver-Burke plots, $P = 0.2$. After the addition of nitroprusside the r-values calculated with linear regression were 0.979 (0.933 to 0.994) and with Lineweaver-Burke plots were 0.989 (0.953 to 0.999), $P = 0.2$.

The TCUF max increased from 771 ml (381 to 986 ml) with icodextrin to 1288 ml (635 to 2355 ml) with icodextrin and nitroprusside, $P = 0.009$. The TCUF 0-1min was 3.4 ml/min (2.1 to 7.9 ml/min), but this difference was not significant ($P = 0.3$).

Transport of low molecular weight solutes and proteins

The MTACs of the low molecular weight solutes urea (molecular wt 60 Da), creatinine (molecular wt 113 Da) and urate (molecular wt 168 Da) increased after the addition of nitroprusside (Table 1). The median increase for urea was 15%, for creatinine 26% and for urate 40%. The clearances of urea and creatinine are shown in Table 2. The addition of nitroprusside caused a 13% increase in the clearance of urea and a 19%
increase in the clearance of creatinine during the eight-hour dwell. Also, the protein clearances were higher with nitroprusside. This nitroprusside induced increase of clearances was more pronounced the larger the protein: 19% for β2-microglobulin (molecular wt 11,800 Da), 47% for albumin (molecular wt 69,000 Da), 63% for IgG (molecular wt 150,000 Da) and 95% for α2-macroglobulin (molecular wt 820,000 Da). The albumin loss during this period increased 0.92 grams with nitroprusside (P = 0.02). The restriction coefficient calculated on the four proteins decreased from 2.36 (1.75 to 2.49) to 2.06 (1.66 to 2.33) with nitroprusside (P = 0.01).

A positive correlation was found between the restriction coefficient for macromolecules and the time treated with CAPD (r = 0.7, P = 0.04), using icodextrin. This correlation disappeared after the addition of nitroprusside (r = –0.1, P = 0.70). Figure 2 shows the restriction coefficient for macromolecules with icodextrin and nitroprusside.

Table 2. Peritoneal clearances of urea and creatinine and the albumin loss during 8-hour dwells

<table>
<thead>
<tr>
<th></th>
<th>7.5% Icodextrin</th>
<th>+ Nitroprusside</th>
<th>P value</th>
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<tbody>
<tr>
<td>Clearance ml/min</td>
<td></td>
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<tr>
<td>Urea</td>
<td>4.8 (3.2–6.5)</td>
<td>5.4 (3.7–7.1)</td>
<td>0.008</td>
</tr>
<tr>
<td>Creatinine</td>
<td>4.2 (2.8–6.3)</td>
<td>5.0 (3.3–7.0)</td>
<td>0.006</td>
</tr>
<tr>
<td>Albumin loss g/8 hr</td>
<td>1.48 (0.89–2.69)</td>
<td>2.40 (1.25–2.76)</td>
<td>0.02</td>
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</table>

Values are given as medians with ranges.

The kinetics of fluid and solute transport with 7.5% icodextrin based dialysate during eight-hour exchanges were in accordance with expectations based on four-hour exchanges. The addition of nitroprusside induced increase in the MTAC of creatinine, an indication for an increase in the vascular surface area, was accompanied by an increase in intraperitoneal volume, as shown in Figure 3 for each individual patient.

**Parameters of nitric oxide**

The D/P ratio of nitrate was higher with nitroprusside both after four hours and after eight hours: after four hours 0.73, range 0.54 to 0.90 (icodextrin) and 0.83, range 0.72 to 0.88 (icodextrin with nitroprusside), P = 0.04. The D/P ratio of nitrate after eight hours was 0.82, range 0.76 to 1.06 (icodextrin) and 0.87, range 0.83 to 1.19 (icodextrin with nitroprusside), P = 0.01. Regardless of the addition of nitroprusside, the observed D/P ratios of nitrate were not higher than the expected values based on its molecular weight, both after four and after eight hours (Fig. 4).

The D/P ratio of cGMP was 0.39 (0.13 to 0.55) after four hours and 0.62 (0.26 to 0.74) after eight hours, during the icodextrin dwell. These D/P ratios of cGMP were not greater than expected on the basis of its molecular weight (Fig. 4). After the addition of nitroprusside the D/P ratio of cGMP increased to 0.82 (0.36 to 1.39) after four hours (P = 0.01) and 0.76 (0.32 to 1.13) after eight hours (P = 0.08). This increase in the D/P ratio was greater than expected; P < 0.001, both after four and after eight hours (Fig. 4). After four hours the D/P ratio of cGMP even exceeded 1.0 in four patients and after eight hours this occurred in two patients. During the icodextrin dwell the D/P ratio of cGMP was greater after eight hours in comparison with values after four hours (P = 0.01). With nitroprusside the D/P ratio of cGMP was greater after four hours (P = 0.05) compared to values after eight hours.

**DISCUSSION**

The nitroprusside induced increase in the MTAC of creatinine, an indication for an increase in the vascular surface area, was accompanied by an increase in intraperitoneal volume, as shown in Figure 3 for each individual patient.
nitroprusside lead to marked increments in the transport of fluids and solutes. These findings will be discussed according to physiological mechanisms and to potential clinical relevance.

**Fluid transport**

Icodextrin 7.5% is a solution hypotonic to uremic plasma. It induces ultrafiltration across the capillary wall by colloid osmosis. This process is based upon the principle that fluid flow across a membrane permeable to small solutes, occurs in the direction of relative excess of impermeable large solutes, rather than along the osmolality gradient. The TCUF induced by the 7.5% icodextrin-based dialysis solution increased in a linear way during an eight-hour dwell. When 4.5 mg/liter nitroprusside was added to the icodextrin based dialysate, the ultrafiltration could be augmented by almost 50%. These observations extend the findings that the ultrafiltration increases linearly during a four-hour exchange [8]. Furthermore, they support the clinical data showing that icodextrin is especially effective during long exchanges and in situations with impaired ultrafiltration on glucose based solutions due to a large vascular surface area [6, 7]. The effects of a nitroprusside induced increase in the peritoneal vascular surface area on the TCUF are in accordance with previous studies. Patients with a large effective peritoneal surface area, due to ultrafiltration failure or peritonitis, showed the largest benefit by using a glucose polymer solution in stead of glucose based dialysate [5, 9]. The relationship found previously between the MTAC of creatinine, as a marker of the effective peritoneal surface area, and the TCUF rate during icodextrin [8] could be confirmed in the present study (without nitroprusside $r = 0.6$ and $P = 0.07$; with nitroprusside $r = 0.7$ and $P = 0.03$). Increasing the vascular surface area with nitroprusside increased the ultrafiltration rate even more. During dwells with glucose dialysate the positive effect of nitroprusside on ultrafiltration is only present during the initial phase of a dwell, because it is counteracted by the increased absorption of glucose by diffusion [15]. As icodextrin disappears from the peritoneal cavity by uptake into the lymphatic system, diffusion can probably be neglected. None of the patients included in the present study had ultrafiltration failure. The presence of a large vascular surface area is the most frequent cause of impaired ultrafiltration [28]. It cannot be predicted from our results whether the addition of nitroprusside to icodextrin would increase their vascular surface area even more with a subsequent increase in ultrafiltration.

The best fit for the TCUF during a glucose dwell is the Lineweaver-Burke plot [17]. Linear regression was found to fit best for four-hour dwells with icodextrin [8]. In the present study,

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Fig. 4. Regression lines based upon the relationship between the median D/P ratios of urea, creatinine, urate and β2-microglobulin and their molecular weights (●). The positions of nitrate and cGMP (○) are given in relation to their molecular weight during various conditions. (A) Icodextrin at 240 minutes. (B) Icodextrin with nitroprusside at 240 minutes. (C) Icodextrin at 480 minutes. (D) Icodextrin with nitroprusside at 480 minutes. *$P < 0.001$ for increase in the observed D/P ratio cGMP with regard to the expected D/P ratio cGMP.
both linear regression and the Lineweaver-Burke plot fitted well for the TCUF during eight-hour icodextrin exchanges. Neither fit was significantly better, but it was evident that the TCUF increased during the whole dwell. The TCUFmax reported for 1.36% glucose dwells averaged 641 ml [17]. The present study shows a 20% higher TCUFmax with icodextrin and a 101% increase with icodextrin and nitroprusside.

The TCUF0-1min was not significantly higher after the addition of nitroprusside, probably because the icodextrin dialysate is hypotonic compared to uremic plasma. Consequently, the initial crystalloid osmotic pressure gradient causes ultrafiltration from the dialysate to the circulation during the first part of the dwell. This will be even more pronounced after the nitroprusside induced increase of the vascular peritoneal surface area.

**Transport of low molecular weight solutes**

The absolute values of MTACs of low molecular weight solutes were somewhat lower than previously reported for glucose- and icodextrin based dialysate during four-hour dwells [8, 15, 29]. This is most likely due to the eight-hour duration of the dwells in the present study. The nitroprusside induced increase in the MTACs was, however, similar during four and eight-hour dwells and averaged 15 to 40% [15]. The combination of higher MTACs and higher ultrafiltration rates resulted in a median increase in the peritoneal creatinine clearance of 15% or 0.8 ml/min during the eight-hour dwell with icodextrin and nitroprusside. It can be calculated from our data (median creatinine clearance 4.2 ml/ min) that the daily use of an eight-hour overnight dwell with icodextrin during seven days a week will add 14 liters per week (4.2 × 60 × 8 × 7) to the total creatinine clearance obtained by the exchanges during daytime. For comparison, the contribution of the night dwell to total creatinine clearance in a patient with ultrafiltration failure, who drains only 1800 ml of a 2 liter glucose solution, averages only 11 liters per week. The routine addition of nitroprusside to icodextrin for one long dwell everyday would further increase the total creatinine clearance by 3 liters to 17 liters per week, compared to the total clearance obtained with daytime ambulatory peritoneal dialysis. This may be of significance in clinical practice, because the CANUSA study has shown that an increment of the creatinine clearance of 5 liter/week/1.73 m² reduced the relative mortality risk by 7% [30]. Although it cannot be concluded from these observational data that increasing peritoneal creatinine clearance will prolong the survival of peri-toneal dialysis patients, the increase of 6 liters per week in creatinine clearance makes it more feasible to meet the recently formulated adequacy targets [31].

**Transport of serum proteins**

The median values for the peritoneal clearances of individual serum proteins and the peritoneal restriction coefficient calculated on these proteins was similar to previously published values. In accordance with earlier published cross-sectional and longitudinal data by our group [32, 33], the restriction coefficient was higher in long-term CAPD patients. As the restriction coefficient can be considered a reflection of the large pore radius, these observations suggest a smaller radius of these pores in long-term CAPD. However, the relationship with time disappeared after the addition of nitroprusside. This suggests that the dilating capacity of these pores is unaffected by the duration of CAPD. Park et al [34] compared new CAPD patients to long-term CAPD patients and found that the nitroprusside induced increase in drained protein concentration was more pronounced in the new CAPD patients. This is in contrast with the results of our present study where a positive correlation was found between the CAPD treatment time and the proportional increase in albumin loss during eight-hour dwells. The difference of our results with that of Park et al might be that short exchanges were used in the latter study. It should also be realized that the number of patients is small and interpretation of the relationship between protein kinetics and time on CAPD is speculative, as the anatomic equivalent of these large pores has not been established with certainty [35]. When one assumes that venular interendothelial gaps, that can be provoked by local administration of vasodilators such as histamine, represent the large pore system [36] the following hypothesis can be raised. Mesothelial cells synthesize many vasoactive substances such as prostaglandin E₂ and prosta-cyclin [37]. Long-term peritoneal dialysis can lead to a reduction of mesothelial cell mass. This may lead to a lower basal vasodilating tone in the peritoneal microvasculature and therefore higher restriction coefficients. The addition of nitroprusside causes so much vasodilation that the effect of the basal vasodilating tone is overruled.

The effect of nitroprusside administration on peritoneal albumin clearance led to an increased albumin loss in peritoneal effluent. The median increase was, however, only 0.92 grams per eight-hour exchange. This would increase peritoneal albumin loss from 3 to 4 grams per 24 hours to 4 to 5 grams per 24 hours [38]. This is unlikely to influence the serum albumin concentration especially as Kaysen and Schoenfeld found that albumin synthesis in CAPD patients increased with increased albumin loss [39]. Moreover, various studies have shown that the main determinants of serum albumin concentration in CAPD patients were age and the presence of a systemic disease such as diabetes mellitus, and not peritoneal albumin loss [40, 41]. It can be expected that the favorable effects of nitroprusside on ultrafiltration and small solute clearances outweigh the limited increase in peritoneal protein loss.

**Parameters of nitric oxide**

The D/P ratios of nitrate increased with nitroprusside, due to the larger effective peritoneal surface area. Nitrate, formed from the degradation of nitric oxide in the circulation, will diffuse from the circulation to the dialysate. Therefore, the D/P ratio increases during the dwell. The D/P ratio of nitrate during the administration of nitroprusside could totally be explained by transperitoneal transport. This implies that there was no detectable local production of nitrate in the peritoneal cavity. It suggests that nitric oxide, released from nitroprusside, diffuses from the peritoneal cavity to the circulation, where the oxidation to nitrate takes place. In a previous study the D/P ratios of cGMP were higher than expected on the basis of its molecular weight after the addition of nitroprusside [15]. We concluded that this could be explained by local generation of cGMP, induced by nitric oxide. This has been confirmed in the present study. Both after four and after eight hours the D/P ratios of cGMP were above the transport line. D/P ratios exceeding 1.0 with nitroprusside is a second reason for local generation of cGMP. The third indication is the higher D/P ratio of cGMP after four hours in comparison with eight hours. It is likely that the locally generated cGMP diffused from the dialysate to the circulation.
It can be concluded that the addition of nitroprusside enlarged the vascular surface area, leading to an increase in the MTACs of low molecular weight solutes and in the clearances of urea, creatinine and proteins. Furthermore, this increase in effective peritoneal surface area enhanced the icodextrin induced ultrafiltration during eight-hour dwells. The adequacy of peritoneal dialysis in CAPD patients can therefore be improved by the addition of nitroprusside to a 7.5% icodextrin dialysis solution. The benefit will especially be during long exchanges, like the night dwell for CAPD patients and the exchange during the day for automated peritoneal dialysis patients.

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Reprint requests to Caroline E. Douma, M.D., Ph.D., Academic Medical Center, University of Amsterdam, Department of Nephrology, F4-215, P.O. Box 22700, 1100 DE Amsterdam, The Netherlands.

APPENDIX

Abbreviations used in this article are: CAPD, continuous ambulatory peritoneal dialysis; cGMP, cyclic guanosine monophosphate; D/P ratio, dialysate/plasma ratio; ICO, icodextrin; MTAC, mass transfer area coefficient; NO, nitric oxide; NP, nitroprusside; RC, restriction coefficient; D/P ratio, peritoneal dialysis in CAPD; cGMP, cyclic guanosine monophosphate; D/P ratio, peritoneal transport characteristics of water, low-molecular weight solutes and proteins during long-term continuous ambulatory peritoneal dialysis. Perit Dial Bull 9:129–141, 1991

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