

The effects of low-sodium peritoneal dialysis fluids on blood pressure, thirst and volume status

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Abstract

Background. Poor ultrafiltration is associated with worse outcomes in peritoneal dialysis (PD) patients. This might in part reflect problems associated with salt and water excess. Increasing the diffusive component of peritoneal sodium removal using low-sodium PD fluids might have beneficial effects on blood pressure (BP), thirst and fluid status that could translate into clinical benefits.

Methods. Using a multicentre, prospective, baseline controlled (1 month), non-randomized intervention (2 months) design, two novel solutions designed from predictions using the three-pore model were investigated. In group A ($[Na^+] = 115$ mmol/l), the glucose (G) was increased to 2.0% to compensate for reduced osmolality whereas in group B ($[Na^+] = 102$ mmol/l), it was unchanged (2.5%). Both solutions were substituted for one 3- to 5-h exchange per day and no change was made to the rest of the dialysis regime.

Results. Ten patients in group A and 15 in group B completed the study. Both solutions resulted in significant increases (30–50 mmol/dwell) in diffusive sodium removal during the test exchanges, $P < 0.001$. Ultrafiltration was maintained in group A but reduced in group B. Ambulatory nocturnal mean BP fell in group A [93.1 ± 10.6 mmHg (\pm SD) versus 85.1 ± 10.2 mmHg, $P < 0.05$], but was stable in group B (95.4 ± 9.4 versus 95.1 ± 10.7 mmHg, NS). Thirst reduced independent of appetite and mood in both groups by 2 months, more markedly in group A. Indices of fluid status, including TBW by bioimpedance and D dilution also improved in group A, $P < 0.05$, whereas weight increased in group B.

Conclusions. Increasing the diffusive component of sodium removal whilst maintaining ultrafiltration is associated with improvements in BP, thirst and fluid status. The lack of effect seen with uncompensated low-sodium dialysate suggests that these benefits cannot be achieved

by manipulation of dialysate sodium removal alone. These observations provide valuable information of the design of future randomized studies to establish the clinical role for low-sodium dialysis fluids.

Keywords: bioimpedance; blood pressure; deuterium; fluid status; thirst

Introduction

As in all types of renal replacement therapy, long-term maintenance of adequate fluid and electrolyte balance is of crucial importance for the survival of patients on peritoneal dialysis (PD). Observational data from large PD cohorts show that poor peritoneal salt and water removal is associated with decreased survival, independent of residual renal function, inflammation and cardiac biomarkers [1–3]. There is also evidence that when the residual renal function is low, many PD patients become fluid overloaded [4]. It is likely that volume overload aggravates not only hypertension, but also left ventricular hypertrophy, often present already at the start of PD. Salt and water overload may be the result of excess intake, especially when there is increased thirst, insufficient ultrafiltration (UF), which is the primary determinant of peritoneal sodium removal in PD [5,6], or a combination of these. The problem increases with time on treatment, not only as a consequence of loss of residual renal function, but also due to changes in peritoneal membrane function and the desire to avoid excessive glucose exposure [7].

In clinical practice, various strategies are currently used to manage fluid excess: dietary salt and fluid restriction, diuretics, anti-hypertensive drugs, icodextrin, addition of an extra day dwell, and, as a last option, PD combined with haemodialysis (HD), or switch to HD [8]. Another possibility would be to enhance sodium removal during PD. When using conventional PD fluid, where the $[Na^+] \sim 132$ mmol/l, sodium removal is predominantly due to convection and typically ~ 10 mmol Na^+ /dl of UF volume in 4 h. Increasing the glucose concentration to obtain more ultrafiltration will

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increase absolute sodium removal, but due to aquaporin-mediated fluid transport, an essential component of healthy UF, the relative proportion of sodium to fluid removal will decrease, especially in short exchanges [6]. This gap between sodium and fluid removal may in part explain the increased thirst reported by PD patients [9]. Theoretically, this problem could be improved by designing low-sodium dialysis solutions so that the sodium removal by diffusion would be increased, closing the gap between salt and water losses. However, no such solutions are presently commercially available.

The role of low-sodium dialysis solutions in the management of hypernatraemia due to the excessive aquaporin-mediated ultrafiltration associated with the short exchanges employed in intermittent PD patients was first described by Ahearn and Nolph [10]. More recently, Nakayama *et al.* [11] studied nine patients on CAPD with a dialysis solution containing Na⁺ 120 mmol/l in either 1.36% or 2.27% glucose (G), replacing all four exchanges. Compared to conventional solutions, sodium removal over a 4-week period increased from 38.5 ± 25.8 mmol/day to 85.0 ± 27.5 mmol daily with the low-sodium solutions. All patients showed a significant fall in blood pressure, and two patients dropped out because of hyponatraemia and overhydration. Nakayama *et al.* also reported the effect of ultra-low-sodium dialysis fluid ([Na⁺]: 98 mmol/l) during CAPD in two studies [12]. In one of these, the authors used ultra-low-sodium dialysis fluid in one exchange daily for 7 days in overhydrated CAPD patients. There was a significant increase in sodium removal and UF. Furthermore, mean arterial pressure (MAP) and body weight (BW) decreased significantly. Similarly, increased sodium removal with variable clinical effects has been demonstrated in a number of subsequent small-scale investigations of low-sodium solutions [13–16].

The design of low-sodium solutions needs careful consideration because sodium is osmotically active, so unless this is compensated there will be a fall in the ultrafiltration obtained that might be counter-productive. Computer simulations of sodium removal as a function of dialysate sodium concentration according to the three-pore model have recently been reviewed [17], and corroborated by clinical observations [6]. These simulations show how Na⁺ removal could be strikingly increased by reducing dialysis fluid Na⁺ concentration and the effect this would have on net UF could be predicted. We have used these simulations to design three possible low-sodium dialysates called 'DeltaSol-low/medium/high' intended to replace low (1.5%), medium (2.5%) and high (3.9%) standard G solutions for once-daily clinical use. Each would increase the total sodium removal by 20–30 mmol/day, but the low and high replacement fluids were compensated with an increase in the glucose to ensure maintained UF, whereas the medium replacement solution was not. The purpose of this study was to establish whether our predictions of sodium removal and UF were valid, establish their safety and investigate whether the use of these solutions had any effect on BP, thirst and volume status. In the event, we were unable to recruit sufficient patients to the regular use of the high G (3.9%) replacement solution to warrant statistical analysis, so the data presented here are for the low G (compensated, group A) and medium G (uncompensated, group B) solutions.

Table 1. The composition with respect to Na and glucose concentrations, respectively, for Deltasol and Gambrosol[®] trio

Solution	Group A (compensated)	Group B (uncompensated)
Sodium (mmol/l)		
Gambrosol [®] trio	133	132
Deltasol	115	102
Glucose (%)		
Gambrosol [®] trio	1.5	2.5
Deltasol	2.0	2.5

sated, group A) and medium G (uncompensated, group B) solutions.

Methods

Study design: population

This was an open-label, multicentre, prospective intervention study, performed at the University Hospitals of North Staffordshire (Stoke-on-Trent, UK), Lund and Malmö (Sweden). The study product (Deltasol-low/medium) was compared with conventional solution (Table 1) given as a single 3- to -6-h dwell per day in patients on either CAPD or APD, using either G or icodextrin in the long dwell. The patients had to be at least 18 years old, should not be participating in another interventional study, should not be pregnant or lactating, should have a technique and patient survival compatible with the study duration and had to be able to give their full consent. Patients were excluded from the study if they had a positive screen for HIV and/or hepatitis B and C, a 24-h urine volume exceeding 2000 ml, plasma sodium <125 mmol/l on two consecutive readings, low blood pressure (<110 mm systolic pressure) or postural blood pressure drop. Furthermore, patients who had a serious illness or injury or an episode of peritonitis within 1 month prior to the run-in period were excluded. Approval for the study was granted by the local research ethics committees as well as the competent authorities in United Kingdom and Sweden. All subjects provided written informed consent.

Study design: intervention

After giving informed consent the patients were stabilized on their normal regime for 1 month (T₁-T₀). Patients not usually using Gambrosol[®] trio were appropriately trained and used this for the study exchange during this period. The Deltasol study period lasted 2 months during which one bag of Gambrosol[®] trio, a glucose-lactate-containing, low-GDP fluid, per day was replaced by the Deltasol low-sodium solution. Patients were allocated into groups A (low-strength G, compensated) or B (medium-strength G, uncompensated) according to their baseline prescription as a major change in G prescription was considered a potential hazard. As with Gambrosol[®] trio, Deltasol is a three-compartment bag allowing the constitution of three different low-sodium solutions depending on which are mixed together prior to instillation. In group A, one bag of 1.5% G Gambrosol[®] trio was replaced with Deltasol constituted

from mixing compartments A and C ($G = 2.0\%$, $\text{Na}^+ = 115 \text{ mmol/l}$). In group B, 2.5% G Gambrosol® trio was replaced with Deltasol by mixing compartments B+C ($G = 2.5\%$, $\text{Na}^+ = 102 \text{ mmol/l}$); see Table 1.

Longitudinal measurements

Following the stabilization period (T_0) and at 1 (T_1) and 2 months (T_2) during the test period, the patients were assessed by BW, multifrequency bioelectrical impedance analysis (Xitron and Tanita instruments, respectively, see below). Total body water (TBW) was further determined by deuterium oxide (D_2O) dilution at T_0 and T_2 . Blood pressure (BP) was measured by 24-h ambulatory monitoring and as office readings. Blood, urine and dialysate samples were collected for measurements of electrolytes, glucose, dialysis adequacy, peritoneal membrane transport characteristics and residual renal function (calculated as the mean of urine clearance of urea and creatinine). In a subgroup of patients, thirst, mood and appetite were assessed using a specially designed palmtop utilizing an electronic appetite rating system (EARS) to record serial visual analogue scores (VAS) six times daily previously validated in PD patients [9]. Changes in anti-hypertensive medication were prohibited unless needed for patient safety; diuretics were not changed. Any change in hypertensive medication was noted. Dialysis prescription remained the same throughout the study period and identical to the one used for the stabilization period except for the test bag dwells.

Blood pressure was measured manually with a validated device at each visit; two measurements were performed after at least 5 min in sitting position with at least 2 min between the measurements. This was followed by one measurement in standing position to detect postural hypotension.

Twenty-four-hour ambulatory blood pressure readings were recorded using the same device in all three centres (SpaceLabs Medical, model 90217, Hertfordshire, UK). Measurements were performed hourly during the entire 24-h period and divided into day- and nighttime periods with the nighttime period from 2200 to 0600 h. At least 60% of the measurements during the entire day or a single period had to be properly measured or the measurement was repeated.

Body composition was determined using two multiple-frequency bioimpedance devices: the Hydra analyzer (Model 4200, Xitron Technologies, San Diego, CA, USA) and Tanita body composition scale (TBF 300 MA, Tanita UK Ltd, Yiewsley, Middlesex, UK). With the Xitron equipment, measurements were performed using the standard bipolar technique with electrodes placed on the dorsum of wrist and anterior aspect of the ankle. The patient was supine for at least 10 min before measurements without dialysis fluid present. During the measurements, values for TBW, extracellular fluid (ECF), intracellular fluid (ICF) and lean body mass (LBM) were determined by the instrument. The Tanita measurements were performed by having the patients standing on the scale with the feet in direct contact with the four measuring electrodes and the following results were recorded: BW, TBW, fat mass (FM), fat-free mass (FFM), and body mass index (BMI).

Sodium removal and UF volume measurements

Assessing UF volume and sodium removal took careful account of the problems associated with 'flush-before-fill' systems, which due to variable overfill and length of flush variably over-estimates the UF volume (50–200 ml, and sodium removal 5–20 mmol) [18,19]. To avoid these errors, bags were weighed before and after instillation and drainage, respectively. Flush time was recorded and appropriate corrections were made.

Analytical methods

All samples were analysed according to current hospital routines using a Beckman synchronic LX20 auto-analyzer (Beckman, Colter, Fullerton, CA, USA). Glucose was determined using the hexokinase method. Sodium was measured using flame photometry (Model 420 Flame Photometer, Sherwood Scientific Ltd, Cambridge, UK). C-reactive protein was analysed with an accredited high-sensitivity-rate turbidimetric method according to routine instructions at the Clinical Chemistry department at Malmö University Hospital, Malmö, Sweden. TBW was determined by the D_2O dilution. Patients drank 15 or 30 ml of D_2O , depending on BW, followed by at least 100 ml of tap water. Dialysate samples were taken before ingestion and after the following dwell (>6 h to ensure full equilibration). TBW was determined from the isotope dilution in equilibrated dialysate measured by flowing-afterglow mass spectrometry; following correction for instilled dialysate volume, this method allows determination of body water to within 1% on repeated measures [20].

Calculations

Computer simulations using the three-pore model were performed according to the principles given in Rippe *et al.* 2004 [17] for an average patient, setting $A_0/\Delta X$ at 23 000 cm and the mass transfer area coefficient (PS) for Na^+ at 6 ml/min.

Total sodium removal was calculated from drained Na^+ corrected for flushed Na^+ (mmol) minus infused Na^+ (mmol). Diffusive ('free') Na^+ removal is defined by

$$\text{Na}_{\text{Diff}} = \text{NaR} - \frac{\text{Na}_P + \text{Na}_D}{2} \cdot S \cdot \text{UFV}, \quad (1)$$

where NaR is the total Na^+ removal (in mmol), Na_P is plasma Na^+ corrected for plasma water (in mmol/l), Na_D is (mean) dialysate Na^+ (in mmol/l), S is the fraction of total UF volume that normally occurs through small pores (0.6) according to the three-pore model and UFV is the total UF volume (in l) during the period of observation (corrected for flush volume).

Statistical power and analyses

The study was powered to detect significant increases in free-sodium removal in the test exchanges (primary endpoint, T_0 compared to T_1). A previous pilot study including seven patients [16] showed a standard deviation (SD) for sodium removal per exchange of 12.9 mmol. The expected

Table 2. Demographics and treatment modality of all recruited patients and those completing the study in groups A and B

	All recruited patients (<i>n</i> = 40)	Group A (<i>n</i> = 10)	Group B (<i>n</i> = 15)
Age (range)	69 (19.6–80.7)	54	60
Gender (M/F)	31/9	8/2	13/2
Height (m)	1.71 (1.43–2.00)	1.71	1.71
APD/CAPD	11/29	3/7	3/12
Icodextrin		4 (40%)	6 (40%)
Average number of 2.5% glucose exchanges per day	1.4	1.3	2.21*
Time on PD (months)	28.5	41.9	19.5

**P* = 0.012 between groups A and B.

free sodium removal determined from computer simulations predicted an increase of free-sodium removal for the low-, medium- and high-G concentrations of 23.2, 50.4 and 29.2 mmol, respectively. With 80% statistical power using a two-sided paired *t*-test, significance *P* < 0.05, increased free-sodium removal would be detected with the following sample sizes: low G, *n* = 8, medium G, *n* = 4 and high G *n* = 6. We failed to recruit sufficient patients to the high group, so data were not further analysed. We deliberately over-recruited to the other groups in order to explore the potential effects on the secondary clinical measures so that future randomized studies could be adequately designed.

Data were analysed in an intention to treat basis. Values are given as mean ± 1 SD, except in figures of repeated measures (SEM). Data from 24-h collection showed considerable variability and are expressed as median values and analysed using both parametric and non-parametric statistics. Comparisons within groups were performed using paired *t*-test and between the groups using unpaired *t*-test. Analysis of the EARS data was performed using a three-way mixed ANOVA to compare the therapy groups. The two repeated factors were 'visit' with three levels (*T*₀, *T*₁, *T*₂) and 'time' with six levels (measurements taken every 2 h during the day, a.m., +2, +4, +6, +8, +10 h). The between-subject (independent) factor was therapy group with two levels (A, B). Bonferroni comparisons were used when appropriate.

Results

Demography, drop-out rate and exclusion

The demographic characteristics of the patients recruited to the study and those in groups A and B who completed the study are shown in Table 2. They represented a typical dialysis population: 30% were diabetic, 62.5% had cardiovascular disease and 45% hyperlipidaemia. Underlying diagnoses were diabetic nephropathy (30%), glomerulonephritis (25%), adult polycystic kidney disease (10%), interstitial/chronic pyelonephritis (10%), nephrosclerosis (7.5%) and others/unknown (17.5%). Of the 40 patients initially recruited, 11 left the study, 6 before using the study product (3 due to peritonitis, 1 wrongly included, 1 due to hypotension and 1 due to consent withdrawal). Two patients left the study within 1 month on the study product: 1 due to con-

Table 3. Baseline parameters for patients in groups A and B

Group	A (<i>n</i> = 10)	B (<i>n</i> = 15)
Systolic office BP (mmHg)	137 ± 18.6	142.3 ± 23.5
Diastolic office BP (mmHg)	87.7 ± 5.9	82.4 ± 13.7
Body weight (kg)	74.7 ± 3.1	82.4 ± 3.4
Body mass index (kg/m ²)	25.7 ± 2.7	28.0 ± 4.4
Solute transport (D/P _{creat} , h)	0.78 ± 0.1	0.77 ± 0.11
24-h urine volume (ml)	738 ± 612	642 ± 459
24-h urine Na ⁺ loss (mmol)	48.7 ± 38	33.1 ± 35
TBW _{Tanita} (l)	40.3 ± 6.6	44.3 ± 6.05
TBW _{Deuterium} (l)	44.6 ± 7.9	47.2 ± 7.5
ECF:ICF ratio _{Xitron}	0.92 ± 0.17	0.88 ± 0.15
Thirst _{EARS} (mean of baseline score profiles)	46.5 ± 18.1	36.8 ± 18.5
Hunger _{EARS} (mean of baseline score profiles)	31.4 ± 15.9	30.6 ± 21.7
Mood _{EARS} (mean of baseline score profiles)	60.65 ± 17.5	61.6 ± 17.1

Figures denote ±1 SD.

There were no significant differences at baseline in any of the parameters in this table.

sent withdrawal (group A) and 1 due to peritonitis (group B). Three patients left the study after more than 1 month on the study product: two due to transplantation and one consent withdrawal (group B). Twenty-nine patients completed the entire study with four on the high-G product who were withdrawn from the analysis. The numbers of patients at baseline and at each time point by group are shown in Tables 3 and 4. No patient left the study due to adverse effects attributable to the study product.

Changes in achieved UF and sodium removal and comparisons with computer simulated data

At baseline, the total daily peritoneal UF was 355 ± 690 ml for group A and 855 ± 411 ml in group B (*P* = 0.002), Figure 1. As predicted, there was a significant decrease in UF volume after 1 month in group B (*P* = 0.034), due to a fall in UF with the test exchange that was not seen in group A. There were no significant changes in daily urine volume or urinary sodium losses over the observation period and these were not different between groups (Figure 2 and Table 4). The simulated and achieved total net sodium removal (NaR) for the test exchanges is shown in Figure 3. In group A, the achieved NaR for the test dwell was close to the values predicted by the three-pore model for the stabilization period (−0.10 ± 11.1 mmol/dwell versus the three-pore model simulated value of 5 mmol/dwell), although the UF was slightly negative (−69 ml). Deltasol markedly improved the NaR that reached 32.4 ± 50.1 mmol/dwell, *P* = 0.0021, in close agreement with the three-pore model simulated value (32 mmol/dwell). In group B, the achieved sodium removal for Gambrosol[®] trio was lower than the predicted value (10.6 ± 27.6 mmol/dwell versus a simulated NaR of 37 mmol/dwell), due to a lower than predicted UF volume (113 ± 24.2 ml). For Deltasol in group B, the increase in NaR was excellent, being 62.5 ± 26.3 mmol/dwell, *P* < 0.001, compared to 53 mmol/dwell in the simulation. The improvement in sodium removal by Deltasol was nearly entirely (~90%) due to diffusive

Table 4. Longitudinal changes in dialysate and urinary sodium losses, residual renal clearance and plasma sodium

	Baseline (T ₀)	1 month (T ₁)	2 months (T ₂)
Group A (<i>n</i>)	10	10	10
Median (inter-quartile range) 24-h dialysate Na ⁺ removal	37.3 (-3.6–74.6)	53.1* (28.8–108.7)	53.8** (18.4–102.8)
Median 24-h urinary Na ⁺ removal	27.7 (0–86)	28.4 (0–76)	18.0 (0–99)
Residual creatinine clearance (l/week)	11.3 ± 7.1	11.1 ± 6.2	11.6 ± 5.7
Plasma sodium (mmol/l)	137.6 ± 1.9	137.6 ± 3.3	137.2 ± 2.4
Group B (<i>n</i>)	15	15	15
Median (inter-quartile range) 24-h dialysate Na ⁺ removal	52.7 (24.1–99.6)	59.9 (51.9–84.7)	73.5 [‡] (58.4–122.8)
Median 24-h urinary Na ⁺ removal	25.8 (0–94)	24.2 (0–121)	28.7 (0–117)
Residual creatinine clearance (l/week)	7.4 ± 5.1	5.9 ± 5.3	8.0 ± 6.2
Plasma sodium (mmol/l)	137.2 ± 3	136.2 ± 3.5	136.3 ± 4.1

P* = 0.048, *P* = 0.06, [‡]*P* < 0.02 compared to baseline.

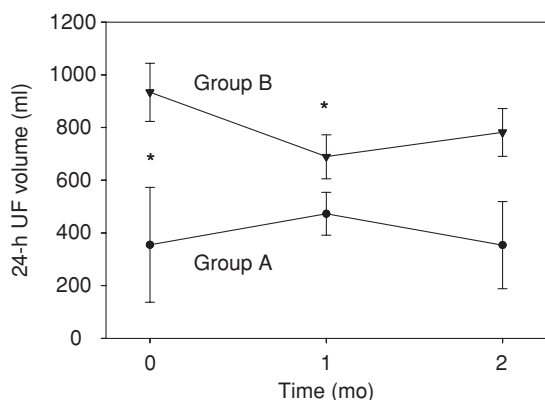


Fig. 1. Twenty-four-hour peritoneal UF at baseline (0 months, T₀) and during Deltasol treatment (1 and 2 months, T₁ and T₂) for groups A (●) and B (▼). The two groups differed significantly with respect to UF volumes at baseline and there were significant differences between baseline and 1 month in the B group (**P* < 0.05).

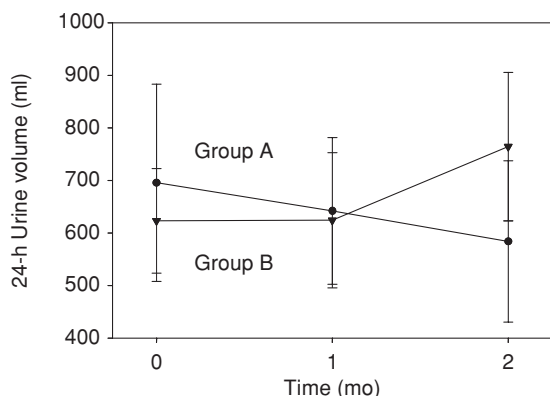


Fig. 2. Urine volumes during baseline (0 months) and during Deltasol treatment (1 and 2 months) for groups A (●) and B (▼). There were no significant differences in between groups or as a function of time.

sodium removal for group A and exclusively (~98%) due to diffusive sodium removal for group B. These increases in sodium removal from the test exchanges translated into increases in the total daily peritoneal sodium loss (see Table 4). For group A, the mean and median increases in 24-h peritoneal sodium removal were 41.9 (*P* = 0.07) and 28.4 mmol (*P* = 0.048) at T₁ and 21.1 (*P* = 0.049) and

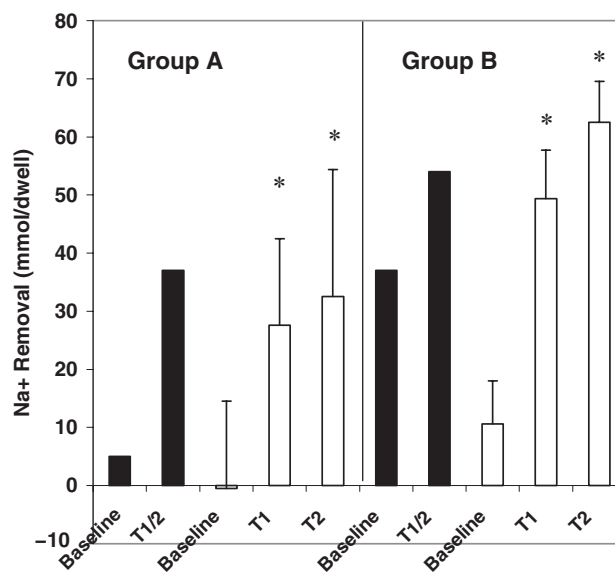


Fig. 3. Simulated (black bars) and measured (open bars) sodium removal (mmol/dwell) for baseline control fluid and low-sodium solutions at T₁ and T₂. For both groups, there was a highly significant increase in measured sodium removal between baseline, 1 and 2 months (**P* ≤ 0.0002).

14.3 (*P* = 0.06) at T₂, respectively. In group B, mean and median increases were 13.3 (*P* = 0.27) and 21 mmol (*P* = 0.15) at T₁ and 29.5 (*P* = 0.023) and 32.4 (*P* = 0.016) at T₂, respectively.

Blood pressure and anti-hypertensive medication

At baseline, there were no differences between groups A and B in clinic or 24-h blood pressure measurements (*P* = 0.435). In group A, the nocturnal mean arterial ambulatory blood pressure (MAP) fell significantly from T₀ to T₂ from 93.1 ± 10.6 mmHg to 85.1 ± 10.2 mmHg (*n* = 9, *P* = 0.045) whereas this was not affected in group B [95.4 ± 9.4 mmHg at T₀ versus 95.1 ± 10.7 mmHg at T₂ (*n* = 14, *P* = 0.52)] (see Figure 4). Between-group differences in nocturnal MAP T₁ and T₂ became significantly different (*P* = 0.019, *P* = 0.006, respectively). These differences in group A were due to a fall in both nocturnal systolic (125.4 ± 12.7 mmHg to 113.9 ± 16.4 mmHg, *n* = 9, *P* = 0.025) and diastolic blood

pressure (77.0 ± 11.5 mmHg to 70.7 ± 8.5 mmHg, $n = 9$, $P = 0.078$). There was a trend towards a reduction in daytime ambulatory systolic pressure ($P = 0.07$) and office MAP ($P = 0.068$) in group A that was not observed in group B. A total of 76.5% of the patients were taking anti-hypertensive medication at the start of the study. Six patients experienced nine episodes of hypotension necessitating a reduction in their BP medication but this was not statistically different between groups.

Thirst, appetite and mood evaluation

Analysis of the EARS was undertaken in six patients in group A and nine from group B. Throughout the study, group A patients consistently reported greater thirst than Group B that was not statistically significant. There was a significant effect of visit on thirst [$F(2,20) = 4.86$, $P < 0.05$], with both groups reporting a reduction between T₁ and T₂ ($P < 0.05$). This effect was larger in group A (see Figure 5). There was an effect of both visit [$F(2,20) = 4.76$, $P < 0.05$] and time of day [$F(5,50) = 2.98$, $P < 0.05$] on hunger, with a significant increase occurring in both groups

at T₁ ($P < 0.05$), but no between-group differences. There were no effects of group, visit or time of day on mood.

Changes in body composition

The longitudinal changes in body composition by group are summarized in Table 5. In group A, all the measures to varying degrees demonstrated a reduction in the body water content; the multifrequency bioimpedance (Xitron) indicated that this change was mostly due to a reduction in the ECF volume. In contrast, there were no significant changes in the fluid status of patients in group B, in which, if anything, there were increases in weight and the ECF:ICF ratio. We also examined the internal consistency of the body composition data. For the whole population, there were significant positive correlations between the change in TBW_D from baseline and the changes in weight ($R = 0.6$, $P = 0.002$), TBW_T ($R = 0.55$, $P = 0.004$) and ECF_X ($R = 0.43$, $P = 0.04$), and the changes in TBW_T and ECF_X, (month 1: $R = 0.63$, $P = 0.001$; month 2: $R = 0.85$, $P < 0.001$).

Residual renal function, serum albumin, C-reactive protein and safety parameters

No significant changes were obtained in any of these measurements. Plasma and urinary sodium and residual function (see Table 4) and osmolality remained stable throughout the study in all patients. Serum albumin was on average 34.8 ± 3.8 g/l at T₀ and 34.7 ± 4.3 g/l at T₂. C-reactive protein was 4.67 ± 0.59 mg/l at T₀ and 6.01 ± 1.25 mg/l at T₂. There were no significant within-group differences observed.

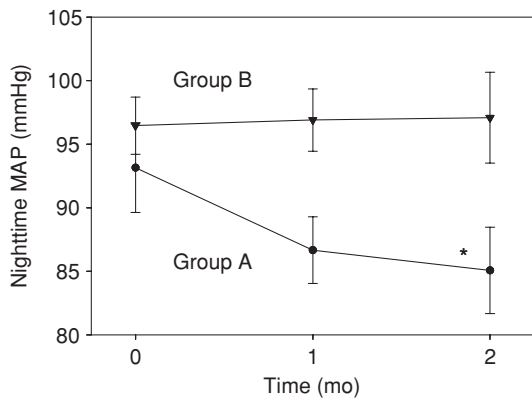


Fig. 4. Mean arterial pressure (MAP) during nighttime during baseline (0 months) and during Deltasol treatment (1 and 2 months) for groups A (●) and B (▼) (* $P < 0.05$).

Discussion

This study used computer simulations to design and then clinically test two novel low-sodium dialysis solutions. There was a strong agreement between the simulations

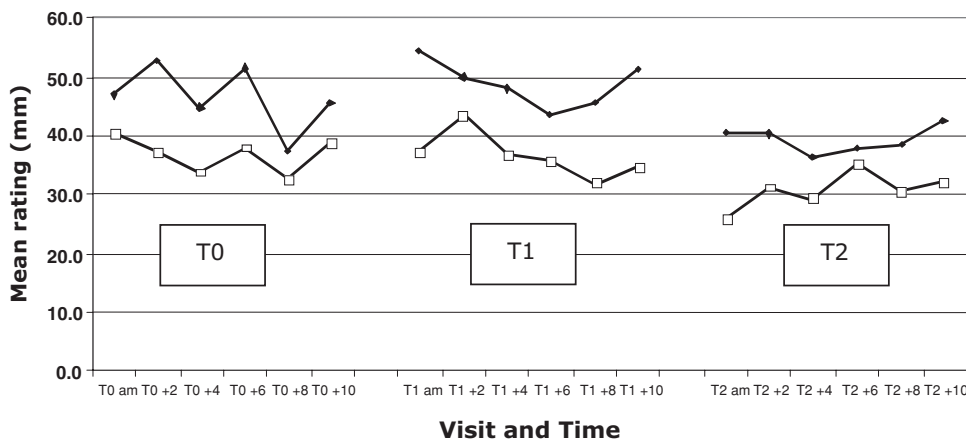


Fig. 5. Daytime profiles of thirst measured in every 2 h at baseline (T₀), 1 (T₁) and 2 (T₂) months in groups A (◆) and B (□). There was a significant decrease in subjective sensations of thirst between T₁ and T₂ in both groups (three-way mixed ANOVA), more marked in group A.

Table 5. Changes in body composition—mean difference ($\pm 95\%$ CI)

	Month 1	<i>P</i> -value	Month 2	<i>P</i> -value
Group A (<i>n</i>)	10		10	
Weight (kg)	-0.27 (+0.68, -1.2)	0.53	-0.47 (+0.32, -1.3)	0.21
TBW (Tanita) (L)	-0.81 (-0.04, -1.57)	0.04	-0.97 (-0.5, -1.4)	0.001
TBW (Xitron) (L)	-0.89 (-0.04, -1.7)	0.04	-0.04 (+0.71, -1.5)	0.43
TBW (Deuterium) (L)	-	-	-2.3 (-0.34, -4.4)	0.049
ECF (Xitron)	-2.5 (+1.2, -6.25)	0.16	-0.61 (-0.1, -1.12)	0.025
ECF/ICF ratio (Xitron)	-0.035 (+0.02, -0.09)	0.16	-0.036 (0.00, 0.07)	0.049
Group B (<i>n</i>)	17		15	
Weight (kg)	-0.02 (+0.72, -0.75)	0.96	+0.88 (+1.7, +0.5)	0.04
TBW (Tanita)	-0.18 (+0.96, -1.3)	0.73	+0.33 (+1.4, 0.79)	0.54
TBW (Xitron)	-0.51 (+0.78, -1.2)	0.53	-0.49 (+1.5, -2.4)	0.61
TBW (D)	-	-	-0.087 (+1.5, -1.6)	0.91
ECF (Xitron)	-0.107 (+0.43, -0.65)	0.68	+0.49 (+0.77, -0.67)	0.89
ECF/ICF ratio (Xitron)	+0.02 (+0.05, -0.01)	0.23	+0.02 (+0.07, -0.03)	0.32

and observed increase in sodium removal during test dwells that was predominantly due to an increase in the diffusive component. This was associated with an increase in the total daily peritoneal sodium removal without significantly affecting urinary sodium losses, despite the marked between-patient heterogeneity in daily sodium removal and the associated increase in error when determining losses from multiple exchanges. There appeared to be clear differences in the observed effects on the secondary clinical endpoints according to whether the glucose concentration was increased in order to maintain ultrafiltration. In the compensated group, there were reductions in blood pressure, ECF and more marked decrease in thirst; no changes in the clinical measures were observed in the uncompensated group. These observations have implications for our understanding of membrane physiology, the role of sodium in controlling blood pressure in PD patients and for the design of future randomized controlled trials to determine the clinical role of low-sodium solutions.

The three-pore model remains the most powerful descriptor and predictor of peritoneal fluid and solute transport. In this study, it was used to predict sodium and fluid transport for a typical PD patient, setting the membrane area parameter ($A_0/\Delta X$) at 23 000 cm, equivalent to a D/P creatinine ratio during a 4-h peritoneal equilibration test of ~ 0.72 . The PS value for sodium was reduced (6 ml/min) to take account of previous observations that suggest it is lower than would be expected from its molecular weight [17]. When comparing the simulations to the observed sodium removal and ultrafiltration, it is apparent that the predictions of the former were very close; there was a tendency for the model to over-predict ultrafiltration, although the expected fall in ultrafiltration observed in the non-compensated group B was seen. This relative accuracy in predicting sodium removal, in particular the diffusive component, as compared to ultrafiltration was also seen in a comprehensive testing of the model in over 1800 exchanges [6], and would thus justify the selection of the PS value for sodium.

The actual daily increase in sodium removal observed (~ 30 mmol), regardless of the solution used, is likely to be clinically significant. There is some confusion in the literature as to the typical daily sodium removal in PD patients. This is mainly due to variability in the measurement of net

ultrafiltration in CAPD patients due to the presence of over-fill of dialysate in each bag needed to take into account the flush before fill procedure and to a lesser extent evaporation [18,19]. This differs by manufacturer and may account for 50–200 ml per exchange, 200–800 ml per day in a typical CAPD patient, equivalent to 20–80 mmol of sodium. The discrepancy in measured sodium intake (~ 80 mmol/day) and removal (180 mmol/day), initially reported by Asghar *et al.* can largely be explained by this error [21, 22]. The rather high average daily sodium losses reported by Ates (180 mmol/day) are also associated with relatively high reported ultrafiltration; although this might reflect a high daily salt intake (> 11 g/day for the peritoneal component alone), the relationship between fluid removal and mortality reported is much different to more recent studies, where increased mortality is seen at much lower levels of ultrafiltration (400–750 ml/day). In one of the centres in this study (UHNS), regular audit of total daily sodium removal indicated average losses of 70–80 mmol/day ($> 50\%$ from urine), although there is a very wide variation. In this context, an increase in peritoneal losses of 30 mmol per day is likely to be clinically significant. Although there is undoubtedly a role for sensible salt restriction in PD patients, it can be seen that even a relatively strict low-sodium diet of 5 g a day would not be sufficient for some, especially those with an increased mortality associated with low ultrafiltration in whom peritoneal losses can be estimated at ~ 40 –55 mmol/day (~ 3 –4 g) as seen in the EAPOS and ADEMEX studies [1,2].

The clinical observations in this study appeared to be different according to the type of low-sodium solution used. The combination of effects seen with the compensated solution that included lower blood pressure, especially for the nocturnal readings, changes in fluid status in keeping with a reduction in extracellular water and a greater reduction in thirst independent of appetite and mood strongly suggest that benefits can be obtained from increasing the sodium removal whilst maintaining ultrafiltration in PD patients. In contrast, the lack of any effects in the uncompensated group implies that these benefits cannot be achieved by manipulation of sodium removal alone. This is a potentially important clinical message for the management of PD patients but must be interpreted cautiously. This was not a

randomized study and patients were allocated to groups A and B on the basis of their current treatment regimes and therefore to some extent were pre-selected. Most of their baseline characteristics are similar (Tables 2 and 3), except for the greater peritoneal ultrafiltration in group B reflecting their higher glucose prescription. Interestingly, this did not translate into significantly higher sodium removal at baseline, possibly due to sodium sieving leading to a greater gap between sodium removal and ultrafiltration. Patients in group A had spent longer on treatment but were not proportionately more likely to be on APD or be using icodextrin. Although these differences were not statistically significant, it remains possible that poorly understood or unmeasured selection factors such as dietary salt intake that was not measured independently in this study contributed to the different clinical effects seen with the two solutions tested. The lack of effect in group B might have been because the incremental increase in the peritoneal sodium removal was less in these patients (35% versus 55% in group A) and thus not sufficient to cause a change. In the study of Nakayama [12], sodium removal was higher than that achieved in the present study, causing a marked influence on both body fluid status and BP, even in the absence of glucose compensation of the low-sodium solutions. It is conceivable that an additional low-sodium exchange in the present study would have caused more clear-cut effects on body fluid status and BP, even at the price of reduced UF (group B), than those achieved with only one daily low-sodium exchange.

The rationale behind designing a solution that was not compensated was that over time this would lead to decreased thirst and thus a lower fluid intake that would more than make up for the expected loss in ultrafiltration. The level of thirst measured at baseline was similar to that reported by Wright using the same methodology [9] and again supports the impression that PD patients experience increased thirst; if this were as a result of sodium sieving then low-sodium solutions by increasing diffusive sodium removal will close the gap between salt and water removal and thus be expected to be of benefit. Both groups experienced a reduction in thirst, which appeared more marked in group A, possibly because they had a higher mean score at baseline. It is of interest that the effect on thirst did not become significant until the second month of treatment raising the possibility that the lack of effect seen in group B was also due to an insufficiently long observation period; previous studies have found that the maximal effect of salt restriction may not be seen for 6 months in haemodialysis patients [23].

Both the solutions investigated in this study appeared to be safe. Only one patient had to stop the study due to hypotension and five patients had to reduce their BP medication. No patients developed hyponatraemia that probably reflects the decision to use the low-sodium solution for just one of the exchanges during the 24-h period. There was no significant fall in residual renal function in either group suggesting that the impact on blood pressure and fluid status is rather gradual. However, follow-up was just for 2 months and clearly, longer studies are required to confirm safety.

In conclusion, the present study indicates that it is possible to improve BP control, fluid status and thirst in PD patients with the use of low-sodium fluids, as long as the osmolality is preserved to maintain UF volume. Net sodium

diffusive removal per given glucose load was clearly increased by low-sodium solutions, even moderately exceeding the predictions made by computer modelling such that net sodium removal using a 2.0% solution exceeded that removed by a conventional 2.5% dialysate. Finally, over the observation period, a moderate increase in daily sodium removal was safe with no effects on plasma sodium, residual renal function or inflammatory markers. These observations form the basis for future larger randomized controlled trials to establish the clinical value of low-sodium dialysate.

Acknowledgements. This study was supported by Gambro Lundia AB, Sweden and also in part by funding from the Swedish Research Council (grant no. 08285). The support and assistance from the following persons are gratefully acknowledged: Lena Krützén, University Hospital of Lund, Sweden; Ann-Britt Grahed, Malmö University Hospital, Malmö, Sweden; Sandra Garner and Tracey Connor, University Hospital of North Staffordshire, Stoke-on-Trent, United Kingdom and Madeleine Holmquist, Clinical Affairs, Gambro Lundia AB, Sweden.

Conflict of interest statement. O.C., I.L. and A.W. are employees of Gambro, Lund, Sweden. S.D. has received lecture and consultancy fees in connection with the publication. None of the other authors report a conflict of interest.

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Received for publication: 2.9.08

Accepted in revised form: 5.11.08

Nephrol Dial Transplant (2009) 24: 1617–1625

doi: 10.1093/ndt/gfn673

Advance Access publication 9 December 2008

Short-term effects of bicarbonate/lactate-buffered and conventional lactate-buffered dialysis solutions on peritoneal ultrafiltration: a comparative crossover study

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Abstract

Background. This study was designed to compare the effects of a conventional lactate-based peritoneal dialysis (PD) solution (D) and a new biocompatible bicarbonate/lactate-based solution with a low concentration of glucose degradation products (P) on peritoneal ultrafiltration (UF) and other peritoneal membrane indices.

Methods. Twenty-six stable, prevalent PD patients were enrolled in this prospective study. They sequentially underwent 3 months of therapy with the D solution and 3 months with the P solution in a randomized order. Daily, overnight and 4-h UF on PET were measured and other peritoneal membrane indices were also assessed using PET with 2.27% glucose solution.

Results. Twenty-one patients successfully completed the study. The mean daily peritoneal UF with D was 1324 ± 602 ml and 881 ± 633 ml with P ($P < 0.001$) and this

lower daily UF of 443 ml (95% CI 275–610 ml) with P was associated with a similarly lower daily total fluid removal of 394 ml (95% CI 210–577 ml), as urine volume did not differ between D and P. The decrement in UF with the P solution was reversible. There were no significant differences in other peritoneal membrane indices (D/P creatinine, D/D₀ glucose, 4-h UF at PET, weekly creatinine clearance, weekly urea Kt/V) or blood pressure and body weight between the solutions whereas calculated peritoneal fluid absorption rate was significantly higher with the P than with the D solution.

Conclusion. This study shows that the daily UF with the P solution may be lower than with the D solution. The mechanism for this short-term and reversible effect that conceivably reflects differences in biocompatibility is not clear although our results implicate that the peritoneal fluid absorption rate may differ between the two solutions.

Keywords: bicarbonate/lactate buffered solution; peritoneal dialysis; PET; prospective study; ultrafiltration

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