Icodextrin Improves the Fluid Status of Peritoneal Dialysis Patients: Results of a Double-Blind Randomized Controlled Trial

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Abstract. Worsening fluid balance results in reduced technique and patient survival in peritoneal dialysis. Under these conditions, the glucose polymer icodextrin is known to enhance ultrafiltration in the long dwell. A multicenter, randomized, double-blind, controlled trial was undertaken to compare icodextrin *versus* 2.27% glucose to establish whether icodextrin improves fluid status. Fifty patients with urine output <750 ml/d, high solute transport, and either treated hypertension or untreated BP >140/90 mmHg, or a requirement for the equivalent of all 2.27% glucose exchanges, were randomized 1:1 and evaluated at 1, 3, and 6 mo. Members of the icodextrin group lost weight, whereas the control group gained weight. Similar differences in total body water were observed, largely explained by reduced extracellular fluid volume in those receiving icodextrin, who also achieved better ultrafiltration and total sodium losses at 3 mo ($P < 0.05$) and had better maintenance of urine volume at 6 mo ($P = 0.039$). In patients fulfilling the study's inclusion criteria, the use of icodextrin, when compared with 2.27% glucose, in the long exchange improves fluid removal and status in peritoneal dialysis. This effect is apparent within 1 mo of commencement and was sustained for 6 mo without harmful effects on residual renal function.

The widely applied emphasis on small solute clearance targets has overshadowed the attention that fluid status and BP control deserve in the clinical management of dialysis patients. Cardiovascular disease is the major cause of death in dialysis patients, accounting for well over 40% of deaths (1,2). Left ventricular hypertrophy (LVH) is the most common abnormal echocardiographic finding in dialysis patients (3), and its presence is an important independent determinant of survival in these patients (4). Hypertension has been suggested to be one of the strongest risk factors for LVH in dialysis patients, and its high prevalence suggests that fluid removal is inadequate in peritoneal dialysis (PD) (5) as well as in hemodialysis patients (6). Fluid overload itself is also believed to be a causative factor in the development of LVH–left ventricular dysfunction, independent of BP. In a recent multicenter PD study, increased extracellular fluid volume (ECF) was significantly correlated to left ventricular end diastolic diameter as a parameter of eccentric hypertrophy (7).

Fluid overload may be the result of excess fluid intake, insufficient ultrafiltration, or a combination of these. As residual renal function declines, osmotically driven peritoneal ultrafiltration becomes critical, and ultrafiltration failure remains an important cause of technique failure (8). The incidence of this complication increases with time on treatment (9), in part because of loss of residual renal function but also because of acquired changes in peritoneal membrane function (10,11). A high rate of peritoneal transport is the most common explanation for poor ultrafiltration, caused by the rapid absorption of glucose and consequent loss of the osmotic gradient. Patients with high transport characteristics often have to use hypertonic glucose exchanges in their long-dwell period to prevent net reabsorption of fluid. This use of hypertonic glucose solutions may lead to increased body fat (12) and adverse effects, both locally in the peritoneal membrane (13), as well as systematically through metabolic abnormalities such as hyperlipidemia and hyperinsulinemia.

Since the early 1990s, icodextrin, a glucose polymer derived from starch, has been used as an alternative osmotic agent to glucose for the long overnight dwell in continuous ambulatory

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peritoneal dialysis (CAPD) or the long daytime dwell in automated peritoneal dialysis (APD), enhancing fluid removal while avoiding use of hypertonic glucose for long periods of time. It is of particular value in patients with high solute transport (14), and several randomized trials have demonstrated better ultrafiltration compared with 2.27% glucose (15–17). A recent open study in APD patients, where icodextrin was used in the daytime dwell compared with 2.27% glucose, demonstrated clinically important changes in fluid content and BP control (18). In this study, we describe the results of a randomized, double-product, blinded, controlled trial of icodextrin *versus* 2.27% glucose in the long exchange designed to evaluate its effects on fluid status, body composition, BP, and cardiovascular risk factors.

Materials and Methods

Study Design

The study had a prospective, multicenter, controlled, randomized, double-blind design. The goal was to recruit 50 patients from centers in Germany, Sweden, and the United Kingdom, with the aim of 40 patients completing at least 3 mo of the study. After giving consent to participate, patients not receiving 1.5 to 2.5 L of 2.27% glucose (Dianeal; Baxter) for the long dwell entered a 1-mo screening period, during which the long-dwell solution was 2.27% glucose (Dianeal). Those already receiving 2.27% glucose for the long dwell entered a 2-wk baseline period, during which the long-dwell prescription was unchanged.

At the end of the baseline period, patients were randomized 1:1, with stratification for center/country, dialysis modality (CAPD or APD), and presence of cardiovascular disease, defined as previous myocardial infarction or cerebral stroke, angina pectoris, or LVH. Randomization was to either 7.5% icodextrin or 2.27% glucose for the long-dwell exchange, with the length and fill volume of the long exchange during the treatment phase being the same as that in the baseline period. After randomization, further study assessment visits were at 1, 3, and 6 mo, with statistical analysis of variables primarily based on change of value from baseline after 3 mo of treatment. During the treatment period, patients were assessed by body weight, multifrequency bioelectrical impedance analysis, and deuterium oxide dilution (3 and 6 mo only). In addition, BP was assessed by 24-h ambulatory monitoring. Blood, urine, and dialysate samples were collected for assessment of electrolytes, high-resolution C-reactive protein, total cholesterol and triglycerides, dialysis adequacy, peritoneal membrane transport characteristics, and residual renal function.

After commencement of the study product, patient medications, including antihypertensive drugs, could be altered according to clinical need, other than changes in diuretics. Changes could also be made as necessary to short-dwell fill volume glucose concentrations.

Inclusion and Exclusion Criteria

The principal inclusion criteria for the study were (*1*) either untreated hypertension (BP $>$ 140/90 mmHg), treated hypertension, or a dialysis prescription with a daily average glucose concentration of 2.27% or greater, (*b*) high or high-average peritoneal solute transport (corrected 4 h D/P creatinine ratio $\geq$0.65, and (*3*) urine output $\leq$750 ml/d. Patients had to tolerate a dialysis regime that included a long dwell of $\geq$6 h with 2.27% glucose with fill volume of 1.5 to 2.5 L, as demonstrated in the screening period. All patients were over 18 yr of age, were able to give written informed consent, and had to have been on PD for at least 90 d.

Patients were excluded if they had received icodextrin in the 30 d before randomization, used other nonglucose solutions in the 30 d before randomization, had been treated for peritonitis in the 30 d before randomization, were considered noncompliant, or were considered to have hypertension despite being clinically volume depleted (although in practical terms, while this was in the protocol, it did not lead to exclusions), used a 1.36% glucose concentration for all exchanges, were allergic to starch, had a glycogen storage disease, had a life expectancy less than 12 mo, had a serious illness or injury in the 30 d before randomization that would invalidate study entry, were participating in another interventional study, were pregnant or lactating, or had a significant psychiatric disorder that would interfere with their ability to provide informed consent and/or comply with the study procedures.

The identity of the long-dwell solution was blinded to patients, investigators, and clinical monitors; specially created packaging was used to conceal which solution was which. The treatment codes were supplied to study sites in sealed envelopes, which were checked at the end of the study. Approval for the study was granted by the local research ethics committees of all centers, and all subjects provided written informed consent.

Statistical Analyses

Analysis of outcome variables was by ANCOVA for changes from baseline with the patient's baseline value as covariate. Analysis of baseline variables for differences between treatment groups was by ANOVA for continuous variables, with χ^2 test or Fisher's exact test for categorical variables.

Changes with time were analyzed in two ways: a between-group comparison of the change from baseline by unpaired *t* tests (or Mann-Whitney *U* test for nonparametric variables), and a within-group comparison of change from baseline using paired statistics allowing for repeated measures. The intent-to-treat analysis is presented, although an analysis of assessable patients was also undertaken. The assessable population was the subset of intent-to-treat group who completed the baseline period and at least 3 mo of the treatment period, with exclusions of patients who were off the investigational product for a cumulative time of more than 30 d, did not receive PD for more than 30 cumulative days, changed diuretic medication (except withdrawal of diuretics in those with urine output $<$300 ml/24 h), and those changing dialysis category. The outcome of these analyses did not differ.

The sample size was based on previous experience of trials comparing icodextrin with 2.27% glucose. These calculations indicated that with a type 1 error of 0.05 and power of 0.80, a minimum of 19 patients per treatment group would have to complete the study to detect a treatment weight difference of 1.6 kg or greater change from baseline.

Clinical and Laboratory Procedures

The simplified Standardized Permeability Analysis test, which used a 3.86% glucose dwell, was used to assess peritoneal membrane transport characteristics, with collection of dialysate samples at 0, 1, 2, and 4 h and a plasma sample within 1 h. Twenty-four-hour ambulatory BP was measured with a Spacelabs 90207 monitor; readings were performed at hourly intervals. Mean 24-h systolic and diastolic BP were determined, as were mean systolic and diastolic BP for night (23:00 to 07:00 h) and day (07:00 to 23:00 h).

Multiple-frequency bioelectrical impedance analysis was performed with the Hydra analyzer (Xitron Technologies, San Diego, CA). Measurements were performed by means of the standard tet-

rapolar technique, with electrodes placed on the dorsum of wrist and anterior aspect of the ankle on the left side of the body. The patient was supine for at least 10 min before measurements with dialysis fluid present were performed. Three consecutive measurements were performed over a 2-min period, with recording of values for total body water (TBW), ECF, and intracellular fluid volume, which are determined by the analyzer by a bioelectrical impedance spectroscopy method (19). The coefficient of variation, determined from readings taken a month apart in the screening phase of the study, was 5.3% for TBW and 5.8% for ECF.

TBW was also estimated by deuterium oxide dilution. Patients drank 4 g of deuterium oxide (^2H_2O) with 100 ml of tap water. Blood samples were drawn before ingestion and after 2 and 4 h. TBW was determined from isotope enrichment in plasma via isotope ratio mass spectrometry (20), with a coefficient of variation of 5.4% in the control limb of the study between baseline and 3 mo.

Results

Demographics

Of 57 patients screened for inclusion in the study, 50 (88%) met the criteria for randomization. All were using lactate-buffered glucose-based dialysis solutions (Dianeal). Exclusions were the result of lower-than-required solute transport in four patients and excess residual urine volume in three. There was some inequality in the number of patients randomized to each group as a result of the block randomization, but the baseline characteristics of the groups were not significantly different from each other (Table 1). The number of patients remaining in the study at each time point is summarized in Figure 1. Three withdrawals from each group were associated with clinical adverse events: peritonitis and catheter leak (one from each group, respectively), perianal abscess (icodextrin), and pancreatitis (Dianeal). Additional withdrawals from the 2.27% glucose group were for ultrafiltration failure and patient

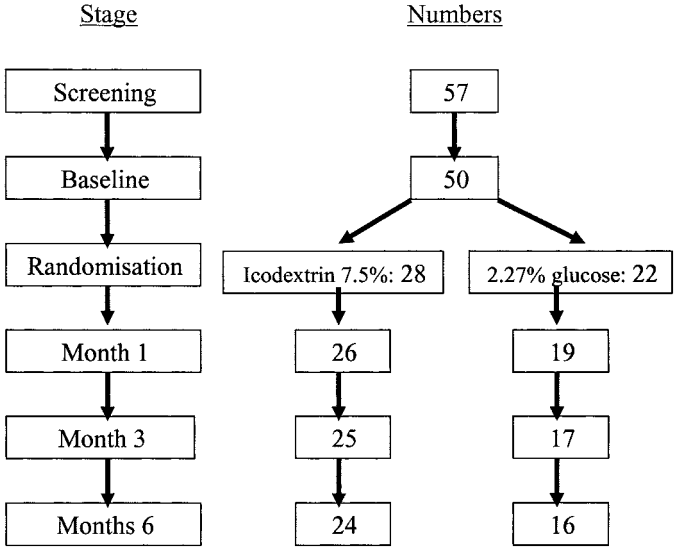

Figure 1. Summary of patient flow through the study, with numbers at each time point.

Table 1. Patient characteristics at randomization[a]

Treatment Group	Icodextrin	2.27% Glucose	*P* Value
No. of patients	28	22	
Age (y)	56 ± 15	54 ± 15	0.69
Gender (% male)	54	45	0.77
Race (% white)	96	95	0.69
Ambulatory peritoneal dialysis (%)	34	34	0.98
Cardiovascular disease (%)	32	27	0.95
Diabetic	0	3	0.32
Primary disease			0.82
diabetic nephropathy	0	2	
hypertensive nephropathy	2	2	
glomerulonephritis	8	6	
polycystic kidney disease	0	1	
interstitial nephritis	3	2	
obstructive nephropathy	2	1	
autoimmune disease	1	1	
other	12	7	
Height (cm)	168 ± 6.9	168 ± 10.6	0.99
Weight (kg)	75.5 ± 14.9	71.6 ± 14.5	0.35
Residual urine volume (ml)	291 ± 282	257 ± 294	0.67
Solute transport (D/P_{creat})	0.76 ± 0.09	0.78 ± 0.09	0.54
Clinic systolic BP (mmHg)	139.3 ± 5.3	143.8 ± 3.8	0.48
Clinic diastolic BP (mmHg)	83.8 ± 3.0	83.2 ± 2.1	0.89

[a] Data are expressed as mean ± SD. Other primary diseases include small kidneys ($n = 7$), renovascular disease ($n = 4$), reflux nephropathy ($n = 4$), stone disease, multicystic disease, cyclosporin toxicity, and Alport syndrome.

preference. Peritonitis rates and vital signs (pulse, respiration, and body temperature) did not differ between groups throughout the study. No adverse events attributable to icodextrin (*e.g.*, skin rash) were experienced.

Changes in Achieved Ultrafiltration, Sodium Removal, and Residual Urine Volume

Achieved ultrafiltration, sodium removal, and residual urine volume are summarized in Table 2 as change from baseline according to treatment group. Statistically significant between-group differences were observed at 3 mo in the achieved ultrafiltration and total fluid losses as a result of maintained ultrafiltration in the icodextrin group and a decline in ultrafiltration in the 2.27% glucose controls. Urine volume was relatively better maintained in the icodextrin group, especially at 6 mo, although this did not quite reach statistical significance. If all patients were included in the analysis, when nonparametric statistics are used, the between-group difference at 6 mo was 89 ml ($P = 0.039$). Absolute sodium losses were consistently and significantly less in the glucose-treated group throughout the study, again the result of a decline in sodium losses in the control group. Plasma albumin, often considered a marker of hydration status in PD patients, diverged during the study, but the differences did not quite reach statistical significance. There was a negative relationship between the change in albumin and ECF-BIA at 3 mo from baseline ($r = -0.44$, $P = 0.004$), which was absent at 6 mo.

Table 2. Change from baseline and between-group differences for a variety of criteria according to treatment group

Criterion	Month 1	Month 3	Month 6
Urine volume (ml)			
icodextrin	−44.3	−34.6	−10.7
control	−44.1	−56.6	−126.6
difference	−0.2	21.9	115.9[a]
Ultrafiltration volume (ml)			
icodextrin	+166.8	+87.9	+193.4
control	−50.1	−311.1	−201.7
difference	216.9	399.0[b]	395.1
Total fluid loss (ml)			
icodextrin	+138.8	+66.0	+258.6
control	−37.2	−307.8	−141.8
difference	176.1	373.8[b]	400.3
Dialysate sodium loss (mmol)			
icodextrin	+11.5	+0.9	+1.4
control	−11.4	−60.8	−25.0
difference	22.9	61.7[b]	26.5
Total sodium loss (mmol)			
icodextrin	+8.3	+4.3	+5.4
control	2.4	−53.0	−19.9
difference	5.9	57.3[c]	25.2
Plasma albumin (g/L)			
icodextrin	0.0	+1.0	+1.0
control	−1.5	−1.0	+1.0
difference	1.5	2.0[d]	0.0
Plasma cholesterol (mmol/L)			
icodextrin	−0.1	0.0	−0.05
control	−0.2	−0.2	−0.2
difference	0.1	0.2	0.15
Plasma triglycerides (mmol/L)			
icodextrin	0.2	0.2	−0.1
control	+0.05	0.0	−0.25
difference	0.15	0.2	0.15
Median plasma C-reactive protein (mg/L)			
icodextrin	—	+2.0	+0.1
control	—	−1.0	0.00
difference	—	3.0	0.1

P values are as follows: [a] $P = 0.059$ (nonparametric test, $P = 0.039$); [b] $P < 0.05$; [c] $P = 0.023$; [d] $P = 0.08$. All other comparisons resulted in $P > 0.1$.

Changes in Body Composition

Significant between-group differences in the longitudinal change in the primary end point, drained body weight, were observed, such that patients randomized to icodextrin lost weight early, whereas those using 2.27% glucose steadily gained weight throughout the study (Figure 2a). The between-group differences were 1.45 kg ($P = 0.015$) at 1 mo, 1.67 kg

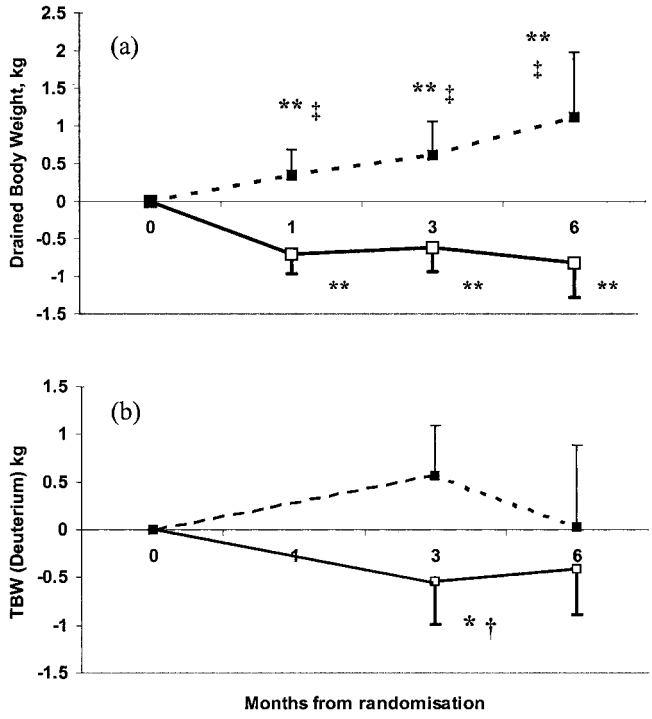

Figure 2. Changes in (a) drained body weight and (b) total body water determined from deuterium dilution. At each time point, values represent mean ± SEM change from baseline for patients randomized to icodextrin (□) or 2.27% glucose (■). Between-group differences, † $P < 0.05$, ‡ $P < 0.04$. Longitudinal differences from baseline, * $P < 0.04$, ** $P < 0.001$.

($P = 0.026$) at 3 mo, and 2.3 kg ($P = 0.036$) at 6 mo. These differences were reflected in changes in the TBW as estimated by multifrequency bioimpedance following a similar, but not identical, pattern. The continued increase in weight in the 2.27% glucose group was not reflected in a further increase of body water at 6 mo (Figure 3a). Between-group differences were 1.7 kg ($P = 0.006$), 1.53 kg ($P = 0.003$), and 1.39 kg ($P = 0.036$) at 1, 3, and 6 mo, respectively. These differences were largely accounted for by changes in the extracellular fluid component as estimated by bioimpedance, being 1.06 kg ($P = 0.008$), 0.85 kg ($P = 0.035$), and 0.82 kg ($P = 0.1$), respectively (Figure 3b). In each case, there were significant changes from baseline values observed in the icodextrin group, with the exception of drained weight, where both groups changed longitudinally from baseline (Figures 2 and 3).

Significant changes in TBW, measured independently by deuterium dilution, also occurred (Figure 2b). The change in ECF estimated from bioimpedance and the change in TBW using deuterium dilution correlated at 3 mo ($r = 0.37$, $P = 0.02$) and at 6 mo ($r = 0.58$, $P < 0.001$).

BP Control, Antihypertensive Medication, Lipids, and C-Reactive Protein

There were no significant differences in the mean and median 24-h BP readings between the treatment groups at any time point. The number of patients receiving antihypertensive drugs was similar in both groups at the start of the study (icodextrin 87%; Dianeal 81%). Patients randomized to icodextrin were more likely to reduce their hypertensive medication ($n = 9$, 33%) compared with the dianeal group ($n = 3$, 14%), but they were also more likely to increase their medication ($n = 5$, 19%, *versus* $n = 2$, 10%), and the multiple changes in some patients made this difficult to analyze. There was no correlation between longitudinal changes in BP and changes in weight, achieved ultrafiltration, or extracellular fluid as estimated from BIA. There were no between-group changes from baseline in the total cholesterol, triglycerides, or C-reactive protein measurements.

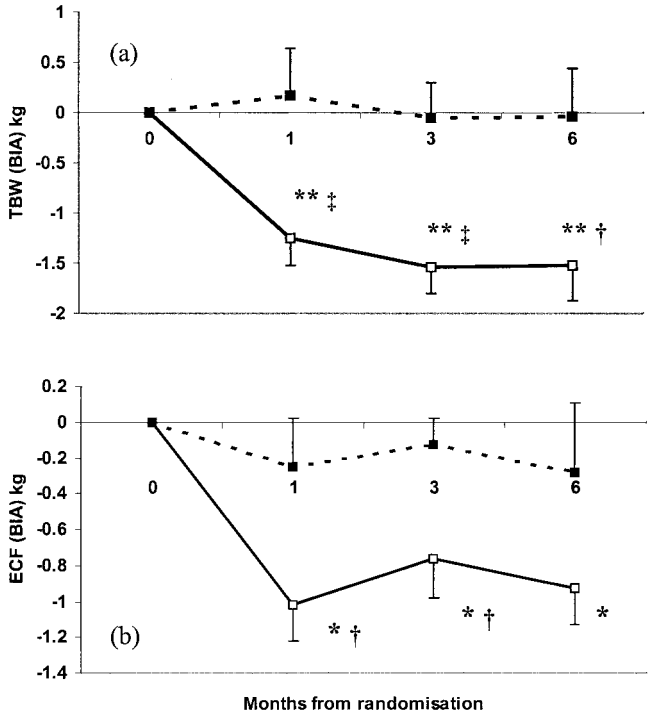

Figure 3. Changes in (a) total body water and (b) extracellular fluid determined from bioelectrical impedance. At each time point, values represent mean ± SEM change from baseline for patients randomized to icodextrin (□) or 2.27% glucose (■). Between-group differences, † $P < 0.04$, ‡ $P < 0.008$. Longitudinal differences from baseline, * $P < 0.002$, ** $P < 0.001$.

Discussion

We report what is to our knowledge the first randomized, double-blind, controlled trial in PD patients in which manipulation of achieved ultrafiltration is linked to a clinically relevant end point, specifically the fluid status of the patient. We found that when icodextrin is used during the long exchange compared with 2.27% glucose, ultrafiltration is better preserved and a sustained reduction in weight, primarily attributable to changes in the ECF, occurs. This supports the changes in weight observed in a recent randomized study (17) and in uncontrolled studies of manipulation of fluid status in PD patients, although in these reports, the changes in BP were greater (18,21,22). Furthermore, this change does not appear to have a detrimental effect of residual urine volume.

Several previous randomized trials have demonstrated that icodextrin compared with 2.27% glucose used in the long exchange results in improved net ultrafiltration (15–17). It does not necessarily follow, however, that this will translate into an improvement in the fluid status of the patient. For example, patients may simply drink more under these circumstances, and it has been argued that thirst might be increased in patients receiving icodextrin as a result of the buildup of osmotically active metabolite in the circulation, leading to increased thirst (23). Another possibility, as has been found in open studies of increasing ultrafiltration to control BP, is that volume depletion will result in a drop in residual urine volume, thus counterbalancing the beneficial effects of increased ultrafiltration (22). Neither of these concerns appear to have been borne out in this study; the changes in fluid status were maintained in the icodextrin group throughout the study, and if anything, these patients also had better preservation of urine volume. The explanation for the latter observation is not absolutely clear but may reflect either an osmotically driven maintenance of diuresis in the icodextrin group or the effect of a marked reduction in the ECF seen in two of the patients randomized to glucose that occurred between 3 and 6 mo. This was associated with loss in urine volume in these individuals that might have resulted from dehydration. It is likely that a more gradual and even control of fluid status throughout the 24-h period is beneficial to the maintenance of residual renal function. This is supported by a recent report of slower reduction in residual function loss in patients randomized to a dialysis regime combining icodextrin, amino acid, and bicarbonate-buffered glu-

cose compared with conventional all-lactate buffered glucose prescriptions (24).

In this study, we attempted to utilize several complementary measures of fluid status in our patients to build an overall picture of changes in body composition. It is clear that these different measurements, although all resulting in significant between-group differences, especially at 3 mo, differ from one another in the information they provide. For example, body weight and TBW estimated from deuterium dilution both diverge at 3 mo, whereas the BIA measurements remain stable in the control patients, only changing in those randomized to icodextrin. It is important to emphasize that the estimate of TBW by deuterium dilution is independent of body weight, whereas estimates of both fluid compartments from BIA use measured weight in the derivation of TBW and ECF volumes.

These data would suggest that BIA is particularly sensitive to relative changes in extracellular fluid rather than absolute TBW. Interestingly, there was a good correlation at 6 mo between changes in TBW-D (total body water measured by deuterium dilution) and changes in ECF but not TBW from BIA, supporting this view. At 6 mo, it is apparent that drained body weight continued to diverge, whereas TBW-D in the control group reverted to baseline. This was in part the result of the above-mentioned two patients whose ECF-BIA and TBW-D fell substantially during the second part of the study, but also due an apparent relative increase in fat mass in the control group. Because BIA can only indirectly estimate body fat, on the basis of the assumptions of the two-compartment model of body composition, it is likely to be insensitive to changes in body fat in a situation where changes in hydration of the fat-free compartment are occurring. Taking these observations together as a whole, it would seem that the patients randomized to icodextrin had an early but sustained reduction in ECF, whereas the picture was more complex in the control patients but included a worsening of fluid status at 3 mo combined with continued increase in body weight by 6 mo that is in part attributable to fat gain. The relative reduction in calories absorbed from the peritoneum when using icodextrin may be the reason for this (16).

The lack of influence of improved ultrafiltration on BP control in this study is on the surface disappointing and differs from the findings of uncontrolled studies (18,21,22). It should be noted, however, that achieved BP control throughout the study in both patient groups was very satisfactory, reflecting both a good quality of care by participating physicians and the freedom to use drug therapy as required in the study protocol. It was not felt ethical by the study investigators to stop antihypertensive medication upon entry to the trial. BP control in the icodextrin group was, in fact, rather better at the start of the study, and any changes observed might reflect a regression to the mean, especially because these patients were more likely to have their antihypertensive treatment reduced. The inability to relate changes in BP to those in ECF may not be that surprising, however, because the extracellular fluid expansion seen in PD patients does not necessarily reflect an increase in intravascular volume (25).

It is apparent from these data that the differences in achieved 24-h fluid removal at 3 and 6 mo were due as much to a decrease in achieved ultrafiltration and urine output in the control group as they were to improvements in the icodextrin group. This is despite a run-in period before randomization to ensure that patients could tolerate use of 2.27% glucose during the day's long exchange. It can also be seen that the net sodium removal in the icodextrin group was stabilized rather than significantly enhanced. The lack of increase in sodium removal by icodextrin for a given improvement in ultrafiltration is in part the result of the slightly higher dialysate sodium concentration (133 *versus* 132 mmol/L) and the modest reduction in plasma sodium, typically 4 to 5 mmol/L, well described in patients using this product (which also occurred in this study) (16,23,26). Both of these effects will have resulted in less diffusive removal of sodium, which would otherwise be maximized in long exchanges, which cancels out the increased convective loss of sodium. This may also contribute to the lack of effect on BP, raising the possibility that increased sodium removal, either by using a lower dialysate sodium concentration or by combining this solution with a low glucose concentration, could be substantially enhanced.

We have shown that patients with above-average solute transport, treated or untreated hypertension, or excessive dependence on hypertonic (average of 2.27% glucose exchanges during day) dialysate and a urine volume of <750 ml will benefit from icodextrin in their fluid management. An additional advantage would include the avoidance of excess glucose exposure and thus preservation of membrane function and avoidance of fat weight gain. There were relatively few patients with diabetes in this study. This was due in part to the somewhat lower percentage of people with diabetes in the European dialysis population compared with North America, although the main reason was difficulty in recruitment. Use of icodextrin in patients with diabetes in Europe is already common because of its higher peritoneal solute transport characteristics and the immediate metabolic benefits these patients receive. Clinicians were unwilling to stop this treatment under these circumstances required for enrollment onto the study. There is no reason to believe, however, that patients with diabetes would not also benefit in terms of their fluid status.

In summary, it is our opinion that this product should be used proactively in these patients. Of further importance, our study has demonstrated that the fluid status of PD patients can be influenced by therapeutic maneuver, and it provides evidence that longitudinal fluid status can be monitored by complementary measures of body composition that could form the basis of both future trials and clinical practice.

Acknowledgments

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