Nephrol Dial Transplant (1997) 12: 550–553

Nephrology
Dialysis
Transplantation

Original Article

Icodextrin instead of glucose during the daytime dwell in CCPD increases ultrafiltration and 24-h dialysate creatinine clearance

N. Posthuma[1], P. M. ter Wee[1], H. A. Verbrugh[2], P. L. Oe[1], E. Peers[3], J. Sayers[3] and A. J. M. Donker[1]

[1]Department of Nephrology, Free University Hospital Amsterdam; [2]Department of Clinical Microbiology, University Hospital Rotterdam, The Netherlands; [3]ML Laboratories plc, St Albans, UK

Abstract

Background and methods. Icodextrin 7.5% is an iso-osmolar, glucose polymer-containing peritoneal dialysis solution with an ultrafiltration potential similar to glucose 3.86%. We compared in an open, randomized, prospective study the ultrafiltration potential of icodextrin with that of glucose during the daytime dwell of 23 patients treated with automated peritoneal dialysis (CCPD).

Results. Daytime ultrafiltration volume and 24-h ultrafiltration volume increased significantly in icodextrin-treated patients ($n=11$) at 3 and 6 months, allowing patients a less rigid fluid restriction or an adapted treatment schedule. This improved the patients' subjective well-being. Although ultrafiltration at 9 and 12 months also increased it did not reach statistical significance. Similar to the gain in ultrafiltration volume, 24-h dialysate creatinine clearance per 1.73 m^2 (D_{Cl}/1.73 m^2) and D_{Cl}/1.73 m^2 per litre used dialysate (D_{Cl}/1.73 m^2/l) increased in icodextrin-treated patients. D_{Cl}/1.73 m^2/l per litre ultrafiltrate (D_{Cl}/1.73 m^2/l/UF) did not increase. No side-effects of icodextrin were encountered, although serum disaccharide levels increased.

Conclusion. Icodextrin enhances ultrafiltration during the daytime dwell in CCPD patients. As a result of an increased 24-h ultrafiltration volume, D_{Cl}/1.73 m^2 and D_{Cl}/1.73 m^2/l improve. D_{Cl}/1.73 m^2/l/UF does not rise, which suggests that the increase in D_{Cl}/1.73 m^2 and D_{Cl}/1.73 m^2/l is caused by convective transport.

Key words: CCPD; dialysate creatinine clearance; icodextrin; peritoneal dialysis; ultrafiltration

Introduction

Continuous peritoneal dialysis is associated with a risk of peritonitis and changes in the peritoneal membrane which can, over time, lead to loss of ultrafiltration capacity [1–4]. The latter may be related to the use of hyperosmolar glucose solutions, which have inadequate biocompatibility.

Glucose-based dialysis fluids are particularly suited for short dwells, since they achieve optimal ultrafiltration over 4–6 h. The long daytime dwell in automated peritoneal dialysis (CCPD) exceeds this optimum by about 10 h, resulting in limited or even negative ultrafiltration during the daytime dwell. Consequently, some CCPD patients leave their peritoneum dry during the day. However, this strategy significantly reduces the solute clearance, and therefore compromises dialysis adequacy [5].

Loss of ultrafiltration is an important cause of treatment failure in long-term peritoneal dialysis patients. Recently, the use of an iso-osmolar glucose polymer solution was advocated in order to maintain adequate ultrafiltration in CAPD patients [6]. This may even extend CAPD technique survival in patients that have failing ultrafiltration when using glucose monomer solutions [7].

Icodextrin is a glucose polymer of weight average molecular weight (Mw) 16 200 dalton and number average molecular weight (Mn) of 5 800 dalton. Icodextrin 7.5% contains a glucose polymer chain length varying between 4 and 250 glucose units. The total osmolality of 7.5% icodextrin solution is 282 mOsm/kg, pH is 5.3 [8]. Potentially, the iso-osmolar icodextrin may be less damaging to the peritoneum and the local host resistance compared to the hyperosmolar [346–486 mOsm/kg) glucose solutions currently used [6,9]. In the present study we investigated the ultrafiltration profile of CCPD patients using icodextrin during the daytime dwell and compared them to CCPD patients using the standard glucose solutions. In addition the effect of icodextrin on 24-h dialysate creatinine clearance, and total creatinine clearance was studied. In the this paper we present the results of our interim analysis after 1-year follow up.

Subjects and methods

We started an open, randomized, prospective study in CCPD patients, consisting of a 2-year treatment period on either

Correspondence and offprint requests to: N. Posthuma MD, Department of Nephrology, Academisch Ziekenhuis der Vrije Universiteit, Postbus 7057, 1007 MB Amsterdam, The Netherlands.

icodextrin or glucose for the daytime dwell (14–15 h). Both established CCPD patients and patients new to CCPD were included. The patients had to be compliant, in a stable clinical condition (no peritonitis in the previous month) with an estimated life expectancy of more than 2 years, and aged over 18. Women of child-bearing potential were excluded unless taking adequate contraceptive precautions. The study was approved by the local ethical commitee and written informed consent was obtained from each patient.

Clinic visits were made every 3 months. Icodextrin was manufactured and supplied by ML Laboratories plc. (St Albans, UK). It was bagged as 2-litre 7.5% w/v by Fresenius AG, Bad Homburg, Germany. The glucose solutions were those commercially available from Baxter BV (Utrecht, The Netherlands). These were bagged as 2-litre 1.36, 2.27 or 3.86% w/v solution. Ultrafiltration volumes were recorded automatically by the patients' CCPD machines and transcribed into a file by the patients. Concentrations of the glucose bags used during the CCPD cycles were recorded as well. Dialysate and urine creatinine clearances were calculated according to the standard formula $((D \times V)/P)$ from a 24-h dialysate or urine sample, and expressed per 1.73 m^2. Blood and dialysate samples were analysed with an automated analyser (Hitachi 747, Boehringer, Mannheim, Germany). Serum disaccharides were calculated by using standard methods of area under the curve after determining the well-defined peak on gel-permeation chromatogram and expressed as a percentage of total carbohydrate in the sample.

Results are expressed as mean values $\pm$ SEM. The changes from baseline have been compared between the groups and within the groups using a one-way analysis of variance (ANOVA). Group differences were tested using a paired two-tailed Student's *t* test. Analysis was done in SPSS B for Windows™ 6.01. $P < 0.05$ was considered to be significant.

Results

Recruitment began in February 1994. Of the 38 patients currently entered, 23 have had a follow-up period of 9 months or longer in March 1996 (11 glucose, 12 icodextrin). Twenty-one patients have had a follow-up of 12 months (11 glucose, 10 icodextrin).

At baseline, all patients used standard glucose solutions prior to entry into the study, daytime ultrafiltration was similar in both groups. As shown in Table 1, daytime ultrafiltration volumes increased significantly from baseline in the icodextrin group (all visits: $P \leqslant 0.005$, within the group), this in contrast to glucose users. After 3, 6 and 9 months a significant difference in ultrafiltration between glucose and icodextrin users existed (ANOVA glucose *versus* icodextrin from baseline: $P \leqslant 0.01$). The total (24-h) ultrafiltration volumes were also larger in icodextrin users at all visits (Table 1), but a significant difference between the groups was not reached. Within the icodextrin group the total ultrafiltration increased significantly from baseline at 3 and 6 months ($P = 0.02$).

The glucose concentrations used during the night-time CCPD cycles at baseline, were similar in glucose patients and icodextrin patients (average glucose concentrations 2.34 ± 0.24 *versus* 2.29 ± 0.18% respectively; NS). However, the glucose concentrations used during CCPD cycles tended to increase over time in both groups (Table 2). At study entry three patients had a dry abdomen because of ultrafiltration failure (1 glucose and 2 icodextrin).

Although serum creatinine concentration was slightly higher in icodextrin patients, this difference was not statistically significant. However, calculated dialysate clearances (D_{Cl}) per 1.73 m^2 increased significantly in icodextrin users at all intervals, but not in glucose patients (ANOVA between the groups 1–12 months: $P \leqslant 0.05$, and within the icodextrin group 1–12 months: $P < 0.0005$). Expressed as $D_{Cl}/1.73$ m^2 per litre of used dialysate, the difference between icodextrin and glucose persisted (Table 3). This difference only disappeared when the dialysate clearance was corrected for the ultrafiltration in litres (data not shown in Table 3). Urine creatinine clearance (Table 3) and diuresis (Table 1)decreased in both groups over time, but did

Table 2. Mean glucose concentrations ($\pm$SEM) used during the daytime and overnight dwells in CCPD patients using glucose (G) or icodextrin (I) for the daytime dwell

Months (*n* pts in study	Daytime		Night-time	
	G (%)	I (%)	G (%)	I (%)
0 (23)	2.41 ± 0.27	2.16 ± 0.23	2.34 ± 0.24	2.29 ± 0.18
3(23)	2.25 ± 0.22	I	2.39 ± 0.24	2.34 ± 0.20
6 (23)	2.25 ± 0.22	I	2.39 ± 0.21	2.34 ± 0.17
9 (23)	2.25 ± 0.22	I	2.51 ± 0.23	2.39 ± 0.18
12 (21)	2.38 ± 0.26	I	2.50 ± 0.23	2.38 ± 0.23

Table 1. Mean ultrafiltration volume and diuresis ($\pm$SEM) in glucose (G) and icodextrin (I) users during 12-months follow up

Months (*n* pts in G & I gps)	Daytime UF (ml)		Total UF (ml)		Diuresis (ml)	
	G	I	G	I	G	I
0 (11&12)	5 ± 159	-129 ± 88	916 ± 205	970 ± 205	677 ± 269	550 ± 154
3 (11&12)	42 ± 139	168 ± 57#	1025 ± 237	1220 ± 169	559 ± 285	490 ± 169
6 (11&12)	36 ± 115	218 ± 57#	1080 ± 289	1287 ± 159	546 ± 232	388 ± 126
9 (11&12)	-30 ± 87	224 ± 71#	1019 ± 270	1240 ± 192	578 ± 226	280 ± 110
12 (11&10)	75 ± 99	204 ± 95	1050 ± 228	1270 ± 145	449 ± 258	345 ± 147

#$P \leqslant 0.02$, G *versus* I from baseline (ANOVA).
Note. At study entry three patients (1 G and 2 I) had a dry abdomen during the daytime because of previous ultrafiltration failure. Zero daytime dwell ultrafiltration was taken in these patients.

Table 3. Mean (±SEM) serum creatinine concentration, dialysate creatinine clearance, and urine creatinine clearance in CCPD patients using glucose (G) or icodextrin (I) solutions for the daytime dwell

Months	Creatinine (mmol/l)		D_{Cl}/1.73 m^2 (ml/min/1.73 m^2)		D_{Cl}/1.73 m^2/l (ml/min/1.73m^2/l)		U_{Cl}/1.73 m^2 (ml/min/1.73 m^2)	
	G	I	G	I	G	I	G	I
0	1010±98	1083±117	4.5±0.4	3.8±0.2	0.45±0.03	0.37±0.03	2.8±1	2.4±0.8
3	1082±105	1064±108	4.2±0.3	4.5±0.3	0.44±0.03	0.46±0.03	2.0±1	2.6±0.9
6	1006±70	1081±100	4.3±0.3	4.8±0.3#	0.46±0.03	0.48±0.02	2.2±0.8	1.9±1
9	1036±78	1151±121	4.4±0.2	4.3±0.2*	0.48±0.02	0.43±0.03*	2.7±0.9	1.9±0.9
12	1078±65	1121±103	4.3±0.3	4.4±0.2*	0.47±0.03	0.44±0.02#	1.7±0.7	1.7±0.9

ANOVA G *versus* I from baseline, * $P \leqslant 0.005$, #$P < 0.05$

not reach statistical significance (nor the decrease from baseline, nor the difference between the groups). Total creatinine clearance (dialysate and urine combined) fluctuated around baseline in the glucose users and was higher at all follow-up visits in icodextrin users, but was not significant.

Body-weight remained stable in glucose patients (71.9±3.4 kg at baseline and 72.4±3.9 kg after 12 months), and increased in icodextrin patients (73.7±3.5 kg to 76.6±3.5 kg; NS). Mean arterial pressure decreased significantly after 6 months in glucose users and remained stable in icodextrin patients (105±3 to 93±4 mmHg, $P \leqslant 0.03$ and 102±5 to 101±6 mmHg respectively). At the same time antihypertensive medication prescription decreased in glucose patients and tended to increase in icodextrin patients.

No clinical side-effects or complaints were associated with icodextrin. Serum disaccharide levels increased in the icodextrin group from 0.049±0.01 to a steady state of 1.20±0.2 g/l.

Discussion

In a previous randomized multicentre clinical trial, isosmolar icodextrin was compared with hyperosmolar glucose solutions in CAPD [6]. Long-term safety and efficacy were evaluated by comparing overnight use of icodextrin with conventional glucose exchanges over a period of 6 months. The mean ultrafiltration with icodextrin was similar to that of 3.86% glucose at 8 and 12 h. Furthermore, a small drop in serum sodium and chloride concentrations in the icodextrin group occurred, together with a rise in the serum maltose level. None of these findings was associated with any adverse clinical effects. Using icodextrin instead of glucose neither increased or decreased the peritonitis rate, nor alter the outcome of it [10].

So far, the published experience with icodextrin has been confined to CAPD over a period of 6 months. Long-term data and extended dwell periods are necessary to further establish its safety and efficacy.

We compared in the present study icodextrin used for the daytime dwell in CCPD with glucose. The daytime dwell averaged 14 h 35 min in our study, which is considerably longer than the usual night-time dwell in CAPD. As shown in Table 1, daytime ultrafiltration increased markedly in icodextrin patients at all intervals. At 12 months follow-up however, it was not statistically different from glucose users. This may in part be explained by the number of patients in the study. During the study period, total ultrafiltration increased after initiation of icodextrin treatment, but because of the large interindividual variation in ultrafiltration, the difference compared with glucose-treated patients did not reach statistical significance. Within the icodextrin patients there was a significant increase from baseline up to 9 months. In addition, six patients adjusted their dialysis schedule according to their social needs after starting on icodextrin. Usually they increased their daytime dwell volume and they skipped one exchange in the night, resulting in a constant amount of used litres dialysate. As can be deduced from Table 2, patients used the UF gain to drink more instead of decreasing their glucose concentration. Diuresis did not decrease significantly during follow-up in both groups, despite a larger ultrafiltration volume in icodextrin patients. Total fluid loss (diuresis and ultrafiltration) can be seen in Table 1. It increased in icodextrin patients and decreased in glucose patients from baseline (1520±180 to 1615±188 ml and 1593±181 to 1499±187 ml respectively). It is also worth noticing that the three patients who had a dry abdomen during the day (because of ultrafiltration failure) were recorded as having a zero daytime dwell ultrafiltration at study entry. These patients would definitively have had a large negative daytime dwell ultrafiltration if so tested with glucose. Therefore, the difference between the icodextrin and glucose groups regarding the gain in daytime ultrafiltration is, at least theoretically, even larger.

D_{CL}/1.73 m^2 increased as did the D_{Cl}/1.73 m^2/l, the latter being a more accurate way of describing the clearance for a certain dialysis fluid. The increase in clearance was approximately identical to the gain in ultrafiltration. When expressed as D_{Cl}/1.73 m^2/l/UF, the difference between glucose and icodextrin disappeared, indicating that the intrinsic clearance capability of icodextrin is probably the same as that of glucose, and that the observed increase in 24-h UF, although statistically not significant at all intervals, probably accounts for the increase in clearance. The increase in

measured D_{Cl} is thus mainly due to 'colloid'-induced osmotic convective transport. This is in accordance with previous findings [11]. Total clearance (residual renal function and dialysate clearance) fluctuated around baseline values in glucose patients and were higher at all intervals in icodextrin patients, as can be calculated from the values in Table 3.

The increased D_{Cl}, however, did not lead to a decrease in serum creatinine concentration. Probably the measured differences were not sufficient to produce such a decrease, although it is possible that the patients were consuming more protein. Changes in body-weight may reflect this possible increased intake, although mean arterial pressure and antihypertensive medication suggest a fluid gain in icodextrin patients.

Finally, serum disaccharide levels appeared to be at about the same level as in CAPD use [6], despite the longer exposure time in CCPD.

Conclusion

We conclude that the daytime dwell use of icodextrin in CCPD will significally increase daytime ultrafiltration volumes, and consequently improve 24-h dialysate creatinine clearances. As a result also total creatinine clearance increased from baseline at all intervals in icodextrin patients. This was not accompanied by clinical side-effects, despite the increase in serum disaccharide levels in icodextrin users.

Acknowledgements. This study was supported by the Dutch Kidney Foundation (Grant no. C93.1286). NP is supported by ML laboratories plc.

References

1. Bronswijk H van, Verbrugh HA, Heezius HCJM, Meulen J van der, Oe PL, Verhoef J. Dialysis fluids and local host resistance in patients on continuous peritoneal dialysis. *Eur J Clin Microbiol Infect Dis* 1988; 7: 368–373
2. Fijter CWH de, Verbrugh HA, Peters EDJ, Oe PL, Meulen J van der, Verhoef J. In vivo exposure to the currently available peritoneal dialysis fluids decreases the function of peritoneal macrophages in CAPD. *Clin Nephrol* 1993; 39: 75–80
3. Dobbie JW, Lloyd JK, Gall CA. Categorisation of ultrastructural changes in peritoneal mesothelium, stroma and blood vessels in uraemia and CAPD patients. In: Khanna R *et al. Advances in Peritoneal Dialysis 1990*. Perit Dial Bull Inc., Toronto 1990; 3–12
4. Verger G, Luger A, Moore JU, Nolph KD. Acute changes in peritoneal morphology and transport properties with infectious peritonitis and mechanical injury. *Kidney Int* 1983; 145: 391–411
5. Diaz-Buxo JA, Farmer CD, Chandler JT, Walker PJ, Burgess WP. CCPD—Wet is better than dry. *Perit Dial Bull* 1987; 17: S22 (abstract)
6. Mistry CD, Gokal R, Peers EM. A randomized multicenter clinical trial comparing isosmolar icodextrin with hyperosmolar glucose solution in continuous ambulatory peritoneal dialysis: a six month study. *Kidney Int* 1994; 46: 496–503
7. Peers EM, Scrimgeour AC. Icodextrin can prolong technique survival in CAPD patients with ultrafiltration failure. *J Am Soc Nephrol* 1995; 6: 513 (abstract)
8. Davies DS. Kinetics of icodextrin. *Perit Dial Int* 1994; 14 [Suppl 2]: S45–50
9. Fijter CWH de, Verbrugh HA, Oe PL *et al.* Biocompatibility of a glucose-polymer containing peritoneal dialysis fluid. *Am J Kidney Dis* 1993; 21: 411–418
10. Gokal R, Mistry CD, Peers EM *et al.* Peritonitis occurrence in a multicenter study of icodextrin and glucose in CAPD. *Perit Dial Int* 1995; 15: 226–230
11. Imholz ALT, Brown CB, Koomen GCM, Arisz L, Krediet RT. The effect of glucose polymers on water removal and protein clearances during CAPD. In: Khanna R *et al. Advances in Peritoneal Dialysis*. Perit Dial Bull Inc, Toronto, 1993; 9: 25–30

Received for publication: 20.6.96
Accepted in revised form: 15.11.96