Nephrol Dial Transplant (1998) 13: 2341–2344

Nephrology
Dialysis
Transplantation

Preliminary Report

Icodextrin use in CCPD patients during peritonitis: ultrafiltration and serum disaccharide concentrations

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Abstract

Background and methods. In a randomized study on the biocompatibility of icodextrin (I) versus glucose (G) in CCPD we used icodextrin or glucose for the long daytime dwell. During the night-time dwells glucose was used in all patients. In case of peritonitis icodextrin was continued. In all patients ultrafiltration (UF) was recorded and serum icodextrin metabolites were determined every 3 months and during peritonitis in I-users when available.

Results. Thirty-eight patients (19 G, 19 I) entered the study and suffered 30 peritonitis episodes (16 G, 14 I). During peritonitis (P), daytime dwell UF decreased significantly in G ($P=0.001$), but remained stable in I patients compared to non-peritonitis (NP) episodes. Total 24-h UF decreased in G ($P=0.001$) and in I patients ($P=0.04$), as the result of a decreased daytime UF and night-time UF, respectively. There was no difference in the used glucose concentrations during the P versus NP episodes.

In five I-patients serum disaccharides increased from 0.05 ± 0.01 to 1.26 ± 0.23 mg/ml during follow up. During peritonitis serum disaccharide concentrations did not increase further (1.47 ± 0.24 mg/ml, $P=0.56$). In I patients total carbohydrate minus glucose rose to 5.72 ± 1.2 mg/ml during follow up, and to 6.63 ± 1.04 mg/ml during peritonitis ($P=0.7$). These concentrations are comparable to CAPD patients despite the longer dwelltime in CCPD (8–10 versus 14–16 h, respectively). Adverse reactions attributable to icodextrin were not encountered.

Conclusions. In contrast to glucose, icodextrin preserved the daytime dwell ultrafiltration during peritonitis. Serum icodextrin metabolites increased during icodextrin use, but remained stable during peritonitis. Adverse effects were not observed.

Key words: disaccharides; icodextrin; maltose; peritoneal dialysis; peritonitis; ultrafiltration

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Introduction

During peritonitis in peritoneal dialysis (PD) patients, ultrafiltration (UF) decreases in the first days as a result of increased glucose absorption and an increase in dialysate absorption via the lymphatic system [1]. Sometimes, this decrease in UF leads to overhydration. However, nausea and vomiting, increased insensible loss, and possibly fluid sequestration, often equal or even overcome this loss of UF.

A PD solution containing larger molecules than glucose will, theoretically, better maintain its UF capability during peritonitis. Icodextrin, a glucose polymer derived from starch (molecular weight 16 200 dalton), is used for long dwells, i.e. the night-time dwell in CAPD and the daytime dwell in CCPD. Icodextrin 7.5% contains a glucose polymer chain length varying between 4 and 250 glucose units. In CAPD patients without peritonitis, icodextrin results in an UF equal to that of 3.86% glucose at 8 and 12 h [2]. In CCPD patients without peritonitis, the daytime UF with icodextrin is greater than with, on average, 2.28% glucose [3].

A persistent finding during icodextrin use is accumulation of maltose, a disaccharide breakdown product of icodextrin after hydrolyzing by amylase. Concentrations up to 36 times that found in uraemic plasma have not been associated with any recognisable adverse effect up to 6 months except for a small decrease in serum sodium and chloride concentration [2]. We found no adverse effects associated with plasma concentrations up to 26 times in CCPD patients using icodextrin for 12 months [4]. We now report on ultrafiltration and icodextrin metabolites when icodextrin was continued in patients developing peritonitis.

Patients and methods

An open, randomized, prospective study was carried out on the biocompatibility of icodextrin versus glucose use for the long daytime dwell in CCPD patients, with an intended follow up of 2 years. Patients established on CCPD as well

as patients new to PD were included. Patients had to be compliant, in a stable clinical condition (no peritonitis in the previous month) with an estimated life expectancy >2 years, and aged over 18 years. Women of childbearing potential were excluded unless taking adequate contraceptive precautions. Icodextrin was continued in case of peritonitis. We treated all peritonitis patients with intraperitoneal antibiotics, starting with gentamycin (20 mg/l once a day) and rifampin (50 mg/l every exchange), unless there was serious suspicion of a specific organism, for example in case of concomitant exit site infection [5]. As soon as the culture results became available, antibiotics were adjusted according to culture sensitivity. The local ethical committee had approved the study and written informed consent was obtained from every patient.

Icodextrin (I) was manufactured and supplied by ML Laboratories plc. (Liverpool, UK). Fresenius AG (Bad Homburg, Germany) bagged it as 2–l 7.5% w/v. The glucose (G) solutions (1.36, 2.27, and 3.86%) were from Baxter BV (Utrecht, The Netherlands).

UF volumes were calculated from the data recorded by the patients' CCPD machines, and transcribed into a file by the patients themselves. Concentrations of the G-bags used during the CCPD cycles and used volumes were recorded as well. At 3-month intervals a study visit to the clinic was made, at which time clinical data, blood samples for haematology, biochemistry, and icodextrin metabolites, 24-h dialysate and urine collection were obtained. If necessary, material was stored at -20°C or -70°C, as appropriate. In case of peritonitis, UF and G-concentration of the used dialysate were carefully recorded every day. Afterwards a mean value was calculated of the days during which the dialysate leukocyte count was elevated. Blood and dialysate samples were obtained when possible. The residual renal function and diuresis were measured every 3 months, but not extra during peritonitis.

Biochemistry tests were performed with an automated analyzer (Hitachi 747, Boehringer, Mannheim, Germany). Icodextrin metabolites were calculated by using standard methods of area under the curve after determining the well-defined peak on gel permeation chromatography and expressed as a percentage of total carbohydrate in the sample. Disaccharides ('maltose') and the total carbohydrate minus glucose (CHO–G1) are given as the smallest metabolite and total icodextrin metabolites, respectively.

Results are expressed as mean values $\pm$SEM. Group differences were tested using a two independent samples test (Mann–Whitney) and differences within the groups in P and NP were tested with a 2-tailed Wilcoxon Signed Ranks test as nonparametric tests. Analysis was done in SPSS 7.5 for Windows™. $P<0.05$ was considered to be significant.

Results

Starting in February 1994, 38 patients entered the study. Demographic data are given in Table 1. These 38 patients had 30 peritonitis episodes (16 G, 14 I) during 287 and 306 months follow up, resulting in once every 17.9 and 21.9 months, respectively (once every 19.8 months in the whole group). Before the study these patients had experienced 56 peritonitis episodes, 37 in patients subsequently assigned to G-use and 19 in patients assigned to I-use, during 486 and 307 months, respectively (once every 13.1 and 16.2 months, $P=0.3$). All these data are not significantly different. Three G- and one I-patient accounted for 27 and seven episodes before study; during the study these patients had five and no peritonitis episodes, respectively. The microorganisms causing peritonitis were predominantly staphylococcal species and other Gram positive bacteria (Table 2). Ultrafiltration volumes and the mean G concentrations as used by the patients during peritonitis and in non-peritonitis episodes are provided in Table 3. Volumes and the mean used G-concentrations were compared with the mean volumes of a normal week in a non-peritonitis period just before the peritonitis episode. The daytime UF in I-patients was preserved, this in contrast to G patients, who lost an extra 578 ± 89 ml (366%) on top of their normal daytime UF (-158 ± 197 ml). The total UF decrease in I patients was the result of the decreased night-time dwell UF, again in contrast to the G users, in whom the UF loss was a combined daytime and night-time loss. The difference between the daytime UF in I and G patients was significant ($P<0.001$). Total UF (24-h) was also significantly higher in I patients ($P=0.002$), completely caused by the daytime difference. The daytime UF decrease between peritonitis (P) and non-peritonitis (NP) was significant in G ($P=0.001$), but non-significant in I patients. Almost the same results were obtained for the total UF (G: $P=0.001$), but now the total UF decreased also in I patients ($P=0.04$) caused by a decreased night-time

Table 1. Demographic data of the patients in the study

	Daytime dwell	
	Glucose	Icodextrin
Number of patients	19	19
Male : female	17 : 2	10 : 9
Age (mean $\pm$SEM)	51.7 ± 3.6	52.9 ± 2.6
Diabetes mellitus	2	0
Time on PD before study (months)	26 ± 6	16 ± 4
Follow-up during study (months)	15 ± 2	16 ± 2
Peritonitis episodes during study	16	14

Table 2. Microorganisms causing peritonitis in 38 CCPD patients

Species	Number of episodes of peritonitis in	
	Glucose patients	Icodextrin patients
Staphylococcus aureus	8	5
Coagulase-negative Staphylococci	2	4
Diphteroid rod	1	
Enterococcus faecalis	3	
Escherichia coli		1
Pseudomonas aeruginosa	1	1
Faecal flora	1	
Undetermined Gram negative rods		1
Candida albicans	1	
Culture negative		2

Note: one icodextrin patient had a combined *S. aureus* and *E. coli* peritonitis.

Table 3. Ultrafiltration volumes and used glucose concentrations in glucose- and icodextrin patients during peritonitis and non-peritonitis.

Daytime dwell PD fluid:		Glucose ($n=15$) UF (ml)	G (%)	Icodextrin ($n=14$) UF (ml)	G (%)
Daytime dwell:	peritonitis	-736 ± 81[a,c]	2.22 ± 0.23	296 ± 82	icodextrin
	non-peritonitis	-158 ± 97[b]	2.13 ± 0.19	293 ± 61	icodextrin
	ΔP–NP (ml)	-578 ± 89[c]		3 ± 72	
Total (24-h) ultrafiltration:	peritonitis	-72 ± 193[b]	2.08 ± 0.24	1107 ± 202	2.14 ± 0.22
	non-peritonitis	571 ± 233[b]	2.08 ± 0.22	1479 ± 159[d]	2.24 ± 0.16
	ΔP–NP (ml)	-643 ± 213[d]		-372 ± 181	

Note that, the glucose concentration given for the total ultrafiltration is only for the night-time dwells.
Abbreviations: Δ difference in ultrafiltration, UF: ultrafiltration, P: peritonitis, NP: non-peritonitis.
Mann–Whitney test: glucose vs icodextrin: [a]$P<0.001$, [b]$P<0.01$.
Wilcoxon test: P versus NP: [c]$P<0.001$, [d]$P<0.05$.

UF ($P=0.02$). The lower night-time glucose concentration used during P in I patients was not significantly different from NP.

Serum for I-metabolites determination was obtained in five I patients. Serum I-metabolites (disaccharides and the total carbohydrate minus glucose: 'CHO–G1') are given in Table 4. Serum disaccharides increased 25 times during I treatment (from 0.05 ± 0.01 to 1.26 ± 0.23 mg/dl). The serum disaccharide concentration measured during peritonitis did not increase significantly (1.47 ± 0.24), and neither did CHO–G1. The residual renal function in these five patients was 1.16 ± 0.65 ml/min/1.73 m^2 with a diuresis of 400 ml/day. Two patients were anuric. The whole group had a creatinine clearance of 0.72 ± 0.3 ml/min/1.73 m^2 with a diuresis of 271 ml/day. However, one patient with a clearance of 3.46 ml/min/1.73 m^2 had higher serum concentrations than two anuric patients. During P it is possible that the clearance was lower than measured in NP. We were able to obtain only two dialysate samples for I fractions and in one of these two patients a NP dialysate sample. These results are also shown in Table 4. Dialysate concentrations during peritonitis were lower than before suggesting higher absorption during peritonitis. Patients experienced no adverse effects during I-use, and adding antibiotics to I did not give any problem.

Table 4. Serum and dialysate icodextrin metabolites ($\pm$SEM) during peritonitis and non-peritonitis in icodextrin-treated patients

	Number of patients	Non-peritonitis	Peritonitis
Disaccharides			
serum (mg/ml)	5	1.26 ± 0.23	1.47 ± 0.24
dialysate (mg/ml)	2	1.08 ± 0	1.19 ± 0.2
CHO–G1			
serum (mg/ml)	5	5.72 ± 1.2	6.63 ± 1.04
dialysate (mg/ml)	2	40.5 ± 0	37.3 ± 1.16

Note: CHO–G1 is total carbohydrate minus glucose.

Discussion

The peritonitis incidence before the study was once every 13.1 and 16.2 months in G and I patients, respectively. During the study the peritonitis incidence was once every 17.9 and 21.9 months, respectively. All these results are not significantly different. There was no surplus risk of peritonitis in the I patients, which makes our results similar to MIDAS [6].

Our results further show that UF was preserved during peritonitis in I-users, this in contrast to G-users. Icodextrin users had a significant loss in night-time UF and, as can be seen in Table 3, they started to use lower G concentrations during the night. Thus, the preserved daytime UF can lead to lower G concentration use, which can be favourable to the peritoneal membrane especially in peritonitis. In peritonitis the mesothelium is denuded, subjecting the sub-mesothelial layers to an excessive glycation by dextrose [7].

Renal failure causes accumulation of maltose, since further metabolism is limited by the absence of maltase activity in the human circulation, the enzyme being most notably present in the brush border and the apical membrane of the proximal renal tubules of the kidneys [8]. Steady state levels of maltose are reached within two weeks of I-use, suggesting transperitoneal elimination, and the levels fall to previous values after cessation of PD with I-containing fluids [9]. Complete clearance from the systemic circulation is eventually achieved by the kidneys and by metabolism to glucose [10]. Serum I-metabolites did not significantly rise in the five patients studied, compared to their non-peritonitis episodes. Still there was a non-significant increase. Dialysate samples were obtained in only two patients for I-metabolite measurements. These two patients seem to absorb more CHO–G1 during a P episode than during a NP episode. However, only one NP dialysate was obtained and that patient absorbed 36,5 and 36.6%, in P and NP respectively. Still, higher serum I-metabolite concentrations and higher I-metabolite absorption from the dialysate point into the same direction. Further study is needed. The NP

I-metabolite concentrations we found were approximately the same as found earlier in CAPD patients [2]. The average duration of the night-time dwell in these CAPD patients was 8–10 h. Our patients had an average daytime dwell time of 13–16 h (14 h 31′). Despite this longer dwell time the levels are the same. During P disaccharide concentrations in our five patients seem somewhat higher than previously found in four CAPD patients: 1.47 ± 0.28 vs 1.16 ± 0.24 mg/ml, respectively [6]. In this CAPD paper the NP disaccharide concentration was higher than the P concentration. Residual renal function was low in our patients, but will influence the disaccharide concentrations. In the five patients the creatinine clearance was slightly higher than in this total I group. The whole study I group (19 patients) had a creatinine clearance declining from 2.9 ± 0.7 to 2.5 ± 0.9 ml/min/1.73 m^2 and serum disaccharide concentrations similar to that found in these five patients [4]. Consequently we feel these data can be accepted as representative of the group.

Conclusion

Daytime dwell UF was preserved in I patients during peritonitis, this in contrast to G-users in whom a significantly decreased UF was established. During peritonitis icodextrin patients tended to use lower glucose concentrations during their night-time dwells. Serum I-metabolites did not increase during peritonitis. There was no excess of peritonitis episodes in I patients.

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Received for publication: 20.1.98
Accepted in revised form: 8.4.98