Review of clinical trial experience with icodextrin

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Icodextrin-based dialysis solutions have been introduced to address an unmet clinical need in peritoneal dialysis, namely the difficulties inherent in ultrafiltration management during the long dwell [1–4]. These solutions take advantage of the physiologic principle of colloid osmosis and the high reflection coefficient of the glucose polymers allows for ultrafiltration to proceed with dialysis solutions iso-osmotic to plasma. While the efficacy and safety of icodextrin have been described in multiple publications (abstracts; Douma et al, *J Am Soc Nephrol* 8:282A, 1997; Wolfson et al, *J Am Soc Nephrol* 12:317A, 2001; Wolfson et al, *J Am Soc Nephrol* 317A, 2001; Woodrow et al, *Perit Dial Int* 14:140, 1998) [5–11], an integrated summary of the major controlled clinical trials is in order as the use of this new class of osmotic agents widens around the world.

Evaluation of ultrafiltration during peritoneal dialysis can be examined in two complementary approaches. A quantitative approach examines the values of net ultrafiltration achieved under various therapeutic conditions. A normative approach, however, is more clinically relevant as it relates the ultrafiltration response to the therapeutic intent of the physician applying it. In the case of ultrafiltration, the normative approach would examine the occurrence of negative net ultrafiltration with the various interventions, as this occurrence is contrary to the therapeutic intent. Hence, negative net ultrafiltration can be labeled as therapeutic failure and the relative occurrence of this condition can be used as a normative measure to compare interventions.

TRIALS DESCRIPTION

MIDAS Trial

The Multicenter Study of Icodextrin in Continuous Ambulatory Peritonal Dialysis (MIDAS Trial) was an open, randomized, active controlled study comparing 7.5% icodextrin with dextrose (1.5 to 4.25%) for the long/overnight dwell in patients on continuous ambulatory peri-

toneal dialysis (CAPD). A total of 209 patients in the United Kingdom were enrolled and were treated for up to six months. The objectives of the study were to evaluate the efficacy of 7.5% icodextrin compared with low (1.5%) or high (4.25%) dextrose solutions when the dwell time was 8 or 12 hours overnight. Approximately 40% of patients in the dextrose group used 4.25% dextrose bags overnight prior to the study and the other patients used 1.5% dextrose bags overnight prior to the study.

One hundred five patients were randomized in the low dextrose arm of the study (55 patients, 1.5% dextrose; 50 patients, 7.5% icodextrin). The mean age (approximately 57 years of age) was comparable between the 1.5% dextrose and 7.5% icodextrin groups. Seventy-three patients were randomized in the high dextrose arm of the study (38 patients, 4.25% dextrose; 35 patients, 7.5% icodextrin). The mean age was 55 years in both treatment groups.

Patients randomized to the icodextrin group received 7.5% icodextrin solution in place of their usual dextrose solution for the nighttime dwell for six months. Patients in the control group continued to receive their usual long dwell solution of either 1.5%, or 4.25% dextrose solutions for the nighttime dwell. When dextrose concentration usage for the long dwell was reviewed from the baseline period, no patient reported using 2.5% dextrose in their usual prescription. Patients in both treatment groups continued their normal daytime exchanges using dextrose-based solutions. Overnight dialysis dwell times were controlled during six study weeks (weeks 3, 4, 12, 13, 20, and 21), in which all patients received their usual 8-hour (weeks 3, 12, and 20) or a standardized 12-hour (weeks 4, 13, and 21) overnight dwell.

North American CAPD Trial

This study was a prospective, randomized, double-blind parallel group, active-controlled study of 175 continuous ambulatory peritoneal dialysis (CAPD) patients enrolled in the United States and Canada. The objectives of the study were to evaluate the efficacy and safety of 7.5% icodextrin compared with 2.5% dextrose peritoneal dialysis solution. Patients were treated for one month. Of the 175 patients enrolled in this study, 85 received di-
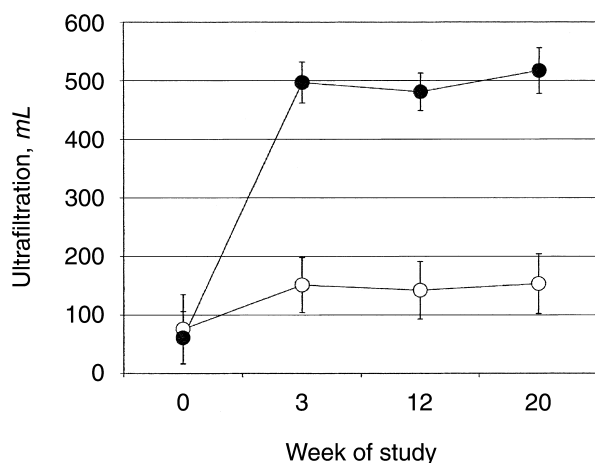
Fig. 1. MIDAS Study: Mean ultrafiltration (UF) in 1.5% dextrose-treated patients (○) versus 7.5% icodextrin-treated continuous ambulatory peritoneal dialysis (CAPD) patients (●) for the 8-hour dwell.

Fig. 2. MIDAS Study: Mean UF in 1.5% dextrose-treated patients (○) versus 7.5% icodextrin-treated CAPD patients (●) for the 12-hour dwell.

alysis treatment with 2.5% dextrose, and 90 patients received 7.5% icodextrin. Net UF for the long nighttime dwell was measured at weeks 2 and 4. Overnight dialysis dwell times in this study were 12 ± 4 hours.

European APD Trial

This study was a prospective, randomized, open-label parallel group, active-controlled study comparing the safety and efficacy of icodextrin 7.5% with 2.5% dextrose in patients treated with automated peritoneal dialysis (APD). A total of 39 patients were enrolled in this 16-week study (2 weeks of baseline evaluation, 12 weeks treatment, 2 weeks follow-up). Of the 39 patients enrolled in this study, 19 received 2.5% dextrose for the long daytime dwell and 20 patients received 7.5% icodextrin. The primary efficacy parameter for this study was net UF for the long daytime dwell. Daytime dialysis dwell times in this study were 14 ± 2 hours. Primary efficacy variables were measured at baseline, weeks 1, 6, and 12, and during follow-up when only glucose-based dialysis solutions were used.

EFFECTS ON NET ULTRAFILTRATION IN CAPD

7.5% icodextrin versus 1.5% dextrose

The 8-hour dwell. Figure 1 illustrates the net ultrafiltration (UF) during the 8-hour nighttime dwell at baseline and weeks 3, 12, and 20 for the 1.5% dextrose and 7.5% icodextrin treatment groups. The mean net UF at baseline was comparable between the 7.5% icodextrin group and the 1.5% dextrose group (61 mL vs. 76 mL, respectively; $P = 0.846$). Mean net UF was increased in the 7.5% icodextrin group compared with the 1.5% dextrose group at week 3 (497 vs. 151 mL), week 12 (481 vs. 142 mL), and week 20 (517 vs. 153 mL).
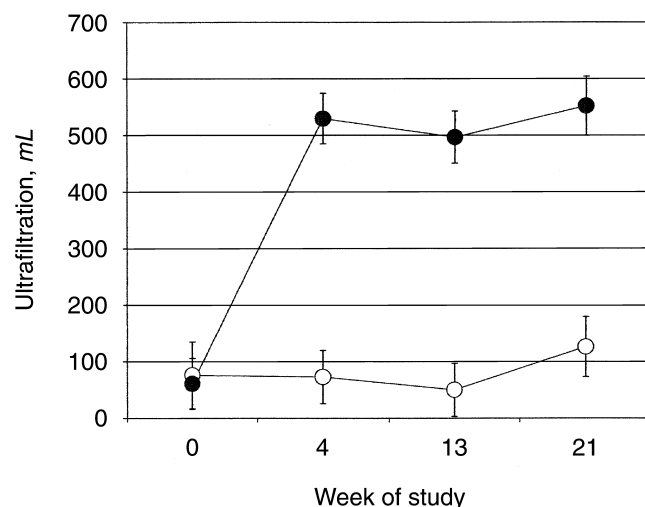
In addition to comparisons of net ultrafiltration at discrete time periods, the mean change from baseline in net UF was evaluated. Analysis of covariance (ANCOVA) revealed that the mean changes in UF were significantly greater in the 7.5% icodextrin group compared with the 1.5% dextrose group at weeks 3, 12, and 20 ($P < 0.001$ at all 3 visits).

12-hour dwell. Figure 2 illustrates the net UF of the 12-hour nighttime dwell at baseline and weeks 4, 13, and 21 for the 1.5% dextrose and 7.5% icodextrin treatment groups. The mean net UF at baseline was comparable between the 7.5% icodextrin group and the 1.5% dextrose group (61 mL vs. 76 mL, respectively; $P = 0.846$). Mean net UF was increased in the 7.5% icodextrin group compared with the 1.5% dextrose group at weeks 4 (530 vs. 73 mL), 13 (497 vs. 50 mL), and 21 (552 vs. 126 mL).

In addition to comparisons of net ultrafiltration at discrete time periods, the mean change from baseline in net UF was evaluated. Analysis of covariance revealed that the mean changes in UF were significantly higher in the 7.5% icodextrin group compared with the 1.5% dextrose group at weeks 4, 13, and 21 ($P < 0.001$ at all 3 visits).

7.5% icodextrin versus 2.5% dextrose

Figure 3 illustrates the net UF at the completion of the 12 ± 4 hour dwell at baseline, week 2 and week 4 for the 2.5% dextrose and 7.5% icodextrin treatment groups. The mean net UF at baseline was comparable between the 7.5% icodextrin group and the 2.5% dextrose group (262 vs. 329 mL; $P = 0.230$). Mean net UF was increased in the 7.5% icodextrin group compared with the 2.5% dextrose group at both the week 2 (578 vs. 390 mL) and week 4 visits (606 vs. 380 mL).

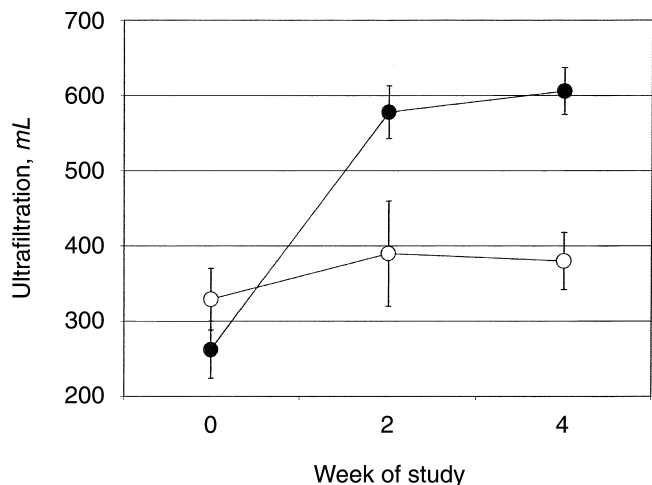In addition to comparisons of net ultrafiltration at

Fig. 3. North American CAPD Trial: Mean UF in 2.5% dextrose-treated patients (○) versus 7.5% icodextrin-treated patients (●) for the 12 ± 4-hour dwell.
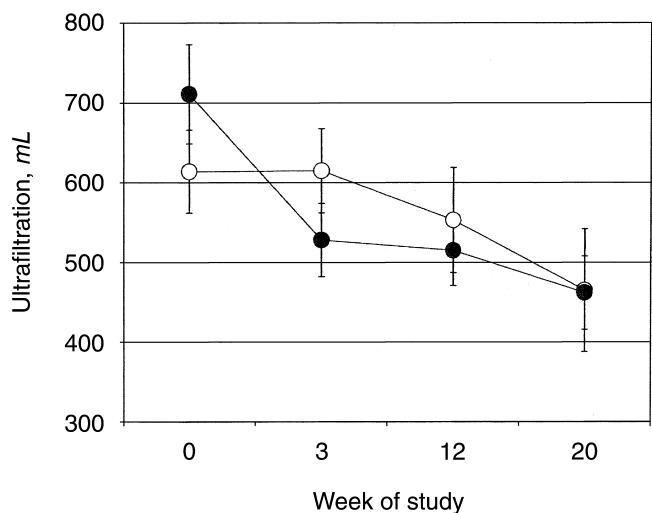

Fig. 5. MIDAS Study: Mean UF in 4.25% dextrose-treated patients (○) versus 7.5% icodextrin–treated CAPD patients (●) for the 12-hour dwell.

Fig. 4. MIDAS Study: Mean UF in 4.5% dextrose-treated patients (○) versus 7.5% icodextrin-treated CAPD patients (●) for the 8-hour dwell.

(528 vs. 615 mL), week 12 (515 vs. 553 mL), and week 20 (462 vs. 465 mL).

In addition to comparisons of net ultrafiltration at discrete time periods, the mean change from baseline in net UF was evaluated. ANCOVA revealed that the mean changes in net UF between the 7.5% icodextrin and the 2.5/4.25% dextrose treatment groups were significantly different at week 3 ($P = 0.011$), but not significantly different at weeks 12 ($P = 0.246$) and 20 ($P = 0.372$).

12-hour dwell. Figure 5 illustrates the net UF at the completion of the 12-hour nighttime dwell at baseline and weeks 4, 13, and 21 for the 4.25% dextrose and 7.5% icodextrin treatment groups. The mean net UF at baseline was comparable between the 7.5% icodextrin group and the 4.25% dextrose group (711 vs. 614 mL; $P = 0.232$). Mean net UF was greater in the 7.5% icodextrin group compared with the 4.25% dextrose group at week 4 (607 vs. 498 mL), week 13 (592 vs. 458 mL), and week 21 (510 vs. 427 mL).

In addition to comparisons of net ultrafiltration at discrete time periods, the mean change from baseline in net UF was evaluated. Although the net UF was greater in the 7.5% icodextrin group compared with the high dextrose group, ANCOVA revealed that the mean changes in UF were not significantly different between the two treatment groups at weeks 4 ($P = 0.405$), 13 ($P = 0.400$), and 21 ($P = 0.687$).

EFFECT ON THERAPEUTIC FAILURE IN CAPD

7.5% icodextrin versus 1.5% dextrose

8-hour dwell. Figure 6 illustrates the percentage of patients with negative net UF at baseline and weeks 3, 12, and 21 in patients using either 1.5% dextrose or 7.5%

discrete time periods, the mean change from baseline in net UF was evaluated. ACOVA revealed that the mean changes in UF were significantly higher in the 7.5% icodextrin group compared with the 2.5% dextrose group at both weeks 2 ($P = 0.008$) and 4 ($P < 0.001$).

7.5% icodextrin versus 4.25% dextrose

8-hour dwell. Figure 4 shows the net UF at the completion of the 8-hour nighttime dwell at baseline and weeks 3, 12, and 20 for the 4.25% dextrose and 7.5% icodextrin treatment groups. The mean net UF at baseline was comparable between the 7.5% icodextrin group and the 4.25% dextrose group (711 vs. 614 mL; $P = 0.232$). Mean net UF was comparable between the 7.5% icodextrin group and the 4.25% dextrose group at week 3
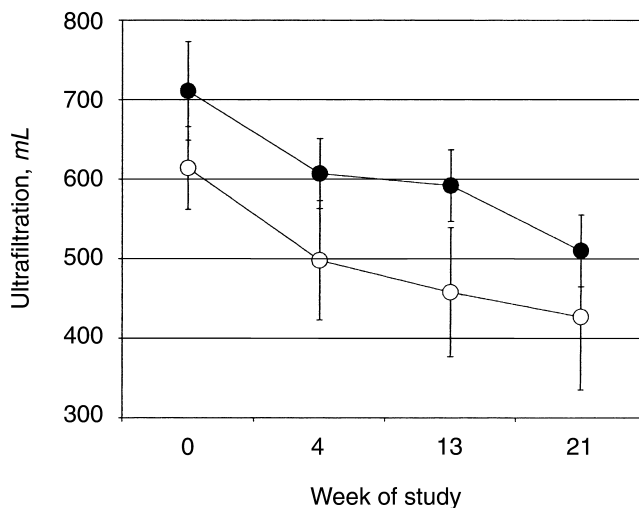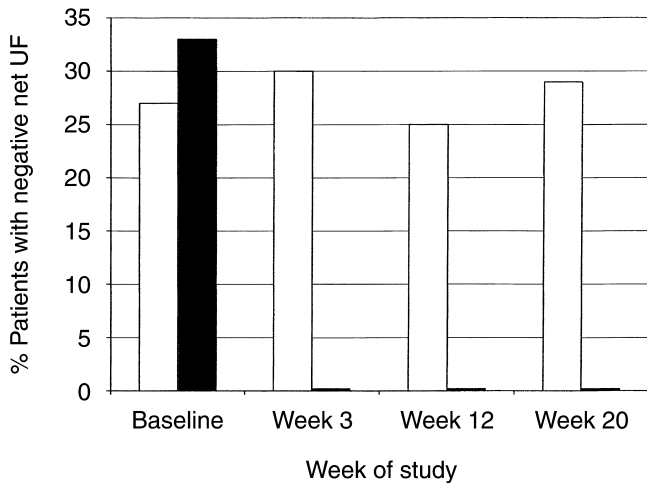
Fig. 6. MIDAS Study: Percent of CAPD patients with negative net UF for the 8-hour dwell. Symbols are: (□) 1.5% dextrose, (■) 7.5% icodextrin.
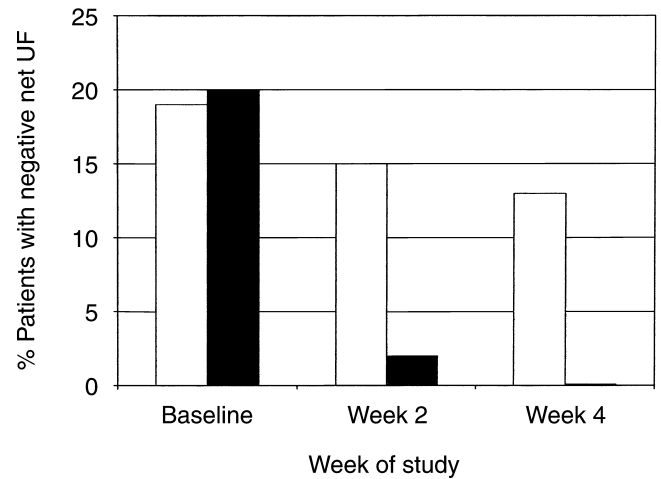

Fig. 8. North American CAPD Trial: Percent of patients with negative net UF for the 12 ± 4-hour dwell. Symbols are: (□) 2.5% dextrose, (■) 7.5% icodextrin.
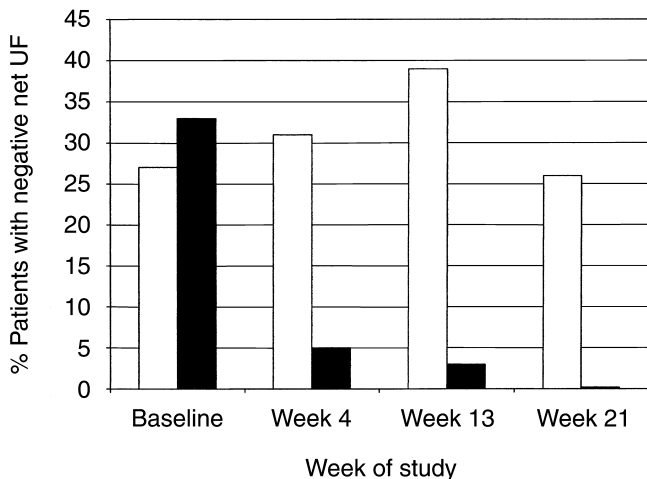

Fig. 7. MIDAS Study: Percent of CAPD patients with negative net UF for the 12–hour dwell. Symbols are: (□) 1.5% dextrose, (■) 7.5% icodextrin.

percentage of patients with negative net UF was significantly reduced in the 7.5% icodextrin group compared with the 1.5% dextrose group at weeks 4 (5 vs. 31%; $P = 0.001$), 13 (3 vs. 39%; $P < 0.001$), and 21 (0 vs. 26%, $P = 0.001$).

7.5% icodextrin versus 2.5% dextrose

Figure 8 illustrates the percentage of patients with negative net UF at baseline, and weeks 2 and 4 in 20 in patients using either 2.5% dextrose or 7.5% icodextrin for the 12 ± 4-hour nighttime dwell. The percentage of patients with negative net UF at baseline was comparable between the 7.5% icodextrin group and the 2.5% dextrose group (20 vs. 19%; $P = 0.844$). The percentage of patients with negative net UF was significantly reduced in the 7.5% icodextrin group compared with the 2.5% dextrose group at weeks 2 (2 vs. 15%; $P = 0.004$) and 4 (0 vs. 13%; $P < 0.001$).

7.5% icodextrin versus 4.25% dextrose

8-hour dwell. Figure 9 illustrates the percentage of patients with negative net UF at baseline and weeks 3, 12, and 20 in patients using either 4.25% dextrose or 7.5% icodextrin for the 8-hour nighttime dwell. The percentage of patients with negative net UF at baseline was 3% in both the 7.5% icodextrin and the 4.25% dextrose treatment groups. Although the percentage of patients with negative net UF was lower in the 7.5% icodextrin group than in the 4.25% dextrose group, the reduction was not statistically significant. The percentages of patients with a negative net UF in the 7.5% icodextrin group compared with the 4.25% dextrose group weeks 3, 12, and 20, respectively, were: 4 versus 7% ($P = 1.000$), 0 versus 7% ($P = 0.497$), and 5 versus 13% ($P = 0.618$).

12-hour dwell. Figure 10 illustrates the percentage of

icodextrin for the 8-hour nighttime dwell. The percentage of patients with negative net UF at baseline was comparable between the 7.5% icodextrin group and the 1.5% dextrose group (33 vs. 27%; $P = 0.652$). The percentage of patients with negative net UF was significantly reduced in the 7.5% icodextrin group compared with the 1.5% dextrose group at weeks 3 (0 vs. 30%; $P < 0.001$), 12 (0 vs. 25%; $P < 0.001$), and 20 (0 vs. 29%, $P < 0.001$).

12-hour dwell. Figure 7 illustrates the percentage of patients with negative net UF at baseline and weeks 4, 13, and 21 20 in patients using either 1.5% dextrose or 7.5% icodextrin for the 12-hour nighttime dwell. The percentage of patients with negative net UF at baseline was comparable between the 7.5% icodextrin group and the 1.5% dextrose group (33 vs. 27%; $P = 0.652$). The
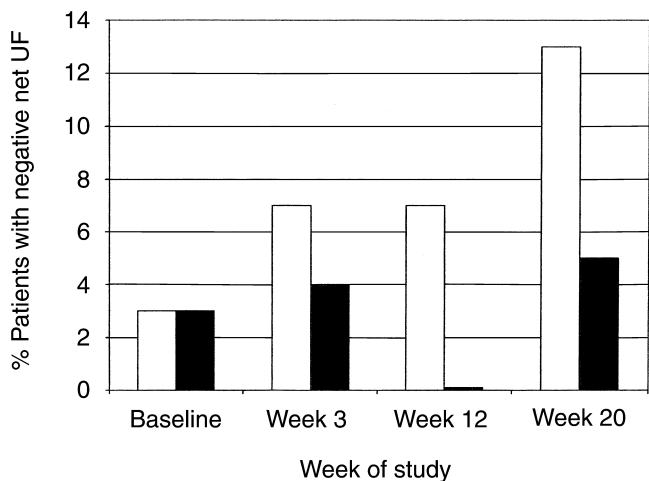
Fig. 9. **MIDAS Study: Percent of CAPD patients with negative net UF for the 8-hour dwell.** Symbols are: (□) 4.5% dextrose, (■) 7.5% icodextrin.
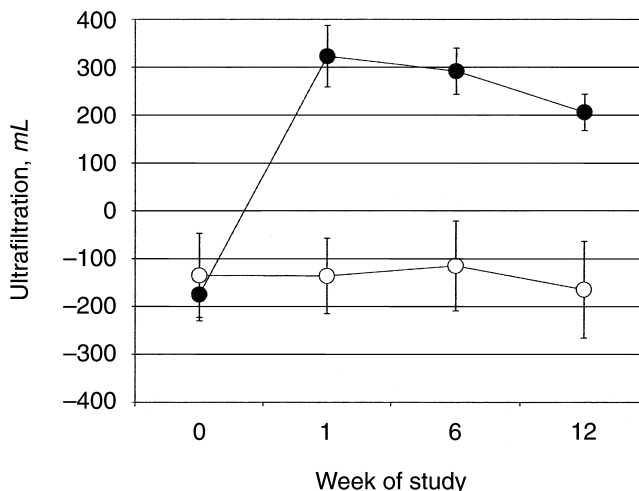

Fig. 11. **European Automated Peritoneal Dialysis (APD) Trial: Mean UF in 2.5% dextrose-treated patients (○) versus 7.5% icodextrin-treated patients (●) for the 14 ± 2-hour dwell.**
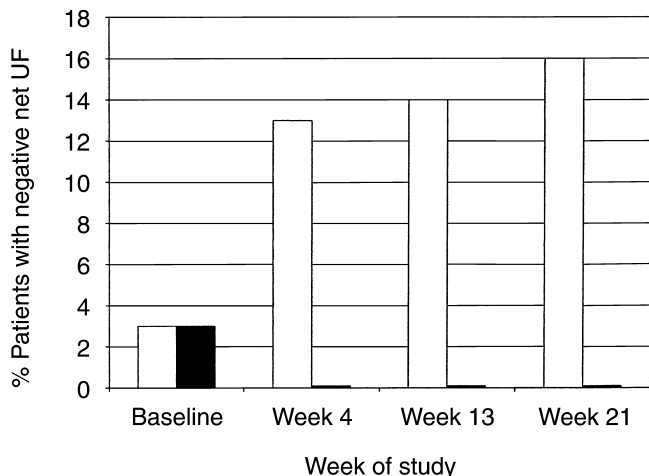

Fig. 10. **MIDAS Study: Percent of CAPD patients with negative net UF for the 12-hour dwell.** Symbols are: (□) 4.5% dextrose, (■) 7.5% icodextrin.

EFFECTS ON NET ULTRAFILTRATION IN APD

Net UF from the long daytime dwell exchange in APD was determined at the completion of the 14 ± 2 hour dwell at baseline, weeks 1, 6, and 12, and during follow up for the 2.5% dextrose and 7.5% icodextrin treatment groups (Fig. 11). Both treatment groups had a negative net UF during the long dwell at baseline while receiving 2.5% dextrose. The mean net UF at baseline was comparable between the 7.5% icodextrin group and the 2.5% dextrose group (-175 vs. -135 mL; $P = 0.697$). Within the first week the mean net UF was increased in the 7.5% icodextrin group to a positive net UF (323 vs. -136 mL). Similar results were obtained at weeks 6 (292 vs. -115 mL) and 12 (206 vs. -165 mL).

In addition to comparisons of net ultrafiltration at discrete time periods, the mean change from baseline in net UF was evaluated. ANCOVA revealed that the mean changes in net UF were significantly higher in the 7.5% icodextrin compared with the 2.5% dextrose groups at weeks 1, 6, and 12 ($P < 0.001$ at all 3 visits).

EFFECT ON THERAPEUTIC FAILURE IN APD

Figure 12 illustrates the percentage of patients with negative net UF at baseline and weeks 1, 6, and 12 during the 14 ± 2-hour long daytime dwell. The percentage of patients with negative net UF at baseline was comparable between the 7.5% icodextrin group and the 2.5% dextrose group (75 vs. 74%; $P = 1.000$). The percentage of patients with negative net UF was significantly reduced in the 7.5% icodextrin group compared with the 2.5% dextrose group at weeks 1 (15 vs. 68%; $P < 0.001$), 6 (6 vs. 67%; $P < 0.001$), and 12 (6 vs. 71%; $P < 0.001$).

patients with negative net UF at baseline and weeks 4, 13, and 21 in patients using either 4.25% dextrose or 7.5% icodextrin for the 12-hour nighttime dwell. The percentage of patients with negative net UF at baseline was 3% in both the 7.5% icodextrin and the 4.25% dextrose groups. Although the percentage of patients with negative net UF was reduced in the 7.5% icodextrin group compared with 4.25% dextrose group at weeks 4, 13, and 21, this reduction was not statistically significant. The percentages of patients with a negative net UF in the 7.5% icodextrin group compared with the 4.25% dextrose group at weeks 4; 13, and 21, respectively, were: 0 versus 13% ($P = 0.113$), 0 versus 14% ($P = 0.117$), and 0 versus 16% ($P = 0.114$).
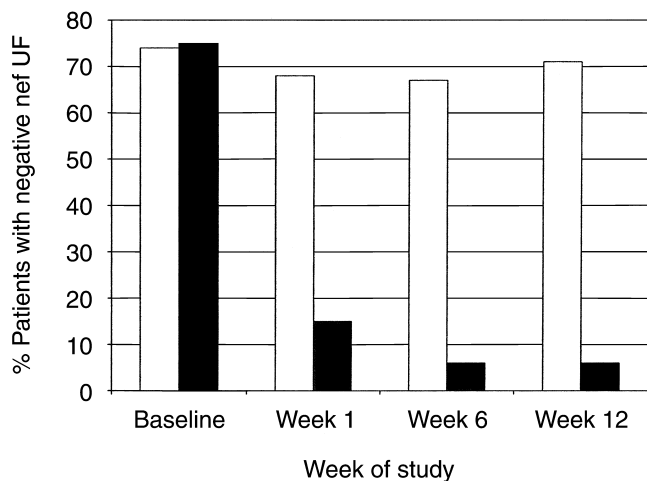
Fig. 12. European APD Trial: Percent of patients with negative net UF for the 14 ± 2-hour dwell. Symbols are: (□) 2.5% dextrose; (■) 7.5% icodextrin.

Table 1. Incidence of skin rash

	Dextrose		Icodextrin	
	Group size *N*	Incidence %	Group size *N*	Incidence %
Overall	347	4.6	493	10.1
Age >65 years	95	6.3	123	8.1
Male	175	2.3	278	6.8
Female	172	7.0	215	14.4
Caucasian	257	4.3	360	10.0
Black	62	4.8	90	8.9
Diabetes mellitus	94	5.3	132	10.6

ADVERSE EVENTS

The adverse events profile of icodextrin-based solutions is similar to that of peritoneal dialysis solutions in general except for a few specific areas that warrant detailed description. Two such adverse events are discussed: the first, skin rash, because it is the most common treatment-related adverse event observed in clinical trials, and the second, peritonitis, because it is has been the subject of confusion in the literature [12].

Skin rash

The development of a new skin rash is the most common treatment-related side effect of the use of icodextrin [abstracts; Prichard et al, *Perit Dial Int* 21(Suppl 2):S81, 2001; Russo et al, *Perit Dial Int* 20:145, 2000; Goldsmith et al, *Perit Dial Int* 20:125, 2000] [13–17]. Because skin disorders are common in patients on dialysis, it is important to always contrast the incidence of this event with the background incidence observed in patients using exclusively glucose-based dialysis solutions. Such a side-by-side comparison based on all clinical trials combined is shown in Table 1. The incidence rates listed in the Table reflect the occurrence of de novo skin rashes observed during the course of the trials. Patients on icodextrin had a higher incidence of rash (10.1%) compared to patients on dextrose-based solutions for the long dwell (4.6%; *P* < 0.003). Because the occurrence of rash is recognized to be influenced by a variety of factors, subgroup analysis was performed to determine how these factors influence the incidence rate of rash (abstract; Russo, *ibid*). In both patients on dextrose-based solutions for the long dwell and patients on icodextrin, the incidence of rash appeared not to be influenced by age, race, or the presence of diabetes, but to be affected significantly by gender with women having a higher incidence rate than men (Table 1). Further, no association was found between the development of the rash and the steady state blood levels of oligosaccharides.

The rash related to icodextrin usually occurred in the early phase of therapy. This is reflected in the observed declining incidence over time in the clinical studies: while the overall rate was 10.1%, it declined to 4.7% in patients on treatment for more than 180 days, and to 2.6% in patients on treatment for more than one year. The rash was mild or moderate in the majority of patients (mild 46.4%, moderate 48.2%), and resolved with discontinuation of icodextrin use without any sequelae (Baxter Healthcare Corporation, data on file). The rash typically involved the palms and soles and in a minority of patients was associated with mild peeling of the skin.

Bacterial peritonitis

A recent review has suggested that the incidence of bacterial peritonitis may be increased in patients using icodextrin-based solution for the long dwell [12]. The review examined the rates of peritonitis reported in the initial trials of icodextrin, and while acknowledging the differences at baseline between the two groups that may account for the observed differences, left the impression that the numerical tendencies of higher peritonitis rates with icodextrin may be representative [12]. The review failed to mention that the apparent differences between the two groups were not statistically significant. The review also failed to report the findings of Posthuma et al that found no difference in the incidence of peritonitis between patients using dextrose and patients on icodextrin (1 per 17.6 months and 1 per 21.9 months, respectively) [9].

We examined the incidence of peritonitis in the controlled clinical trials of icodextrin including the earlier studies mentioned above. Peritonitis occurred in 25.4% of 347 patients in the control group and 26.4% of 493 patients in the icodextrin group (Baxter Healthcare Corporation, data on file). The peritonitis led to withdrawal from the studies in 4% of patients in the control group and 3.7% of patients in the icodextrin group (Baxter

Healthcare Corporation, data on file). Hospitalization due to peritonitis, however, was lower in the icodextrin group (5.3%) than in the control group (8.6%, $P = 0.013$; Baxter Healthcare Corporation, data on file). These results show that the incidence of peritonitis in patients using icodextrin is not different from that of patients using dextrose for the long dwell.

CONCLUSION

The efficacy data from the clinical trials provide evidence that patients treated with icodextrin have an improved UF profile compared with either the 1.5% or 2.5% dextrose solutions, as it provides both significantly greater UF and also reduces the percentage of patients with negative net UF. In addition, it provides enhanced waste solute clearance as compared to 1.5% and 2.5% dextrose solutions. The safety data from the clinical trials provide evidence that icodextrin is a well-tolerated dialysate with an adverse event profile generally similar to dextrose dialysate. Dermatological adverse events (particularly rash and exfoliative dermatitis) are more common in icodextrin-treated patients, but are usually mild or moderate in intensity, appear during the first three weeks of therapy, and often resolve with discontinuation of icodextrin.

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