Author's response to reviews

Title: Icodextrin as salvage therapy in peritoneal dialysis patients with refractory fluid overload

Authors:

David W Johnson Dr (david_johnson@health.qld.gov.au)
Mary Arndt Ms (Cot_Ambulatory_Dialysis_CAPD@health.qld.gov.au)
Amanda O'Shea Ms (Cot_Ambulatory_Dialysis_CAPD@health.qld.gov.au)
Rhonda Watt Ms (Cot_Ambulatory_Dialysis_CAPD@health.qld.gov.au)
Jan Hamilton Ms (Cot_Ambulatory_Dialysis_CAPD@health.qld.gov.au)
Kaia Vincent Ms (Kaia_Vincent@health.qld.gov.au)

Version: 2 Date: 9 Nov 2001

PDF covering letter
RESPONSE TO REVIEWER #1

1. The main concerns relate to the “gaps in knowledge” that is filled by this paper

Despite the reviewer’s assertions that “the accumulated data on icodextrin use in patients with loss of ultrafiltration capacity has been recognised for several years”, there have actually been no prospective trials of icodextrin use in patients with ultrafiltration failure or fluid overload prior to our study. The ISPD guidelines for management of ultrafiltration failure do recommend icodextrin for patients with a net ultrafiltration less than 400 ml/4 hours and a high transport profile of small solute clearance. However, these guidelines primarily reflect opinion. The best available evidence supporting this recommendation is the observation in 10 stable CAPD patients (without ultrafiltration failure) of a weakly positive linear correlation ($r^2=0.43$) of borderline statistical significance ($p=0.05$) between the mass transfer area coefficient of creatinine and transcapillary ultrafiltration rate with icodextrin during a 4-hour standard peritoneal permeability analysis (SPA) [1]. Woodrow et al [2] similarly identified a positive linear correlation ($r^2=0.26$, $p<0.05$) between the dialysate:plasma creatinine ratio at 4 hours and the difference in ultrafiltration achieved between icodextrin and 3.86% glucose dialysate in 17 APD patients without ultrafiltration failure. Both of these studies were already cited in the paper (Background Page 4 Paragraph 1 Line 5, Discussion Page 12 Paragraph 12) and are suggestive that icodextrin may promote better fluid removal compared with glucose-based dialysates in patients with higher peritoneal membrane transport characteristics (who constitute the bulk of patients with ultrafiltration failure). However, these
studies are hypothesis-generating rather than hypothesis-testing and do not address the more important questions of how icodextrin impacts on net daily ultrafiltration in patients with fluid retention problems or on hard clinical end-points, such as technique survival.

These issues were addressed by our study, which is the first prospective examination of the ability of icodextrin to enhance peritoneal ultrafiltration and prolong technique survival in a clearly and practically defined group of patients with symptomatic fluid overload. As already mentioned in the manuscript (Background Page 4 Paragraph 2 Line 1), the previous evidence that icodextrin prolonged technique survival in such patients consisted only of two retrospective studies, which were potentially limited by recall bias and by the lack of a clear or consistent definition of “ultrafiltration failure,” thereby introducing uncertainty as to the true extent of PD prolongation. The studies may also have overestimated prolongation of technique survival as a result of censoring the data for patient death (since impaired ultrafiltration and fluid overload could conceivably have contributed to mortality). Our prospective study addressed these limitations and provided new information regarding the clinical factors, which were predictive of a satisfactory ultrafiltration response to icodextrin and subsequent enhancement of technique survival. In particular, low daily ultrafiltration volume was predictive of a satisfactory response. This information is novel and of substantial importance to clinicians who are trying to determine whether or not their patients with refractory, symptomatic fluid overload are likely to respond to icodextrin therapy. A further novel finding of our study was the demonstration of an improvement in glycaemic control in diabetic peritoneal
dialysis patients with ultrafiltration difficulties. This has not been previously studied. All of these points have already been made in the paper.

2. Additional relevant publications are not discussed

The Imholz et al [3] reference has now been cited in the Discussion section of the manuscript (Page 12 Paragraph 1). The other references cited by the reviewer were not included because they were either tangential to the main thrust of our paper or were reviews of relevant studies that were already cited in our paper. The paper by Neri and associates [4] was essentially a study of the impacts of posture and physical activity on the differences in ultrafiltration with icodextrin between 10 CAPD and 10 APD patients. The evidence provided by Krediet et al [5] in their review cited the results observed in the small transport study by Ho dac Pannekeet et al [6], which is referenced in our paper. Peers and Gokal [7] reviewed the literature pertaining to icodextrin. All of the articles cited in this review that were relevant to icodextrin use in patients with fluid overload had already been cited in our manuscript. The relevant paper by Stein et al was unable to be found in Peritoneal Dialysis International.

3. The paper would have been considerably enhanced by provision of clear objective criteria (endorsed by the ISPD) for the diagnosis of ultrafiltration

The ISPD criterion for diagnosis of ultrafiltration failure was published in mid-2000 and was not available when we commenced the study on 30 January 1999. In the absence of the availability of this criterion, we opted to define ultrafiltration failure based on a widely recommended adequacy target of 1 L/day [8] (The ISPD has not
yet defined a daily adequacy target for ultrafiltration). This is a clear, objective and practical definition that is no less evidence-based than the ISPD recommendation. The ISPD definition of ultrafiltration failure (< 400 mL/4h) was based on standard peritoneal permeability analyses in 68 stable PD patients and validated against a dubious “gold standard” of net negative ultrafiltration with 1.36% glucose dialysate. In support of the definition that we employed in our study, Davies [8] has demonstrated that net daily ultrafiltration < 1L/day correlates very well with a PET ultrafiltration capacity of less than 200 ml (equivalent to a SPA < 400 ml). The Davies reference has now been cited in the manuscript (Results Page 9 Paragraph 2). To avoid confusion with the ISPD definition of ultrafiltration failure, patients in our study with net daily ultrafiltration volumes below and above 1 L have been reclassified as low daily ultrafiltration (LDUF) and normal daily ultrafiltration (NDUF), respectively. Information about the infused glucose amounts has been provided (Methods Page 7 Paragraph 1 Line 1). As stated in the Methods section (Page 6 Paragraph 1 Line 4), all patients were placed on a fluid restriction of 800 ml/day. The numbers of patients at-risk in each group have now been provided in the Kaplan-Meier survival curve in Figure 2.

4. The lack of randomisation is a short-coming of the paper

This has already been acknowledged in our paper (Discussion Page 13 Paragraph 2 Line 1).
RESPONSE TO REVIEWER #2

1. **Page12 Sentence 2: Leave the sentence out of the paper. This is an irrelevant conclusion.**

   This conclusion is based on the results of the multivariate Cox regression analysis, which identified net ultrafiltration < 1L/day as a strong independent predictor of prolongation of technique survival by icodextrin. We believe that this is an important and novel finding that belongs in the conclusions because it assists clinicians in predicting which of their fluid overloaded patients are likely to respond to icodextrin therapy. The sentence has been reworded to provide greater clarity of meaning.

2. **Please present data for “UFF” and “No UFF” groups separately, because this is necessary to justify the conclusion that patients with poor baseline ultrafiltration are high or high average transporters and the other group is not.**

   The section of the Discussion to which the Reviewer is referring (Page 12 Paragraph 1 Line 5) is misleading. We intended to refer to the whole study group rather than patients with low daily ultrafiltration volumes. This has been rectified so as to avoid creating the impression that patients with poor baseline ultrafiltration were high or high-average transporters and the other group was not. Given that the vast majority of the study population were high and high-average transporters, the proportion of high/high-average transporters was considerable in both patients with and without UFF (88% vs 89%, respectively). An explanation for the lack of
correlation between transport status and icodextrin-associated ultrafiltration has additionally been provided (Discussion Page 12 Paragraph 1). As mentioned in Response 3 to Reviewer #1, we have also reclassified “ultrafiltration failure” (UFF) as low daily ultrafiltration (LDUF) and “no UFF” as normal daily ultrafiltration (NDUF) in order to avoid confusion with the ISPD definition of ultrafiltration failure.

3. **Is it “frusemide” or “furosemide”**

   “Frusemide” and “furosemide” are valid alternative names for the same drug.

4. **Counts for UFF group in Figure 1.**

   Kaplan-Meier survival curves depict event rates as a proportion of the patients “at-risk” for each time point. Since patients were followed up for variable periods of time (recruitment took place between 1999 and 2001) and the data were censored at the end of the study period (31 May 2001), the number of patients at-risk decreased with time. In order to make this clearer, the number of patients at risk has been provided at the tops of both figures.
REFERENCES


SUMMARY OF CHANGES MADE

1. Title Page: Coauthor’s name changed from “Robyn Watt” changed to “Rhonda Watt.”

2. Abstract Page 2 Results Last Line: Added “daily” between “baseline” and “peritoneal.”

3. Methods Page 7 Line 1: Changed paragraph from,

   “patients) glucose exchange. The remaining glucose exchanges were not altered at any stage.”

   To,

   “patients) 4.25% glucose exchange. The remaining glucose exchanges (all 2.5% glucose exchanges except for 2 patients who each had an additional 4.25% glucose exchange) were not altered at any stage.”

4. Results Page 9 Paragraph 2 Line 7: Changed sentences from:

   “Patients who had ultrafiltration failure, defined as a net daily ultrafiltration of less than 1L, remained on PD for a considerably longer time period following icodextrin administration than those who did not have ultrafiltration impairment (Fig. 2).”

   To,

   “Patients who had low daily ultrafiltration, defined as a net daily ultrafiltration of less than 1L[10], remained on PD for a considerably longer
time period following icodextrin administration than those who had normal daily ultrafiltration (Fig. 2)."

5. Discussion Page 12 Paragraph 1: Changed paragraph from:

“The extension of PD life in our study appears to have been related to a substantial increase in peritoneal fluid removal and was most marked in those patients who had poor initial ultrafiltration (<1 L/day). For each additional litre/day of peritoneal ultrafiltration prior to icodextrin commencement, the adjusted risk of subsequent early technique failure was increased by approximately 150%. In keeping with previous studies [10-12], most (89%) of the patients with poor baseline ultrafiltration were high or high-average transporters. Their favourable response to icodextrin is consistent with the reported observation that the mass transfer area coefficient of creatinine was positively correlated with transcapillary ultrafiltration induced by icodextrin, but not glucose dialysate [3]. Similarly, Woodrow et al [4] noted that the difference in daytime ultrafiltration between icodextrin and 3.86% glucose was positively correlated with the dialysate:plasma creatinine ratio, suggesting that icodextrin achieves superior fluid removal compared with glucose-based dialysates in subjects with higher peritoneal membrane transport characteristics.”

To,

“The extension of PD life in our study appears to have been related to a substantial increase in peritoneal fluid removal and was most marked in those patients who had poor initial daily ultrafiltration (<1 L/day). For each
additional litre/day of peritoneal ultrafiltration prior to icodextrin commencement, the adjusted risk of subsequent early technique failure was increased by approximately 150%. These results are supported by Imholz et al [11], who demonstrated that icodextrin promoted a greater net ultrafiltration in 5 CAPD patients with low ultrafiltration than those with normal ultrafiltration (918±85 vs 657±104 ml, respectively, p=0.06).

In keeping with previous studies of patients with refractory fluid overload [12-14], most (89%) of the patients in this investigation were high or high-average transporters. Their generally favourable response to icodextrin is consistent with the reported observation in stable peritoneal dialysis patients that the mass transfer area coefficient of creatinine was positively correlated with transcapillary ultrafiltration induced by icodextrin, but not glucose dialysate [3]. Similarly, Woodrow et al [4] noted in euvolaemic CCPD patients that the difference in daytime ultrafiltration between icodextrin and 3.86% glucose was positively correlated with the dialysate:plasma creatinine ratio, suggesting that icodextrin achieves superior fluid removal compared with glucose-based dialysates in subjects with higher peritoneal membrane transport characteristics. Such a correlation was unable to be demonstrated in our patients with symptomatic fluid overload, possibly because of the great preponderance of high and high-average transporters and the consequent narrowing of the range of dialysate:plasma creatinine ratios.”
“Those individuals with impaired ultrafiltration (< 1L/day) appear to be most likely to derive benefit from incorporation of icodextrin into their PD regimens.”

To,

“Those individuals with low net daily ultrafiltration volumes (< 1L/day) appear to be more likely to derive benefit from incorporation of icodextrin into their PD regimens than patients with higher ultrafiltration volumes.”

7. Abbreviations Page 14: Deleted UFF and added LDUF and NDUF.


9. Figures 1 & 2: Add numbers of at-risk patients to tops of both figures.

10. Figure 2 Legend reworded to incorporate new abbreviations for low and normal daily ultrafiltration.