The contribution of combined crystalloid and colloid osmosis to fluid and sodium management in peritoneal dialysis

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The achievement of euvolemia is essential to the successful management of peritoneal dialysis patients. However, the concern that hypertonic glucose exchanges may have a role in long-term changes to the peritoneal membrane has lead to an alternative strategy to enhance ultrafiltration (UF) over the long dwell by combining crystalloid and colloid osmosis. This review summarizes the experience of mixing glucose or amino acids with polyglucose (icodextrin), with particular focus given to data from studies using glucose/icodextrin in combinations of 1.36%/7.5% and 2.61%/6.8%. Both combinations demonstrate a significant increment of UF volume and sodium removal compared with the component osmotic agents used individually over long dwells, with the 2.61%/6.8% mixture having an effect over dwells extending to 15 h. Hypothetically, the mechanism of the enhanced UF is the attenuation by the colloid osmotic force of the backflow of water through small pores from dialysate to the peritoneal capillary circulation once the crystalloid osmotic force has dissipated. This experience provides promising data that deserves further examination in longer term clinical studies.

Kidney International (2008) **73,** S102–S111; doi:10.1038/sj.ki.5002610

KEYWORDS: combination dialysate; icodextrin; glucose; ultrafiltration

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While recent studies have questioned the relevance of small molecule clearance targets in peritoneal dialysis (PD),[1] the importance of fluid and sodium balance on outcome in anuric patients treated with long-term PD has been highlighted.[2] Results from earlier studies that had suggested the need for elevated clearance targets led to the implementation of high-dose automated peritoneal dialysis (APD)/continuous ambulatory peritoneal dialysis (CAPD) strategies to enhance small solute clearances, which required the prescription of high volumes of glucose-based dialysate. However, there is concern that such an approach has the potential to cause metabolic consequences for the patient and long-term structural changes to the membrane.[3,4] Awareness of the potentially deleterious effect of glucose-based dialysis solutions on the peritoneal membrane, combined with the significant impact of salt and water overload on patient outcome, places PD in a double-bind situation requiring an alternative approach.

There are several difficulties that can arise through the use of APD to enhance ultrafiltration (UF). First, the long dwell may last up to 15 h and is not suited to glucose-based dialysate, since glucose absorption leads to loss of UF and reduced sodium clearance. It has been demonstrated that 7.5% icodextrin would be clearly beneficial in this setting.[2] Second, rapid exchanges with glucose may result in a reduction in sodium clearance due to the effect of sodium sieving.[5] Further, frequent dialysate exchanges reduce the opportunity to equilibrate the peritoneal physiology before the next exchange commences, with concerns about the long-term effect on the peritoneal membrane. However, the problem is not with APD itself, but rather the unsuitability of the currently available dialysate solutions. Indeed, the long dwell in CAPD and APD can be seen as the lost therapeutic opportunity; if it were possible to implement an active UF strategy, the long dwell could contribute significantly to fluid and sodium balance with increased convective clearance of small solutes and more importantly for middle molecules that approach equilibrium over that period of time. The ability of icodextrin to induce UF over the long dwell via colloid osmosis and to reduce glucose exposure has

been an important advance. An important aspect of its use is a relative increase in sodium removal since water movement with icodextrin is through the small pores. Despite this, the osmotic effect of 7.5% icodextrin alone has been insufficient to achieve fluid balance in many patients on APD without recourse to hypertonic glucose during the overnight exchanges. Thus, there remains for many patients the unmet need for a dialysate solution that would combine enhanced osmotic effects with reduced glucose exposure.

An approach to this problem is to mix existing osmotic agents combining colloid and crystalloid osmosis in the same exchange with the tantalizing possibility that the effects on UF may be more than additive. The challenge has been to identify the appropriate concentrations of the components of the dialysate mix, which has been aided considerably by the development of mathematical modeling using the three-pore model by Rippe and Levin,[6] allowing the selection of component mixes of glucose and icodextrin that have predictable effects on UF. There are, of course, limitations to the concentrations of icodextrin that can be used due to the potential accumulation of oligosaccharides in plasma.[7] Equally, we are conscious of the potentially undesirable effects of high glucose concentrations. Ultimately, it should be possible to develop a portfolio of solutions to suit a range of peritoneal membrane and patient characteristics, similar to how glucose concentrations are used today.

This paper sets out to review the development of combination (bimodal) dialysis solutions for PD. To date, the experimental experience has been limited to single exchange studies or short clinical trials involving small numbers of patients. It is anticipated that by presenting this information, interest will be stimulated in the possibilities for the development of efficacious solutions with excellent UF and sodium clearance profiles, while at the same time exposing the peritoneal membrane to relatively low concentrations of glucose, and with the potential for incorporation within modern biocompatible technology. The objective would be to develop solutions that are kind to the peritoneal membrane while at the same time optimizing long-term survival of the dialysis technique.

THE FIRST INVESTIGATION OF ICODEXTRIN PLUS GLUCOSE COMBINATIONS FOR USE IN CAPD

The results from the studies described below are presented in Tables 1 and 2. In 1996, Elizabeth Peers and ML Laboratories[8] set up a project investigating the power of various mixes of icodextrin with glucose-based solutions for continuous use in CAPD, with the aim of avoiding long-term exposure of the peritoneal membrane to hyperosmolar solutions. They studied the net drained UF volumes (net UF calculated from drained volume) from single dwell exchanges in which a formulation containing 2% or 2.5% icodextrin mixed with 0.68% glucose was compared with 1.5% glucose-based dialysate. Despite important inter- and intra-subject variation, data reported from 12 CAPD patients for 4- and 10-h dwells demonstrated equivalence of the overnight UF (10-h dwell) between isotonic glucose and the dual osmotic formulation with less than half the caloric load due to diminished glucose absorption. In their conclusion, the authors speculated on the further development of a process likely leading to a glucose-free iso-osmolar dialysis regimen.[9,10]

REPLACING 3.86% GLUCOSE BY A COMBINATION OF POLYGLUCOSE AND AMINO ACIDS FOR THE NIGHT EXCHANGE IN CAPD

Following preliminary tests in an animal model, Faller *et al.*[11] designed a study to randomly compare the efficacy of a 4% polyglucose (PG)/1.0% amino acid (AA) (PGAA) combination solution with 7.5% icodextrin during the long dwell (10 h) exchange in CAPD. During baseline and washout periods (1 week), patients were prescribed 3.86% glucose-

Table 1 | Single dwell exchange studies using various combinations of crystalloid and colloid osmotic agents in PD

Mixed osmotic agents	PGAA 4% IcoD/1% amino acid Faller *et al.*[11] *n*=20	Sheffield experience 7.5% IcoD/1.36% glucose Jenkins *et al.*[23] *n*=11	French experience 6.8% IcoD/2.61% glucose Freida *et al.*[14] *n*=7
Glucose (%)	0%	1.36%	2.61%
IcoD (%)	4.0%	7.5%	6.8%
Amino acid (%)	1.0%	0%	0%
Sodium (mmol l^{-1})	132	134.1	121
Osmolality(mosM per kg H_2O)	344	334	410
Dwell time (min)	600	420	900
Time of assessment (i.p. volume)	1, 2, 4, 6, and 10 h[a]	Every 30 min[a]	0, 2, 4, 8, 12, and 15 h[b]
UF volume (ml)	836 at 2 h and 462 at 10 h	703 $\pm$ 266	990 $\pm$ 300
Control UF volume (ml)			
1.36% glucose	NA	143 $\pm$ 199 at 7 h	NA
3.86% glucose	1060 at 2 h and 460 at 10 h	929 $\pm$ 320 at 7 h	-85 ± 347 at 15 h
7.5% IcoD	400 at 2 h and 430 at 10 h	210 $\pm$ 155 at 7 h	462 $\pm$ 374 at 15 h

IcoD, icodextrin; i.p., intraperitoneal; NA, not applicable; PD, peritoneal dialysis; PGAA, polyglucose/1% amino acids; UF, ultrafiltration.
[a]Use of a dextran 70 as volume marker or [b]complete drainage of the cavity at each time point.