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THE BEGINNING OF ICODEXTRIN

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In the history of peritoneal dialysis (PD), 1976 marked a significant step forward when Popovich and Moncrief revolutionized the practice by introducing the concept of equilibration PD and extending the duration of dwell time to 4 – 10 hours (1). Despite this fundamental change in the practice of PD, the basic principle used to generate osmotic forces across the peritoneum remained unaltered. This principle relied on the traditional concept of osmotic flow across an "ideal" semipermeable membrane, necessitating making dialysis solution hypertonic to plasma with the addition of glucose as osmotic agent. Unfortunately, not being an "ideal" semipermeable membrane but being partially permeable to solutes, the peritoneum allows rapid absorption of glucose with progressive dissipation of the osmotic gradient and ultrafiltration of short duration. While this is of little significance during short dwell exchanges (30 – 60 minutes' dwell in intermittent PD), it is not the case for long exchanges, such as in continuous ambulatory PD (CAPD) and automated PD, where reabsorption of initially ultrafiltered peritoneal fluid occurs. In addition, the continuous daily absorption of glucose aggravates long-term metabolic complications, including hyperlipidemia and obesity (2,3).

Even as early as the 1980s there was clear recognition for an alternative osmotic agent that would minimize metabolic derangements and provide the ultrafiltration profile to suit long dwell exchanges. A range of different macromolecules was evaluated based on the simplistic concept that large molecular weight (MW) agents are less readily absorbed through the peritoneum and are likely to produce sustained ultrafiltration while reducing metabolic complications. Early investigations clearly identified the problems associated with use of nonphysiological hyperviscous macromolecules and defined the need for a neutral substance that is soluble, nonallergenic, and readily metabolized (3).

Glucose polymer (GP), derived from hydrolyzed cornstarch, seemed a natural contender and several groups already held patents of diverse MW fractions. Among them, the Abbott group led the way by studying a narrow MW fraction (MW 1000 Da) in both animals (4) and humans (5). In Manchester, we were well placed to explore the potential of this novel agent as considerable experience had been developed while investigating GP (Caloreen) as an intravenous high-energy nutrient source in the management of patients with renal (6) and hepatic failure (7). We worked closely in collaboration with Jerry Milner, the holder of the patent for Caloreen, Fisons Pharmaceutical, who had established expertise in fractionating GP technology, and J. Fox, Department of Biochemistry, University of Birmingham, who had extensive experience in methods of carbohydrate analysis.

For the initial clinical studies carried out in July 1983, we utilized a readily available dextrin formulation (Caloreen) with a bimodal MW distribution consisting of a 67% "low" MW fraction (chain length < 12 glucose units) and a 33% "high" MW fraction (chain length > 12 glucose units); weight average MW (Mw) was 7000 Da and number average MW (Mn) was 960 Da. In contrast to glucose solution, predicting osmotic performance of a polydisperse GP sample with a relatively unknown peritoneal permselectivity proved difficult. Our preliminary studies suggested that 5% (52 mmol/L) and 10% (104 mmol/L) GP solutions were probably comparable to 1.36% (76 mmol/L) and 3.86% (214 mmol/L) glucose respectively (8).

The first formal Phase 1 study, using solutions containing 5% (52 mmol/L) and 10% (104 mmol/L) of this GP formulation over a 6-hour dwell, was exciting and

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exceeded our expectation by producing net ultrafiltration 1.5 – 2.5 times greater than glucose solutions, with substantially reduced transperitoneal absorption of carbohydrate: 53% – 55% versus 66% – 69%. However, the metabolism of GP was incomplete, resulting in accumulation of maltose, with a peak serum level reaching 1148 mg/L with 5% GP solution, and this almost doubled with 10% solution (9). Even though subsequent investigations led to identification of a low level of circulating maltose and isomaltose in uremic and dialysis patients (10), a 32- to 64-fold increase following a GP exchange was considered unacceptable, especially in the absence of any previous report of this level of exposure in uremic patients. A similar conclusion reported by Winchester *et al.* in a multicenter trial involving 88 patients (5) led to the apparent abandonment of further research in this field in the USA. In contrast, we were encouraged by the results of our detailed analysis of oligosaccharide fractions in serum and dialysate. It seemed clear that there were differential rates of transperitoneal absorption of oligosaccharides: those with chain length < G12 were absorbed (75% – 80%) at rates not too dissimilar to glucose, whereas the remaining fractions > G12 were poorly absorbed (20% – 30% of the load). Furthermore, the rapidly absorbed fraction < G12, particularly G5–G9, was preferentially hydrolyzed by circulating amylase and was the major source of maltose generation. Thus, it seemed possible that removal of this fraction from the original polymer profile would substantially reduce the accumulation of maltose. However, it was uncertain whether the high MW fraction (>G12) on its own would be osmotically effective.

Following a casual comment by colleague Colin Ricketts, and having reviewed the publication by Kiil (11), we reconsidered the principles of osmotic forces as applied to solute-permeable biological membranes, such as the peritoneum. The recognition that the direction of osmotic force across a solute-permeable membrane is governed by the differences in the size of the sum of the products of the reflection coefficients and molar concentrations of solutes rather than the traditional total osmolality gradient (12) was the key to further development. Therefore, it was theoretically possible that a "large" MW GP fraction at a low concentration could exert an osmotic effect across the peritoneum, provided it was largely impermeable, and might even reduce the systemic load of maltose.

We were fortunate in our collaboration with Fisons Pharmaceutical, who successfully fractionated Caloreen into two component parts using the conventional solvent-based fractionation process. The high MW fraction of GP was isolated, with 95% of the profile containing glucose chain length > 12 glucose units with Mw 16 823 Da and Mn 5304 Da. A pilot study using a 5% GP solution (9.4 mmol/L) containing high MW fraction, with osmolality similar to uremic serum, produced remarkably good ultrafiltration compared to glucose solutions over a 6-hour dwell (13). Unfortunately, 2 patients developed severe chemical peritonitis with polymer solution contaminated with pyrogens (8). Even in these patients it was interesting to note that the GP fraction resulted in net ultrafiltration. This was the first indication that GP probably exerted its effect by a mechanism resembling colloid osmosis and could be adapted as a novel osmotic agent in CAPD. Following refinement of the manufacturing process, our clinical studies progressed rapidly and demonstrated superior ultrafiltration with 5% iso-osmolar GP solution for dwells up to 12 hours. Furthermore, only 14% – 28% of polymer was absorbed transperitoneally, compared to 62% – 83% of glucose, during the exchanges, resulting in a lower potential calorie load per milliliter ultrafiltration (14). Interestingly, the pattern and magnitude of peritoneal absorption of GP was similar to that described for much larger molecules (15), suggesting GP is absorbed primarily via peritoneal lymphatics (16). This lower rate of absorption also led to an 80% reduction in systemic accumulation of maltose compared to the original formulation. Although the metabolic clearance of maltose was minimal in the absence of dialysis, some transperitoneal maltose clearance was expected during multiple-exchange regimes. This was confirmed in subsequent studies, with estimated transperitoneal clearance of maltose 3.5 mL/min (8). Therefore, it seemed likely that maltose accumulation would achieve a steady state level with continuous use of polymer solution.

With the change in the manufacturing process from solvent-based to membrane-based fractionation, we obtained a slightly larger (Mw 22 000 Da; Mn 7000 Da) but more reproducible fraction. A 7.5% solution (10.7 mmol/L) yielded ultrafiltration similar to the previous 5% GP solution but was hypo-osmolar (277 mOsm/kg) to uremic serum. This was the first clinical demonstration of osmotic flow against the conventional osmolality gradient using a hypo-osmolar dialysate that finally consolidated the role of GP as a colloid osmotic agent (17). Furthermore, it provided a wonderful opportunity to prove the hypothesis that ultrafiltration profiles over varying dwell times could be optimized using different proportions of colloid and crystalloid agents combined in an iso-osmolar dialysate (18).

A series of studies using solutions containing this fraction overnight and conventional glucose exchanges during the daytime clearly demonstrated sustained ul-

trafiltration with very little day-to-day variation: maltose levels reached steady state within 6 days without apparent tissue accumulation (19). While this was reassuring, the fundamental question remained whether these elevated but steady state levels would be harmful in the long term. Therefore, we undertook a 3-month study (20), the favorable results of which paved the way for the MIDAS study, the first large, long term, randomized controlled study undertaken in CAPD to compare the efficacy and safety of icodextrin with conventional glucose solutions (21).

For almost a decade, the development of GP was based primarily at a single center with a small highly focused group of clinicians and nurses, and a faithful committed group of patients. Over this period, more than 11 separate clinical trials were conducted with only 33 patients, many of whom volunteered on a number of occasions, contributing to the rapid progress we made. There is no doubt that the critical step in the project was the 3-month study, and all those involved were apprehensive regarding the potential risk of maltose accumulation. It was perhaps the advantage of being in a single center with almost a decade of experience and the many patients that had already been repeatedly exposed to the product that allowed us to take this step. We were naturally reassured by our previous experience, despite the lack of long-term toxicity data, and fortunate to have a special relationship with our patients, who were enthusiastic to continue their involvement with the development of GP.

Initially, in 1983 the funding for the project was limited, with the Manchester & North West Region Kidney Research supporting the research registrar's salary and Jerry Milner meeting the expenses for dextrin assays. During this phase, all nursing assistance was voluntary, mostly out of hours and on weekends. After 2 years of rapid clinical progress, and with potentially a promising product, a high level of interest was shown by the pharmaceutical industry. In 1987, the withdrawal of support by a leading pharmaceutical company at a crucial step almost ended the development of GP. However, the project was salvaged when Jerry Milner, in partnership with Kevin Leech, an entrepreneur, formed a new biopharmaceutical company: M L Laboratories Plc. In 1988, Fisons withdrew from the project and M L Laboratories Plc set up a small manufacturing unit at Wavertree Technology Park in Liverpool, UK, with the capacity to manufacture the product by a new process involving membrane fractionation. Using this process, the optimal GP fraction (Mw 22 000 Da; Mn 7000 Da) for ultrafiltration that minimized maltose accumulation was subsequently used in all long-term studies. This fraction, originally referred to as "dextrin 20," was later renamed "icodextrin," from the Greek *icosa*, meaning twenty. In 1991, M L Laboratories embarked on a randomized, controlled, multicenter trial of icodextrin in CAPD involving 11 centers and 209 patients to evaluate safety and efficacy over a 6-month period (21). Following this, icodextrin received a product license in the UK in January 1993, European Marketing approval in March 1994, and, finally, USA Marketing approval in 2002. Initially, M L Laboratories reached an agreement with Fresenius AG to collaborate in the field of PD and to launch the product in Europe and the USA, but that agreement was terminated in March 1996, and 2 months later M L Laboratories granted an exclusive worldwide license to Baxter Healthcare. In 2005, ML Laboratories was acquired by Quadrant Technologies (as Innovata plc), and in 2007 this was taken over by Vectura Group plc.

Icodextrin has now been in clinical use for more than 15 years and has been an important step forward in the history of PD. It is not only a successful alternative osmotic agent to glucose but the first novel agent developed to exploit the physiological process of colloid osmosis, thereby providing sustained ultrafiltration with many metabolic advantages (22,23) particularly suited to long-dwell PD regimens. Its success is undoubtedly attributable to its humble beginning in Manchester, UK, where a unique blend of highly motivated clinical staff and 33 loyal and courageous patients created a promise of a successful product and inspired the formation of a new pharmaceutical company, M L Laboratories Plc, which secured the necessary expertise and resources to complete the development of icodextrin. It is estimated that icodextrin is used by more than 30 000 patients worldwide in more than 55 countries, and in richer countries penetration probably exceeds 50% (24). It is a great tribute to all those involved and, after 15 years, it is particularly satisfying to see that the use of icodextrin goes from strength to strength.

DISCLOSURES

The author does not have any conflict of interests to declare

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