ICODEXTRIN: OVERVIEW OF CLINICAL EXPERIENCE

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.Objective: To review all clinical studies and experience gained with icodextrin to date; primarily its use in peritoneal dialysis in patients with end-stage renal failure, but also its use as an intraperitoneal vehicle.

.Data sources: Peer-reviewed original research articles in the literature; abstracts from international scientific meetings; data generated from the compassionate use programme.

.Study selection: All published studies to date are included, some 10-20 studies being included in this review.

.Data extraction: Data have not been specifically extracted from studies; results have been described in the context of overall experience.

.Results: Over ten years of clinical experience with icodextrin have now been accumulated, in both continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD). A small number of patients have received icodextrin for over five years, with no loss of effect. Icodextrin produces sustained ultrafiltration over long dwells while being iso-osmolar, by the process of colloid osmosis.

.Conclusion: Icodextrin represents the first viable alternative osmotic agent to glucose, for use in solutions for peritoneal dialysis. It also has a potential use as a vehicle solution for intraperitoneal drug delivery.

KEY WORDS: Icodextrin; peritoneal dialysis, intraperitoneal vehicle; glucose polymer; ultrafiltration failure.

Continuous ambulatory peritoneal dialysis (CAPD) has been used to treat patients in end-stage renal failure for about 20 years now. Current CAPD solutions based on dextrose are hyperosmolar, exerting their effect by crystalloid osmosis across the peritoneal membrane. However, dextrose, while effective over short dwells and relatively cheap, is associated with various metabolic disadvantages (obesity, hyper-lipidemia, hyperinsulinemia), and its absorption leads to dissipation of the osmotic gradient and ultrafiltration (UF) of short duration. This is more evident in long dwell situations (overnight in CAPD, daytime in automated peritoneal dialysis APD[1]). The developments in CAPD have had to be adapted to these limitations of dextrose.

There have been several attempts to identify a suitable alternative (e.g. glycerol, amino acids) to dextrose as a low molecular weight agent; these have had their disadvantages, limiting widespread use. The absorption of amino acids across the peritoneal membrane has been utilized to improve nutrition in malnourished CAPD patients (2). High molecular weight agents have also been evaluated, but their use has been abandoned (dextran-problems associated with its accumulation and lack of biometabolism; gelatin-allergenicity; albumin-prohibitive cost).

Icodextrin has been developed in part as a response to some of the disadvantages of dextrose. The need for a CAPD solution iso-osmolar with uremic serum, to avoid damage associated with dextrose solutions (3), has been met. Also, the icodextrin solutions are able to provide sustained UF over long dwell times of 8-12 hours in CAPD (4) and up to 16 hours in APD (5). Over the last 10 years, a wealth of clinical experience has evolved in these areas, and other exciting developments are being studied. This paper reviews this vast clinical experience.

EARLY CLINICAL STUDIES

Hyperosmolar solutions are unphysiological and can have detrimental effects on the peritoneum (6), which in addition is not an ideal semipermeable membrane, being permeable to lower molecular weight solutes. In principle, the use of colloid osmosis is possible in such a situation, if the dialysis solution is iso-osmolar and contains an excess of large molecules relative to uremic serum. This lay behind the first use of a high molecular weight dextrin to provide an osmotic agent in peritoneal dialysis (7,8). It was
shown that dialysate osmolality remained constant and iso-osmolar to uremic serum over the course of dwells up to a 12-hour dwell. It was also clear that with dextrin, net UF increased between 6 and 12 hours, whilst with dextrose, UF decreased (8). The peritoneum is much less permeable to large molecules, such as those of icodextrin or albumin. This explains the relatively low absorption of icodextrin compared with dextrose across the peritoneal membrane (8). It is likely that icodextrin is absorbed via the lymphatic pathways at a constant rate, rather than across the peritoneum. This implies that increasing the molecular size of a colloid osmotic agent will lead solely to the disadvantage of requiring a greater mass of osmotic agent to induce the same UF volume (9).

The absorbed dextrin is rapidly metabolized by amylase, for which its\(\alpha\)-1,4linking bonds are a prime substrate. This metabolism leads to the production of maltose which, in the absence of circulating maltase, can be measured in the serum of patients on icodextrin, in the same way that most drugs are detectable in the blood. The maltose thus generated is subject to a constant peritoneal clearance of 3 m/L min. in the presence of CAPD, leading to steady state levels in blood within two weeks of starting treatment(10). Its well established that the enzyme maltase is abundant within the intracellular lysosomes (11,12), so that any intracellular maltose is swiftly metabolized.

Early studies with various dextrin fractions led to the identification of a particular fraction for use in peritoneal dialysis, which has been named icodextrin, (from the Greek \textit{icosa}, meaning twenty). Icodextrin’s molecular weight is expressed as weight-average molecular weight (Mw) of 16,800, and as number-average molecular weight (Mn) of 5,300. This represents a profile close to the ideal for inducing osmotic flow across the peritoneum in the absence of an osmotic gradient, while at the same time limiting its absorption predominantly to the lymphatic pathway.

**MIDAS CLINICAL STUDY**

The early studies showed that iso-osmolar icodextrin 7.5% (282 mosmol/kg) produced UF equivalent to 3.86% dextrose solutions (486 mosmol/kg) (8,9), and that its breakdown products, including maltose, reached a plateau level in serum after two weeks of treatment and remained at that level for up to three months (13). However, a large multicenter study of longer duration was needed, and the Multicenter Investigation of Dextrin in Ambulatory Dialysis Study (MIDAS) was set up in the United Kingdom. The study, which included about 5% of the country’s CAPD population, involved 11 hospitals and six months of treatment with icodextrin. One exchange of icodextrin 7.5% was combined with three of dextrose. The results of the MIDAS study have been widely reported elsewhere (4), and it suffices here to summarize the results: icodextrin produced at least as much UF as 3.86% dextrose (in dwell times up to 12 hours) and maintained its efficacy over the six-month trial period; CAPD symptoms were significantly reduced in the icodextrin group; and maltose levels remained stable throughout the study, with no associated adverse effect. The MIDAS database, in addition, demonstrated that there was no excess risk of peritonitis in the icodextrin patients, and that the outcome of episodes of peritonitis was also similar (14). This is important because the mesothelium is denuded during peritonitis, subjecting the sub-mesothelial layers to glycation by dextrose (15).

The long-term consequences of such glycation may be associated with loss of UF and technique failure.

The propensity of the osmotic agent to glycate peritoneal proteins, which may ultimately result in advanced glycation end-products (AGEs) is receiving increasing attention. It has been shown in vitro that icodextrin is much less able to glycate proteins than even the weakest dextrose solution (16). Similarly, during peritonitis, UF is poor with dextrose solutions (17), because the membrane is hyperpermeable; in order to maintain fluid balance, higher-strength dextrose solutions are needed. Icodextrin, in contrast, has the advantage of maintaining or even increasing the UF it produces during peritonitis (14).

**LONG-TERM ICODEXTRIN USE**

The MIDAS study evaluated icodextrin over six months. Most of the MIDAS patients continued on icodextrin beyond this; a few patients have now remained on icodextrin for five years under the MIDAS-2 protocol, and their peritoneal dialysis treatment continues satisfactorily. Long-term tracking of hematology, biochemistry and other laboratory variables indicates that these parameters remain stable while patients are on long-term icodextrin treatment (ML Laboratories, data on file, 1995). There has been no excess of adverse events in the patients and none considered to be related to icodextrin. No patients withdrew because of icodextrin’s lack of efficacy; UF is maintained.

Of patients who received icodextrin on a long-term basis (more than two years), a small group was further studied to investigate the effect on icodextrin metabolite levels (including maltose) of stopping icodextrin treatment. The levels fell to pretreatment values within two weeks. On recommencing icodextrin after three weeks, the maltose and icodextrin metabolite levels rose just as during the initial treat
ment phase, to reach a plateau within two weeks (18). These kinetics confirm that there can be no capacity-limited compartment for icodextrin metabolites in man. Deposition of icodextrin in tissues is therefore unlikely, not only based on its pharmacokinetics, but also on its biochemistry.

Total clinical experience with icodextrin also includes patients treated in the compassionate use programme (CUP). Patients received icodextrin for 1 to 30 months under the CUP for a variety of reasons, the main one being UF failure on dextrose (see below). Data obtained on a group of 40 patients pre and post-icodextrin showed no changes in laboratory data except for a small fall in serum sodium, as expected (19). Adverse events reported in the CUP patients were related to the patients' pre-existing conditions, and icodextrin was well tolerated by this group. Patients who ceased icodextrin treatment generally did so because CAPD treatment itself was no longer appropriate. Relatively little clinical experience was required to evaluate and establish icodextrin's efficacy (pre-MIDAS studies); however, all the experience since that time (including the MIDAS trial) has been necessary to document icodextrin's safety profile. A total of 240 patient years of experience has been accumulated to date (Table 1).

**LOSS OF ULTRAFILTRATION**

In the years since icodextrin was introduced as a new treatment for CAPD, it has found particular use in the treatment of UF failure. The most common reason for UF failure is type I membrane failure, where the peritoneal membrane becomes hyperpermeable. Icodextrin is a large molecule and therefore is unaffected by the membrane hyper-permeability whether caused by type I membrane failure (permanent) or by peritonitis (temporary) (14). It has been shown that icodextrin provides patients who have UF failure with a means to gain adequate UF to remain on CAPD for an average of 12-16 months (20), allowing patients to remain on their chosen dialysis modality, and gaining time in the wait for a renal transplant.

**AUTOMATED PERITONEAL DIALYSIS**

APD is becoming more widely available in the United States and in Europe. Its principle advantages are the relative convenience for patients and the use of larger volumes of PD fluid, thereby achieving higher clearances than in CAPD. Some patients require a "wet" day to achieve adequacy targets (21), but this daytime dwell is long-up to 16 hours-and negative UF is common with dextrose even using stronger solutions.

**FUTURE DIRECTIONS**

Icodextrin is a versatile agent. It has so far been used for long dwell in peritoneal dialysis treatment, both ambulatory and automated. Its ability to maintain intraperitoneal volume over longer periods than dextrose or saline led to the proposal that it could be used as a vehicle to maintain a "reservoir" of fluid in the peritoneum, from which active ingredients could be absorbed locally, into the lymphatic system or directly into the blood stream via the peritoneal capillaries. This principle has been demonstrated in a kinetic...
study using 2.0 L icodextrin for a 24-hour dwell with 5fluorouracil (5-FU) as the active chemotherapeutic agent
(25). It was shown that using intraperitoneal icodextrin as
vehicle for 5 FU achieved a concentration 1,000 times
higher in the abdomen than was achieved by using
conventional intravenous administration. These patients
had functioning kidneys, but achieved "UF volumes" of
500-600 mL over a 24-hour dwell.

Using a similar approach to the intraperitoneal
chemotherapy outlined above, icodextrin has also been
used as vehicle to administer an antiviral agent
intraperitoneally, in order to gain access to the lymph nodes
where the HIV virus is believed to reside (26). Using the
same principles as above, a peritoneal catheter was
implanted in patients with acquired immune deficiency
syndrome (AIDS), and antiviral treatment administered in
1.5 L of 7.5% icodextrin in 24-hour dwells. To date, there
have been no peritonitis episodes, of great concern in these
patients, and "UF volumes" of about 350 mL have been
achieved over a 24-hour dwell (ML Laboratories, data on
file).

Experience with icodextrin 7.5% as a vehicle for the
intraperitoneal administration of antineoplastic and
antiviral drugs has shown satisfactory progress so far.
However, the trials have been small and highly intensive;
widder clinical experience of this therapeutic modality will
emerge in the future.

Finally, icodextrin might be used in combination with
other osmotic agents in peritoneal dialysis patients: with
dextrose (27) or amino acids, or in differing concentrations
to provide UF profiles over dwell times of differing
durations; as well as offering reduced calorie absorption
and/or protein supplementation in patients with diabetes, or
malnourished CAPD patients. Such combinations, prepared
in bicarbonate solutions to normalize pH, would be
approaching the characteristics of the "ideal solution."

CONCLUSION

There now exists about ten years of clinical experience
with icodextrin in peritoneal dialysis, ranging from single
dwell to full-scale multicenter studies, and into clinical use
on a licensed commercial basis. Icodextrin has different
attributes to dextrose, principally its iso-osmolar nature and
ability to provide sustained UF over long dwells. Its
sustained osmotic effect relies on the large size of its
molecules to produce UF by colloid osmosis. It is likely
that icodextrin produces this effect across intercellular
pores of diameter 8 nm, leading to increased clearances of
smaller proteins such as Beta2-microglobulin (28).

Icodextrin provides patients in ESRF with the first
viable alternative osmotic agent to dextrose, and as such
represents a major advance in the solutions used for the
treatment of ESRF by peritoneal dialysis.

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