

5 Peritoneal dialysis solutions

Guidelines

A. Although the solutions containing low glucose degradation products (GDPs), buffered with either lactate, bicarbonate or both, have not yet proven to have long-term clinical benefits, their use as first choice should be considered (*Evidence level C*) because of their better biocompatibility over the conventional glucose/lactate-based solutions (*Evidence level B*). However, there may be economic/resources implications.

(*Evidence level C*)

B. A 7.5% icodextrin-containing solution could be used in patients with fluid overload related to insufficient peritoneal ultrafiltration in the long dwell (CAPD and APD) and to avoid excessive glucose exposure. This is especially recommended for patients with a transient or permanent highly permeable peritoneal membrane. Icodextrin should only be administered once daily to avoid excessive plasma maltose and high molecular weight polymer concentrations.

(*Evidence level A*)

C. The use of an amino acid-containing solution should be considered in malnourished patients as part of a strategy aimed to improve nutritional status. Amino acid solutions should only be administered once daily (4–6 h dwell) to avoid uraemic symptoms and metabolic acidosis.

(*Evidence level B*)

D. Low calcium-containing solutions should be used in patients with hypercalcaemia. However, the serum calcium concentration should be monitored in order to avoid hypocalcaemia.

(*Evidence level A*)

E. Low magnesium-containing solutions should be used in patients with hypoparathyroidism.

(*Evidence level B*)

F. High buffer-containing solution should be used in patients with metabolic acidosis (venous serum bicarbonate <25 mmol/l). However, the serum bicarbonate concentration should be monitored in order to avoid metabolic alkalosis (venous serum bicarbonate >29 mmol/l).

(*Evidence level A*)

Commentary to Guideline 5: peritoneal dialysis solutions

Guideline A. Glucose and glucose degradation products

The extremely high glucose concentrations in the standard peritoneal dialysis solutions may lead to hyperglycaemia, hyperinsulinaemia and a decrease in plasma glucagon [1–3]. These effects are known to increase the risk for the development of atherosclerosis and obesity in the normal population (reviewed in [4]).

In vitro studies have underlined local glucose toxicity towards mesothelial cells, leukocytes and host defence mechanisms (reviewed in [5]). High concentrations of glucose are also toxic for mesothelial cells in animal models [6]. Deposition of advanced glycosylation end-products (AGEs) is described in peritoneal tissues [7–9].

Glucose is also likely to be involved in the development of peritoneal neoangiogenesis. This is supported by the diabetiform alterations of the peritoneal microvessels that are present in patients [10] and that can be induced in animal models [11]. Also, the number of peritoneal vessels is higher in long-term peritoneal dialysis (PD) patients [12] and in those with peritoneal membrane failure [13]. The peritoneal exposure to glucose-based solutions is higher in patients with peritoneal sclerosis than in time-matched controls [14] and also higher in patients who develop an increase in the dialysate/plasma ratio of creatinine than in those where this ratio remains stable during follow-up [15].

Also, glucose degradation products (GDPs), induced by heat sterilization, are toxic to peritoneal cells and induce the formation of AGEs at a faster speed than glucose itself [16,17]. In cultured mesothelial cells, it has been demonstrated that impaired viability and function of cells are mainly related to the presence of GDPs and, to a significantly lesser extent, to the presence of glucose *per se* [18]. Dialysis solutions that are glucose based but contain a reduced amount of GDPs are available, either buffered with lactate [17], with a combination of a bicarbonate/lactate buffer [19] or bicarbonate buffer only [20]. These solutions are delivered in a double chamber system and have a pH that is either 6.3 (lactate buffered) or 7.4 (bicarbonate/lactate and bicarbonate buffered). Since bags are divided into two or more compartments, glucose can be sterilized

separately from the other substances at a very low pH, resulting in a very low formation of GDPs during the autoclaving procedure [16]. *In vitro* studies demonstrated a significant biocompatibility benefit of these solutions when compared with the conventional solutions [21].

In clinical practice, the use of these solutions in randomized controlled trials in prevalent continuous ambulatory peritoneal dialysis (CAPD) patients is associated with an increase in dialysate cancer antigen 125 (CA125) concentrations and a decrease in the levels of hyaluronan [22–24]. The former is considered to be a reflection of mesothelial cell mass or turnover in stable CAPD patients (reviewed in [25]). Dialysate hyaluronan may reflect peritoneal inflammation. These results are promising, but more data have to be awaited since studies with long-term administration are not yet available.

The impressive results of the *in vitro* and in animal studies, and the effects on surrogate markers of biocompatibility in patients prompted the committee to suggest low GDPs solutions as first choice in CAPD despite the fact that their effectiveness in the long-term preservation of the peritoneal membrane has not yet been demonstrated. However, the cost of these solutions is slightly higher than that of the conventional solutions. Thus, where economic resources for PD are scarce, a balanced cost/benefit analysis should be done.

Guideline B. Use of icodextrin

Icodextrin is a high molecular weight osmotic agent that induces ultrafiltration mainly by a colloid osmosis-like phenomenon [26]. Its average molecular weight is 16 800 Da. Its uptake during a dwell averages 10–20% and is mainly into the lymphatics. Consequently, it induces sustained ultrafiltration, which makes it especially suitable for long dwells. A 5% icodextrin dialysis solution yielded more ultrafiltration than a 1.36% glucose-based solution [27]. The currently available 7.5% icodextrin solution is able to induce similar ultrafiltration to a 3.86% glucose-based solution during 8 and 12 h dwells [28] and superior ultrafiltration to a 2.5% dextrose solution [29]. It does not affect the diffusive transport of low molecular weight solutes, but increases the peritoneal clearance of β_2 -microglobulin due to a higher convective flow [30,31]. Icodextrin also increases ultrafiltration during the diurnal long CCPD exchange of 14–15 h [29,32].

Fast solute transport rates indicate the presence of a large vascular peritoneal surface area. In principle, it allows high ultrafiltration rates. However, this is counteracted by a fast absorption of glucose, leading to a rapid disappearance of the osmotic gradient, when the current solutions are used. Because of its high molecular weight, icodextrin hardly diffuses across the peritoneal membrane. Therefore, prolonged ultrafiltration can be expected when patients with a large vascular peritoneal surface area are treated with icodextrin. This has indeed been found in patients with impaired ultrafiltration due to the presence of a

large vascular surface area [33], during peritonitis [34] and in long-term patients with very severe ultrafiltration failure [35].

These PD patients are particularly at risk for overhydration that in turn could lead to hypertension and left ventricular hypertrophy. Recent randomized studies show a significant reduction of the body weight, total body and extracellular water, and left ventricular mass in the group treated with icodextrin [36,37].

The 7.5% icodextrin solution can only be used once daily in order to avoid excessive accumulation of maltose in the extracellular volume [28]. The accumulation of maltose is likely to be responsible for the decrease in plasma Na^+ of on average 2 mmol/l that has been described during treatment with icodextrin [30]. It also may lead to spuriously high blood glucose concentrations when some home monitoring methods based on glucose dehydrogenase are used [38] and also to spuriously low plasma amylase levels because of interference with the substrate used to measure amylase activity [39]. No other side effects are described that can be attributed to accumulation of maltose. Hypersensitivity to icodextrin has been reported, consisting of skin rashes and culture-negative peritonitis. The prevalence of skin reactions varies from 0.6 to 15% [40–42]. An incidence of 1 per 60 patient-years has been found in a large post-marketing survey [43]. In 2001/2002, an outbreak of culture-negative peritonitis was reported [44,45], with a prevalence of up to 8.7% [46]. It has now become very likely that a peptidoglycan concentration exceeding 60 ng/ml was the most probable source. After a modification of the production of icodextrin leading to a reduction of the peptidoglycan concentration below the detection limit of 7.4 ng/ml, the frequency of culture-negative peritonitis has decreased to values similar to those before the outbreak (Baxter, unpublished data).

Guideline C. Use of amino acids

Several mixtures of amino acids have been studied with the dual aim of nutritional support and osmotic agent. The solution that is currently commercially available contains 1.1% amino acids, mainly essential amino acids. The short-term use of one exchange per day of this solution results in an increased nitrogen balance in malnourished patients [47]. This is accompanied by higher serum transferrin and total protein levels, as well as a decrease in total CO_2 . A 3 month clinical study in patients with a wide range of nutritional status reports an increase in serum albumin and transferrin levels [48]. A randomized multicentre study showed no changes in albumin and prealbumin serum levels, an increase in serum insulin-like growth factor-1 and a decrease in serum potassium and phosphate associated with the use of an amino acid solution [49]. However, a significant increase of blood urea and decrease in blood bicarbonate has been recorded when more than one exchange per day was used and with solutions containing amino acids with different formulations [50].

Guideline D. Use of low calcium solutions

Commercially available PD solutions contain 1–1.75 mmol/l of calcium. Since the normal concentration of diffusible ionized calcium ranges from 1.15 to 1.29 mmol/l, calcium is absorbed or lost depending on the diffusive gradient direction [51]. A 1.75 mmol/l calcium-containing solution has been used for many years in order to provide an additional source of calcium in uraemic patients in whom the vitamin D deficiency usually leads to a reduced calcium absorption in the bowel. The clinical use of phosphate binders containing calcium salts and vitamin D exposes patients in dialysis to a risk of hypercalcaemia [52] that in turn could lead to vessel and soft tissue calcifications (reviewed in [53]). With the use of a lower calcium-containing solution, hypercalcaemic patients have reduced serum calcium levels, and an increased amount of phosphate binders containing calcium salts can be used [54–56]. However, the serum calcium concentration should be carefully monitored, since low serum levels worsen uraemic osteodystrophy [57].

Guideline E. Use of low magnesium solutions

Commercially available PD solutions contain 0.25–0.75 mmol/l of magnesium. With the solution containing 0.75 mmol/l of magnesium, supraphysiological levels of plasma magnesium are usually recorded in the majority of patients [58]. Whether a high plasma magnesium level may have clinical effects is very controversial [59]. Cross-sectional studies [60] have shown an inverse correlation between parathyroid hormone (PTH) and magnesium serum concentration independently from the other most important factors regulating parathyroid gland function (calcium, phosphate and calcitriol). Since a low PTH level is a typical feature of adynamic bone disease, it is possible that the hypermagnesaemia, caused or worsened by the high concentration of magnesium in the PD solution, plays a role in the pathogenesis of this disease. Therefore, it seems prudent to reduce these levels. A lower magnesium-containing solution (0.25 mmol/l) is effective in reducing serum magnesium levels [58]. Despite the fact that a severe hypomagnesaemia has been associated with neurological and cardiac derangements [61,62], in CAPD patients clinically relevant hypomagnesaemia has never been recorded [54,58,63].

Guideline F. Buffers

The catabolic effects of metabolic acidosis on protein and amino acid metabolism can only be reversed by a full correction of this condition [64]. In a randomized study on 200 CAPD patients [65], normal venous bicarbonate (27.2 mmol/l) was associated with nutritional benefits such as an increase in body weight and midarm circumference, and decreased morbidity as compared with mildly low venous bicarbonate

(23.0 mmol/l). Commercially available PD solutions contain 35–40 mmol/l of lactate, 34 mmol/l of pure bicarbonate and a mixture of 25 mmol/l bicarbonate and 15 mmol/l lactate. With the 35 mmol/l lactate-buffered solution, a moderate to mild acidosis is usually recorded in the majority of patients [66]. With the 40 mmol/l lactate-buffered solution, the percentage of patients with normal acid–base status increases [58]. The 34 mmol/l bicarbonate-buffered solution improved blood bicarbonate as compared with the 35 mmol/l lactate-buffered solution [67]. The 25 mmol/l bicarbonate- plus 15 mmol/l lactate-buffered solution had a similar effect on acid–base status compared with the 40 mmol/l lactate-buffered solution [68]. Both bicarbonate-based solutions had no local and systemic side effects. These solutions improved peritoneal pain or discomfort experienced by some patients during the infusion of the lactate-buffered solutions [67,69]. There are very few data in the literature about the clinical consequences of alkalosis. Alkalosis depresses the central nervous system, increases neuromuscular excitability, causes hypokalaemia and cardiac arrhythmias, enhances digitalis intoxication and increases binding of oxygen to haemoglobin, preventing the release of oxygen to peripheral tissues (reviewed in [70]). These effects have been described in acute alkalosis, while the clinical effects in long-term mild chronic alkalosis are still unknown. From a physical–chemical point of view, a higher pH favours calcium precipitation and thus alkalosis could contribute to soft tissue calcification. However, only one report describes periarticular calcifications associated with alkalosis in patients treated with a 40 mmol/l lactate-buffered CAPD solution [71]. Despite the lack of evidence on the detrimental clinical effects of chronic alkalosis, it still seems prudent to try to avoid it in dialysis patients. *In vitro* studies highlight the contribution of low pH and high lactate content in the solution to the bioincompatibility of PD fluids (reviewed in [5]). Bicarbonate-buffered PD solutions show a decrease of such bioincompatibility *in vitro* because of the physiological pH and the absence or the low dialysate concentration of lactate. In addition, in the bicarbonate-containing solutions, a reduced amount of glucose degradation products is present because it is manufactured in a double-bag system (see above). Furthermore, studies in an animal model show that a bicarbonate-containing solution has no vasoactive effect on peritoneal vessels [72] and does not inhibit the physiological response to inflammatory stimuli [73] compared with conventional solutions.

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