

Dialysate as food as an option for automated peritoneal dialysis

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Abstract

Protein-energy malnutrition is frequently found in dialysis patients. Many factors play a role in its development including deficient nutrient intake as a result of anorexia. Peritoneal dialysis (PD) solutions containing a mixture of amino acids and glucose in an appropriate ratio could serve as a source of food. The authors of this article found that such a dialysis solution when administered to fasting patients who were on nightly automated peritoneal dialysis (APD), as part of a regular dialysis schedule, induced an acute anabolic effect. Also in PD patients in the fed state, dialysis solutions containing both amino acids and glucose were found to improve protein metabolism. It appears that the body responds similar to intraperitoneal and oral amino acid:dialysate as food. Like dietary proteins, intraperitoneal amino acids can bring about generation of hydrogen ions and urea as a result of oxidation. No rise of serum urea levels was found and serum bicarbonate remained within the normal range when a total buffer concentration of 40 mmol/L in the mixture was used. The use of this approach may be an option for PD patients who cannot fulfil dietary recommendations.

Keywords: amino acid dialysate; malnutrition; metabolic acidosis; peritoneal dialysis

Introduction

Protein-energy malnutrition (PEM) is frequently found in patients with chronic renal failure and is reported to occur in ~40% of dialysis patients [1,2]. Besides inadequate intake of proteins and calories, various other factors are involved in the development of PEM in patients with renal failure including acidosis, insulin resistance and uraemic toxins [3]. With haemodialysis, loss of amino acids via dialysate may amount to 10 g per dialysis session, whereas with peritoneal dialysis (PD), protein loss in infection free patients is ~5–10 g per 24 h in addition to a loss of 2–4 g of amino acids. In the past few years, the role of inflammation has been in the spotlight. A strong association has been found

between malnutrition, inflammatory parameters and cardiovascular mortality [4–7]. It is poorly understood which pathophysiological mechanisms underlie this connection. Many strategies have been proposed to improve dietary nutrient intake in PD patients, but actual protein intake is frequently below the recommended amount of 1.2 g/kg body weight. In continuous ambulatory PD (CAPD) patients, amino acid containing dialysate has been used to compensate for a low dietary protein intake and peritoneal loss of amino acids and proteins [8–13]. Till date, convincing clinical benefits have not been demonstrated unequivocally although amino acids containing dialysis solutions may lead to a significant increase in serum urea levels and metabolic acidosis. Currently, amino acid dialysates are not widely used for the improvement of nutritional status or as supplement to food intake. It has been generally recommended to use amino acid dialysate together with a meal containing enough calories. Lately, it has been shown convincingly that simultaneous ingestion of calories is really of utmost importance to obtain an optimal anabolic effect of intraperitoneal amino acids [14]. However, anorexia may restrain patients from taking enough calories together with intraperitoneal amino acids. Recently, the authors could show that in patients on nightly automated peritoneal dialysis (APD), a dialysis solution that contains a mixture of amino acids and glucose, as part of a regular dialysis schedule, induced an acute anabolic effect [15]. In that study, the proportion of energy and protein given via dialysate varied between 160 and 340 kcal/gN although the western diet contains ~150–200 kcal/gN. Taken together, these findings suggest that the body's response to the amino acid–glucose dialysis solution is similar to food; this article is a discussion on 'dialysate as food'. In the next sections, a more detailed discussion is made on whether this concept could make sense as nutritional support in clinical practice. First, the role of diet and inflammation in the nutritional status is dealt with.

How much protein does the patient on PD need?

According to the Kidney Diseases Outcomes Quality Initiative (DOQI) guidelines, recommended daily dietary protein intake (DPI) should be at least 1.2 g/kg/day for PD patients [16]. This target is based on nitrogen balance studies in clinically stable patients assuming that the intake is within the safe limit in 97.5% of the population [17,18]. Many patients, however, have a neutral or positive nitrogen

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balance with a DPI of 1.0 g/kg/day and some patients even at a value as low as 0.7 g/kg/day [18]. Various studies have shown that actual DPI in many PD patients is <1.2 g/kg/day even though these patients usually receive diet counselling. The European Best Practice Guideline working group on PD allows for a lower DPI target (>1.0 g/kg/day) if the patient remains in a stable nutritional status. Poor appetite is central to low intake of proteins and energy. Nutrient intake is closely correlated with the nutritional status, comorbid conditions, inflammatory parameters (see the section on inflammation) and the stage of renal insufficiency [19]. Pro-inflammatory cytokines such as TNF α and IL-1 β that are known to be implicated in anorexia and cachexia may be the connecting link.

Malnutrition, inflammation, atherosclerosis and risk of death

In various epidemiological studies of dialysis, a strong association of PEM, inflammation and increased risk of morbidity and mortality has been found [4,5,19]. Various factors including volume overload, comorbid conditions such as infections, atherosclerosis and decreased clearance of pro-inflammatory cytokines and glucose degradation products may contribute to an inflammatory state in end-stage renal disease (ESRD). Of note, atherosclerosis itself is an inflammatory process, which may deteriorate further by infections and other inflammatory conditions, as frequently found in dialysis patients [20–22]. Several authors argue that PEM is the result of inflammation and is a secondary marker rather than the cause of poor outcome. It is suggested that PEM without inflammation has only minor harmful effects on outcome. However, associations, as found in cross-sectional epidemiological studies, cannot be simply explained in terms of cause and effect. There is evidence to suggest that inflammation, whatever its cause, may not be the sole explanation of PEM in ESRD, as suggested by imprecise association of several nutritional and inflammatory parameters [6]. Preliminary data suggest that PEM may independently promote and increase the risk of clinical illness, leaving room for the viewpoint that part of the association of PEM and poor outcome is because of deficient nutrient intake as a result of anorexia [6]. Further research is required to elucidate the pathophysiological mechanisms underlying the aforementioned associations. To assess the relative contribution of nutrient intake to outcome, interventional studies including large groups of patients are needed, selected on the basis of nutritional status, DPI and inflammatory parameters.

Amino acid dialysis solutions in CAPD

To improve the nutritional status in patients on CAPD, glucose in PD solutions was replaced with amino acids. Using a 1.1% amino acid solution ultrafiltration is similar to a 1.36% glucose solution. During a dwell of 4–6 h, ~80% of the amino acids, that is 18 g, are absorbed using a dwell volume of 2 L [14]. Currently, the commercially available solutions (Nutrineal[®]) are composed of a mixture of all

essential amino acids and six nonessential amino acids, three of which are considered to be essential for ESRD patients. Various studies have been performed to investigate the clinical effectiveness. These studies differed in their design, including patient selection, DPI, nutritional status and duration of follow-up although different nutritional parameters were used as endpoint [8–13,23]. Although in some studies improvement was found according to selected parameters, overall there was no consistent amelioration of nutritional status. In a prospective-controlled interventional study, it was found that 1–2 bags of a 1.1% amino acid solution induced a significantly positive nitrogen balance [24]. In this study, malnourished PD patients were included who were ingesting 1.0 g protein/kg/day or less, whereas during the study, the patients were fed a constant diet containing 0.8 g protein/kg/day and 28 kcal/kg/day energy. The amino acid solutions were exchanged in the postprandial state. It is really of utmost importance that intraperitoneal administration of amino acids is accompanied by simultaneous intake of calories, as was convincingly shown by Delarue [14] who compared the effects of intraperitoneal amino acids with and without consuming a meal composed of carbohydrates and lipids in CAPD patients. The amino acids stimulated protein synthesis and the oral calories induced an inhibition of protein breakdown (i.e. proteolysis) thereby reinforcing the positive effects of the amino acids solution on protein balance. In this study, oral energy and absorbed intraperitoneal amino acids were given in a proportion of ~200 kcal/gN. The normal western diet contains energy and proteins in a proportion of 150–200 kcal/gN. Anorexia, however, may restrain patients from taking enough calories simultaneously with intraperitoneal amino acids.

Combined amino acids and glucose-containing solutions in APD

Considering that the utilization of intraperitoneal amino acids could be optimized by giving them simultaneously with glucose, the hypothesis that in patients who are on nocturnal APD, a dialysis solution that contains a mixture of amino acids and glucose, as part of a regular dialysis schedule, could improve protein metabolism was put forward. In a randomized crossover study, it could be seen that the mixture of amino acids and glucose induced an acute anabolic effect on protein metabolism because of the combined effect of stimulation of protein synthesis and inhibition of protein breakdown [15]. Apparently, the body's response to the administration of intraperitoneal amino acids is similar to food. The acute changes in protein metabolism were studied by primed constant infusion of ¹³C-leucine. Whole body protein (WBP) turnover, oxidation, synthesis and breakdown (i.e. proteolysis) were determined by measuring at isotopic steady state plasma stable isotope enrichment and ¹³CO₂ production. Using this sophisticated technique, the protein gain was estimated at ~13 g of protein during a nightly APD session, which is amply sufficient to compensate for protein losses via dialysate. The results of the 24-h nitrogen balance studies showed a tendency towards improvement in nitrogen retention. The studies were

performed in the fasting state while intraperitoneal amino acids were given in a fixed amount of 27 g, of which ~40–50% was absorbed. The proportion of energy and protein given via dialysate varied between 160 and 340 kcal/gN. As a supplement to deficient nutrient intake, an amount of 13 g of absorbed amino acids is relatively modest and may be inadequate if DPI is far below the targets. The question arises as to whether more intraperitoneal amino acids, for example, a double amount, could be given within the scope of this concept. The optimal energy-to-protein ratio is unknown and remains to be determined. If a ratio of 100 kcal/gN or more is to be assumed, per 54 g of amino acids (2 bags of 2.5 L of a 1.1% solution) 216 g of glucose should be given. This can be achieved roughly when equal volumes of 1.1% amino acid and 3.86% glucose solutions are mixed with final concentrations of 0.55% and 1.93% for amino acids and glucose, respectively. Whether this is acceptable with respect to adverse effects is discussed in a separate section.

The authors also investigated whether this concept could also be utilized for patients in the fed state. This could be of importance for CAPD patients when the amino acids are given in the daytime as a supplement to their (deficient) food intake. Except that the study was performed during the day in patients on CAPD taking liquid food, the study protocol was the same as during nightly APD including the use of an APD cyclor. It could be seen that even in the fed state, intraperitoneal amino acids can make an extra contribution to protein synthesis [25]. Furthermore, similar to intraperitoneal amino acids, feeding itself acted almost exclusively on protein synthesis rather than inhibiting protein breakdown thereby corroborating the concept of ‘dialysate as food’. A two-compartment bag system could make this approach feasible for CAPD patients.

Further, the effects of combined amino acids and glucose solutions on fractional albumin synthesis rate (FSR-albumin) were studied. It was found that neither intraperitoneal amino acids nor food induced a statistically significant stimulation of FSR-albumin. In contrast, both the amino acids/glucose mixture and food exerted a significantly stimulating effect on whole body protein synthesis (WBPS) [26]. These findings demonstrate a differential effect of both oral and intraperitoneal amino acids on the synthesis rates of albumin and WBP. As muscle protein synthesis contributes substantially to WBPS, the stimulating effect of amino acids on WBPS may be attributed to a large extent to increased muscle protein synthesis consistent with previous reports [27]. However, it should be mentioned in this context that the most marked stimulation of albumin synthesis by protein supply has been found under protein-depleted conditions [28]. This study was conducted in a small, relatively stable and well-nourished population of CAPD patients.

Adverse effects of intraperitoneal amino acids

Several studies on CAPD patients have shown that the use of amino acid dialysate is accompanied by acidaemia occurring within 1–4 weeks after starting the daily use of these solutions [8,24]. It is caused by metabolism of the sulfur-

Table 1. Nutrineal and acid generation in APD

	g/L	Absorbed mmol/2.5 L ^a	Liberation of H ⁺ mEq/2.5 L ^b
Methionine	0.850	7.10	14.2
Lysine	0.955	8.16	8.16
Arginine	1.071	7.68	7.68
Histidine	0.714	5.75	2.87 ^c
Total			32.9

^a Assuming 50% absorption.

^b Assuming complete oxidation.

^c Assuming 50% present as cations.

containing amino acid methionine and the cationic amino acids arginine and lysine-HCl. Therefore, the concentration of these amino acids was decreased in the newer commercially available dialysis solutions (Nutrineal[®]). Despite the use of dialysate with lower concentrations of aforementioned amino acids, a trend to acidosis has still been described especially when two bags per day were used giving reason for concern [24,29]. Therefore, it is generally recommended to use no more than one bag of a 1.1% amino acid solution per day. It should be noted in this respect that dietary proteins are the main source of the generation of H⁺ ions (protons) by hydrolysis of dietary phosphate existing as H₂PO₄⁻ and by oxidation of the sulfur-containing amino acids methionine and cysteine as well as the cationic amino acids arginine and lysine, which come available by food intake or endogenously by proteolysis [30,31]. On the other hand, the metabolism of anionic amino acid glutamate and aspartate generates alkali. Collectively, this results in a net hydrogen ion production of 1–2 mEq/kg/day in healthy adults on a normal Western diet. Increasing intake of dietary proteins along with organic H₂PO₄⁻ results in production of increasing amounts of hydrogen ions that have to be removed by the kidney to maintain acid base homeostasis. Halperin estimated that in a diet containing ~120 g of proteins (note: 100 g of beef contain 20 g of protein), ~72 mEq and 138 mEq of H⁺ are generated by metabolism of sulfur-containing amino acids and cationic amino acids, respectively [32]. On the other hand, by metabolism of glutamate and aspartate, 100 mEq of H⁺ are removed, whereas the oxidation of various other dietary organic anions removes additionally 60 mEq of H⁺. This would imply that net acid production by amino acids in such a diet is ~210–100 mEq = 110 mEq. Organic H₂PO₄⁻ has not been taken into account as a source of acid production in the calculations. In patients with renal failure, quantity and class of phosphate binders complicate the role of phosphate in acid generation [33]. Table 1 shows that the estimated hydrogen ion generation by absorbed amino acids in 2.5 L of a 1.1% amino acid solution (~13.5 g) is ~33 mEq if the quantity of absorbed amino acids is completely oxidized. The fact that net acid production by the current intraperitoneal amino acids solution is higher compared with the same amount of dietary protein can be largely explained by the absence of the alkali-generating glutamate and aspartate in the dialysis solution. On the other hand, lactate and bicarbonate are added to dialysis solutions for the provision of alkali [34]. In the fasting state study, a slight decrease of serum bicarbonate

concentrations with amino acids containing dialysate was found, but the bicarbonate levels remained within the normal range when dialysis solutions containing a 40 mmol/L buffer was used. Furthermore, substantial part of the supplied amino acids was not oxidized but was utilized for anabolism as shown in the whole-body protein turnover (WBPT) studies and this may have resulted in a low production of hydrogen ions and urea as well. These findings may suggest that intraperitoneal amino acids, insofar as they are given to supply the deficit of protein intake, bring about only a limited increase in the generation of H⁺ ions and urea. In addition, the findings of this study suggest that metabolic acidosis could be prevented even with higher doses of intraperitoneal amino acids when the concentration of buffer in the mixture of amino acids and glucose containing dialysis solutions is 40 mmol/L.

Feasibility in clinical practice

The intraperitoneal administration of amino acids combined with glucose can take place as part of a regular dialysis schedule in APD patients with the cyler regulating the mixing of amino acids and glucose. Applying an 'empty bag procedure' mixing occurs from the first cycle onward. The dialysis procedure that is described in detail elsewhere is easy to perform at home [15]. Developments in software could further simplify the practice of the dialysis procedure and could make the application of the concept of 'dialysate as food' more versatile.

Conclusion

Automated peritoneal dialysis with a mixture of amino acids and glucose brings about an acute improvement of protein metabolism. Such a response of the body to intraperitoneal amino acids is similar to food-'dialysate as food'. Like dietary protein, intraperitoneal amino acids can bring about the generation of hydrogen ions and urea. No rise of serum urea levels was found with the amount of amino acids given in this study and serum bicarbonate levels remained within the normal range when a buffer concentration of 40 mmol/L in the mixture of amino acids and glucose was used. The use of this approach may be an option for PD patients who cannot fulfil dietary recommendations. APD is very suitable to individualize the dose of intraperitoneal amino acids. The procedure is easy to perform at home. Developments in software could make the application of this approach more versatile. Long-term clinical trials are required to evaluate the effects on morbidity and mortality.

Conflict of interest statement. None declared.

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