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(54) **Titre : COMPOSITIONS NUTRITIVES ET LEURS PROCEDES D'UTILISATION**
(54) **Title: NUTRITIVE COMPOSITIONS AND METHODS OF USING SAME**

(57) **Abrégé/Abstract:**
The invention provides intradialytic parenteral nutrition (IDPN) solutions with low carbohydrate for the treatment of malnutrition in dialysis patients. The IDPN solutions of the invention are particularly advantageous for the treatment of malnutrition in patients who are diabetic or suffer from other glucose management related pathologies or patients who require strict fluid management.

Abstract

The invention provides intradialytic parenteral nutrition (IDPN) solutions with low carbohydrate for the treatment of malnutrition in dialysis patients. The IDPN solutions of the invention are particularly advantageous for the treatment of malnutrition in patients who are diabetic or suffer from other glucose management related pathologies or patients who require strict fluid management.

NUTRITIVE COMPOSITIONS AND METHODS OF USING SAME

FIELD OF THE INVENTION

The invention pertains to nutrition supplement compositions for patients receiving dialysis treatment and methods of using the nutrition supplement compositions. The nutrition supplement compositions include reduced levels of carbohydrates and lower volume to reduce complications in patients who are diabetic or suffer from other glucose management related pathologies, or patients who require strict fluid management.

BACKGROUND OF THE INVENTION

Severe malnutrition remains a problem for patients receiving maintenance hemodialysis (MHD). Dialysis patients often have poor appetites and low energy. This malnutrition is reflected in low serum albumin concentrations, a strong predictor of increased morbidity and mortality. (Moore and Lindenfield, *Support Line* **29**(5):7-16 (Oct. 2007)). Patients are often treated using diet liberalization, oral supplements and enteral feeding. When these methods are not effective intradialytic parenteral nutrition (IDPN) may be utilized for more aggressive nutrition repletion efforts.

IDPN is infused during the hemodialysis procedure. IDPN has been used for decades and has resulted in weight gain and improved protein levels in patients. (U.S. Publication No. 2005/0148647). The typical IDPN treatment delivers 4-6 mg/kg/minute of glucose for patients in need of carbohydrate control and 6-8 mg/kg/minute for patients who do not need carbohydrate control. Blood glucose must be monitored to avoid problems associated with insulin resistance, hyperglycemia and hypoglycemia. In some cases, insulin is also administered either in the IDPN solution or more typically separately administered subcutaneously to modulate blood glucose levels. IDPN generally contains 1.2-1.4 g/kg of amino acids. However, these amounts can be lowered for patients who do not tolerate protein well. Monitoring of serum bicarbonate and carbon dioxide levels must be monitored to check for acidosis caused by administration of amino acids. Lipids are provided in IDPN at a rate between 4 mg/kg/minute and 12-12.5 g/hour depending on tolerance of the lipids by the patient. Generally, these lipids are emulsions of purified vegetable oil from soybean (Intraliipid® from Kabi Vitrum or Travamulsion® from Travenol) or safflower oil (Liposyn® from Abbott). (Powers, *Contemporary Dialysis and Nephrology*:29-31 (Feb. 1990).

IDPN is usually administered in one liter of solution, and occasionally micronutrients, like vitamins and minerals are co-administered in or with IDPN. IDPN has proved effective in decreasing morbidity and mortality in MHD patients, leads to increased levels of serum albumin and creatine levels, and increased body weight. (Moore and Celano, *Nutrition in Clinical Practice*, **20**(2):202-212 (2005)). Hypoglycemia is another potential dangerous result of the administration of insulin during IDPN with symptoms of nervousness, sweating, intense hunger, trembling, weakness, palpitations, and trouble speaking.

Problems associated with IDPN include hyperglycemia, complications in patients with insulin resistance or other problems associated with glucose management, as well as complications in patients who require strict fluid management. The glucose concentrations administered with IDPN can cause hyperglycemia and hypoglycemia in some patients. The administration of insulin can sometimes successfully treat this hyperglycemia, but some patients demonstrate insulin resistance, and may not respond to insulin treatment. (Goldstein and Strom, *Journal of Renal Nutrition* **1**(1):9-22 (Jan. 1991)). Hyperglycemia is a major barrier to effective nutrition support even outside the context of hemodialysis. Many studies report associations between hyperglycemia and increased morbidity and mortality. (McCowen and Bistrian, *Nutrition in Clinical Practice*, **19**(3):235-244 (Jun. 2004)). Moreover, the amount of fluid in typical IDPN treatment is a barrier to use in patients with strict fluid management. Thus, a need exists for an improved IDPN composition for administration to patients that diminishes hyperglycemia associated with IDPN administration and decreases the need for the administration of insulin with IDPN. Moreover, a need exists for a lower volume IDPN dosage form.

SUMMARY OF THE INVENTION

The invention provides intradialytic parenteral nutrition (IDPN) solutions with low carbohydrate content and low volume. The IDPN solutions of the invention are effective in the treatment of malnutrition in patients receiving dialysis treatment. These solutions also reduce the need for insulin administration when administered to patients undergoing maintenance hemodialysis (MHD) patients. Moreover, patients with metabolic conditions that impair their glucose tolerance and metabolism would also benefit from the IDPN solutions of the invention. Also, patients with strict fluid management would benefit from the IDPN solutions of the invention. The IDPN solutions of the invention also include amino acids and, optionally, lipids and/or micronutrients such as vitamins, trace elements and/or minerals. In certain preferred embodiments the IDPN solutions are lipid free. In other

preferred embodiments, the IDPN solutions of the invention are kept in containers for administration to patients, such as bags appropriate for parenteral administration. In one embodiment, each bag contains one dose of IDPN for a patient. In other embodiments, these doses are supplemented with pharmaceuticals, such as insulin. These doses are often administered subcutaneously using a separate administration system.

DETAILED DESCRIPTION

The invention provides intradialytic parenteral nutrition (IDPN) solutions with low carbohydrate and low volume. The IDPN solutions of the invention allow medical personnel to engage in reduced carbohydrate management for MHD patients when they receive IDPN. Moreover, the IDPN solutions of the invention are particularly effective for treating malnutrition in MHD patients who have glucose management difficulties including patients that are insulin resistant, who have type I diabetes or pancreatitis. Also, the reduction of carbohydrate in the IDPN solutions of the invention favors anabolism over catabolism, thus effectively treating malnutrition. In preferred embodiments, the IDPN solutions of the invention have reduced volume, so as to reduce side effects associated with high infusion volumes including dyspnea, increased respiratory rate, rhonchi edema, hypertension, and anxiety. The IDPN solutions of the invention are especially appropriate for patients that have adequate caloric intake but not protein intake. Further, the IDPN solutions of the invention can be administered to normal weight or obese patients.

Preferably, the IDPN solutions of the invention contain carbohydrate and amino acids. In some embodiments of the IDPN solution of the invention, the solution also contains lipids. In other embodiments of the IDPN solution of the invention, the solution also contains micronutrients such as vitamins, trace elements and/or minerals. In other embodiments of the IDPN solution of the invention, the solution also contains pharmaceuticals such as insulin. In preferred embodiments, of the IDPN solution of the invention, pharmaceuticals are coadministered with the IDPN, but are not part of the IDPN solution. For example, insulin can be administered subcutaneously in a separate injection. Preferably, the carbohydrate contained in the IDPN solutions of the invention dextrose (D-glucose). The amino acids contained in the IDPN solutions of the invention include combinations of two or more of the standard 20 amino acids. Preferably, all 20 of the amino acids are administered in the IDPN solutions of the invention. More preferably, 17 amino acids are used. Preferably, the solution of amino acids used to make the IDPN solution of the invention is a concentrated solution and is used in the invention due to the benefits of low volume. Preferably the

concentrated solution contains 15 g/mL of amino acids. More preferably, the concentrated solution contains 20 g/mL of amino acids.

Preferably, the IDPN solutions of the invention contain between 0.02 and 0.10 g/mL of dextrose in solution. Preferably, the IDPN solutions of the invention contain between 0.04 and 0.08 g/mL of dextrose in solution. More preferably, the IDPN solutions of the invention contain between 0.05 and 0.07 g/mL of dextrose in solution. More preferably the IDPN solutions of the invention contains between 0.055 and 0.065 g/mL of dextrose in solution. In various embodiments of the IDPN solutions of the invention, the solutions contain 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09 or 0.10 g/mL of dextrose in solution. In other embodiments of the IDPN solutions of the invention, the solutions contain 0.055, 0.056, 0.057, 0.058, 0.059, 0.060, 0.061, 0.062, 0.063, 0.064 or 0.065 g/mL of dextrose in solution.

Preferably, the IDPN solutions of the invention are packaged in sterile containers for administration to patients. Preferably, the sterile containers are bags used for parenteral administration of IDPN solutions to a patient. Preferably the bags hold between 100 mL of IDPN solution and 2 liters of IDPN solution. More preferably, the bags hold between 300 mL or 1 liter of IDPN solution. More preferably, the bags hold between 419 mL of IDPN solution and 809 mL of IDPN solution. More preferably, the bags hold between 350 mL and 635 mL of solution.

Preferably, the IDPN solutions of the invention are packaged in sterile containers so that the sterile container holds one dose of IDPN solution for administration to a patient. Preferably the dose of IDPN solution has a volume between 100 mL of IDPN solution and 2 liters of IDPN solution. More preferably, the dose of IDPN solution has a volume between 350 mL or 635 mL of IDPN solution. More preferably, the dose of IDPN solution has a volume of 300, 342, 350, 383, 400, 419, 427, 450, 483, 500, 540, 550, 600, 613, 635, 700 or 809 mL. In conjunction with a volume associated with the IDPN solution of the invention, the term "about" means +/- 10 mL per dose.

Preferably, a dose of the IDPN solution of the invention contains between 10 and 50 g of dextrose. More preferably, a dose of the IDPN solution contains between 20 and 45g of dextrose. More preferably, a dose of the IDPN solution contains 20, 23, 26, 30, 35 and 41 g of dextrose. In conjunction with an amount of dextrose associated with the IDPN solution of the invention, the term "about" means +/- 1 g per dose.

In some embodiments of the IDPN solution of the invention, the amount of dextrose in the IDPN solution is dependent upon the mass of the patient receiving the IDPN treatment. Generally, the IPDN solution of the invention contains a dose of dextrose less than 1 g/kg of

body mass of the patient. For example, a patient with a mass between 34 and 39 kg would receive an IDPN solution containing 20 g of dextrose, a patient with a body mass between 40 and 44 kg would receive an IDPN solution containing 23 g of dextrose, a patient with a body mass between 45 and 51 kg would receive an IDPN solution containing 26 g of dextrose, a patient with a body mass between 52 and 59 kg would receive an IDPN solution containing 30 g of dextrose, a patient with a body mass between 60 and 69 kg would receive an IDPN solution containing 35 g of dextrose, and a patient with a body mass of 70 kg, or greater, would receive an IDPN solution containing 41 g of dextrose

Preferably, the IDPN solutions of the invention contain between 0.10 and 0.20 g/mL of amino acids in solution. Preferably the IDPN solutions of the invention contain between 0.12 and 0.18 g/ml of amino acids in solution. More preferably the IDPN solutions of the invention contains between 0.15 and 0.17 g/mL of amino acids in solution. In various embodiments of the IDPN solutions of the invention, the solutions contain 0.10, 0.11, 0.12, 0.13, 0.14, 0.15, 0.16, 0.17, 0.18, 0.19 or 0.20 g/mL of dextrose in solution. In other embodiments of the IDPN solutions of the invention, the solutions contain 0.150, 0.151, 0.152, 0.153, 0.154, 0.155, 0.156, 0.157, 0.158, 0.159, 0.160, 0.161, 0.162, 0.163, 0.164, 0.165, 0.166, 0.167, 0.168, 0.169 or 0.170 g/mL of amino acids in solution.

Preferably, a dose of the IDPN solution of the invention contains between 30 and 120 g of amino acids. More preferably, a dose of the IDPN solution contains between 51 and 110 g of amino acids. More preferably, a dose of the IDPN solution contains 50, 52, 52.5, 55, 60, 65, 68, 70, 75, 78, 80, 85, 90, 95, 100, 105 and 110 g of amino acids. In conjunction with an amount of amino acids associated with the IDPN solution of the invention, the term "about" means +/- 3 g per dose.

In some embodiments of the IDPN solution of the invention, the amount of amino acids in a dose of the IDPN solution is dependent upon the mass of the patient receiving the IDPN treatment. For example, a patient with a body mass between 34 and 39 kg would receive an IDPN solution containing 51 g of amino acids, a patient with a body mass between 40 and 44 kg would receive an IDPN solution containing 60 g of amino acids, a patient with a body mass between 45 and 51 kg would receive an IDPN solution containing 68 g of amino acids, a patient with a body mass between 52 and 59 kg would receive an IDPN solution containing 78 g of amino acids, a patient with a body mass between 60 and 69 kg would receive an IDPN solution containing 90 g of amino acids, and a patient with a body mass of 70 kg, or greater, would receive an IDPN solution containing 105 g of amino acids.

In some embodiments of the IDPN solution of the invention, the solution also contain lipids. Preferably the lipids are emulsions of purified vegetable oil from soybean (Intraliipid® from Kabi Vitrum or Travamulsion® from Travenol) or safflower oil (Liposyn® from Abbott). IDPN solutions of the invention with lipids contain 5-30% lipid by volume. Preferably, IDPN solutions of the invention with lipids contain 10-20% lipid by volume. Lipids should not be added to IPDN solutions administered to patients with hyperlipemia, acute pancreatitis, lipid nephrosis or allergic reactions to eggs.

In preferred embodiments of the IDPN solution of the invention, the solution is lipid free.

In some embodiments of the IDPN solution of the invention, the solution also contains micronutrients such as vitamins, trace elements and/or minerals. Vitamins and minerals that are optionally added to the IDPN solutions of the invention include water soluble vitamins such as vitamin C, folic acid, vitamin B_1, and vitamin B_6, as well as multivitamins lacking vitamin K, and trace elements such as zinc, selenium, copper, chromium, and manganese. Minerals also include mineral salts such as sodium phosphate, and magnesium sulfate.

In some embodiments of the IDPN solution of the invention, the solution also contains pharamaceutical compositions. One example of a pharmaceutical composition appropriate for inclusion in the IPDN solution of the invention is insulin. In some embodiments, insulin is added to the IDPN solution just prior to administration to the patient, because many solution container materials will absorb insulin. Preferably, insulin is coadministered independent of the IDPN solution. For example, the insulin can be subcutaneously injected during treatment with IDPN. Preferably 5-20 units of insulin is added with one dose of IDPN.

Preferably, the IDPN solution of the invention is administered to dialysis patients who are suffering from malnutrition. A dialysis patient suffering from malnutrition can be identified by detecting evidence of protein or energy malnutrition and inadequate dietary protein intake, evidence of the inability to administer or tolerate adequate oral nutrition inclusive of supplements and tube feeding, and evidence that the combination or oral and/or enteral intake when combined with IDPN will meet the patient's nutritional needs.

Administration of the IDPN solution of the invention generally coincides with the start of hemodialysis on a patient. During IDPN solution administration the patient should be monitored for glucose tolerance, protein status and/or fat status. Glucose monitoring includes blood glucose level before, during and after IDPN administration and monitoring the patient

for symptoms of hyper or hypoglycemia. The symptoms of hyperglycemia include nausea, thirst, headache, vomiting and weakness. The symptoms of hypoglycemia include headache, dizziness, tremors, cold sweat, confusion, and faintness. The presence of hyper or hypoglycemia can then be confirmed through blood sugar analysis, such as via a fingerstick or arterial glucose level. To treat hyperglycemia, insulin is administered. To treat hypoglycemia the patient should receive 20-30 g of simple carbohydrates orally. Protein monitoring includes the monitoring of blood urea nitrogen (BUN) prior to dialysis and Kt/V which is a measure of dialysis adequacy.

Fat monitoing includes a pre-dialysis triglyceride test prior to lipid infusion and then another following first lipid infusion to ensure that the patient is clearing lipids from the bloodstream. Also, sodium, potassium, phosphorus and magnesium levels should be monitored for the presence of refeeding syndrome.

Generally, the IDPN solution of the invention is administered through a port post dialyzer of the dialysis machine being used to perform hemodialysis on the patient. In a preferred embodiment, the IDPN infusion is performed through the venous chamber of the dialysis machine. Examples of routes of parenteral administration include intravenous, intradermal, subcutaneous, and intraperitoneal administration. Any pharmaceutically acceptable carrier can be used in conjunction with the IDPN solution of the invention. The IDPN solution of the invention can be administered in the same manner prior art IDPN solutions have been administered.

EXAMPLES

Protein Repletion Formulas

The following IDPN formulas were developed. These formulas are administered to a MHD patient requiring 3.25 hours or longer dialysis treatment time. The formulas are fat free and micronutrient free, but these components could easily be added.

Table 1

WEIGHT	CHO	AA	VOL	Total Kcals	FINAL (g/dl)
34-39 Kg	29ml 20gm	255ml 51gm	(Approx. 50cc fill) 334ml	272kcals	D5.9 15.3AA
40-44 Kg	33ml 23gm	300ml 60gm	383ml	318kcals	D6.0 15.7AA
45-51 Kg	37ml 26gm	340ml 68 gm	427ml	360kcals	D6.1 15.9AA
52-59 Kg	43ml 30gm	390ml 78gm	483ml	414kcals	D6.2 16.1AA
60-69 Kg	50ml 35gm	450ml 90 gm	550ml	479kcals	D6.4 16.4AA
70+Kg	59ml 41gm	525ml 105gm	635ml	560kcals	D6.5 16.6AA

The infusion rate schedule for subjects of each weight class are shown in Table 2, below.

Table 2

Weight class	**Week 1 Infusion Rate**	**Week 2 Infusion Rate**
34-39 kg	50 mL/hour	105 mL/hour
40-44 kg	60 mL/hour	120 mL/hour
45-51 kg	65 mL/hour	135 mL/hour
52-59 kg	75 mL/hour	150 mL/hour
60-69 kg	85 mL/hour	170 mL/hour
70+ kg	100 mL/hour	195 mL/hour

The following formulations were made with a more dilute commercially available source of amino acids.

Table 3

WEIGHT	CHO	AA	VOL	Total Kcals	FINAL (g/dl)
34-39 Kg	29ml 20gm	340ml 51gm	(Approx. 50cc fill) 419ml	272 kcals	D4.8 12.2AA
40-44 Kg	33ml 23gm	400ml 60gm	483ml	318 kcals	D4.8 12.4AA
45-51 Kg	37ml 26gm	453ml 68 gm	540ml	360 kcals	D4.8 12.6AA
52-59 Kg	43ml 30gm	520ml 78gm	613ml	414 kcals	D4.9 12.7AA
60-69 Kg	50ml 35gm	600ml 90 gm	700ml	479 kcals	D5.0 12.9AA
70+Kg	59ml 41gm	700ml 105gm	809ml	560 kcals	D5.1 13.0AA

CLAIMS

1. An aqueous composition formulated based on a body mass of a patient, the aqueous composition comprising:
a) dextrose, wherein the dextrose is present in an amount less than 1 g/kg based on the body mass of the hemodialysis patient; and
b) between 0.10 and 0.20 g/ml of amino acids,
wherein the dextrose and the amino acids are both dissolved in the aqueous composition, which is packaged in a sterile container.

2. The aqueous composition of claim 1, comprising between 0.12 and 0.18 g/ml of amino acids.

3. The aqueous composition of claim 1 or 2, comprising between 0.15 and 0.17 g/ml of amino acids.

4. The aqueous composition of any one of claims 1-3, comprising two or more of the standard 20 amino acids.

5. The aqueous composition of claim 4, comprising a mixture of 17 of the 20 standard amino acids.

6. The aqueous composition of claim 4, comprising a mixture of all 20 of the standard amino acids.

7. The aqueous composition of any one of claims 1-6, further comprising micronutrients.

8. The aqueous composition of any one of claims 1-7, further comprising a pharmaceutical agent.

9. The aqueous composition of claim 8, wherein the pharmaceutical agent is insulin.

10. The aqueous composition of any one of claims 1-9, wherein the aqueous composition has a volume between 300 mL and 1 L, and wherein the sterile container is suitable for parenteral administration of the aqueous composition to a human patient.

11. The aqueous composition of any one of claims 1-10, wherein the aqueous composition is suitable for administration through a port post dialyzer of a dialysis machine.

12. The aqueous composition of any one of claims 1-10, wherein the aqueous composition is suitable for administration through a venous chamber of a dialysis machine.

13. The aqueous composition of any one of claims 1-12, comprising between 30 and 120 g of amino acids, wherein the aqueous composition has a volume between 100 mL and 2 L.

14. The aqueous composition of any one of claims 1-13, wherein the aqueous composition is suitable for parenteral administration.

15. The aqueous composition of any one of claims 1-14, wherein the aqueous composition is lipid free.

16. The aqueous composition of any one of claims 1-14, wherein the aqueous composition comprises lipids.

17. Use of the aqueous composition of any one of claims 1-16 in formulating a medicament for treating malnutrition in a hemodialysis patient in need thereof.

18. The use of claim 17, wherein the hemodialysis patient has insulin resistance, type I diabetes, pancreatitis, or a need for strict fluid management.

19. Use of the aqueous composition of any one of claims 1- 16 in formulating a medicament for promoting anabolism over catabolism in a hemodialysis patient in need thereof.

20. The use of claim 19, wherein the hemodialysis patient has insulin resistance, type I diabetes, pancreatitis, or a need for strict fluid management.

21. A dosage form formulated based on a body mass of a patient, the dosage form comprising an aqueous solution of:
a) dextrose, wherein the dextrose is present in an amount less than 1g/kg based on a body mass of a patient; and
b) between 30 and 120 g of amino acids,
in a volume between 100 mL and 2 L, wherein the dosage form is packaged in a sterile container suitable for parenteral administration to a human patient.

22. The dosage form of claim 21, wherein the aqueous solution is lipid free.

23. The dosage form of claim 21, wherein the aqueous solution comprises lipids.

24. Use of the dosage form of claim 19 in formulating a medicament for treating malnutrition in a hemodialysis patient.

25. Use of the dosage form of claim 19 or 20 in formulating a medicament for promoting anabolism over catabolism in a hemodialysis patient.

26. A composition comprising:
a) between 0.10 and 0.20 g/ml of dextrose; and
b) between 0.10 and 0.20 g/ml of amino acids;
wherein the dextrose and the amino acids are both dissolved in the same aqueous solution, which is packaged in a sterile container.

27. The composition of claim 26, wherein the composition is lipid free.

28. The composition of claim 26, wherein the composition comprises lipids.

29. Use of the composition of any one of claims 26-28 in formulating a medicament for treating malnutrition in a hemodialysis patient.

30. Use of the composition of any one of claims 26-28 in formulating a medicament for promoting anabolism over catabolism in a hemodialysis patient.

31. The use of claim 29 or 30, wherein the hemodialysis patient has insulin resistance, type I diabetes, pancreatitis, or a need for strict fluid management.