Review Article

Metabolic acidosis during parenteral nutrition: Pathophysiological mechanisms

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Abstract

Total parenteral nutrition (TPN) is associated with metabolic complications including metabolic acidosis (MA), one of the main disorders of acid-base balance. The main causes involved in the appearance of MA during TPN administration are the metabolism of cationic amino acids and amino acids containing sulfuric acid (exogenous addition), the titratable acidity of the infused parenteral solution, the addition of acidificant agents (hydrochloric acid, acetic acid), thiamine deficiency, disruption of carbohydrate and lipid metabolic pathways and D-fructose administration. Moreover, hypophosphatemia that appears during TPN therapy contributes significantly to the maintenance of MA. This review describes in a comprehensive way the pathophysiological mechanisms involved in the appearance of MA induced by intravenous administration of TPN products most commonly used in critically ill-patients.

Keywords: Critical illness, metabolic acidosis, total parenteral nutrition

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Introduction

Metabolic acidosis (MA) is a disorder of acid-base balance, which is characterized by reduction of arterial blood pH (increase of hydrogen ions [H^+] concentration) with simultaneous reduction of serum bicarbonate concentration (HCO_3^-) and of carbon dioxide partial arterial pressure. The main causes of this disorder are, the exogenous acid administration or increased endogenous acid production (i.e., lactic acid in cases of tissue hypoxemia, β-hydroxybutyrate in diabetic ketoacidosis), the decreased acid excretion, normally produced on daily basis (i.e., phosphoric and sulfuric acid in chronic kidney disease) and the increased HCO_3^- loss (i.e., diarrhea, renal tubular acidosis). MA could also be observed in cases of acid or acid precursors administration such as sodium chloride (NaCl), ammonium chloride, bromine, valproic acid, acetic anions (through dialysis solution), sulfur and during administration of total parenteral nutrition (TPN).

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In this review, we attempt to present in a comprehensive way the pathophysiological mechanisms involved in the appearance of MA-induced by intravenous (i.v.) administration of TPN products. In-depth knowledge of these mechanisms forms a necessity considering the frequency of TPN administration in everyday clinical practice, especially in critically ill-patients.

Metabolic Acidosis During Total Parenteral Nutrition

During 70's, Dudrick *et al.* first introduced TPN, for the patients who were unable to obtain adequate nutrients by oral route, especially for critically ill-patients, having as a primary goal to supply the substrate necessary to meet their metabolic needs.[1] Another goal of nutritional support is to alter the course and outcome of critical illness, as it is known that malnutrition causes significant postoperative complications, increases the frequency of infections and prolongs patients' hospitalization.[2] However, the early initiation of TPN administration (up to 48 h) does not seem to alter mortality and there is no consistent evidence of improvement in the number of ventilator-free days or length of stay in the Intensive Care Unit (ICU) in critically ill-patients.[3] In addition, metabolic complications presented in malnourished patients after major surgery are partially due to TPN administration

for a long period of time.[4] These complications include hyperglycemia, macro-or micro-nutrient excess or deficiency, refeeding syndrome, serum electrolytes alterations and acid-base disturbances, such as MA the incidence of which has been previously reported fairly high among critically ill patients treated with TPN.[5]

The main causes involved in the occurrence of MA during TPN administration are the metabolism of cationic amino acids and sulfur-containing amino acids (exogenous addition), the titratable acidity (TTA) of the infused parenetral solution, the addition of acidificant agents (hydrochloric acid, acetic acid), thiamine deficiency, disruption of carbohydrate and lipid metabolic pathways and D-fructose administration. Moreover, hypophosphatemia that appears during TPN therapy contributes significally to the maintenance of MA.

Metabolism of cationic amino acids and of sulfur-containing amino acids (exogenous addition)

In the early era of TPN, MA was rarely observed because used solutions were enriched with proteins (protein hydrosylates) and did not cause significant nitrogen retention.[6] The newer TPN solutions contain synthetically produced amino acids (L-amino acids), instead of albumin, in concentrations ranging from 5.5% to 15%. The wide variation in the content of amino acids, provide the opportunity of treatment individualization according to the needs of each clinical case.[7]

L-amino acids according to their charge are subdivided in cationic and anionic amino acids. Cationic amino acids are arginine, lysine and histidine (positive charge), and sulfur-containing amino acids like methionine, cysteine and cystine, while anionic amino acids are lactic, acetic, aspartatic and glutaminic acids (negative charge).[8,9] Solutions containing L-amino acids come in three different types, those containing only cationic amino acids, those with only anionic amino acids and mixed solutions. Metabolism of cationic amino acids of TPN results in production of H^+ according to equation:

$$R\text{-}NH_3 + O_2 \leftrightarrow Urea + CO_2 + H_2O + H^+$$

The H^+ ions produced through metabolism of amino acids remain in extracellular space and are added to those produced from catabolism. Human body is unable to neutralize this excess of acids with the available bases reserves (HCO_3^-), resulting in MA.[9] On the contrary, metabolism of anionic amino acids is characterized by the consumption of H^+. Thus, in mixed TPN solutions, if the content of cationic amino acids is higher than anionic, this results in a greater quantity of produced H^+ than the one which could be consumed during their metabolism, with final consequence the appearance of MA. This difference (excess of H^+) between metabolized cationic and anionic amino acids is characterized as cation gap.[9]

Oxidation of sulfur-containing amino acids leads to the production of sulfate, the addition of which in extracellular space leads to the appearance of MA.[10,11] As sulfate is a not a measured anion, MA arising is characterized by increased anion gap. Moreover, sulfate is not reabsorbed from renal tubules and is excreted by the kidneys as sodium sulfate, leading to extracellular volume contraction and increased reabsorption of (NaCl) with final result the appearance of hyperchloremic MA.[12]

Titratable acidity of parenteral solution administrated

Titratable acidity is defined as the quantity of the base, which should be added to an acid solution in order that solution's pH returns to be 7.40. In human body H^+ must be excreted in a form other than the dissociated acid to maintain a homeostatic pH and this is accomplished by the formation of TTA (H^+ bound to buffers in the urine such as HPO_4^{2-} and SO_4^{2-}).[13] TTA is not considered important for the appearance of MA during TPN, since in the mixed acid solutions is much smaller comparing with the older solutions containing protein.[9] Thus, the quantity of H^+ administrated is not sufficient enough to cause MA. The TTA of parenteral solutions consists of hydrochloric acid and organic acids, such as acetic acid. Terashima *et al.* showed that MA is caused by the high TTA induced not only by the nonmetabolizable acids (hydrochloride acids), but also metabolizable acids (organic acids) in TPN solutions.[14] However, a recent study suggested that the amount of TTA is not related to the incidence of the acid load.[15]

Addition of hydrochloride acid and acetic acid

Preparation of TPN solutions requires pH solution to be maintained in low levels (ideal range 5.0–5.4) aiming to suspend the initiation of chemical interactions between carbohydrates and amino acids (Caramel and Maillard reactions).[16] It is well known that these reactions are promoted by the high amino acids concentrations and the solution alkaline pH leading to the production of advance glycosylation end products and advance lipid end products. However, during production, a number of solutions present higher pH after their thermal sterilization. Thus, for the maintenance of predesigned formula's quality, the addition of acidifying factors becomes necessary. Hydrochloric acid (not metabolized) and acetic acid (metabolized) are the most widely used acidifying mean for the maintenance of desired pH in the commercially available TPN solutions.[8]

Addition of hydrochloric acid in solutions leads to increased chloride plasma concentration with a parallel reduction of HCO_3^- plasma concentration (first line of defense for H^+ neutralization derived from hydrochloric acid). This in turn causes a reduction of HCO_3^- content filtrated by the glomerulus and a competitive increase of Cl^- and Na^+ reabsorption, which are normally equally reabsorbed at the proximal convoluted tubule. The final result is the installation of hyperchloremic MA.

On the contrary, acetic acid is a metabolized anion. During its oxidation consumes H^+ ions, which are produced by metabolized cations.[5] In a recent study Tsai *et al.* showed that TPN solutions containing acetic acid caused MA to a lesser degree compared with solutions containing hydrochloric acid.[8] In a solution containing both hydrochloric and acetic acid the proportion of acetic/hydrochloric determines the degree of MA. A recent research showed that only nonmetabolizable acid might be a risk factor for MA.[16]

Thiamine deficiency (Vitamin B1)

The main sources of thiamine intake for human body are dietary intake and the produced thiamine by the normal flora of intestinal tract. Free thiamine (after hydrolysis of its phosphorylated forms), is absorbed actively through specific receptors, which are independent from sodium, but are dependent from pH and amiloride (amiloride-sensitive).[17] After its absorption, thiamine is phosphorylated in thiamine pyrophosphate (TTP). TTP is involved in a series of enzymatic reactions, which are correlated with the metabolism of carbohydrates, lipids, and amino acids. Normally, thiamine is necessary for the transmutation of pyruvic acid in a-ketoglutaric acid, which then entry Krebs cycle.[18]

However, thiamine is also necessary for the conversion of lactic acid in pyruvic acid, which is then metabolized as mentioned before.[18] Therefore, in situations with thiamine deficiency such as inadequate dietary intake (especially in patients during TPN therapy), reduced enteric absorption, increased peptic or renal loss, in alcoholic patients, in patients with AIDS or malignancies, in pregnancy and breastfeeding, in hyperthyroidism, in chronic kidney disease (especially in hemodialysis patients), in systemic infections and in diabetic mellitus, the inadequate metabolism of lactic acid leads to its tissue accumulation, increased concentration and finally to the appearance of MA.[5,19] MA caused by lack of thiamine is both local and systematic.[17] Recently, it was showed that lack of thiamine in ICU patients is combined with high concentration of lactic acid even in the absence of hepatic dysfunction.[20]

Recent guidelines recommend administration of thiamine in a dose of 100–300 mg/day during the first 3 days of hospitalization for ICU patients who are potentially suspected for thiamine deficiency.[21]

Disruption of metabolic pathways of carbohydrates and lipids

Critically ill-patients have increased caloric requirements for the metabolism of diseased tissue/organ.[22] The endogenous produced quantity of glucose through glucogenolysis is limited and consequently insufficient to cover the increased energy requirements. Under these conditions, glucose is released mainly from endogenous proteins and secondly from lipids (lipolysis), through gluconeogenesis.[23] Therefore, administration of carbohydrates through TPN solutions is the preferred energy source during critical illness because fat mobilization is impaired and exogenous administration of dextrose, plays an important role in inhibition of gluconeogenesis. It is worth noting that the maximum glucose infusion rate in order to maintain normoglycemia both in healthy population and severely ill patients is 4 mg/kg/min.[24,25]

Parenteral nutrition is a mixture of solutions that contains dextrose in a variety of concentration, most commonly 40, 50 and 70%, whereas lipid emulsion may be infused separately or added to the mixture. Dextrose and lipids (commonly long-chain omega-6 triglycerides) are the main sources of daily caloric requirements, which are not derived from proteins (nonprotein calories). However, previous studies refer that the administration of carbohydrates has a special effect on protein metabolism, which causes retention and consequently reduction in renal excretion of nitrogen metabolism products,[26] whereas this effect is not observed with diet based on lipid intake.[27] Recent experimental studies did not confirm these findings.[28]

Another side-effect of dextrose-containing stock solutions is the transient hepatic dysfunction,[29] causing a transient disturbance of lactic acid hepatic metabolism (lactic acidosis type B).[30] Finally, administration of large volume of dextrose-containing stock solutions, fails to suppress completely endogenous lipolysis, increases oxygen consumption with a parallel increase of carbon dioxide production (glucose oxidation), leading to an additional acid-base disturbance, namely respiratory acidosis.[31]

D-fructose administration

D-fructose, regardless the route of administration (orally or i.v.), is converted into lactic acid, causing the appearance of lactic acidosis.[32] In addition, D-fructose causes an

increment of nucleotide catabolism (endogenous acid production depends on the dose and the infusion rate), contributing to the appearance of MA.[33] It is worth noting that large doses of D-fructose are considered toxic.

Hypophosphatemia

Hypophosphatemia, observed during TPN support therapy, is partially responsible for the occurrence and maintenance of MA. Hypophosphatemia observed in critically ill patients, is one of the main electrolyte disorders of the refeeding syndrome. Refeeding syndrome describes a constellation of metabolic disturbances that occur as a result of reinstitution of nutrition to patients who are starved or severely malnourished. In particular, hypophosphatemia occurs due to the utilization of phosphorus for the development of new cells and tissue regeneration.

Hypophosphatemia results in the reduction of serum phosphate levels and a reduction of the phosphate amount filtered through the glomerulus and which participates, together with bicarbonate and ammonium buffer system, in the renal removal of nonvolatile H^+. Reduction of phosphate leads to a reduction of H^+ elimination from renal tubules through the phosphate buffer system (reduction of urinary TTA).[33]

Previous studies have described a syndrome observed during TPN, which was due to hypophosphatemia.[34,35] The syndrome was characterized by paraesthesia, dysarthria, confusion, hyperventilation and lethargy. At cellular level, deficiency of 2, 3 diphosphoglycerate and adenosine triphosphate in red blood cells was the main finding, leading to increased risk for hemolysis and increased O_2 affinity (impaired tissue release, tissue hypoxemia-lactic acidosis).

Conclusions

Apart from the common causes, as diabetic ketoacidosis and kidney dysfunction, MA can be observed during TPN administration, commonly applied in every day therapeutic practice. However, when there is a strong indication for TPN administration, the use of newer solutions could reduce the incidence of MA because they contain a higher concentration of organic acid anions (potential base).[36] Nonetheless, MA represents a potentially dangerous problem in those patients receiving TPN and presenting with conditions as diarrhea or proximal renal tubular acidosis due to increased bicarbonate loss, acute or chronic renal failure due to decrease acid excretion and various forms of shock due to lactic accumulation. Therefore, close monitoring of parameters that are evolved in the assessment of acid-base balance disturbance is necessary in order to achieve the early correction of MA.

Infusion of parenteral nutrition may cause MA of multifunctional reasoning, which should be early recognized and treated, trying to prevent further complications. As a result, in-depth knowledge of pathophysiological mechanisms underlying metabolic disorders of TPN constitutes a very useful tool, especially in the hands of health practitioners responsible for TPN prescription and of clinicians treating critically ill patients.

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