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Effects of Parenteral Infusion of Amino Acid Solutions in Acid-Base Balance in Patients with Advanced Chronic Renal Failure

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Abstract

Malnutrition is a very common condition in patients with chronic kidney disease (CKD), especially after the 3rd stage (GFR 30-59 mL/min/1.73 m^2). It affects virtually every organ and the function of the entire organism as well and therefore influences the survival. Moreover, the supplementation of amino acids could correct the negative nitrogen balance of those patients improving their survival rates, while little is known regarding any possible negative effect of this supplementation of amino acids on the acid-base balance.

We investigated the impact of parenteral infusion of two different kinds of amino acid solutions (specific for CKD patients and nonspecific) in 25 patients (12F, 13M), suffered from chronic renal failure in stages 3 and 4 (GFR 16 to 45.1 mL/min/1.73 m^2). The specific for uremic CKD patients solution A was administrated for 5 days, and after an interval of one week, we treated the same patients for another 5 days with the second non-specific solution B, with usual composition), in order to investigate their influence on patients' acid-base balance. Comparing the results of the first and the last infusion of solution A, neither pH nor blood gases analysis presented significant differences, while solution B induced statistically significant changes in both pH and blood gases, (p=0.0001). Acidosis was resulted in by the reduction of serum levels of HCO_3^- whereas not any significant change observed in serum lactate levels after the infusion of each solution.

These results suggest that for patients with chronic kidney disease in stages 3 and 4 who require the administration of a supplementary amino acid solution, the CKD-specific solution A may be preferred, since it prevents the worsen of the metabolic acidosis, which is commonly present in these patients.

Keywords: Chronic renal failure; Amino acid solution; Parenteral infusion; Metabolic acidosis; Acid-base balance

Introduction

Due to protein restriction, there is a high prevalence of malnutrition and negative nitrogen balance, in both pre-dialysis patients with severe chronic renal failure and in hemodialyzed patients with end-stage renal disease (ESRD) [1-3]. Moreover, epidemiological studies have shown that several markers of malnutrition, such as low serum albumin and high C-reactive protein (CRP) levels are strong predictors of morbidity and mortality in ESRD patients [4,5], mainly due to cardiovascular diseases [6]. Consequently it is of great importance to increase daily protein intake either orally or parenterally, which may enhance the acid production leading to aggravation of metabolic acidosis [7-9]. Several studies in patients on hemodialysis reported the advantages of providing intradialytic proteins [10-12], while data are missing about the effects of given proteins in patients with 3rd and 4th stage of chronic kidney disease (CKD).

In this study, we evaluated the effect of intravenous (I.V.) infusion of two different amino acid solutions, one specific solution for patients with CKD and a non-specific one, on acid-base balance (blood pH, HCO_3^-).

Patients

Twenty five patients (12 female, 13 male), aged 37 to 85 (median age 73), with 3rd and 4th stage of CKD have been studied, 11 of stage 3 and 14 of stage 4, with GFR ranged from 16 to 45.1, 26.6 ± 8.1 ml/min, (mean ± SD), and median = 26 ml/min. The primary diseases of the patients were diabetic nephropathy (11 patients), hypertensive nephrosclerosis (7 patients), adult dominant polycystic kidney disease (2 patients), eclampsia (1 patient) and nephropathy of unknown cause (4 patients).

All the patients were daily prescribed to take a low protein diet of 0.6 gr protein/kg body weight (BW). Also they had been instructed to keep in taking the same amount of protein, during the study period, to avoid severe exercise maintaining approximately the same mild everyday activity, and not to use any medication that could affect the acid-base balance such as soda or antacids with carbonate or/and hydrochloric sevelamer.

Since CKD patients are susceptible to infections, we excluded patients who had clinical symptoms and signs or relative laboratory findings as well as those with increased blood lactate levels and malnourished.

Methods

First of all, the glomerular filtration rate (GFR) of the patients was estimated by MDRD equation [13] and verified if they met the

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inclusion criteria by taking blood sample from a peripheral vein for laboratory tests (Hct, Hb, ESR, serum urea, creatinine, CRP, iron, ferritin, TIBC, total proteins, and albumin) in the morning of the first day of the study. An extra sample of arterial blood was taken, mostly from the radial artery, the first morning and every morning during the study period, before the initiation of amino acid infusion, in order to evaluate the acid-base parameters and blood lactates levels. An extra sample of arterial blood was also taken at the end of the last infusion.

Two different types of amino acid solutions, were evaluated; those which are specific for CKD patients named solution A (Nephrotect, Fresenius), and a commonly used non-specific amino acid solution, named solution B (Aminoplasmal L-10%, B Braun), with a wash-out of period between them of 7 days. The composition of the two amino acid solutions (A and B) is shown in table 1. Both solutions contain similar amounts of total nitrogen (16.3 gr/L [A] vs 16 gr/L [B]), while solution A contains more essential amino acids as compared to solution B. Also solution A contains more acetate (124 mEq/L) than solution B (59 mEq/L) and more malate (15 mmol/L) than solution B (7.5 mmol/L), which are metabolized to bicarbonate (HCO_3^-). Additionally, solution A contains 40 mol NaOH/L (acidity titration), whereas only solution B contains CI^- (Cl^- = 57 mmol/L). Any other difference concerning their composition in amino acids is not important.

We studied the changes in the acid-base parameters before and after a 4-hour intravenous (I.V.) infusion of 500 ml (50 gr of protein), of solutions A and B, in a peripheral vein, each administered for 5 consecutive days. Before the first infusion, and every morning for the next 5 days before the infusion, the changes of pH, HCO_3^- and $PaCO_2$, were evaluated and compared to changes seen in the sample taken after the end of the 5th infusion. Blood gases and lactate levels were estimated directly by automatic analyzer (GEMPremier 3000), while biochemical parameters and hematocrit were determined by automatic biochemical and hematologic analyzer, respectively. Also iron serum levels were measured by automatic analyzer chromatometric (Radox Lab UK), transferrin by anosoenzymatic method (Radox Lab UK), TIBC calculated automatically by analyzer or from the formula TIBC = transferrin x 1.25, ferritin by microsomatic ELISA, and creatinine clearance was estimated by MDRD formula.

	Nephrotect (gr/1000 ml) (Solution A)		Aminoplasmal L-10 (gr/1000 ml) (Solution B)
L-isoleukine	5.8		5.1
L-leukine	12.8		8.9
L-lysinmonoacetate	*16.925*	*HCl lysine*	*7*
L-methionine	2		3.8
L-phenylalanine	3.5		5.1
L-threonine	8.2		4.1
L-tryptophan	3		1.8
L-valine	8.7		4.8
Arginine	*8.2*		*9.2*
L-histidine	*9.8*		*5.2*
L-alanine	6.2		13.7
Acetylcysteine	0.54		0.68
L-cysteine	0.4		0.5
L-proline	3		8.9
L-serine	7.6		0,30
L-tyrosine	3.0		1,30
Glycine	5.31		-

Table 1: Composition of solutions A and B.

The statistical analysis of the results was done with repeated measures one way analysis of variance. We use a mixt model to find out possible differences between the two our different therapeutic interventions. Statistical significance was accepted as $p < 0.05$.

Results

The plasma levels of total proteins of the 25 patients ranged from 6 to 8.3 g/dL (mean ± SD, 7.16 ± 0.6, median 7.1 g/dL) while the levels of albumin ranged from 3.4 to 4.8 g/dL (mean ± SD, 4.01 ± 0.37, median 4 g/dL). Similarly the serum levels of lactate were in normal range without any difference during each solution infusion.

Blood pH did not reveal any statistically significant change before the first infusion and immediately after the last infusion of solution A (7.34 ± 0.04 vs. 7.32 ± 0.06, p = NS), in contrast to infusion of solution B which resulted in pH a statistically significant decrease (7.34 ± 0.05 vs. 7.30 ± 0.06, p = 0.0001). This difference was due to the reduction in HCO_3^-, which was significant for I.V. infusion of both solutions (A from 18.38 ± 3.17 to 16.98 ± 3.76, p = 0.0001, and B from 19.38 ± 3.24 to 15.59 ± 3.6, p = 0.0001), though the difference in the last sample was greater for solution B (solution A vs. B, 16.98 ± 3.76 vs. 15.59 ± 3.6, p=0.026). The differences in the $PaCO_2$ (Table 2) were due to the need of different compensation.

Comparing also the differences of blood gases analysis before the first infusion and after the last one, $PaCO_2$ presented a statistically significant decrease by solution B (35.1 ± 4.1 to 31.4 ± 4.4, p = 0.0001) whereas solution A did not reveal any significant change (34.36 ± 4.30 to 32.52 ± 4.3, NS), (Tables 2).

Discussion

There is a high prevalence of malnutrition and negative nitrogen balance in CKD patients because of several factors such as the decreased protein and energy intake due to protein restriction and low-phosphorus diet, the presence of anorexia, which is related to uremic toxins, the impaired gastrointestinal motility, medicines, and taste disturbances, psychological factors (depression), endocrine and metabolic disorders and concurrent chronic illnesses [12,14].

Metabolic acidosis, even if it is mild, is related both to negative nitrogen balance [15] and enhanced protein catabolism [16] while chronic metabolic acidosis suppresses albumin synthesis, the most sensitive and early predictor of malnutrition in patients with CKD. On the contrary the correction of metabolic acidosis increases albumin synthesis [8] and decreases protein catabolism [7,16].

This is important since, considerable protein restriction in CKD patients does not retard the progression of renal failure while it might probably lead to malnutrition. Consequently some investigators thought that the supplementation of amino acids could correct the negative nitrogen balance of those patients and improve their survival [17]. This beneficial result presupposes that such a supplementation with amino acid solution may not have negatively affected the acid-balance, which may be related to the composition of these solutions. Actually, specific amino acid solutions for parenteral use in hemodialyzed patients could probably protect from such complications.

	Solution A			Solution B		
	Before	After	p	Before	After	p
pH	7.34 ± 0.04	7.32 ± 0.06	NS	7.34 ± 0.05	7.30 ± 0.06	0.0001
HCO_3^-	18.38 ± 3.17	16.98 ± 3.76	0.0001	19.38 ± 3.24	15.59 ± 3.6	0.0001
$PaCO_2$	34.36 ± 4.30	32.52 ± 4.3	NS	35.1 ± 4.1	31.4 ± 4.4	0.0001

Table 2: Changes of the blood gases before and after the end of the last amino acid infusion of solution A and B.

Mortelmans et al. [18] performed a prospective long-term study in 16 malnourished hemodialyzed patients to whom they infused 0.6 gr/kg BW amino acids in each session for 9 months and did not find any difference in the acid-base balance. Similar results have been reported by Navarro et al. [12].

Also, Hisoshige et al. [19], studied the parenteral infusion of a specific amino acid solution in 28 elderly malnourished chronic hemodialysis patients, for at least 2 years, and did not find any effect on the patients' metabolic acidosis. Specifically, they used Amiyu solution (Amiyu, Morishita CO, Tokyo, Japan), containing 14 gr of essential amino acids. It must be mentioned that they used dialyzers with polysulfone, PMMA, and PEPA membranes, which are permeable to amino acids (6-8 gr amino acids are being lost in each 4-hour dialysis session) [20]. Subtracting the quantity eliminated by the dialyzer the amount of amino acids they infused (14 - (6-8) = 6-8 gr) is almost half of that we used (16 gr) in our patients.

Moreover, the effects of intradialytic parenteral infusion for 16 weeks of amino acids during one HD session in 16 malnourished patients on chronic hemodialysis were evaluated by Smolle et al. [10]. They found out that the serum albumin levels increased, while the patients were not acidotic because the pH did not change from the beginning until the end of the infusion at the end of the study (7.37 ± 0.02 vs. 7.39 ± 0.01, p = NS). These results are similar to our findings, though in our pre-dialysis patients there was not any loss of amino acid due to the dialysis as was estimated by Smolle et al. [10] Also they used an every other day estimation of acid-base balance instead of the everyday assessment for 5 consecutive days, we used for the present study.

Concerning the composition related effects, it is well known that synthetic L-amino acids, which were included in parenteral solutions, have measurable quantities of titration acid, which might cause acidosis [21]. It should be particularly noted that cationic amino acids (arginine, histidine, and lysine), can cause acidosis, as a consequence of the metabolic production of H^+ [21]. Additionally, all the amino acids included in both specific (A) and not (B) solutions were in L-form, except for acetylcysteine (Table 2). Besides, solution A vs. B contain more lysine (19.925 gr/L vs. 7 gr/L) and histidine (9.8 gr/L vs. 5.2 gr/L) and less arginine (8.2 gr/L vs. 9.2 gr/L), but these differences did not play any significant role in the changes in acid-base balance. Subsequently where could we yield the different effect of amino acid solutions to the blood gases? Firstly, amino acid solutions commonly used in the past as well as solution B contain Cl^- in high concentration, since it is a component of their amino acid molecules, and this anion may be responsible for acidosis. Secondly specific solution A contains significant quantities of molecules, such as acetate and malate that are precursors of HCO_3. Finally, the specific solution A contains the base NaOH that protects from acidosis.

It is concluded that in pre-dialysis patients with chronic kidney disease, the differential buffer content of each amino acid solution for supplementary use, is very important because it could affect the acid-base balance and thus the CKD-specific solutions must be preferred for uremic patients, since they prevent from worsening the metabolic acidosis that is commonly present in these patients.

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