

Amino acids – Guidelines on Parenteral Nutrition, Chapter 4

Aminosäuren – Leitlinie Parenterale Ernährung, Kapitel 4

Abstract

Protein catabolism should be reduced and protein synthesis promoted with parenteral nutrition (PN). Amino acid (AA) solutions should always be infused with PN. Standard AA solutions are generally used, whereas specially adapted AA solutions may be required in certain conditions such as severe disorders of AA utilisation or in inborn errors of AA metabolism. An AA intake of 0.8 g/kg/day is generally recommended for adult patients with a normal metabolism, which may be increased to 1.2–1.5 g/kg/day, or to 2.0 or 2.5 g/kg/day in exceptional cases. Sufficient non-nitrogen energy sources should be added in order to assure adequate utilisation of AA. A nitrogen calorie ratio of 1:130 to 1:170 (g N/kcal) or 1:21 to 1:27 (g AA/kcal) is recommended under normal metabolic conditions. In critically ill patients glutamine should be administered parenterally if indicated in the form of peptides, for example 0.3–0.4 g glutamine dipeptide/kg body weight/day (=0.2–0.26 g glutamine/kg body weight/day). No recommendation can be made for glutamine supplementation in PN for patients with acute pancreatitis or after bone marrow transplantation (BMT), and in newborns. The application of arginine is currently not warranted as a supplement in PN in adults. N-acetyl AA are only of limited use as alternative AA sources. There is currently no indication for use of AA solutions with an increased content of glycine, branched-chain AAs (BCAA) and ornithine- α -ketoglutarate (OKG) in all patients receiving PN. AA solutions with an increased proportion of BCAA are recommended in the treatment of hepatic encephalopathy (III–IV).

Keywords: amino acids, branched-chain amino acids (BCAA), dipeptide, amino acid metabolism (first pass)

Zusammenfassung

Ein Proteinkatabolismus soll bei parenteraler Ernährung (PE) vermindert und anabole Stoffwechselprozesse gefördert werden. Standard-Aminosäure (AS)-Lösungen werden empfohlen, falls nicht in Sondersituationen z. B. bei schweren AS-Verwertungsstörungen oder bei angeborenen Stoffwechselstörungen spezifisch adaptierte AS-Lösungen eingesetzt werden müssen. Für erwachsene Patienten in ausgeglichenem Stoffwechsellzustand wird eine AS-Zufuhr von 0,8 g/kg/Tag empfohlen, die auf 1,2–1,5 g/kg/Tag oder in Ausnahmefällen auch auf 2,0–2,5 g/kg/Tag gesteigert werden kann. Zur Gewährleistung einer angemessenen Utilisation von AS sollten ausreichend Nicht-Stickstoff-Energieträger zugegeben werden. Das angestrebte Verhältnis zwischen Stickstoff- und Energiezufuhr (Stickstoff-Kalorien-Verhältnis) sollte unter Normalbedingungen 1:100–1:130 (g N:kcal) bzw. 1:16–1:21 (g AS:kcal) betragen. Glutamin sollte parenteral bei kritisch Kranken, sofern indiziert, in Form von Peptiden verabreicht werden, wie z.B. 0,3–0,4 g Glutamin-Dipeptid/kg KG/Tag (entsprechend 0,2–0,26 g Glutamin/kg KG/Tag). Für Patienten mit akuter Pankreatitis, nach Knochenmarkstransplantation sowie für Neugeborene kann derzeit keine Empfehlung für eine Glutaminsupplementierung mit der PE ausgesprochen werden. Der

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Einsatz von Arginin als Supplement in der PE beim Erwachsenen ist derzeit nicht gerechtfertigt. Den N-azetylierten AS kommen als alternative Aminosäurenquellen zur Zeit nur eine begrenzte Bedeutung zu. Für eine generelle Verwendung von AS-Lösungen mit einem erhöhten Gehalt von Glyzin und verzweigtkettigen AS (VKAS) wie auch für Ornithin- α -Ketoglutarat (OKG) besteht keine gesicherte Indikation. Die Wirksamkeit von AS-Lösungen mit erhöhtem Anteil an VKAS in der Behandlung der hepatischen Enzephalopathie (III–IV) wird empfohlen.

Schlüsselwörter: Aminosäuren, verzweigtkettige Aminosäuren, Dipeptide, Aminosäuremetabolismus

Amino acid intake

Introduction

An important objective of parenteral nutrition (PN), in addition to meeting energy requirements, is to maintain vital organ structure and function. Protein catabolism should be decreased and protein synthesis promoted. Amino acids (AA), the building blocks in protein synthesis, are classified as dispensable, indispensable, and conditionally dispensable AA and their precursors (Table 1). Recommended AA supplies with PN are generally based on oral/enteral intake recommendations (Table 2), but data from animal studies [1], [2], [3] and clinical trials [4] point to different AA needs with parenteral and enteral supply.

Indications/Contraindications

Indication and contraindication

- AA should always be infused with PN (A).
- Contraindications to the infusion of standard AA solutions are inborn errors of AA metabolism (e.g. phenylketonuria, maple syrup urine disease, cystinuria) as well as severe disorders of AA utilisation (e.g. severe liver dysfunction). Specially adapted AA solutions should be used when necessary (A).

Commentary

AA solutions are an essential part of complete PN for the maintenance of nitrogen homeostasis [5]. Contraindications to the infusion of *standard* AA solutions are inborn errors of AA metabolism (cf. chapter “Neonatology/Paediatrics” <http://www.egms.de/en/gms/2009-7/000074.shtml>) as well as severe disorders of AA utilisation such as severe liver dysfunction (cf. chapters “Gastroenterology” <http://www.egms.de/en/gms/2009-7/000072.shtml> and “Hepatology” <http://www.egms.de/en/gms/2009-7/000071.shtml>) or renal disorders (cf. chapter “Parenteral nutrition in patients with renal failure” <http://www.egms.de/en/gms/2009-7/000070.shtml>). Specially adapted AA solutions should be used in these situations.

Compounding

Amino acid solutions

- None of the presently available AA solutions meet all the physiological requirements of dispensable and indispensable AA.

Commentary

Crystalline AA solutions used presently in PN contain between 3.5 and 15% of weight as AAs (osmolarity 450 to 1450 mosmol/l) (Table 3 and Table 4). None of the currently available solutions provide ideal quantities of indispensable and dispensable AA [6] because of either poor solubility of individual AA (tyrosine, cysteine) or instability in aqueous solutions (e.g. glutamine dissociates into pyroglutamate and ammoniac). Dipeptide solutions, which have recently become available, allow for an improvement in the intravenous administration of larger amounts of some AA (see below) in the form of complete solutions or supplements.

Requirement

Basic adult requirements

- An AA intake of 0.8 g/kg/day is recommended for an adult patient on total PN with a normal metabolism and normal organ functions, irrespective of age and sex (B). Depending on metabolic requirements, this can be increased to 1.2–1.5 g/kg/day (A), or to 2.0 or 2.5 g/kg/day (C) in exceptional cases.
- Sufficient *non-nitrogen energy sources* should be added in order to guarantee optimum utilisation of AA. A nitrogen calorie ratio between 1:130 and 1:170 (g N/kcal) or 1:21 to 1:27 (g AA/kcal) is recommended under normal metabolic conditions (A).

Commentary

A recently published meta-analysis of nitrogen balance studies, investigating the protein requirements of healthy

Table 1: Classification of amino acids in adults and school children

Dispensable AA	Indispensable AA	Conditionally dispensable AA (precursors)
Isoleucine	Alanine	Arginine (glutamate, aspartic acid)
Leucine	Aspartic acid	Cysteine (methionine, serine)
Lysine	Asparagine	Glutamine (glutamic acid, ammonia)
Methionine	Glutamic acid	Histidine (serine, choline)
Phenylalanine	Glycine	Serine (glutamate)
Threonine	Proline	Tyrosine (phenylalanine)
Tryptophan		
Valine		

Table 2: Dietary reference values for enteral protein intake [55]

Age	g/kg body weight/day		g/day	
	m	f	m	f
19– <25 years	0.8		59	48
25– <51 years	0.8		59	47
51– <65 years	0.8		58	46
≥65 years	0.8		54	44
Pregnant women (>4 months of pregnancy)			58	
Breast-feeding women			63	

Table 3: Recommended intakes for indispensable amino acids (mg/kg body weight/day, [55])

	≥19 years	Pregnant women	Breast-feeding women
Histidine	14	18	19
Isoleucine	19	25	30
Leucine	42	56	62
Lysine	38	51	52
Methionine + Cysteine	19	25	26
Phenylalanine + Tyrosine	33	44	51
Threonine	20	26	30
Tryptophan	5	7	9
Valine	24	31	35

Table 4: Available parenteral amino acid solutions for adults (g/L) (Version 05/2004)

	Amino-plasmal®	Aminoven®	Intrafusin®	Parentamin®	Synthamine V10	Thomaeamin® n
Amino Acid:						
Concentration:	10%/15%	10%/15%	10%/15%	10%/15%	10%	10%/15%
Tryptophan	1.8/2.1	2/1.6	1.4/2.1	1.8/2.1	1.8	1.2/1.8
Isoleucine	5.1/5.85	5/5.2	2.8/4.2	5.16/4.2	6	3.8/5.7
Leucine	8.9/11.4	7.4/8.9	3.8/5.7	8.88/5.7	7.3	6.6/9.9
Valine	4.8/7.2	6.2/5.5	3.1/4.7	4.8/4.7	5.8	4.1/6.15
Lysine	5.6/7.95	6.6/11.1	6.73/6.73	5.6/6.73	5.8	6.6/9.9
Methionine	3.8/5.7	4.3/3.8	3.6/5.5	3.8/5.5	4	2.8/4.2
Phenylalanine	5.1/5.7	5.1/5.5	2.7/4.1	5.16/4.1	5.6	4.1/6.15
Threonine	4.1/5.4	4.4/8.6	3.6/5.4	4.08/5.4	4.2	4.6/6.9
Arginine	9.2/16.05	12/20	9.3/14	9.2/14	11.5	9.2/13.8
Histidine	5.2/5.25	3/7.3	2.3/3.5	5.2/3.5	4.8	4.4/6.6
Glycine	7.9/19.2	11/18.5	10.4/15.6	10.4/15.6	10.3	7.7/11.55
Alanine	13.7/22.35	14/25	17.3/26	13.68/26	20.7	14.3/21.45
Amino Acid	4.6/16.2	-	16.97/22.07	9.2/22.07	-	9.9/14.85
L-asparagine	9.3/0	-	-	-	-	-
Aspartic acid	1.3/7.95	-	-	-	-	1.8/2.7
Proline	8.9/7.35	11.2/17	9.4/14.1	8.88/14.1	6.8	9.2/13.8
Serine	2.4/3	6.5/9.6	9.4/14.1	2.4/14.1	5	5.9/8.85
Tyrosine	1.3/0.5	0.4/0.4	1.22/1.83	1.28/1.827	0.4	0.3/0.3
Cysteine	0.5/0.37	-	0.52/0.52	-	-	0.7/1.05
Ornithine	2.5/0	-	-	-	-	2.5/3.75
Taurine	-	1/2	-	-	-	-

adults, has recommended an oral protein intake of 0.8 g/kg/day irrespective of age and sex [5].

As the objective of PN therapy in critically ill patients is to minimise the loss lean body cell mass, the above-mentioned protein requirement for healthy adults should be adjusted according to the severity of the clinical picture. For example, in non-hypercatabolic patients with acute kidney failure or during the polyuric recovery phase after acute kidney failure, a protein intake of 1.0–1.3 g/kg/day is recommended to maintain nitrogen balance [7]. An intake of 1.2–1.5 g/kg/day is recommended in

patients with severe acute pancreatitis [8]. The previously suggested upper limit of 1.5 g/kg/day may be exceeded in extremely catabolic, critically ill patients depending on their energy requirements. An intake of up to 2.5 g/kg body weight/day is recommended by some authors in order to achieve a positive nitrogen balance, particularly in burns patients with no kidney or liver insufficiency, as well as in critically ill patients requiring dialysis due to renal insufficiency [9], [10], [11]. An adjustment of the protein intake to >1.5 g/kg body weight/day is also recommended in malnourished patients [12]. The level of

intake should generally not exceed an amount allowing for a serum urea value near the upper end of the reference range.

Sufficient *non-nitrogen energy sources* should be added in order to guarantee the optimum utilisation of AAs [13]. A nitrogen calorie ratio between 1:130 and 1:170 (g N/kcal) or 1:21 to 1:27 (g AA/kcal) is recommended under normal metabolic conditions (A). In contrast to data on oral/enteral protein intake, there are no sufficient data to determine the optimal ratio of indispensable/total AA (E/T ratio) in PN.

Conditionally indispensable amino acids

New studies are increasingly questioning the conventional classification of *indispensable* and *dispensable* AA in clinical nutrition. Numerous data point out that some of the so-called dispensable AAs are *conditionally indispensable* in adults under certain medical situations [14], and therefore, should be supplied [15].

Glutamine

In catabolic illnesses (e.g. elective surgery, trauma, pancreatitis, burns, high-dosage chemotherapy), massive intracellular glutamine deficiency occurs in muscles. Many studies have highlighted the fact that in these illnesses glutamine is released from muscle tissue and lungs and is made available for other organs (e.g. intestines, kidney) and immune cells. Thus, glutamine is the most important AA for nitrogen transport between organs and organ systems.

- Critically ill patients receiving no enteral nutrition (including burns and trauma patients) should receive a sufficient amount of glutamine dipeptides (0.3–0.4 g glutamine dipeptide/kg body weight/day = 0.2–0.26 g glutamine/kg body weight/day) in PN (A).
- No recommendation can be made for glutamine supplementation in patients with acute pancreatitis due to the lack of data (C).
- No recommendation can be made for glutamine supplementation in PN for patients after bone marrow transplantation (BMT), and in newborns, due to the availability of limited and inconsistent data (C).

Commentary

Twelve prospective randomised studies and 2 meta-analyses [16], [17] have established the efficacy of glutamine-containing PN in both surgical [18], [19], [20], [21], [22], [23], [24] and other critically ill patients [25], [26], [27], [28]. Administration of glutamine resulted in a *dose-dependent* reduction in infection-related complications as well as length of hospital stay in critically ill patients who had undergone surgery. Likewise, in medical

intensive care patients there was a significant reduction in complications and mortality.

Although, two randomised studies have been published [29], [30] on the effect of glutamine administration on patients with acute pancreatitis, no recommendation can be made due to the small number of patients included in the study. In patients after bone marrow transplantation, no consensus can be reached regarding the administration of glutamine [31], [32], [33].

- When indicated, glutamine should be administered parenterally, in the form of peptides (A).

Commentary

Commercially available AA solutions contain only small amounts of cysteine, tyrosine or glutamine due to their low solubility or instability. These AAs are regarded as semi-essential in certain situations. Recently, di- and tripeptides of cysteine, glutamine and tyrosine have been synthesised that are hydrolysed rapidly to provide the respective AA.

Glutamine-containing parenteral solutions must be freshly prepared, under strict aseptic conditions at 4 °C due to their low solubility in aqueous solutions and their tendency to be degraded to pyroglutamate, which involves a release of ammonia. The concentration of glutamine in the aqueous parenteral solution should not exceed 1–1.5% [w/v] in order to prevent precipitation. The amount of glutamine that can be administered is therefore limited, as large amounts of fluid have to be infused to overcome the low solubility of glutamine.

Arginine

- The application of arginine is not currently warranted as a supplement in PN in adults (C).

Commentary

There are only a few isolated studies on the parenteral use of arginine in patients. In critically ill patients, arginine has a favourable effect on the function of immune cells and on the progression of wound healing [34], [35]. Arginine plays a key role in nitrogen homeostasis, in the formation of creatine and the polyamines, and is the most important substrate in the formation of nitric oxide (NO). In burn patients, for example, a significant drop in serum arginine concentration was observed due to an increased synthesis of ornithine (starting substrate of polyamine synthesis) [34], [35]. An increase in arginine intake from 5% to 7% of total AA may result in immunomodulatory effects [34], [35], [36]. Routine parenteral supplementation of arginine is not recommended due to the insufficient data on safety and efficacy.

N-acetyl amino acids

- N-acetyl AA are metabolised to a limited extent in humans and are, therefore, only of limited use as alternative AA sources in clinical nutrition at the present time (B).
- N-acetyl cysteine is recommended to prevent contrast agent (CA)-induced nephropathy (A).

Commentary

Initial studies on animals provided convincing data that the soluble and stable N-acetyl AA, i.e. acetyl cysteine, acetyl tyrosine and acetyl glutamine, are effectively deacetylated in vivo and the released AA are well metabolised [37]. Subsequent studies on humans, however, did not support this data. In humans, 50% of the substrates are excreted unchanged in the urine. Compared to dipeptides, the half-life of acetyl cysteine after intravenous administration is approximately 40 times higher [38], [39]. However, effectiveness of N-acetyl cysteine (600 mg intravenously 12 hours before and 12 hours after administration of CA) in prevention of renal failure after CA administration has been demonstrated in many studies [40], [41].

Glycine, branched-chain amino acids, ornithine-alpha-ketoglutarate

- There is currently no indication for use of AA solutions with an increased content of glycine, branched-chain AAs (BCAA) and ornithine- α -ketoglutarate (OKG) in all patients receiving PN (I).
- AA solutions with an increased proportion of BCAA are recommended in the treatment of hepatic encephalopathy (III–IV) as they are effective in alleviating the encephalopathy (A).

Commentary

The dispensable, soluble AA glycine is the only naturally occurring AA which is neither chiral nor optically active. It is an essential part of scleroproteins as well as an intermediate in the biosynthesis of porphyrins, purines, creatinine and glutathione. Glycine serves as a flexible bond for proteins, which is necessary for helix formation, and acts as an extracellular signal protein. It is cytoprotective in ischemic insults, hypoxia and reperfusion damage [42]. Orally administered glycine in conjunction with glutamine serves to repair cells, the metabolic adaptation, and protects intestinal mucosa after intestinal resection [43], [44]. Administration of high dose glycine with glutamine resulted in a good compatibility and uptake in patients with polytrauma [45].

The use of parenteral AA solutions, which are concentrated with BCAA, is well-known. BCAA supplementation is used in multiple conditions such as liver disorders (especially hepatic encephalopathy), sepsis, trauma,

disorders of gastric motility, and the prevention of failure of the respiratory musculature during artificial respiration. The effectiveness of BCAA in the treatment of hepatic encephalopathy was tested in seven controlled studies, where the individual results were contradictory, but in meta-analysis showed an improvement in encephalopathy. However, no benefit was observed in the survival rate [46].

Until to date, there are only small randomised studies that have investigated the use of AA solutions with an increased proportion of BCAA, in critically ill patients and demonstrated an improvement in clinical status [47], [48], [49], [50]. The small number of patients in these studies does not justify a general recommendation.

OKG consists of one molecule of α -ketoglutarate (AKG) and 2 molecules of ornithine. After intravenous administration, it dissociates into the two parts in blood [51]. OKG is well tolerated and is associated with the stimulated release of insulin and growth hormone, and it serves as a substrate for polyamine synthesis. The components of OKG participate in glutamine biosynthesis. In small studies, intravenous administration of OKG in post-operative and critically ill patients results in protein conservation, stimulation of protein synthesis in the muscles, and reduction in degradation of the muscular glutamine pool [52], [53], [54].

Notes

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