Nutrition Support in Critical Illness: Amino Acids

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Introduction

The general approach to the nutritional care of the catabolic, malnourished or critically ill patient involves delivery of a balanced diet including energy (in the form of carbohydrates and lipids), an adequate amount of nitrogen, all essential nutrients (amino acids, fatty acids, vitamins, electrolytes) and fluid [1]. Traditionally, the qualitative and quantitative composition of dietetic measures in patients was derived from recommended daily allowances for healthy adults with addition of a so-called ‘safety margin’. In the past 2 decades, this view has been fundamentally modified. Firstly, overwhelming evidence has been brought forward that critical illness is associated with profound alterations in carbohydrate, lipid, and protein metabolism [2, 3]. Consequently, nutrient demands of patients can considerably differ in comparison with healthy adults. Presently, great efforts are being undertaken to define ‘disease-related’ recommendations and, in line with this novel concept, to provide ‘tailor-made’ formulas for specific patient groups like children, renal and liver diseases, and critical illness. Secondly, evidence was found that various nutrients including amino acids and fatty acids possess more than the well-known ‘nutritive’ effects on body function and metabolism [4]. In vitro and in vivo studies showed that nutrients can modify the immune response as well as the integrity of organs and tissues in health and disease in a dose-dependent manner. Moreover, the extent and target of this ‘pharmacological’ effect can be controlled by the timing and the way (oral/enteral, intravenous) of substrate administration. Indeed, this approach opens the possibility to modulate the metabolic response to stress.
This chapter briefly reviews the role of selected amino acids as conditionally indispensable substrates (*nutritive approach*) and as modifying agents (*pharmacological approach*) in the therapy of critically ill patients.

**The Nutritive Approach: Conditionally Indispensable Amino Acids**

On the basis of long-term clinical studies and with the availability of improved analytical technologies, it became evident that some clinical conditions are associated with particular amino acid deficiencies, antagonisms or imbalances which then cause specific changes in amino acid metabolism and requirements. Accordingly, amino acids are nowadays classified as *indispensable*, *conditionally indispensable* and *dispensable* substrates [5, 6] (table 1). This new approach of categorizing amino acids recognizes the functional and physiological properties of a given substrate under various pathological states as well as the ratio of supply to demand. Accordingly, certain amino acids known as nonessential substrates for healthy adults have to be reconsidered as ‘conditionally indispensable’ substrates in stressed patients and, thus, must be part of nutritional support.

In this respect, *glutamine* seems to be of utmost importance for the critically ill. There are numerous data available showing that hypercatabolic and hypermetabolic situations are accompanied by glutamine deprivation. During prolonged starvation [7], after elective operations, major injury, burns, infections [8] and pancreatitis [9], intramuscular glutamine concentrations declined considerably regardless of nutritional efforts. This reduction in the muscle-free glutamine pool (about 50% of normal) can be seen as a typical feature of injury and malnutrition; the extent and duration of the depletion being proportional to the severity of the illness [10]. Recent studies underlined that glutamine deprivation is mainly caused by trauma-induced alterations in the interorgan glutamine flow [10]. Muscle and, as postulated,

<table>
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<th>Table 1. New classification of nutritive amino acids</th>
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<tr>
<td><strong>Indispensable amino acids</strong></td>
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<tr>
<td>Amino acids which cannot be synthesized endogenously</td>
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<td><strong>Conditionally indispensable amino acids</strong></td>
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<td>Amino acids which exhibit a considerably increased need in certain diseased situations</td>
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<td>Amino acids which cannot be synthesized in adequate amounts due to disease-dependent limited/impaired synthesis</td>
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<td><strong>Dispensable amino acids</strong></td>
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<td>Amino acids which can be sufficiently synthesized by transamination</td>
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lung glutamine efflux are accelerated to provide substrate for the gut, immune cells, and the kidneys [11, 12] explaining the profound decline in muscle-free glutamine concentration. Even under maximum glutamine efflux from the muscle, endogenous provision cannot meet the increased demands of glutamine consumers. Based on recent calculations, glutamine balance is negative with approximately 12 g/day (table 2).

Numerous studies in different patient groups have convincingly shown that inadequate glutamine supply contributes to impaired cell metabolism [for references see 8]. Exogenous provision of glutamine is, thus, a necessary replacement of a deficiency rather than a supplementation.

While the role of glutamine as an indispensable substrate in the critically ill is widely accepted, the way and the timing of glutamine administration is still under discussion. Two unfavorable chemical properties hamper the use of free glutamine itself as nutrition substrate in routine clinical setting [13]: (1) instability especially during heat sterilization and prolonged storage, and (2) limited solubility (~3 g/100 ml at 20°C). The rate of breakdown of free glutamine depends on temperature, pH, and anion concentration. Indeed, this decomposition of free glutamine is quantitative and yields the cyclic product pyroglutamic acid and ammonia.

Among the approaches discussed [14], the implication of stable and highly soluble synthetic dipeptides shows great promise as an effective route for the provision of amino acids otherwise difficult to deliver [15]. Dipeptides with a glutamine residue at the C terminal position reveal high solubility in water (glycyl-L-glutamine, Gly-Gln, 154 g/l; L-alanyl-L-glutamine, Ala-Gln, 568 g/l) and sufficient stability during heat sterilization and prolonged storage. These properties qualify the dipeptides to be approved by the authorities as suitable constituents of liquid nutritional preparations.

In various clinical studies, the beneficial effects of parenteral glutamine dipeptide administration on the metabolic response to stress and patient outcome and recovery have been shown [for references see 8]. A recent multicenter study performed between 1997 and 1998 in 11 centers in Europe with a total of 126 patients showed better daily and cumulative nitrogen

### Table 2. Consumers and producers of endogenous glutamine during metabolic stress

<table>
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<tr>
<th>Consumers</th>
<th>Producers</th>
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<tr>
<td>Gastrointestinal tract, g/day</td>
<td>11–15</td>
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<tr>
<td>Kidneys, g/day</td>
<td>4</td>
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<tr>
<td>Immune competent cells, g/day</td>
<td>2–4</td>
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<tr>
<td>Muscle, g/day</td>
<td>8–10</td>
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<tr>
<td>Lung (?), g/day</td>
<td>1–2</td>
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<tr>
<td>Balance, g/day</td>
<td>minus 12</td>
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balances with glutamine dipeptide than in the control group [16, 17]. Despite the heterogenous material, the length of hospital stay was 2.0 days shorter in the test group (21%) as compared with the controls. Plasma-free glutamine was in the low normal range before operation and showed a significantly higher concentration with supplemental Ala-Gln, while in the controls plasma glutamine levels remained unchanged. The length of hospital stay could be calculated in one of the centers with similar degrees of illness showing significantly reduced hospitalization with glutamine peptide [17]. The time of hospitalization for both test and control groups is also depicted by the Kaplan-Meier probability diagram, clearly demonstrating a reduction in hospital stay with Ala-Gln. Group stratification, length of operation, intraoperative blood loss and type of operation were considered independent variables for entry into the model of the Cox regression. This analysis revealed clearly that hospital stay was significantly dependent on the total parenteral nutrition (TPN) regimen and was not influenced by the type of surgery, length of operation or intraoperative blood loss.

In a current study, 95 patients were randomized and treated for more than 5 days and 68 patients for 9 days or more to receive either standard parenteral nutrition or supplemented TPN with Ala-Gln (0.3 g/kg body weight). Fourty-six patients received the dipeptide supplement and 49 served as controls. Six-month survival was improved for patients treated for 9 days or longer with glutamine supplementation (66.7%) vs. patients receiving standard TPN (40%; fig. 1). In the dipeptide-treated group plasma-free glutamine concentrations increased after 6–9 days. These results support the notion that replacement of glutamine deficiency may correct excess mortality in intensive care unit (ICU) patients due to inadequate parenteral nutrition [18].

A novel finding is the striking influence of supplemental glutamine dipeptide on cysteinyl-leukotriene (Cys-LT) metabolism. Cys-LTs are potent lipid mediators. It has been emphasized that diminished release of these mediators is accompanied by an attenuated endogenous host defense [19]. After surgery, the low Cys-LT concentration in isolated polymorphonuclear leukocytes was completely restored with supplemental dipeptide while remaining low with conventional TPN [20]. It is well known that the highly charged glutamic acid molecule, one of the direct precursors of glutathione, is poorly transported across the cell membrane whereas glutamine is readily taken up by the cell. Glutamine is then deaminated and can, thus, be used as a glutamic acid precursor. Accordingly, it is proposed that the capacity of cysteinyl-leukotriene generation might be normalized with supplemental glutamine [21].

In contrast to the beneficial results seen with parenterally supplemented glutamine, there was no improvement in nitrogen balance, protein synthesis and other variables relating to nitrogen economy when glutamine-enriched tube feeds were administered in short-term trials in ICU patients [22, 23]. Enteral tube feeds supplemented with L-glutamine failed to increase or even
to normalize plasma glutamine levels in adult or pediatric ICU patients [24]. Oral glutamine supplementation in cancer patients did not prevent the occurrence of doxifluridine-induced diarrhea and had no impact on tumor response to chemotherapy [25]. The results are somewhat at variance with the findings of Conversano et al. [26], who reported a decrease in both the duration and severity of gastrointestinal symptoms with oral glutamine supplementation.

In adult patients glutamine has been shown to have a beneficial effect on intestinal barrier function when given orally (30 g/day) for several weeks following high-dose chemotherapy or radiotherapy for esophageal cancer [27]. In a pilot study, ‘swish and swallow’ therapy with 4 × 2 g glutamine/day for 28 days reduced the symptoms of severe stomatitis following extensive chemotherapy [28]. Following this pilot study, a large randomized clinical trial was done on the effects of oral glutamine on stomatitis in 195 bone marrow transplant patients [29]. Less mouth pain, less difficulties in eating, and a reduction in the use of opioids were found with a low dose of glutamine, and the 28-day survival rate was improved in the glutamine group. In contrast, a randomized, placebo-controlled, double-blind study in 24 mucositis patients showed no benefit of oral glutamine (16 g/day) over placebo [30].

Fig. 1. Survival plot of a subgroup of parenterally fed patients treated for 9 days and longer under standardized conditions. Ala-Gln = 1.2 g/g body weight standard amino acid solution plus 0.3 g/g body weight/day alanyl-glutamine; control = 1.5 g/g body weight standard amino acid solution. Reproduced with permission from Goeters et al. [18].
The possible reasons for the less favorable results with enteral glutamine supplementation are multifactorial. The presence of bacterial overgrowth in stressed patients might in part explain the observed low circulating glutamine concentrations, as it is well known that bacteria readily consume glutamine as a preferred substrate. It is also possible that prompt splanchnic glutamine utilization may contribute to the inability of glutamine-enriched enteral feeds to increase the plasma glutamine levels. Glutamine is absorbed in the upper part of the small intestine and subsequently metabolized in the liver, and thus it may not be available in sufficient quantity for the target mucosal tissue at the lower sites of the intestine.

In a current study of a more heterogenous group of ICU patients capable of tolerating enteral feeding [31], many of whom were already infected on admission, there was no suggestion of reduced mortality, but overall post-intervention hospital costs were significantly reduced in both enteral and parenteral glutamine recipients. In a randomized, double-blind study oral and parenteral glutamine supplementation was evaluated in 66 bone marrow transplant patients. Unfortunately, the investigators did not distinguish between enteral (oral) and parenteral treatment. Nevertheless, there was a suggestion of a possibly improved long-term survival [32].

In conclusion, it is to mention that lack of glutamine supply in glutamine-deprived critically ill patients will be associated with symptoms such as impaired gut barrier function, immune response and protein economy which then unfavorably influence outcome. An adequate provision of this indispensable amino acid (about 15 g glutamine corresponding to about 25 g glutamine dipeptide) is, thus, mandatory.

The Pharmacological Approach: Amino Acids with Additional Functions

As already outlined in the Introduction, several amino acids possess additional ‘pharmacological’ functions on the molecular/cellular level. Provision of these amino acids outside a potential metabolic need can beneficially modify the metabolic response to a given trauma. Within the ICU, the use of arginine and cysteine as modulating agents are extensively discussed.

Arginine may be of significance in the critically ill because of its potential role in immunomodulation [33, 34]. It is hypothesized that (high-dose) arginine enhances the depressed immune response of individuals suffering from injury, surgical trauma, malnutrition or sepsis. In experimental animals as well as in human studies, supplementation with arginine resulted in an improved cellular response, a decrease in trauma-induced reduction in the T-cell function and a higher phagocytosis rate [33]. Innate host cellular cytotoxicity, mediated in part by natural killer (NK) and lymphokine-activated killer (LAK) cells, is thought to play an important role in the inhibition of tumor growth and the
reduction in metabolic spread. Arginine supplementation has been shown to enhance NK and LAK cytotoxicity [for references see 34]. Interestingly, a daily supply of 30–35 g of arginine is claimed to retard tumor growth and to diminish tumor metastasis [35, 36]. On the other hand, it has been reported that substituting ornithine for arginine in parenteral regimens will ameliorate an arginine-related increase in growth of a Ward colon tumor [37].

Clinical studies administering arginine enteraly have demonstrated moderately improved net nitrogen retention and protein synthesis compared to isonitrogenous low arginine diets in critically ill and injured patients. Following surgery for certain malignancies in elderly postoperative patients, supplemental arginine (25 g/day) enhanced T-lymphocyte responses to phytohemagglutinin and concanavalin A and increased the CD4 phenotype number. Interestingly, IGF-1 levels were about 50% higher reflecting the growth hormone secretion induced by arginine supplementation. A high load of oral arginine (30 g/day) improved wound healing [35] and enhanced the blastogenic response to several mitogens [38]. On the other hand, some of these studies were also associated with in vitro evidence of enhanced immunoactivity [33, 39, 40]. However, these results did not demonstrate improvements in overall patient outcome or length of hospital stay [41].

Recently, arginine was shown to be the unique substrate for the production of the biological effector molecule nitric oxide (NO). NO is formed by oxidation of one of the two identical terminal guanidino groups of L-arginine by the enzyme NO synthase (NOS). Of the three NOS isoenzymes characterized, two are constitutive, Ca$^{2+}$-dependent (endothelial, eNOS, and neuronal, nNOS), and generate lesser levels of NO than their inducible counterpart (iNOS) [42]. iNOS is prominent in inflammatory conditions and it is also most often implicated as the producer of NO during the immune response. According to recent reports, NO plays an essential role in the regulation of inflammation and immunity. Interestingly, parenteral arginine may improve myocardial ischemia in patients with obstructive coronary artery disease by producing nonstereospecific peripheral vasodilation thereby improving endothelium-dependent vasodilation. This effect is certainly due to stimulation of insulin-dependent NO release or nonenzymatic NO generation [43].

There are some highly interesting studies elucidating the potential role of the sulfur-containing amino acid cysteine as a modulating substrate [44]. Macrophages act as cysteine transporters under the action of inflammatory stimuli such as endotoxin and TNF. The uptake of cysteine in macrophages is competitively inhibited by glutamate [45]. During episodes of immunosuppression or in diseases with compromised immunocompetence such as AIDS and malignancy, increased extra- and intracellular glutamate concentrations are observed [46].

Cysteine also enhances a number of lymphocyte functions, such as cytotoxic T-cell activity. A high glutamate/cysteine ratio is associated with a low share of T-helper cells [47]. N-Acetyl-cysteine, reduced glutathione and
Cysteine inhibit the expression of the nuclear transcription factor in stimulated T-cell lines [48]. This observation might provide an interesting approach in the treatment of viral diseases like AIDS, since the transcription factor is necessary to express the human immunodeficiency virus (HIV) mRNA. In fact, in vitro studies demonstrate that the stimulatory effects on tumor necrosis factor, induced by free radicals, on HIV replication in monocytes can be inhibited by sulfhydryl compounds [47]. These basic studies indicate that treatment of inflammatory diseases and AIDS with sulfhydryl compounds may be beneficial, and powerful arguments have been advanced in favor of such treatment [47]. Clinical studies using this strategy are not yet available. One reason might be the lack of suitable preparations.

Conclusion

According to our present knowledge, an adequate provision of amino acids in the ICU is based on two approaches (table 3). (1) It is now widely accepted that a balanced nutritional support (oral/enteral and/or parenteral) considering all indispensable and conditionally indispensable amino acids is a prerequisite to improve/maintain the metabolic status of the ICU patient thereby beneficially influencing patient outcome. (2) The (high-dose) supplementation of specific ‘modulating’ amino acids can help to optimize healing processes. Since these effects are influenced by timing and way of administration as well as the situation of the patient, these measures must be planned and performed individually.

References

Amino Acids in the ICU


Discussion

Dr. De Bandt: I don't know if we have to thank you or Dr. Stehle. Perhaps some of his opinions are not exactly yours, when you state in your first slide that we must see glutamine in the context of balanced nutrition and arginine as an immunonutrient, because you said that you have to test an isonitrogenous diet to assess the effect of this nutrient and, if we take your word, we have to supply a very large amount of nitrogen in order to obtain an isonitrogenous diet compared with a glutamine-supplemented diet. So do you really consider it as a balanced diet?

Dr. Cynober: It is a balanced diet if you are providing extra nitrogen in both groups. This is a matter of controversy and it is an important point which can explain discrepancies in the literature. There are two ways to achieve an isonitrogenous diet. The first one is to provide an amount of nitrogen which will cover the basal requirements and then in 1 group you add the amount of glutamine required, for example 20 g/day, and in the other group you add a mixture of nonessential amino acids to avoid pharmacological or toxic effects. The second way to achieve an isonitrogenous intake is to include glutamine in the basal regimen as well as for the mixture of nonessential amino acids, but by making that you are in fact decreasing the amount of all essential amino acids and also nonessential amino acids, making the glutamine group clearly disadvantaged. This may explain why, for example if we consider that glutamine is efficient in modulating the response to stress and even if there is some pharmacokinetic difference between glycyl-glutamine and alanyl-glutamine, in fact most of the studies indicate positive results with alanyl-glutamine and not with glycyl-glutamine. The difference between the two peptides from a practical point of view is that alanyl-glutamine is a powder you have to add to a standard solution. It is the first way to proceed as I described. On the contrary glycyl-glutamine is included in parenteral nutritional solutions and included in the total nitrogen intake.

Dr. Allison: Let me provoke you on a tendentious part. Overcoming that nitrogen problem you could perhaps give \( \alpha \)-ketogluterate. Can I provoke you on that one?

Dr. Cynober: About what results?

Dr. Allison: As an alternative to glutamine.

Dr. Cynober: It is certainly an interesting molecule for several reasons. One is the fact that it is not only a precursor of glutamine but also a precursor of arginine, polyamines, and also it elicits very strong growth hormone secretion when provided by the parenteral route, and insulin secretion when given by the oral and enteral route. Clearly this molecule appears to be very efficient, for example in burn injury, because 3 different reports indicated that \( \alpha \)-ketoglutarate administration in the range of 20 g/day dramatically improved wound healing [1–3]. Note that there is no report on glutamine in burn patients. I don't know why but it is the fact. Of course it is my point of view and not Dr. Stehle's.

Dr. Rosenfeld: You talked about balanced nutritional support and I feel like an imbalanced solution with this recommendation. I would like your comment about the promotion of ureagenesis or increasing urea production and the necessity of dialysis in these patients with these recommendations, principally in older patients.

Dr. Cynober: You mean about patients suffering organ failure such as kidney failure?

Dr. Rosenfeld: Some patients are not really in renal failure but they have a decrease in renal function.

Dr. Cynober: I am not really competent on the problem of nutrition in kidney insufficiency, but what I heard recently at a congress was that the decreased intake of amino acids in such a situation was a dogma, and the fact that, except in certain cases,
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dr. detchelotte: I would like to add some recent experience in this field because at ASPEN we recently presented a prospective study of 114 patients treated with glutamine dipeptide as glutamine or standard isonitrogenous control. Of course at the beginning we selected patients without renal insufficiency, above 250 μmol/l creatinine for any contraindication of parenteral nutrition, but afterwards during the treatment period, about 5–10 days, we were not able to detect any impairment in renal function even with these patients receiving 1.5 g/kg/day amino acids plus 0.5 g dipeptide/kg/day. So as far as renal function is concerned I think this safety margin with dipeptide was rather high, probably higher than we thought because of the nitrogen intake. And there are some experimental data that could at least lead one to think that glutamine may have beneficial effects on renal function because it increases acid output for instance.

dr. planas vila: Due to the interference between glutamine and growth hormone treatment in the anabolic response, do you know if there are some clinical studies in ill patients on the association of growth hormone and glutamine?

dr. cynober: There are some studies dealing with gastrointestinal patients, studies by SCOLAPIO et al. [4, 5] and by Byrne et al. [6]. A total of 4 or 5 studies, and I saw the first study performed by Byrne et al. [6] which provided positive results combining glutamine and growth hormone, and the last one is a French study by Messin et al. (unpublished). I think, all the subsequent studies failed to show any advantage of providing glutamine and growth hormone together.

dr. baracos: I need you to help me out with an explanation of something. In one of Dr. Stehle’s slides you have two categories, balanced nutritional support I understand that for amino acids, that is only amino acids in the rate balance according to some requirements. And then you have something that you call pharmacointutrition, or immunological nutrition, and since it is not in the category of balanced I think that means imbalanced, and that is the interpretation people take away from that categorization. And I, quite frankly, don’t understand this definition. I think some amino acid feeding is balanced nutritional support and someone is always telling me, oh no, that is pharmacointutrition, and in fact there are other people who are telling me that a certain supplementation of fatty acids is not actually nutritional support, it is pharmacointutrition, and I still don’t understand the distinction.

dr. cynober: I will try to answer. I did not have the opportunity to read Dr. Stehle’s manuscript and I did not discuss it with him but I feel that I understand what he means by this distinction. Clearly glutamine supplementation is helpful and useful when there is glutamine deficiency. If you are providing a glutamine-enriched diet to healthy subjects nothing happens. For example, there was a study some years ago by Fox et al. [7] in healthy subjects or in healthy rats and they provided glutamine-enriched nutrition to rats treated by methotrexate or to control rats. In the control rat group glutamine had absolutely no effect on any parameter but, providing a glutamine-enriched diet in methotrexate-treated animals dramatically improved nitrogen balance and a certain number of other parameters. Clearly glutamine displays anabolic properties, regulatory properties, but when the glutamine levels are normal there is absolutely no reason for these properties to work. There is another example with the administration of a glutamine-enriched diet in heavy sport training, and in that situation the decrease in the glutamine pool is very moderate, and almost all authors failed to identify any improvement in immunological function and so on by providing a glutamine-enriched diet, except perhaps the preliminary study by Parry-Billings et al. [8] some years ago. Now with arginine it is very different because the studies by
Yu et al. [9] with stable isotopes indicate that there is clearly an increase in arginine turnover in stress situations, for example after burn injury, but the requirements of arginine are not fulfilled by de novo synthesis at 80 or 85%, and the arginine pool is very dependent on regular protein intake. And what we are researching by providing a high amount of arginine is to have a true pharmacological effect because by providing a high amount of arginine we are upregulating plasma levels, and therefore the intracellular production of nitric oxide is parallel with arginine availability in plasma in such a situation. This explains this pharmacological effect. This is also the case with the production of growth hormone following an intravenous arginine secretion because this effect on growth hormone secretion is only dependent on the arginine plasma levels. Therefore I feel that we are following two different logics with these two amino acids. And finally I mentioned that to my knowledge there is no positive effect in providing glutamine to healthy subjects. On the contrary, there are several reports, especially from Barbul [10], indicating the benefit of high arginine intake in healthy subjects.

Dr. De Bandt: I will make myself the devil’s advocate in saying that there are some situations, perhaps not in critically ill patients, where small amounts of arginine have beneficial effects, for example in diabetes and atherosclerosis. There can be decreased availability of arginine in this situation, though I don’t think we can make a clear black and white distinction between the two categories.

Dr. Bouletreau: Could you comment a little more on whether something is known about the optimal dosage of arginine in our intensive care unit (ICU) patients and the optimal moment to give it, regarding its role in nitric oxide production?

Dr. Cynober: To date to the best of my knowledge there is no study ranging those effects and there are discussions about the fact. Dr. Stehle presented only the wide side, the study by Gianotti et al. [11], but there are several experimental studies in the same model which clearly indicate that huge amounts of arginine actually decrease survival, and there is a metaanalysis by Heyland et al. [12]. There are a lot of papers, but I am not willing to start such a debate because I know that Dr. Martindale will give a lecture on this topic and it will be unfair to discuss this now, but I will be happy to discuss this fascinating point after Dr. Martindale’s lecture.

Dr. Heyland: I look forward to that further discussion on arginine but I did want to ask you some questions related to glutamine. One point is that none of our critically ill patients are the same and if we say that glutamine deficiency is a result of catabolic stress and, we talked about this this morning, that there are various forms of stress and variations in individual patients’ responses to those stressors, I am just wondering if there is a better way of identifying or characterizing those patients who are truly glutamine-deficient and therefore would benefit from glutamine supplementation, than thinking that all critically ill patients may benefit from glutamine supplementation? Do we need to measure plasma glutamine levels or are there some other biochemical or clinical parameters that would help us discriminate what populations with critical illness would benefit the most?

Dr. Cynober: We can look at proteomics and so on, but the measurements of plasma concentrations of amino acids are very debatable because as you know it is just a reflection between the rate of appearance and the rate of disappearance. In my lecture, I will present some results which indicate that when we are making true kinetics we can have much more interpretable and interesting results. However, I think we can look to plasma glutamine levels to identify patients who are depleted. This is a personal point of view. I want to be clear because probably Dr. Stehle would give another answer. But I am basing this feeling on an article by Parry-Billings et al. [13] published some years ago showing that there was a relationship between plasma glutamine in burn patients and the intensity of stress, and also there was an increased
morbidity in patients with lower glutamine levels, and therefore we can probably look at plasma glutamine levels. Also just to tell a story, and this has not really any scientific value but it is absolutely clear. When I was a young intern in St. Antoine Hospital I was working with the burn center head of department, and in my laboratory we performed amino acid chromatography on a routine basis and patients with a glutamine level of <200 $\mu$mol/l systematically displayed complications. Therefore I think that it is a simple reliable way to assess the disequilibrium between the rate of appearance from muscle and perhaps the rate of consumption by central organs. Otherwise we can look at some immunological markers but you know very well that it is not specific.

**Dr. Neu:** I just want to express a little heresy here. It is a dogma in these kinds of studies to have isonitrogenous controls and I think that that can actually lead to a lot of trouble because the isonitrogenous controls can actually have effects of their own. If we are going to do this correctly we should have a real world control group compared to the experimental treatment group. So if one has to do this totally correctly you will have 3 groups, one is the supplemented group, one is the isonitrogenous control, and the other is the real world group.

**Dr. Cynober:** I agree totally, I published that in the *Journal of Nutrition* 3 years ago and I will be pleased to send you a reprint with exactly 3 such groups [14]. But more seriously I think that it is a key issue and we have to be very careful. For this reason a certain number of research groups, including Déchelotte’s and mine, are actually using as an isonitrogenous control a mixture of 6 or 8 amino acids because, by providing huge amounts of glycine, you cannot exclude a positive or negative effect which could mask or reinforce the effect of the so-called immunonutrient. But fundamentally, although it probably doesn’t matter in the final results, I believe that we need an isonitrogenous group in order not to have this point obscure the results.

**Dr. Neu:** In certain situations the isonitrogenous control can actually cause problems. When we were doing some studies in baby rats a few years ago we tried to use glycine as the isonitrogenous control, and we killed more rats using glycine.

**Dr. Cynober:** I agree.

**Dr. Moore:** I am surprised by the comment that enterally delivered glutamine does not get absorbed since we did a randomized study using a product that was supplemented with glutamine and glutamine levels went up. So maybe you could educate me on that. My second comment is that glutamine as an enteral nutrient in the critical ill may be beneficial because it increases the perfusion to the mucosa and it is an amino acid that, once it is absorbed, the enterocyte can use it to produce ATP. In a recent study, we showed that glutamine actually protected against ischemia reperfusion by maintaining these ATP levels.

**Dr. Cynober:** There are several aspects in your question. The first one, it is absolutely true that most of studies providing glutamine by the enteral route to adult patients provide negative results. This is a matter of fact. Secondly, this is very different to what has been repeatedly observed in very low weight infants with at least two reports providing efficiency. From studies performed on piglets we think that there is some evolution in the enzymatic equipment of the intestine, and this was the last hypothesis by Dr. Stehle, and I think that it must be considered. You know, in a given cell, trafficking has a lot of possibilities and you cannot imagine that the substrate in the cell is looking like that to search an enzyme, and this leads to the concept of compartmentalization. This means that once an amino acid and probably other substances are taken up by a specific transporter, it is immediately metabolized by a given associated enzyme. This allows a reduction in the loss of intermediary nutrient, to drive the substrates in a given pathway, and by the way this explains why, for example, an amino acid such as arginine may be taken up by 4 different transporters. Therefore you can imagine that in adults, but perhaps not in very low birth
weight infants, glutamine taken up at the luminal side is transformed into glutamate which could be associated immediately to a transaminase of dehydrogenase and used for energy purposes, and nothing happens. You can imagine that on the vascular side the transporter is associated with the enzymes which channel glutamine from glutamate to arginine and further to polyamines because if you carefully read the article by Rhoads et al. [15], it indicates that glutamine has a trophic effect in the intestine, stimulating the MAP kinase system. In fact this is a cAMP-dependent inhibitable system, and what makes glutamine is to release the inhibition exerted by cAMP. But what is interesting in the discussion section of this article is that when glutamine metabolism is blocked using amino-oxoacetate, this leads to the disappearance of the glutamine effect. Rhoads speculated that in fact the effect of glutamine at the intestinal level was due to the generation of aliphatic polyamines, which can make sense because this molecule is known to have a very important effect in this tissue. Therefore in my opinion, to explain why in humans and in animals enteral glutamine is not as efficient on the intestinal mucosa as parenteral glutamine, it is the different behavior in the cell. But now we cannot exclude that by providing a very high amount of glutamine a part of the glutamine escapes intestinal metabolism and then returns to the cells via the general circulation and has such an effect. I will present these data later in my lecture, a single article showing a very positive effect with only a supplementation of glutamine, not a mixture. It is the article by Houdijk et al. [16] published in the Lancet. I made the calculation, the patients actually received 33 g glutamine/day, whereas in most of the studies, such as those of Long et al. [17] and Jensen et al. [18], the dose given to the patients was around 15–28 g/day.

Dr. Déchelotte: To go with this point I agree with Dr. Moore that glutamine is very well absorbed. Some years ago with Dr. Baugerie, we made a study in both volunteers and in very short bowel patients; it was published in the American Journal of Clinical Nutrition. Even patients with only 30–40 cm of small bowel left were able to absorb a very high amount of glutamine. That is the first point. The second point, I agree with Dr. Cynober, is that probably most of the studies published previously with enteral glutamine were performed at rather low dosages, about 20 g/day which is quite near to that used by the parenteral route in previous postoperative studies, and we know now that with 30 g enteral glutamine/day we are able to inhibit the de novo synthesis of glutamine both in healthy humans with hypercatabolism and postoperative patients. So it is efficient to influence the endogenous metabolism of glutamine, and if we go ahead with further dosages of enteral glutamine then we are able to detect a quite clear enhancement of the glutamine concentration which means that it is bioavailable. The problem with the previous studies is that perhaps we did not exactly measure the right things with enteral glutamine. We now have effects on several mechanisms of heat shock protein production in the gut or protein synthesis and other mechanisms which are difficult to measure in patients. So I am pretty sure we can go ahead with this enteral supply of glutamine, maybe with higher dosages and maybe other issues too.

Dr. Bozzetti: Are you aware of any study in surgical patients where glutamine was administered prior to the surgical operation? I am asking this because if you look at the experience in preoperative nutrition both total parenteral or enteral nutrition were more successful when support was started preoperatively.

Dr. Cynober: The answer is yes but at this moment I am not able to remember in which recent article I have read such a manipulation with positive results. But I think that there are some recent data providing glutamine preoperatively, yes.

Dr. Labadarios: Thank you for a very nice presentation. In one slide you made a recommendation which I find a little bit too general, in relation to glutamine, arginine and cysteine. What type of evidence do we have at present in relation to the safety of
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this proposal that you are making, in relation to the type of patients who would benefit, and also in relation to the course of the illness? At what point of a given course of illness do you think that this recommendation would be appropriate?

Dr. Cynober: It is Dr. Stehle who should answer the question. With regard to safety, studies published in 1990 by Ziegler et al. [19] indicate that even by providing a very high amount of glutamine there is absolutely no toxicity with this amino acid. Perhaps, but this is only a hypothesis because to the best of my knowledge nobody has checked. It may be toxic in liver failure, but for reasons we can imagine nobody has tried to give high amounts of glutamine to patients suffering from liver failure. Now I should say that unfortunately we have absolutely no dose ranging studies available in patients, so that the suggested dose is a sort of compromise of what is available in the literature. And with regard to the subtype of patients, probably glutamine is very efficient in groups of postoperative patients, but I am not certain that these patients require a glutamine-enriched diet to get better. It probably has marginal effects, but we have to consider that in some groups of sick patients there is an advantage of providing glutamine. Then there is an important question arising from Griffiths et al. [20] with no improvement during the ICU stay, but it was a very short period of administration, 3–5 days, with low glutamine intake, 15 g/day. However, these authors observed a clearly decreasing mortality at 6 months and an associated reduced cost in surviving people. Now this is magical but can perhaps be explained. Just to recall, a former Swedish study by Petersson et al. [21] indicated that in cholecystectomized patients a short period of postoperative administration of glutamine decreased fatigue 1 month after the surgery. I don't know what the mechanism of this action is, perhaps it is related to glutathione and oxidative stress. And then to finish answering your question we have to remember that some studies in very sick patients, patients with major sepsis, with very high levels of stress, did not respond at all to glutamine therapy, and I especially refer to the study of Roth et al. [22] providing a high amount of glutamine by the parenteral route, and they were even not able to restore the muscle glutamine concentrations. To summarize my answer there is clearly a need for further work to designate subgroups of patients who can benefit most from such therapy, and in any case we cannot give an absolute recommendation of dosage.

Dr. Déchelotte: Just to add to the body of knowledge, a French multicenter trial with dipeptide, reported in ASPEN, showed that we are able to reduce the incidence of infectious complications by about 40% and to half the number of cases of pneumonia in very severe ICU patients. So I think it is also another step in the story, which is not quite finished.

Dr. Cynober: Sorry, I should have remembered these very impressive results.

References


