Glutamine-enhanced nutrition in the critically ill patient

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It is well established that critically ill patients have a deficiency of the amino acid glutamine. This article reviews the evidence for supplemental glutamine in the critically ill, focusing on the benefits in terms of reduced mortality and infectious morbidity.

During critical illness, blood and skeletal muscle glutamine concentrations fall, yet the demand from cells of the gastrointestinal and immune system rises. Glutamine, therefore, becomes a conditionally essential amino acid during this situation. Critical illness includes a variety of catabolic states with the common component of increased susceptibility to infection as a result of a combination of increased gut permeability to infectious agents and immune cell dysfunction.

The cells of the immune system require glutamine to retain a variety of optimal functions, including protection against oxidative stress damage, nucleotide synthesis and proliferation. Maintenance of plasma glutamine concentrations in critically ill patients has been shown in human and animal studies to improve immune function. This review will examine the evidence for glutamine involvement in immune function and the effect of supplementing parenteral and enteral feeds for the critically ill with glutamine on mortality and infectious morbidity. Finally, the authors will outline questions that are still posed by the use of glutamine in the critical care setting.

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METHODS

An electronic literature search was carried out using Medline (United States National Library of Medicine, 1980–2001) and the Cochrane Library (2001 edition, issue 4). In addition, the relevant reference lists of articles identified by the electronic search were examined.

GLUTAMINE AND THE IMMUNE SYSTEM

Optimal functioning of the immune system is crucial for survival in intensive care, yet many critically ill patients show evidence of immune dysfunction and are therefore at risk of an overwhelming infection. As the European Prevalence of Infection in Intensive Care study showed, the risk of death in intensive care is significantly increased following intensive care unit (ICU)-acquired infections (Vincent et al, 1995).

Immune cells in critically ill patients are subject to many varying influences, but a striking finding common to lymphocytes, macrophages and neutrophils is their high rate of glutamine utilization (Newsholme et al, 1999). Glutamine is fundamental to protein synthesis where it acts as a nitrogen donor in the synthesis of purines, pyrimidines and nucleotides. In addition, it is a precursor of the major antioxidant glutathione. Chang et al (1999) have demonstrated that T helper type 1 (Th1) lymphocyte cytokine responses are preferentially enhanced by glutamine in vitro: a Th1 as opposed to a Th2 cytokine profile is associated with improved cell-mediated immunity.

There is good evidence for monocyte dysfunction in the critically ill, and studies in vitro (Spittler et al, 1995) and in man (Spittler et al, 2001) have shown that supplemental glutamine preserves monocyte human leucocyte antigen (HLA)-DR expression and function. Neutrophils from postoperative patients show enhanced phagocytic function and reactive oxygen intermediate production when cultured in the presence of additional glutamine (Furukawa et al, 2000).

THE EVIDENCE FOR GLUTAMINE DEFICIENCY IN THE CRITICALLY ILL

Glutamine and critical illness

Glutamine is the most abundant free amino acid in the body and skeletal muscle contains the largest store. Following the onset of critical

illness, there is a profound depletion of muscle free glutamine, as well as a significant reduction in plasma glutamine. The decrease in plasma glutamine is seen particularly in patients with burns, sepsis and major trauma, but it is also seen in other critically ill patients (Parry-Billings et al, 1990; Gamrin et al, 1996).

The regulation of glutamine concentration in muscle in critically ill patients is not fully understood, but stable isotope studies in such patients show an increased metabolic clearance rate from plasma consistent with an increased utilization by other tissues (Jackson et al, 1999). Using arteriovenous balance studies in critically ill burn patients, Biolo et al (2000) have shown that by 2 weeks, the muscle free glutamine pool has become massively depleted with decreased muscle glutamine production.

Plasma glutamine and outcome

It may be hypothesized that if a deficiency of glutamine were a limiting factor in the critically ill, then there would be an increased risk of death from multiple organ failure following 'second hit' episodes of sepsis. In a cohort of 80 critically ill patients admitted to ICU, low plasma glutamine (<420 mmol/litre) was shown to be associated with a higher hospital mortality (60% *vs* 29%); a low plasma glutamine improved mortality prediction when added to the APACHE II predicted mortality rate (Oudemans-van Straaten et al, 2001).

GLUTAMINE SUPPLEMENTATION OF PARENTERAL NUTRITION

Parenteral nutrition is usually reserved for the most severely ill patients, who usually have gastrointestinal failure, which is associated with a high mortality. Griffiths et al (1997) examined the outcome of a heterogeneous cohort of critically ill patients given glutamine-supplemented parenteral nutrition compared with an isonitrogenous control in a block-randomized, double-blind trial. There was no significant difference in survival until 20 days after the initial ICU admission (57% surviving after 20 days in the glutamine group compared with 33% in the control group); this survival difference was also seen up to 6 months. Although infectious morbidity was not examined in this study, the excess deaths in the control group after 20 days were mainly as a result of organ failure following sepsis.

Evidence that glutamine may favourably influence the immune system following major insults was shown by Morlion et al (1998). This study examined the effect of glutamine-supplemented parenteral nutrition in comparison to isonitrogenous parenteral nutrition in patients recovering from major abdominal surgery and demonstrated that glutamine supplementation maintained the total circulating lymphocyte count in contrast to the profound decline seen in the control group. In addition, glutamine normalized the cysteinyl-leukotriene level in postoperative neutrophils, which in turn permits an adequate endogenous host defence. O'Riordain et al (1994) performed a small trial which similarly demonstrated significantly enhanced T cell DNA synthesis in patients receiving parenteral nutrition supplemented with glutamine.

In contrast, Powell-Tuck et al (1999) performed a similar trial using a smaller daily dose of glutamine in the study group (20 g *vs* 25 g for the Griffiths study). This study could find no significant difference in outcome at 6 months, although it should be noted that the patient case mix (mainly surgical and haematology patients) was quite different to the Griffiths study. A non-significant trend in mortality reduction was seen in haematology patients receiving glutamine, but the rate of infectious complications was the same for the two treatment groups.

GLUTAMINE SUPPLEMENTATION OF ENTERAL NUTRITION

Effect on mortality

Enteral nutrition has become the preferred method of feeding in the critically ill because of fewer infectious complications, and because enteral feeding prevents gut atrophy and preserves gut barrier function. Jones et al (1999) reported the results of a randomized clinical outcome study in which critically ill patients were given glutamine-supplemented enteral nutrition. No mortality difference could be detected between the patients receiving glutamine supplementation and the controls, but the effect on infectious morbidity was not examined. The authors acknowledged that this study was underpowered and that there were problems in delivering adequate daily calories to the patients studied.

Effect on infectious morbidity

Studies of enteral glutamine supplementation have, however, demonstrated a reduction in infectious morbidity. Neu et al (1997) described a blinded, randomized study of enteral glutamine supplementation in very low birthweight neonates. Logistic regression analysis of the

results controlled for birth weight showed the estimated odds for developing sepsis were significantly higher in the group of neonates allocated the control feed, and this group also showed a significant increase in lymphocyte activation as measured by lymphocyte HLA-DR expression.

Houdijk et al (1998) reported the results of a randomized, double-blind trial of glutamine-enriched enteral feed *vs* an isonitrogenous control in trauma patients. A major achievement of this study was that enteral feed was delivered using endoscopically-placed jejunal feeding tubes to ensure adequate calorie delivery. This trial demonstrated a reduction in bacteraemia from 42% in the control group to 7% in the glutamine supplementation group in the first 15 days. Significant reductions for pneumonia and sepsis were also seen in the group receiving glutamine supplementation, and serum concentrations of p55 and p75 soluble tumour necrosis factor (TNF) were also lower in this group, consistent with a lower systemic inflammatory response.

Enteral feeding with parenteral glutamine supplementation

Oral glutamine supplements may not lead to rises in plasma glutamine concentration in the critically ill, and it has been proposed that supplemental glutamine should be given parenterally to enterally fed patients. A prospective, randomized, double-blind study of intravenous glutamine *vs* an isonitrogenous control given for at least 7 days in enterally fed burns patients showed that in the group receiving glutamine supplementation there were significantly less Gram-negative bacteraemias over the 30 days following enrolment into the trial (Wischmeyer et al, 2001). There was a significant decrease in C-reactive protein at 14 days in the group receiving glutamine, again consistent with a lower systemic inflammatory response. No significant effect on mortality was seen, but the study only looked at 26 patients.

KEY POINTS

- Glutamine is a dietary non-essential amino acid but a deficiency develops in the critically ill.
- Glutamine is an essential fuel for immune cells, and optimal cell function is dependent on adequate supplies of glutamine.
- Glutamine may be of benefit in preventing late deaths in the critically ill when added to parenteral nutrition.
- Glutamine-enhanced enteral feeding has been shown to reduce infectious morbidity in the critically ill.
- Larger trials are needed to confirm the beneficial effects of glutamine on mortality and infectious morbidity.
- The mechanism by which glutamine improves immune functioning in the critically ill needs to be clarified.

CONCLUSIONS

Glutamine deficiency is a serious risk in the critically ill, and given the pivotal role that glutamine plays in the optimal functioning of the immune system, the addition of glutamine to the feeds of critically ill patients would seem logical. Glutamine-supplemented parenteral feed has been shown to reduce late deaths in a cohort of critically ill patients, and other similar trials in surgical patients have revealed benefits in immune cell function in patients receiving glutamine.

There is now good evidence that infectious morbidity is reduced in patients who receive glutamine-supplemented enteral nutrition, but no effect on mortality has been demonstrated. It must be acknowledged, however, that many of these trials only included small numbers of patients, and in some cases trials may not be directly comparable because of widely varying case mixes. There is the additional problem of achieving adequate nutritional intakes for those patients who are enterally fed. There is an urgent need for large multicentre trials to confirm the initial encouraging findings regarding glutamine supplementation in the critically ill.

A number of other important questions still remain to be answered in relation to glutamine and the critically ill. It needs to be established whether the reduction in plasma glutamine levels seen in the critically ill is directly related to the degree of immunosuppression seen in these patients, or directly related to infectious morbidity. In addition, it will be important to examine whether glutamine-supplemented nutrition improves immune cell function by simply increasing plasma glutamine or via an effect on gut-associated lymphoid tissue. HM

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