Glutamine

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Recent interest in nutritional research in the critically ill patient has focused on key nutrients which, when ingested in excess of daily requirements, can modulate immune, metabolic and inflammatory processes. Of these nutrients, glutamine holds considerable potential to be the first to play a key role in the management of patients with critical illness.

Glutamine, a non-essential amino acid, occupies a central role in many metabolic pathways. It comprises more than 50 per cent of the body's free amino acid pool and is a precursor for synthesis of nucleic acids and glutathione. Glutamine is a 'nitrogen shuttle' between tissues and a fuel for enterocytes, colonocytes, lymphocytes and proliferating cells[1]. The function of the gut is impaired in patients with glutamine deficiency, particularly because of the loss of protection against the translocation of bacteria and/or endotoxin from the gut lumen into the portal circulation. In hypercatabolic states (stress, sepsis and trauma) plasma and intracellular glutamine concentrations fall. These decreases have been shown to be of prognostic value and correlate with patient survival.

In view of its central role, the effects of glutamine supplementation have been examined *in vivo* in patients with a variety of diseases. Beneficial effects have occurred in terms of maintenance of protein synthesis, a reduction in loss of body nitrogen following trauma, enhanced intracellular glutamine levels and stimulation of immune function[2]. Such metabolic and immunological benefits are encouraging and can be achieved by either enteral or parenteral administration, but at least 5 days of supplementation appears to be necessary. However, it is the effect of glutamine supplementation on clinical outcome that is important to the patient. In this era of evidence-based medicine, it must be asked what glutamine supplementation actually achieves in terms of hard clinical endpoints.

The ability of supplementation to prevent infectious complications and reduce hospital stay has been examined. In one study 28 patients undergoing elective operation for colorectal cancer received either glutamine-supplemented total parenteral nutrition (TPN) or isonitrogenous isocaloric TPN for 5 days after operation[3]. Patients receiving glutamine had a 29 per cent reduction in hospital stay. Looking critically at this study, however, it might be asked whether a mean stay of 22 days in the control group could be regarded as usual practice, particularly as no major complications occurred. Furthermore, the surgeon decided the time of discharge, criteria for which were not clearly defined, and factors that determined discharge included nursing considerations.

In a second study, 72 patients with multiple trauma (Injury Severity Score of 20 or more) received either glutamine-supplemented enteral nutrition or a diet with the same nitrogen and calorie content[4]. Again, glutamine supplementation was beneficial and there was a lower incidence of pneumonia in the 60 patients who received nutrition for at least 5 days (17 *versus* 45 per cent); bacteraemia and sepsis were also reduced. However, the duration of hospital stay was increased for glutamine-supplemented patients (P not significant) and the mortality rate was the same in both groups. In contrast, a further study showed a beneficial effect on mortality rate in patients with multiple organ failure who received parenteral glutamine supplementation. Although death was the endpoint of this study, this was at a time point of 6 months, and in the convalescent period factors other than glutamine may have been important[5].

The effect of glutamine in reducing infectious complications has also been examined in patients undergoing bone marrow transplantation[6]. Parenteral glutamine administration reduced both infectious complications and hospital stay by 20 per cent in 42 patients with haematological malignancy undergoing such transplantation. This effect of reducing hospital stay was confirmed in a smaller study of bone marrow transplantation[7]. However, in the latter study two patients in the glutamine group were excluded from the analysis, one dying from sepsis after 86 days in the intensive therapy unit and another from multiple organ failure after 10 days. Furthermore, although there was a trend towards a reduction in infectious complications, this was not statistically significant[7].

The ability of glutamine supplementation to improve absorption in the gastrointestinal tract has also been examined. In an uncontrolled trial involving patients with short bowel syndrome, intestinal function and absorption of nutrients were improved substantially by the administration of a combination of oral glutamine, growth

hormone and a high-carbohydrate low-fat diet[8]. The rationale for using this combination was that growth hormone stimulates intestinal growth and the uptake of nutrients across the intestinal wall, and thus the modified diet allows maximal absorption of nutrients. Beneficial clinical effects occurred only when all three agents were given together. When a randomized controlled trial was carried out to investigate these effects further, the results were disappointing. In a small double-blind randomized placebo-controlled crossover study of eight patients with short bowel syndrome, the glutamine–hormone–diet combination resulted in only a modest increase in electrolyte absorption and delayed gastric emptying; there were no improvements in small bowel morphology, stool losses or absorption of macronutrients[9].

Glutamine supplementation may also play a role in protecting the gastrointestinal tract against chemotherapy-induced toxicity. Initial uncontrolled studies suggested that glutamine might reduce the severity of chemotherapy-induced stomatitis. A randomized controlled trial subsequently confirmed this beneficial effect of oral glutamine supplementation in lessening the severity and reducing the duration of stomatitis occurring during chemotherapy[10].

So what can be drawn from the studies that have addressed clinically important endpoints? It seems that glutamine does indeed reduce the risk of patients developing infectious complications after surgery and trauma, and it improves chemotherapy-induced stomatitis. However, whether these effects translate into a reduction in hospital stay and mortality rate remains unclear, and the role of glutamine and hormone combinations in the treatment of short bowel syndrome is also still unproven. Nevertheless, given the potential benefits outlined above, well designed clinical trials with clearly defined endpoints and adequate statistical power are urgently needed if the place of glutamine in clinical practice is to be confirmed.

References

1 Heys SD, Gough DB, Khan L, Eremin O. Nutritional pharmacology and malignant disease: a therapeutic modality in patients with cancer? *Br J Surg* 1996; **83:** 608–19.

2 O'Riordain MG, Fearon KCH, Ross JA, Rogers P, Falconer JS, Bartolo DCC *et al.* Glutamine-supplemented total parenteral nutrition enhances T-lymphocyte response in surgical patients undergoing colorectal resection. *Ann Surg* 1994; **220:** 212–21.

3 Morlion BJ, Stehle P, Wachtler P, Siedhoff H-P, Koller M, Konig W *et al.* Total parenteral nutrition with glutamine dipeptide after major abdominal surgery. *Ann Surg* 1998; **227:** 302–8.

4 Houdijk AP, Rijnsburger ER, Jansen J, Wesdorp RIC, Weiss JK, McCamish MA *et al.* Randomised trial of glutamine-enriched enteral nutrition on infectious morbidity in patients with multiple trauma. *Lancet* 1998; **352:** 772–6.

5 Griffiths R, Jones C, Palmer TE. Six-month outcome of critically ill patients given glutamine supplemented nutrition. *Nutrition* 1997; **13:** 295–302.

6 Ziegler TR, Young LS, Benfell K, Schletinga M, Hortos K, Bye R *et al.* Clinical and metabolic efficacy of glutamine-supplemented parenteral nutrition after bone marrow transplantation. A randomized, double-blind, controlled study. *Ann Intern Med* 1992; **116:** 821–8.

7 Schloerb PR, Amare M. Total parenteral nutrition with glutamine in bone marrow transplantation and other clinical applications (a randomized, double blind study). *JPEN J Parenter Enteral Nutr* 1993; **17:** 407–13.

8 Byrne TA, Persinger RL, Young LS, Ziegler TR, Wilmore DW. A new treatment for patients with short-bowel syndrome. *Ann Surg* 1995; **222:** 243–55.

9 Scolapio JS, Camilleri M, Fleming CR, Oening LAV, Burton DB, Sebo TJ *et al.* Effect of growth hormone, glutamine, and diet on adaptation in short bowel syndrome: a randomized controlled study. *Am J Gastroenterol* 1997; **113:** 1074–81.

10 Anderson PM, Schroeder G, Skubitz KM. Oral glutamine reduces the duration and severity of stomatitis after cytotoxic cancer chemotherapy. *Cancer* 1998; **83:** 1433–9.