**Enteral versus Parenteral Glutamine Supplementation in the Critically ill Patient: Pros and Cons**

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**INTRODUCTION**

It is now 30 years since the concepts of immunonutrition and pharmaconutrition emerged. These exciting developments stimulated intense and sometimes controversial debate with an exponential increase in scientific and clinical investigations.

In this review the term “pharmaconutrient” will be used in preference to “immunonutrient” for glutamine (GLN) because this amino acid has many unique pharmacological and metabolic functions in addition to immune modulation. LGLN is a precursor for purines and pyrimidines, plays an important role in gluconeogenesis, renal ammoniagenesis and in the maintenance of acid-base balance. It serves as the primary fuel for enterocytes, lymphocytes and other rapidly dividing cells of the immune system.
There is substantial animal work demonstrating that GLN becomes conditionally essential under stressful situations, where the body cannot make sufficient quantities. GLN is also a rate limiting substrate for the antioxidant glutathione. Intestinal mucosa produces reactive oxygen species during ischaemia and is therefore susceptible to free radical damage when blood circulation is restored. Additionally surgical trauma and severe illness are associated with profound glutathione and GLN depletion in muscle and blood. Supplementary GLN has been shown to give mucosal protection and attenuate glutathione levels via conversion to glutamate, a constituent of the tri-peptide glutathione which may explain some of the beneficial effects of GLN. GLN also enhances the ability of the gut to withstand chemical and radiation injury and stimulates the immune system to mount an effective defence in response to infection. Good human evidence now exists that GLN provision has beneficial effects on morbidity and mortality in critically ill adult and paediatric patients.

All patients should receive optimal nutritional support. However, the on-going debate between Parenteral (PN) and Enteral Nutrition (EN) now encompasses pharmaconutrition. Side effects, complications and limitations of both modes of administration can be listed ad nauseam but favouring one or the other will not benefit the patient. When used inappropriately, overfeeding or refeeding syndrome can be a problem with PN. Conversely mortality rates have been higher with EN and the patient’s total nutritional needs are difficult to meet enterally. Consequently, responsible use of both therapies where necessary in combination, taking the patient’s condition into account is the best approach.

GLN stability and formulation issues, have now been largely resolved by aseptic and lyophilisation technologies or by the industrial manufacture of artificial heat stable glutamine dipeptides. Pharmaconutrition is still complicated by the heterogeneity of patient groups and difficulties in interpreting the results of therapy, but there is now good evidence to support the benefits of GLNPN. Current evidence for GLNEN is growing although less compelling, but neither method of supplementation is harmful. But which route should we choose?

**GLUTAMINE DEPLETION IN METABOLIC STRESS**

In critical illness and conditions of catabolic stress, the body’s demand for LGLN exceeds the capacity for synthesis. Up to 60% GLN depletion occurs following multiple trauma, burns, serious infections, inflammatory intestinal disorders or in those who remain critically ill for more than a few days after major surgery. It can have serious detrimental effects on immune function and gut integrity, thus increasing susceptibility to infection. Immune system activation with its requirement for increased protein synthesis and GLN utilisation is one explanation for the large fluxes of GLN from skeletal muscle and provides a rationale for GLN supplementation.

Muscle GLN levels recover very slowly and may not return to normal for many weeks after trauma. Plasma GLN is more responsive and may be a good surrogate parameter to titrate the dosage of GLN necessary to restore GLN balance. High ICU mortality correlates well with low plasma GLN, despite only a marginal difference in APACHE II scores. Thus, plasma GLN has high specificity as an indicator of intracellular depletion and can serve as a useful outcome predictor independent of illness severity. In practice this means that low plasma GLN concentration warrants exogenous PN or EN supplementation. But what are the pros and cons of each?

**PARENTERAL GLUTAMINE SUPPLEMENTATION**

Patients are more likely to receive the prescribed dose of GLN from GLNPN than by the oral or enteral route. Moreover PN guarantees systemic distribution of GLN including the GI tract and immune system where GLN restores T-cell mediated immunity, reduces the inflammatory response and reinforces antioxidant defences.

In a groundbreaking study by Griffiths et al the mortality after 6 months in a mixed medical and surgical ICU with one or more organ failures was significantly reduced to 43% with L-GLN enriched PN (GLNPN) at 0.26g/kg/d compared with the controls (67%). GLN supplementation also resulted in a 25% reduction in the cost of intensive care and a 15% reduction in hospital costs for all GLNPN patients. Moreover the total ICU and hospital cost per survivor was reduced by 50% and average length of stay (LOS) in the ICU was reduced from 48 to 25 days (p< 0.012).
The author’s subsequent analysis of microbiological data21 and overall rates of intensive care acquired infections (ICAI) suggest that the improved survival may be related to reduce mortality from multiple organ failure (MOF). Patients receiving GLN developed fewer Candida infections after a longer ICU stay and none of those infected died, whereas many control patients on “standard” PN became infected earlier and died from MOF (p=0.02). Specifically, renal failure deaths were lower with GLN (p<0.02). The incidence of Candida infection was in fact halved in the GLN group. Not only did it take longer for infections to develop but also the GLN patients appeared to be able to survive infection better.

Patients in this study were extremely ill (APACHE II 17-18) and if they survived, would have been expected to stay in the ICU for many days. Long stay patients frequently suffer from one or more infections, of which Candida albicans is the most common fungal organism. The difference in mortality almost exclusively relates to those patients requiring medium to long term PN and who were likely to die of MOF.

The importance of dose and duration of PN has been emphasised in recent European studies. Glutamine-dipeptide (GDPN) at 0.3g GLN/kg was associated with a significant reduction in complications: 41.4% vs. 60.7% (P<0.05) with reduced infection rate and pneumonias (10 vs 19, P<0.05) but outcome could not be determined from median feed durations of only 6-7 days22. In contrast ICU patients receiving a lower dose of GDPN (equiv to 0.2g GLN/kg) for over 9 days survived better than those fed for a shorter time (22/33 versus 13/35, p<0.05)23. In patients with secondary peritonitis, GDPN at 0.4g/kg/body weight/day (equiv to 0.26g/kg GLN) significantly decreased incidence of complications due to infection (4 vs 12, p=0.005) and improved nitrogen balance. IgA returned to normal, along with a trend to improved CD4/CD8 lymphocytes24. GDPN for at least 14 days also prevented the occurrence of pancreatic infection as reported by Chinese investigators25.

In summary; GLNPN may not always decrease the risk of infection, but it can decrease the risk of dying from an infection if therapy is continued for long enough.

**ENTERAL GLUTAMINE SUPPLEMENTATION**

Absorption of GLN by the gut is good in most ICU patients. Enteral GLN (GLNEN) is utilised by the enterocytes and immune competent cells in the upper gastrointestinal tract. However, the proportion of GLN that actually reaches the general circulation is low26. Since correcting a deficiency is central to the pharmacological effect of GLN the failure of many studies can be explained by this limited systemic availability of GLN from enteral feeds.

Several investigations have confirmed that GLNEN improves immune function27-29. In a controlled study with 72 ICU patients infectious morbidity was significantly reduced in the GLN group: pneumonia: 5/29 vs. 14/31, (p<0.02), bacteraemia: 2/29 vs. 13/31, (p<0.005), and sepsis: 1/29 vs. 8/31, (p<0.02)28. Another prospective randomised single-blind trial in 84 patients with systemic inflammatory response syndrome had to be finished earlier than planned due to the significantly higher infection rate in the control group (17/33 versus 11/43 in the GLN group, p=0.02)29. For the GLNEN arm of the Liverpool study patients actually received less energy per day than LGPN patients, reflecting the practical limitations with enteral feed delivery in ICU’s27-30. Nitrogen intake was similar in both groups during the first five days but there was a tendency for control patients to need longer ICU stays (median 16.5d) and receive enteral feeding for longer. Nevertheless, LOS and cost of GLN survivors were reduced.

In another randomised trial, multiple trauma patients with depressed HLA-DR expression on monocytes, showed enhanced recovery after two weeks with GLNEN compared with controls31 and in a recent prospective, controlled randomised trial involving 41 adult burn patients32 GLNEN reduced blood infection threefold and prevented bacteraemia with P. aeruginosa. Mortality was significantly lower in patients receiving GLN (0 versus 8 deaths in control group, p < 0.01).

Neu et al8 randomly assigned very low birth weight (vlbw) babies to a mixed regimen of PN and EN with or without GLN. In the unsupplemented group 10/35 (30%) babies developed bacteraemia and hospital-acquired sepsis compared to only 4/34 (11%) in the GLNEN group (0.3g /kg/day) (p=0.048). Hospital costs with GLNEN treated vlbw babies33 were also less.
Whilst it has been difficult to show an effect on mortality with continuous GLNEN, it must be remembered that patients who are successfully fed by the enteral route are generally less seriously ill with a lower mortality rate. This makes it more difficult to demonstrate a significant outcome effect. Consequently the demonstrable benefits in this group of patients reflect morbidity parameters. GLNEN has been shown to reduce LOS in hospital and ICU as well as the total cost per survivor\(^3\). The sicker the patient the greater the likelihood of GLN deficiency and therefore increased mortality risk, yet the more difficult it is in practice to deliver adequate GLNEN to significantly influence survival, making clinical evidence less powerful than data from GLNPN.

**DOSAGE AND ADMINISTRATION**

As a pharmaco-nutrient L-GLN may have a direct effect on the immune system and its efficacy is probably related to the dose\(^3\) but the precise mechanisms are unclear. Pharmacological doses of GLN, achieving 4mM plasma levels decrease TNF-alpha release and increase HSP 72 expression in human peripheral blood mononuclear cells\(^3\). In stressed patients the production rate of GLN may be near normal but there is increased metabolic clearance from plasma, consistent with increased utilisation by other tissues\(^3\).

GLNPN dosages to reduce mortality are typically 15-24g GLN every 24hrs\(^2,3\). Dosing studies show that up to 40g of parenteral GLN per day restores plasma levels to normal\(^26,37\). Consequently dosage of 0.3-0.4g/kg/d for adults with early initiation of nutrition support and at least 5 days of GLN supplementation is usually recommended\(^3\). The dosage can be adjusted up to 40g per day (0.57g/kg/d) for larger patients, major burns\(^39\) or severe malabsorption such as short bowel syndrome\(^40\). Certainly, at a GLNPN dose of 0.57g/kg/d Wischemeyer et al\(^39\) have demonstrated that patients with severe burns show improvement in nutritional status with significant rise in serum transferrin and albumin coupled with fewer inflammatory and bacteraemic episodes and a significant reduction in septicaemia.

Paediatric doses normally range from 0.2-0.3g/kg/d\(^8\), however in a recent study a safe upper dose of 0.65g/kg/d was established for oral GLN\(^41\).

Delivery of 30g/day of GLN jejunally in multiple-trauma patients led to a significant reduction in pneumonia, bacteraemia and severe sepsis. Trauma patients showed a potentially beneficial rise in the CD4-CD8 T-cell ratio\(^42\). A recent study in adult patients given GLNEN showed a reduction in systemic infections and a lower mortality rate but importantly, the supplemented GLN was not given as a constant infusion, rather by 4-hour boluses up to a total of 26g/d\(^3\). Bolus enteral delivery is potentially more likely to alter GLN levels in the systemic circulation so that one might consider a combination of GLNEN with GLNPN to guarantee the patient the prescribed GLN dose regardless of which therapy is deemed most appropriate.

**SAFETY AND EFFICACY**

All the reported studies of oral and enteral supplementation have utilised pure L-GLN, which is moderately soluble in water and common drinks\(^43\) with good clinical tolerance. After oral administration absorption leads to increased plasma GLN levels within 30 minutes in healthy volunteers\(^44\). No adverse effects have been shown for doses up to 0.65g/kg/d and there are so far no contraindications. Similarly there are no reports that intravenous GLN, using L-GLN or a GLN-dipeptide, produces toxic effects. Addition of 20-40g of dietary GLN during stress will not dramatically change the turnover of GLN, estimated at 60-100g/24hrs in normalsized adults. The quantities supplemented in GLN-enriched feeds can therefore be handled according to normal physiological pathways\(^45\) with no marked differences in nutritional status or plasma aminogram between GLNEN and GLNPN for most patients\(^46\).
Large prospective randomised controlled trials may not be suited to pharmaconutrition studies. Inclusion/exclusion criteria may limit study size, patient enrolment or deny life-saving nutrition support in many institutions. Meta-analysis of multiple clinical studies helps to provide statistical significance from combined data and has confirmed that a conditional deficiency of GLN, which adversely influences outcome, occurs in the critically ill.

Analysis of 14 randomised supplementation studies with 737 critically ill and surgical patients confirmed that GLNPN reduces the rate of infectious complications (risk ratio 0.79, 95% CI 0.67-0.99) and LOS in hospital with a trend towards reduction in mortality (7). A more recent meta-analysis47 strongly supports the hypothesis that GLNPN reduces mortality (RR 0.71, 95% CI 0.51-0.99) and is associated with lower infection rates (RR0.81, 95CI - 4.5 -0.7days). It confirms that GLNEN has no effect on mortality (RR 1.08, 95% CI 0.57-2.01), compared to GLNPN, but overall GLN is associated with lower infection rates (RR 0.81:95% CI, 0.64-1.0) supporting the earlier systematic review of 16 studies with 583 patients concluding that GLNEN improves immune function in multiple trauma, reduces costs in critical illness and improves mucositis in post-chemotherapy cancer patients46.

Based upon a new meta-analysis of five studies, including two level 1 studies the Canadian Guidelines advise that where available in ICU, PN should contain GLN48. This conclusion has been endorsed by a European consensus group49. Although some different conclusions were reached by both aforementioned Spanish meta-analyses46,47, all investigators recommend the use of GLN pharmaconutrition for ICU patients.

CONCLUSION

Nutrition support is of fundamental importance to critically ill patients. While it is preferable for patients to receive their nutrition by the enteral route, this is not always possible and parenteral supplementation may be required. Nutrition support provided on an ‘intention to treat’ basis means that patients are fed enterally as long as necessary. For the majority of ICU patients this approach is beneficial but long-stayers who can only be fed parenterally, should receive supplementary GLN.

The principal objective of intensive care is to prevent death from MOF and correction of GLN deficiency can help improve the chance of survival. Insufficient GLN supply to important tissues explains why low plasma GLN can be an independent predictor for poor outcome. It is reasonable to assume it could take months for the immune system to return to strength after leaving ICU, which is why the Griffiths six months outcome publications20, 21 are so important for relating pharmaconutrition to the risk of death associated with ICU stay. GLN therapy may not reduce the overall incidence of ICAI but could be valuable supportive therapy to reduce the risk of dying from infection or MOF and make more efficient use of ICU resources.

As Hammerqvist50 has eloquently stated: “Nutrition in the ICU involves a large amount of Gut Feeling, some Gut Feeding, but not uncritical Gut Filling”. We can confidently add that Gut Fuelling requires Glutamine supplementation by Parenteral or Enteral Nutrition.

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