Parenteral glutamine in critical illness: just what the gut needs

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Abstract

The role of glutamine as a metabolic fuel for the starving intestines, its capacity to limit bacterial translocation, lung sepsis and a pro-inflammatory cytokine response are reviewed in the context of uncertainities regarding current recommendations for glutamine supplementation in parenterally-fed critically ill patients. Weaknesses in the evidence-base showing benefit of intravenous glutamine supplementation are discussed together with aspects of glutamine supplementation via the enteral route.

Keywords

Glutamine, parenteral nutrition, bacterial translocation, critical illness, systemic inflammatory response syndrome

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Why glutamine?

Over the past decade, the amino acid glutamine has repeatedly come under the spotlight as one of the intravenous nutritional supplements that may rescue the critical care patient from developing the systemic inflammatory response syndrome (SIRS) and multi-organ dysfunction syndrome (MODS) [1] resulting from unrestricted release of proinflammatory cytokines that often follows severe sepsis, shock or trauma.

The candidate molecule for such a rescue operation should not only supply the right cellular metabolic fuels for the scenario but should also have immuno-modulating abilities such as the capacity to regulate the inflammatory response so that it kills enough bacteria without causing fatal damage to the patient's vital organs and their microcirculation.

The glutamine molecule has some outstanding nutritional credentials which should make it eligible for this task. For example, it is the most abundant amino acid in the body, it exhibits the highest concentration in peripheral blood and (taurine excluded) it has the next highest concentration in the cytosol in the cells of vital organs. Its five-carbon chassis can be oxidized (i.e. burnt) as a metabolic fuel or used anabolically as a building block to make other amino acids. Glutamine also stands out amongst its competitors because it has not one but two nitrogen moieties, the α amino group which can carry ammonia and the amide group which supplies nitrogen for the synthesis of nucleotides in rapidly dividing immune cells such as macrophages or lymphocytes.

Glutamine: the key to interorgan nitrogen exchange

Glutamine is the currency responsible for the major part of the flux of nitrogen that occurs between organs undergoing protein breakdown and those undergoing build-up respectively. This ability to shuttle large amounts of nitrogen quickly is complemented by glutamine's capacity to regulate the rate of protein synthesis. Glutamine can also carry toxic ammonia to the kidney where it releases it as a buffer to bind to H^+ ions in the urine. Glutamine is both a nitrogen carrier and a metabolic fuel. The oxidation of its carbon

chassis yields almost as much energy in the form of ATP, the energy currency of the cell, as when glucose is oxidized (endnote 1).[2]

Muscle glutamine: food for the starving gut

Most tissues have the faculty to both synthesise and to breakdown, and therefore to utilize, glutamine. Muscle and brain are the main manufacturers of glutamine while the gut is the main consumer. The starving gut uses muscle-derived glutamine as its main fuel (endnote 2).[3] The gut is also capable of utilizing glutamine delivered through the enteral or parenteral route. The liver can flip from net synthesis to net utilisation according to metabolic demands. Synthesis involves the addition of ammonia (NH_3) to the amino acid glutamate while break down releases NH_3 from glutamine. For obvious reasons the enzymes responsible for these two reactions are located in different compartments of the cell in order to prevent wasting energy through the phenomenon of futile substrate cycling.

The post absorptive state: a happy time of glutamine balance

The biggest stores of glutamine occur in skeletal muscle. This is not surprising as muscle tissue contains 80% of the body's total amino acids, muscle glutamine concentrations being 30 times higher than those of plasma. During the postabsorptive state e.g. 6 hours after a meal when neither feeding nor fasting are influencing metabolism, muscle tissue releases its glutamine stores into the blood for use by the intestinal cells or enterocytes as a fuel. Here glutamine liberates NH_3 and glutamate is oxidised to CO_2 and water via the Krebs cycle to energise gut metabolism.

Toxic ammonia is produced by the gut as a by-product but, unlike in other organs with a systemic drainage, blood from the gut returns to the heart via the portal vein and the liver. The liver detoxifies NH_3 by converting it into urea except in liver disease when ammonia escapes into the blood and brain causing the syndrome of hepatic encephalopathy. In the fed state muscle export of glutamine is balanced by gut consumption and plasma glutamine levels are steady. After a protein meal (meat protein contains 50% glutamine) any surplus glutamine can be converted to the amino acid alanine and together with alanine derived from muscle glutamine, it can be metabolised by the liver to produce glucose (Figure 1).

The critically ill starving patient: a time of glutamine need

During starvation gut utilisation of glutamine continues, muscle glutamine stores becomes depleted, plasma glutamine falls and the liver switches to glutamine synthesis to try to make up the deficit. Acidosis is common during starvation especially in critical illness and this

unfortunately increases the kidneys' demand for (and utilisation of) glutamine. Replicating immune cells place a further new demand on glutamine stores. Muscle synthesis of glutamine cannot keep up with consumption in gut, kidney, and immune system and progressive glutamine depletion sets in (endnote 3).[4]
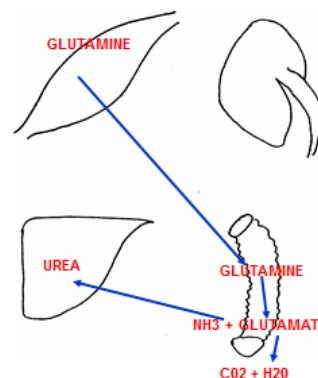

Figure 1: Glutamine metabolism in the post absorptive state.

Progressive muscle wasting further depletes muscle glutamine reserves. The liver cannot synthesize enough glutamine even if the patient is fed with intravenous amino acids. Glutamine supplementation of parenteral nutrition (PN) corrects much of this depletion, improves nitrogen balance and leads to desirable clinical benefits. Intravenous infusions of free glutamine in critically ill patients at doses up to 0.86 g/kgBW/day normalized plasma glutamine levels but did not affect muscle glutamine concentrations (Figure 2).[5]
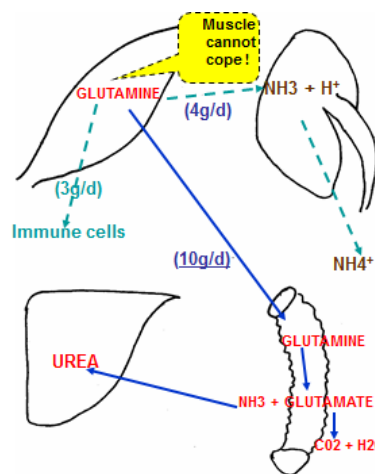

Figure 2: Glutamine metabolism during sepsis, starvation and acidosis.

Glutamine on the ground: how does it work?

Glutamine attenuates the derangement in physiology of many critically ill patients as shown by human, (clinical and volunteer) and animal experimental studies (see below). A common scenario where glutamine may be of benefit is that of a severely burnt ICU patient, suffering from septic shock who requires inotropic support. Here gut ischaemic injury leads to a number of dangerous sequelae (Figure 3) each of which has a potential for correction by glutamine.
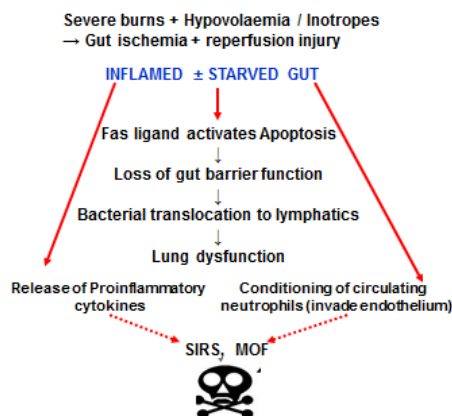

Figure 3: Typical sequelae of gut ischaemia and starvation.

Firstly, gut ischaemia releases excess proinflammatory cytokines. Glutamine metabolism, through NADPH production, increases the ratio of reduced glutathione (GSSH) to oxidized glutatathione (GSSG). This redox change lowers synthesis of a number of harmful proinflammatory cytokines such as TNF through regulation of transcription of NF-κB, the nuclear factor kappa-light-chain-enhancer of activated B cells.[6]

The other way in which glutamine may help is by increasing the synthesis of Heat Shock Protein (HSP) which acts as a chaperone to nascent polypeptides that are otherwise damaged by inflammation. HSP strengthens the cytoskeleton of epithelial cells and increases epithelial integrity and down regulates the expression of harmful cytokines such as interleukin 1 (IL-1), increasing tolerance to endotoxaemia.[7]

Intravenous glutamine enhanced pulmonary HSP production, attenuated lung histologic damage and lowered indices of lung tissue metabolic function and mortality in a rat model of sepsis.[8] Significant correlations between clinical outcome and circulating HSP level augmentation have been observed in critically ill patients supplemented with intravenous glutamine.[9] Supplementation of patients with multiple trauma and a high injury severity score with oral glutamine was associated with a reduced incidence of bacteraemia and pneumonia.[10] Oral glutamine has also been reported to improve intestinal barrier function after high dose chemotherapy.[11]

Secondly, gut ischaemia through the release of Fas ligand increases enterocyte apoptosis, which results in loss of gut barrier function and more bacterial translocation. Here glutamine may increase survival by its ability to suppress a number of kinases which mediate apoptosis or cell suicide in response to binding of ligand to Fas "death receptors."[12]

Thirdly the inflamed ischaemic gut conditions circulating neutrophils to invade the endothelium as part of a systemic inflammatory response. Glutamine is well placed to reduce neutrophil adhesion to gut vascular endothelium and its subsequent migration. Hou *et al* reported reduced vascular CAM-1 expression on, and leucocyte transmigration through, human umbilical vein endothelial cells stimulated by arsenic.[13]

Glutamine has also been shown to improve glycaemic control in critical illness which often causes insulin insensitivity and obligatory gluconeogenesis. Glutamine supplementation decreased insulin requirements in critically ill patients requiring TPN.[14] Although glutamine is itself a substrate for gluconeogenesis it has the incretin potential to increase insulin secretion by raising circulating Glucagon-like peptide (GLP-1) and glucose dependent insulinotropic factor (GIP).[15]

Glutamine: can we deliver it?

The low solubility of free glutamine (35g/l at 20ºC), which may drop further after admixture with parenteral amino acid solutions, often necessitates unwanted bulky additions to the PN regimen. Variations in pH and temperature during manufacture and storage may promote non enzymatic degradation of glutamine to pyroglutamic acid (pGlu and ammonia (NH_3) which can cause cerebral toxicity. Peter Furst[16] pioneered the commercial synthesis of a dipepetide containing Alanine-Glutamine (Ala-Glu, Dipeptiven®, Fresenius Kabi). Ala-Glu is 16 times more soluble than free glutamine and is stable with a shelf life of 24 months when stored below 25ºC. When Ala-Glu was infused continuously intravenously into healthy volunteers, it was rapidly hydrolised by circulating and membrane bound extracellular dipeptidases causing a 30% rise in plasma free glutamine.[17]

Dipeptides are stable and do not decompose to PGlu or NH_3 which could cause cerebral toxicity. Ala-Glu infusions almost abolished trauma-induced muscle glutamine depletion and reversed negative nitrogen balance after major surgery.[18]

Urinary and dialysate losses are well balanced by the infusion and NH_3 derived from glutamine metabolism does not reach toxic levels except in patients with severe hepatic impairment. Dipeptiven provides 82 g alanine and 135 g glutamine per ml. The maximum daily dose of 2mls/kg recommended by the manufacturer would supply 0.27 g glutamine/kg BW which is within the ESPEN recommended dose range.

An alternative dipeptide glycyl-glutamine (Gly-Glu, Glamine®, Fresenius Kabi) is also available as part of a complete well balanced aminoacid solution for use in PN regimens. A daily infusion of 1 litre Glamin in a 70 kg patient would supply 0.32g N/kgBW/day and 0.28g glutamine/kgBW/day.

Glutamine: enteral or parenteral?

Protein-based enteral feeds contain typically 5-8g glutamine per 100 g protein. Glutamine enriched enteral feeds deliver more glutamine e.g. Reconvan® Fresenius Kabi supplies 18 g glutamine per 100 g protein. Enteral glutamine supplementation would supply the preferred metabolic fuel to enterocytes and minimise the depletion of muscle gut glutamine stores that is required to correct the fall in plasma glutamine level induced by critical illness. However glutamine absorbtion may be impaired in critically Ill patients, e.g. those with intestinal ileus, while excess intestinal bacteria may consume significant amounts of enterally infused glutamine. Since glutamine is mostly absorbed in the upper jejunum it may not reach the lower intestine which is better "fed" via the parenteral route. Replenishment of the body glutamine pool is slower with the enteral route[16] and plasma glutamine levels have not been shown to normalize consistently after enteral glutamine supplementation[19] as has been observed after parenteral glutamine. The carrier for glutamine (free or protein bound), the rate and site of enteral infusion (bolus or continuous, gastric or intestinal) may alter glutamine delivery to the systemic circulation. Only a fraction of absorbed glutamine is recovered from portal venous blood[20] which undergoes hepatic first pass elimination before it reaches the systemic circulation. Although plasma glutamine may not mirror intracellular glutamine stores, failure to find reports of normalization of plasma glutamine after enteral supplementation suggests that enteral glutamine often fails to restore negative glutamine balance unless accompanied by parenteral glutamine supplementation. This is unfortunate since enteral feeding is generally the preferred route of feeding over PN for the critically ill patient who requires nutritional support. The Canadian 2009 guidelines (see below) state that enteral glutamine should be considered in burn and trauma patients but there are insufficient data to support the use of enteral glutamine in other critically ill patients.

Parenteral glutamine in ITU: who should receive it?

The American Society of Parenteral and Enteral Nutrition (ASPEN) recently published a position statement advocating the use of FDA-approved parenteral glutamine preparations in critically ill postoperative or ventilator-dependent patients. These recommendations are based on five meta-analysis of 46 studies involving 2780 critical care treatments.[21]

The relative risk (RR) ratios for mortality and infections after glutamine supplementation versus unsupplemented controls and their 95% confidence intervals are shown in forest plots (Figures 4 and 5) calculated using the Comprehensive Meta-analysis Package Ver. 2.0.[22] The size of the square symbols is proportional to the weighting given to individual studies. The pooled relative risk ratios for mortality (0.741) and infection (0.791) significantly favoured intravenous glutamine supplementation; the ideal dose being estimated as close to 0.5 g glutamine /kgBW/day.
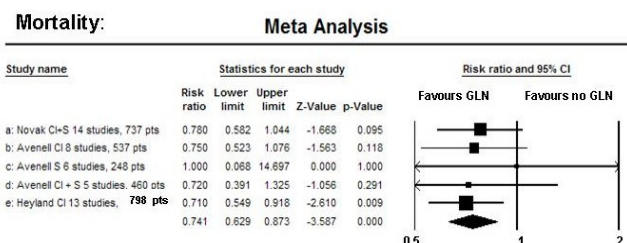

Figure 4: Forest logarithmic plot of relative risks (RR) of death with and without glutamine infusion in critically ill patients and associated confidence limits. RR<1 favours glutamine, RR> 1 favours no glutamine. Weighting of different studies indicated by size of squares. Pooled risk ratio of 0.741 and its confidence limit (parallelogram) significantly favour glutamine infusion.
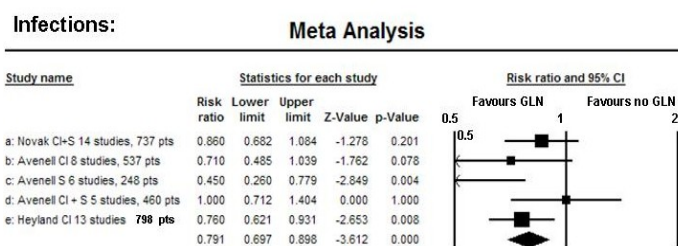

Figure 5: Forest logarithmic plot of relative risks (RR) of severe infections with and without glutamine infusion in critically ill patients and associated confidence limits. RR<1 favours glutamine, RR> 1 favours no glutamine. Weighting of different studies indicated by size of squares. Pooled risk ratio of 0.791 and its confidence limit (parallelogram) significantly favour glutamine infusion.

The American ASPEN / SCCM 2009 guidelines state that when PN is used in a critical care setting consideration should be given to parenteral glutamine supplementation.[23] The Canadian CCCN 2009 guidelines state that when PN is prescribed to critical care patients parenteral glutamine supplementation is strongly recommended whereas data was insufficient to recommend enteral glutamine supplements[24]. The European ESPEN 2009 guidelines state that when PN is indicated in intensive care unit patients the amino acid solution should contain 0.2 to 0.4 grams L glutamine /kgBW/day, e.g. 0.3 – 0.6 g/kg/day alanyl-glutamine dipeptide.[25]

The inclusion of critcally ill and / or surgical patients makes the ASPEN pool of five meta-analysis heterogenous. The study group with the highest weighting (Heyland, 13 studies) differed from the other four study groups in reporting uniformly significant benefit of intravenous glutamine. No overall attempt was made to select patients who may benefit more from supplementation (e.g. by using biomarkers or by selecting low-BMI patients). Moreover meta-analysis does not allow for publication bias or exclusion of studies not reported in English. Despite the positive signal given by the combined meta-analysis the recommendations need further statistical backing.

Glutamine supplementation of PN did not significantly reduce new infection or mortality in the SIGNET[26] and earlier Avenell [27] trials (502 and 279 critically–ill patients respectively). The findings of the ongoing REDOXS trial[28] of combined enteral and parenteral supplementation is therefore eagerly awaited.

Conclusion

Glutamine is a nutritionally non-essential amino acid that becomes conditionally essential during critical illness. Glutamine released from muscle in large amounts (typically eight grams per day) becomes a major metabolic fuel in this scenario. Depletion of muscle glutamine stores deprives the gut of its prime metabolic fuel. Effective repletion of whole body glutamine stores has the potential to restore gut barrier function, to reduce lung sepsis and to fuel immune cells to modulate the cytokine response to injury and sepsis away from the profile associated with SIRS / MODS and to normalize REDOX state in vital organs. American, European and Canadian guidelines recommend parenteral glutamine supplementation in critical care patients receiving PN. These recommendations need to be strengthened by carefully designed clinical trials with specific primary endpoints in selected subgroups of critically ill patients receiving PN. The therapeutic potential of combinations of glutamine with other intravenous immunomodulators (e.g. arginine, ω-3 fatty acids) or antioxidants (e.g. Vitamin E, ascorbic acid and in particular selenium) also merit further investigation.

Endnotes

1. Metabolism of glutamine to α-ketoglutarate and subsequent complete oxidation in the Kreb's cycle yields 30 moles ATP per mole glutamine compared to 36 moles of ATP released by the complete oxidation of one mole of glucose.
2. During starvation glutamine, acetoacetate and hydroxybutyrate constitute 35, 24 and 26 percent respectively while glucose constitute only 7 percent of the total fuel oxidized by the rat intestine.
3. During postoperative trauma in a 70 kg patient typical daily glutamine uptakes by the intestine, kidney, and immune system are 10-14 g, 4g, and 2-4 g respectively while daily glutamine efflux from muscle is typically 8-10g. This results in a daily negative glutamine balance of minus 6 to 14g.

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