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Gut mucosal and plasma concentrations of glutamine: a comparison between two enriched enteral feeding solutions in critically ill patients

Jean-Charles Preiser[1], Daliana Peres-Bota[2], Pierre Eisendrath[3], Jean-Louis Vincent[2] and André Van Gossum[3]

1 Department of Intensive Care, Centre Hospitalier Universitaire de Liège, Belgium
2 Department of Intensive Care, Erasme University Hospital, Brussels, Belgium
3 Department of Gastroenterology, Erasme University Hospital, Brussels, Belgium

author email corresponding author email

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Abstract

Background

Addition of glutamine to enteral nutrition formulas is consistently associated with a significant decrease in septic morbidity in critically ill patients, possibly related to the attenuation of gut dysfunction. This pilot study was undertaken to compare the effects of enteral administration of two glutamine-enriched formulas containing either additional free glutamine or glutamine-rich proteins, with a standard solution on plasma and mucosal concentrations of glutamine in patients admitted in the Department of Intensive Care.

Methods

Following randomization, glutamine concentration was determined in endoscopically sampled duodenal biopsies and plasma, before and after a 7-day period of continuous administration of the designated solution.

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Results

The mucosal concentration of glutamine increased in the duodenal biopsies sampled from patients randomized to the solution containing the glutamine-rich proteins (from 3.6 ± 2.2 to 6.7 ± 5.2 micro-mol/g protein), but not from the others. There were no differences between the 3 groups in the plasma concentrations of glutamine, which remained stable over time.

Conclusion

The source of supplemental glutamine can influence gut mucosal glutamine concentrations, suggesting differences in its availability or utilization.

Background

Addition of glutamine to the nutritional support provided to critically ill patients has been suggested, namely to prevent gut dysfunction and subsequent multiple organ failure. The beneficial effects of glutamine supplementation to critically ill patients have been shown in at least two controlled studies [1,2], where patients randomized to a glutamine-enriched regimen had improved long-term survival [1] and reduced septic morbidity [2]. Although incompletely elucidated, the beneficial effects of these enriched solutions may have been related to the intestinal effects of glutamine. Reported intestinal effects of glutamine include the maintenance of gut barrier function, intestinal cell proliferation and differentiation, increased DNA and protein content and synthesis, and decreased production of pro-inflammatory cytokines [3-9]. The intestinal extraction rate of glutamine is higher than other amino acids [10,11].

The enteral route is preferred for nutritional support in critically ill patients [12]. In addition, the gut barrier function is better preserved when glutamine is supplied on the apical rather than the basolateral side of the enterocyte [13]. Therefore, the enrichment of the glutamine content of enteral feeding solutions is a logical and attractive therapeutic approach. New feeding formulas including supplemental glutamine (13–15 g/L) have been marketed recently. Glutamine is added in its free (unbound) form immediately before use of the solution, or is already present in the vegetal proteins incorporated in the solution.

This pilot study compared the effects of these solutions on the gut and plasma concentrations of glutamine, in order to select one for future studies on gut functional parameters.

Methods

This prospective, randomized, single-blind, placebo-controlled, pilot study enrolled adult patients referred to the Department of Intensive Care of the Erasme University Hospital. The hospital ethic's committee approved the study and signed consent was obtained from the patients' next-of-kin. The inclusion criteria consisted of a loss of consciousness and a reasonable expectation of at least 7-days' requirement for nutritional support and survival. Exclusion criteria consisted of any contra-indication to naso-gastric tubing, eso-gastro-duodenal endoscopy, duodenal biopsy (prothrombin time < 60% and/or platelet count < 100,000/mm^3) or the absence of signed informed consent.

At the time of inclusion, primary diagnosis and usual demographic parameters were recorded. Arterial blood samples were drawn at inclusion, centrifuged (3000 rpm for 10 min) and stored (-80°C) for the determination of plasma glutamine concentration. After intravenous infusion of butylscopolamine (40 mg), an oeso-gastro-duodenal endoscopy was performed (Olympus, PCF10, Tokyo, Japan), and 8 duodenal biopsies were sampled. The samples were kept in dry tubes at -80°C.

Patients were then randomized using a computerized random number table and sealed envelopes to receive the control solution (Nutrison Standard®, Nutricia, Bornem, Belgium), the free glutamine-enriched solution (Alitraq®, Ross-Abbott, Columbus, OH), or the solution containing glutamine from wheat-derived proteins (Stresson®, Nutricia, Bornem, Belgium). The solutions were kindly provided by their respective manufacturers. The composition of the solutions is detailed in

the table 1.

Table 1. Composition of the formulas

The solutions were continuously administered at a rate of 30 mL/h (720 mL/day) from day 0 to day 1, and at a rate of 60 mL/h (1440 mL/day) from day 1 to day 7, using a peristaltic pump. Gastric residues were checked once daily and the administration was interrupted for 4 hours if it was higher than 300 mL, and a pro-kinetic agent (Cisapride, Prepulsid®, Janssen, Beerse, Belgium) was then prescribed. In the case of diarrhea, the administration rate was slowed by half and an anti-diarrheal medication (Loperamide, Imodium®, Janssen) was administered. The patients were dropped from the study if they recovered the ability to eat before the end of the 7-day period. Plasma and duodenal samples were taken on day 7, four hours after administration of the feeding solution was stopped. Patient outcome was followed until ICU discharge.

For determination of plasma glutamine, blood was centrifuged (3000 rpm for 10 minutes) and the plasma was stored at -70°C. The duodenal biopsies were immediately frozen at -70°C. Once defrosted, the duodenal tissue was homogenized. Determination of glutamine concentration by selected ion monitoring quantification by gas chromatography/mass spectrometry (GCMS), using HFBA-glutamine [14].

Statistical analysis included an analysis of variance for repeated measures and a Student's *t*-test for comparison of the biochemical parameters between day 7 and baseline. A p value < 0.05 was considered as significant. Results are expressed as mean ± standard deviation (SD).

Results

This study was performed over an 8-month period. A total of 12 patients were eligible, of whom two died and one recovered the ability to eat during the study period. The characteristics of the 9 remaining patients are shown in Table 2. Mean age was 57 ± 11 years.

Table 2. Characteristics of the patients

Over the 7-day study period, the patients actually received 80–90% of the prescribed amount of their designated solution, i.e., Nutrison Standard (7600 ± 2447 mL), AlitraQ (8430 ± 217 mL), or Stresson (8433 ± 1100 mL). The total amounts of glutamine received were 30.4 ± 9.8 g, 129.8 ± 3.3 g and 109.6 ± 15.4 g for Nutrison Standard, AlitraQ and Stresson, respectively.

Plasma glutamine concentrations (Fig 1, upper panel) increased slightly from 322 ± 84 µmol/L at baseline to 389 ± 134 µmol/L (NS). There was no significant difference in the time course of the plasma glutamine concentration between the groups.

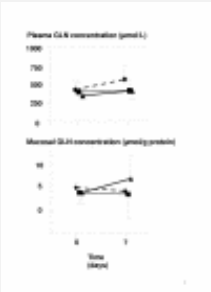

Figure 1. Concentrations of glutamine (mean ± SD) in samples drawn from patients randomized to Nutrison Standard (broken line, diamonds), Alitraq (dotted line, squares) or Stresson (continuous line, triangles). The samples were taken before (day 0) and after (day 7) administration of the designated formula.

In each patient randomized to "Stresson", mucosal glutamine concentrations increased to reach 1.3–2.0 times the baseline value at the end of the 7-day period. Hence, the values of mucosal concentrations of glutamine increased from 3.86 ± 1.37 to 4.71 ± 3.25 µmol/g protein in the "Stresson" group. There was no change in the other groups (Fig 1, lower panel).

Discussion

This pilot study suggests that the mucosal glutamine concentration was increased after administration of an enteral feeding solution containing glutamine-rich proteins but not additional free glutamine.

The duodenal samples were taken approximately 20–30 cm distally to the tip of the naso-gastric catheter, as in a previous study of enteral glutamine absorption in volunteers [15]. The discontinuation of the administration of the enteral solution four hours before the second duodenal sampling may represent a limitation to the interpretation of the results. However, this delay was the shortest possible to allow appropriate viewing and sampling of a duodenal biopsy, especially in this patient population in whom gastric emptying is often delayed.

Three studies have investigated the effects of glutamine-enriched enteral solutions in critically ill patients [2,16,17]. The solutions used in these studies were enriched with free glutamine. In the two studies using AlitraQ [2,16], as in the present one, the plasma concentrations of glutamine in the samples drawn were not increased after 7 days, probably because glutamine is rapidly metabolized. The baseline glutamine concentrations measured in the present study were in the same range as previously reported in critically ill patients [2,16,18]. In volunteers, the peak post-absorptive plasma glutamine concentration was higher after ingestion of glutamine in its free form than protein-bound [19], while the splanchnic extraction was similar [10]. In contrast, our data indicate that the mucosal concentration of glutamine can be influenced by the source of glutamine. However, an increase in the mucosal concentration may indicate an enhanced availability or a reduced utilization of glutamine, but provides no information about the concentration of glutamine in different cell types. Importantly, the absorption of peptides can be better than that of free amino-acids [20].

A limitation of this pilot study lies on the small size of the study population, which does not allow statistical analysis. However, these data could be of interest for the selection of an enteral formula for future studies on the effects of glutamine on gut physiology.

In conclusion, the data presented here suggest that the source of glutamine in enteral formulas can influence its metabolism. Further studies are required to assess whether this can translate into an improvement in intestinal function and a clinical benefit.

Competing interests

None declared

Authors' contributions

JCP, DBP and JLV collected and analysed the data. PE and AVG performed the endoscopies and biopsies.

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