**L-Glutamine**

*Oral glutamine to prevent chemotherapy induced stomatitis: A pilot study*

Keith M. Skubitz and Peter M. Anderson

a Departments of Medicine and Pediatrics, the University of Minnesota Medical School, Minneapolis, Minnesota, USA
b Masonic Center, Minneapolis, Minnesota, USA

*Journal of Laboratory and Clinical Medicine, Volume 127, Issue 2, February 1996, Pages 223-228*

**Abstract**

Mucositis is a common toxicity of cancer chemotherapy. Glutamine appears to be the major energy source for intestinal epithelium, and animal studies have suggested that dietary supplementation with glutamine may protect the gut from both radiation and chemotherapy. Patients experiencing stomatitis after a course of chemotherapy were offered the opportunity to enter the current study if no clinical parameters precluded receiving the same chemotherapy doses during the next course of treatment. Patients received the same chemotherapy regimen as during the previous treatment but in addition received a suspension of L-glutamine, 4 gm swish and swallow twice a day, from day 1 of chemotherapy for 28 days or for 4 days past the resolution of any post-chemotherapy mucositis. Twelve patients receiving doxorubicin, 1 receiving etoposide, and 1 receiving ifosfamide, etoposide, and carboplatinum were entered into the study. The maximum grade (CALGB criteria) of mucositis decreased in 12 of 14 patients with glutamine supplementation (median score 2A vs 0.5, p < 0.001). Similarly, after glutamine supplementation, the total number of days of mucositis was decreased in 13 of 14 patients (2.7 ± 0.8 (mean ± SEM) vs 9.9 ± 1.1, p ≥ 0.001). Thirteen of the 14 patients felt that the mucositis was less severe with the addition of glutamine. No change in the nadir neutrophil count was noted with glutamine, and no toxicity of glutamine was observed. We conclude that oral supplementation with glutamine can significantly decrease the severity of chemotherapy-induced stomatitis, an important cause of morbidity in the treatment of patients with cancer. Glutamine supplementation in patients receiving therapy for cancer warrants further study.

1. Supported in part by the Minnesota Medical Foundation (CO15–91) and by the Vikings Children's Fund.

Glutamine and the preservation of gut integrity
R. R. W. J. van der Hulst MD, M. F. von Meyenfeldt MD, N. E. P. Deutz MD, P. B. Soeters MD, Prof, R. J. M. Brummer MD, B. K. von Kreel PhD and J. W. Arends MD, Prof

a Department of Surgery, Academisch Ziekenhuis, P.O. Box 5800, 6202 AZ, Maastricht, the Netherlands
b Department of Gastroenterology, Academisch Ziekenhuis, P.O. Box 5800, 6202 AZ, Maastricht, the Netherlands
c Department of Clinical Chemistry, Academisch Ziekenhuis, P.O. Box 5800, 6202 AZ, Maastricht, the Netherlands
d Department of Pathology, Academisch Ziekenhuis, P.O. Box 5800, 6202 AZ, Maastricht, the Netherlands

The Lancet, Volume 341, Issue 8857, 29 May 1993, Pages 1363-1365

Abstract

Parenteral glutamine dipeptide improves nitrogen balance in postoperative patients on total parenteral nutrition (TPM). Animal studies show that the structure and function of the gut is preserved by glutamine. It is not known if this is the case in human beings. 20 patients admitted to hospital for total parenteral nutrition were randomly allocated to receive parenteral nutrition enriched with glycyl-\textit{L}-\textit{glutamine} (Gln TPN), or standard parenteral nutrition (STPN). Mucosal biopsy specimens were taken from the second part of the duodenum before starting parenteral nutrition, and after two weeks. The ratio between the urine concentrations of lactulose and mannitol after enteral administration was used to measure intestinal permeability. After two weeks of parenteral nutrition in the GlnTPN group, intestinal permeability was unchanged, whereas permeability in the STPN group increased. Villus height was unaltered in the GlnTPN group but in the STPN group it decreased. The addition of glutamine to parenteral nutrition prevents deterioration of gut permeability and preserves mucosal structure.
Glutamine and macrophage function

Claire Wallace and David Keast

University of Western Australia, Department of Microbiology, QEII Medical Centre, Nedlands, Western
Australia, Australia.

Metabolism, Volume 41, Issue 9, September 1992, Pages 1016-1020

Abstract

The effects of glutamine concentration on the phagocytosis of an opsonized antigen, the synthesis of RNA, and the production of interleukin-1 (IL-1) by macrophages were investigated in vitro. A minimum of 0.125 mmol/L glutamine was required for a significant increase in phagocytosis of opsonized sheep erythrocytes, compared with that recorded for macrophages cultured in the absence of glutamine. The synthesis of 3H-RNA by macrophages also required 0.125 mmol/L glutamine in the culture medium before it was significantly increased above the levels of control cultures. A minimum of 0.03 mmol/L glutamine was required for the induction of significant levels of IL-1 by lipopolysaccharide (LPS)-stimulated macrophages. Therefore, recent findings suggesting that decreases in plasma glutamine resulting from major burn injury, sepsis, trauma, and surgery may be partly responsible for the associated impairment of immune function now have a basis in both phagocytosis and in modulation of the synthesis of IL-1 (the first cytokine of the interleukin cascade that leads to specific immunity) by macrophages, in addition to the previously established dependency of lymphocytes on external sources of glutamine for their replication.
EFFECT OF PARENTERAL GLUTAMINE PEPTIDE SUPPLEMENTS ON MUSCLE GLUTAMINE LOSS AND NITROGEN BALANCE AFTER MAJOR SURGERY


a Institute for Biological Chemistry and Nutrition, University of Hohenheim, Stuttgart, Federal Republic of Germany
b Department of Anaesthesia and Intensive Care, University of Münster, FRG

The Lancet, Volume 333, Issue 8632, 4 February 1989, Pages 231-233

Abstract

Twelve patients admitted for elective resection of carcinoma of colon or rectum were allocated at random to experimental and control groups (six in each) and received a total parenteral nutrition regimen providing 230 mg N/kg and 166 KJ/kg daily over the first 5 postoperative days. In the experimental group the parenteral fluid was supplemented with a synthetic glutamine-containing dipeptide, L-alanyl-L-glutamine (54 mg peptide-N/kg per day) and the control group received corresponding amounts of alanine-N and glycine-N. On each postoperative day nitrogen balance was better in the experimental group; mean daily nitrogen balance with alanyl-glutamine was -1·5 (SE 0·4) g N/day and with the control solution -3·6 (0·2) g N/day. The cumulative nitrogen balances on the fifth postoperative day were -7·1 (2·2) and -18·1 (1·7) g N, respectively. With the peptide-containing solution intramuscular glutamine concentration remained close to the preoperative value whereas with the control solution it decreased from 19·7 (SE 0·9) to 12·0 (0·6) mmol/l intracellular water.
The effect of **glutamine** on prevention of glucocorticoid-induced skeletal muscle atrophy is associated with myostatin suppression


Division of Endocrinology, Metabolism, and Molecular Medicine, Charles R Drew University of Medicine and Science, Los Angeles, CA 90059, USA

*Metabolism, Volume 55, Issue 9, September 2006, Pages 1239-1247*

**Abstract**

Excess glucocorticoids (GCs) cause muscle atrophy. Glucocorticoid-induced muscle atrophy is associated with increased intramuscular myostatin expression. Myostatin is a negative regulator of skeletal muscle mass. **Glutamine** prevents GC-induced muscle atrophy. We hypothesized that **glutamine** effect on reversal of GC-induced muscle atrophy is mediated in part by suppression of myostatin. We administered daily to male Sprague-Dawley rats dexamethasone, dexamethasone plus **glutamine**, saline or saline plus **glutamine**, all pair-fed. Animals were killed on day 5. Body weight and weights of gastrocnemius muscles were measured. Myostatin expression was measured by Northern and Western blots, and was compared with glyceraldehyde-3-phosphate dehydrogenase. Myoblast C2C12 cells were exposed to dexamethasone, or dexamethasone and **glutamine**, and their myostatin messenger RNA and protein expression compared with glyceraldehyde-3-phosphate dehydrogenase. Myostatin promoter activity was measured by luciferase activity of transfected C2C12 cells, grown in medium including dexamethasone, or dexamethasone plus **glutamine**. Rats that received dexamethasone showed significant body and muscle weight loss accompanied by an increase in intramuscular myostatin expression, compared with their saline-treated controls. Pair-fed rats given dexamethasone plus **glutamine** had significantly less reduction in body and muscle weights and lower myostatin expression when compared with those treated with dexamethasone alone. In C2C12 myoblast cells, addition of **glutamine** to dexamethasone prevented the hyperexpression of myostatin induced by dexamethasone. Myostatin promoter activity increased in cells exposed to dexamethasone, but this increase was partially blocked by addition of the **glutamine**. Administration of **glutamine** partially prevents GC-induced myostatin expression and muscle atrophy, providing a potential mechanism for the prevention of muscle atrophy induced by glucocorticoids.
Double-blinded, placebo-controlled trial on intravenous L-alanyl-L-glutamine in the incidence of oral mucositis following chemoradiotherapy in patients with head-and-neck cancer

The present work was, in part, presented and awarded at the 17th International Symposium of the Multinational Association of Supportive Care in Cancer, Geneva, Switzerland on 2005; and in the First International Congress of the Latin American and Caribbean Society of Oncology, Buenos Aires, Argentina on 2005.

Leandro C.A. Cerchietti M.D, Alfredo H. Navigante M.D., Ph.D., Maribel A. Lutteral M.D, Monica A. Castro M.D, Ricardo Kirchuk M.D., Marcelo Bonomi M.D., Maria Esther Cabalar M.D, Berta Roth M.D, Graciela Negretti Pharm.D, Beatriz Sheinker Pharm.D and Patricia Uchima Pharm.D.

§Pharmacy Department, Instituto de Oncologia Angel H. Roffo, Universidad de Buenos Aires, Buenos Aires, Argentina
†Internal Medicine Department, Instituto de Oncologia Angel H. Roffo, Universidad de Buenos Aires, Buenos Aires, Argentina
‡Radiotherapy Department, Instituto de Oncologia Angel H. Roffo, Universidad de Buenos Aires, Buenos Aires, Argentina
Translational Research Unit, Instituto de Oncologia Angel H. Roffo, Universidad de Buenos Aires, Buenos Aires, Argentina

International Journal of Radiation Oncology *Biology* Physics, Volume 65, Issue 5, 1 August 2006, Pages 1330-1337

Summary

Purpose: We performed this double-blinded, placebo-controlled study to determine the safety and efficacy of L-alanyl-L-glutamine in the prevention of mucositis in patients with head-and-neck cancer.

Results: Fourteen patients received L-alanyl-L-glutamine and 15 received placebo. Mucositis was assessed by the Objective Mucositis Score (OMS) and the World Health Organization (WHO) grading system. There was a significant difference in incidence of mucositis developed in patients receiving placebo compared with those who received L-alanyl-L-glutamine ($p = 0.035$). The number of patients with severe objective mucositis (OMS >1.49) was higher in the placebo group compared with the L-alanyl-L-glutamine group (67% vs. 14%, $p = 0.007$). L-alanyl-L-glutamine patients experienced less pain (three highest Numeric Rating Scale scores of 1.3/10 vs. 6.3/10 respectively, $p = 0.008$) and need for feeding tubes (14% vs. 60% respectively, $p = 0.020$) compared with placebo patients. No adverse effects related to the drug or the infusions were noted in either group.

Conclusion: For patients with head-and-neck cancer receiving CRT, intravenous L-alanyl-L-glutamine may be an effective preventive measure to decrease the severity of mucositis.

Collaborators to this study: Professor Dr. Roberto Pradier, Dr. Raul Giglio, Mrs. Viviana Candlish, Mrs. Elsa Gomez, RN (all from the Instituto Angel Roffo), Mr. Raul Honig, Dr. Graciela Merino, and Dr. Mario Perman.
Glutamine protects articular chondrocytes from heat stress and NO-induced apoptosis with HSP70 expression


†Department of Orthopaedics, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan
‡Department of Microbiology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan

Osteoarthritis and Cartilage, Volume 14, Issue 6, June 2006, Pages 545-553

Summary

Objective

To investigate the effect of L-glutamine (Gln) on stress responses of chondrocytes exposed to heat stress or nitric oxide (NO).

Results

Gln demonstrated dose-dependent enhancing effect on stress-mediated induction of HSP70, while in the absence of any stress HSP70 was not induced by Gln alone. After heating or SNP loading, chondrocytes showed severe reduction in viability, while the cytotoxic outcome was almost completely abrogated by conditioning with Gln. The protective effect of Gln was significantly blocked by Que that effectively suppressed stress-induced HSP70 expression in chondrocytes. The Gln also rendered chondrocytes unsusceptible to NO-induced apoptosis that was frequently seen in SNP-treated culture.

Conclusion

This study demonstrated that the treatment of chondrocytes with Gln protected the cells from heat stress and NO-induced apoptosis. These chondroprotective effects of Gln may be mediated by HSP70.

Supported by a Grant-in-Aid for Scientific Research (No. 17390419) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.