Original - Opinion

Pharmaconutrition: The End of an Era?

Farmaconutrición: ¿El fin de una era?

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Resumen

La farmaconutrición ha sido un área interesante de investigación en cuidados intensivos. Al inicio, los ensayos con dosis altas de glutamina o selenio informaron resultados alentadores, pero a menudo no tuvieron el poder estadístico suficiente. No obstante, las revisiones sistemáticas y los meta-análisis realizados hasta 2015 encontraron reducciones significativas en las tasas de infección y/o mortalidad de los enfermos en estado crítico. Sin embargo, los meta-análisis posteriores no han mostrado mejoría en los resultados clínicos. En consecuencia, las directrices actuales no hacen ninguna recomendación para el tratamiento con altas dosis de nutrientes. ¿Es éste el fin de la era de la farmaconutrición? No necesariamente! Es hora de volver a lo básico y adoptar un enfoque más farmacéutico clasificando los farmaconutrientes como medicamentos; establecer mejor su estabilidad, farmacología, toxicología y seguridad *in vitro* e *in vivo*, y luego determinar las interacciones fármaco-fármaco o fármaco-nutriente antes de proceder a los estudios de farmacocinética y farmacodinámica. Además, debemos investigar la verdadera naturaleza de la deficiencia de nutrientes en las personas gravemente enfermas. ¿Cuál es la diferencia entre una deficiencia en una población con cifras de Selenio naturalmente bajas y una población con cifras "normales"? ¿Qué sucede con una dosis alta de un dipéptido de glutamina sintética en un paciente con deficiencia de nutrientes, o con insuficiencia orgánica, y qué sucede con el exceso de farmaconutriente que no es utilizado por un paciente en buen estado nutricional? Estas preguntas básicas no fueron investigadas en forma adecuada en el pasado, donde se administraron dosis suprafisiológicas fijas a todos los pacientes, de los cuales una proporción significativa no tenía deficiencia de nutrientes. Cuando se han generado datos de calidad sobre estos parámetros preclínicos, podemos determinar con mayor precisión las indicaciones, la posología óptima y las mejores guías para nuevas investigaciones clínicas e iniciar una nueva era de la Nutrición Farmacéutica.

Palabras clave: farmaconutrición, glutamina/dipéptidos de glutamina, selenio, cuidados intensivos.

Summary

Pharmaconutrition has been an interesting area of research in critical care. Initially, trials with high dose glutamine and/or selenium reported promising outcomes but were often underpowered. Notwithstanding, systematic reviews and meta-analyses conducted up to 2015 found significant reductions in infection and/or mortality rates in the critically ill. However, later meta- analyses have not shown improvement in clinical outcomes. Consequently, current guidelines do not make any recommendations for high dose nutrient therapy. Is this the end of the pharmaconutrition era? Not necessarily! It is time to return to basics and adopt a more pharmaceutical approach by categorising pharmaconutrients as drugs; better establish their *in vitro* and i*n vivo* stability, pharmacology, toxicology and safety, then determine any drug-drug or drug-nutrient interactions before proceeding to pharmacokinetics and pharmacodynamics studies. We must additionally investigate the true nature of nutrient deficiency in the critically ill. How different is a deficiency in a naturally low Selenium population versus a 'normal' population? What happens to a high dose of a synthetic glutamine dipeptide in a nutrient deficient patient, or one with organ failure, and what happens to the excess pharmaconutrient that is not utilised by a nutritionally replete patient?

These basic questions were inadequately investigated in the past, where fixed supraphysiological doses were administered to all patients, a significant proportion of whom were not nutrient deficient. When quality data have been generated on these preclinical parameters, we can more accurately determine indications, optimum posology and better guidelines for new clinical investigations and begin a new era of Pharmaceutical Nutrition.

Keywords: Pharmaconutrition; Glutamine dipeptides; Selenium, Critical care.

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INTRODUCTION

Glutamine (GLN), Arginine (ARG) and/or Selenium (Se) administered as pharmacologically high dosage (HD) pharmaconutrition therapy has been an interesting area of nutrition research in the last three decades. Many small, single centre, randomized controlled trials (RCT) reported promising outcomes but were often underpowered[1]. Notwithstanding, most systematic reviews and meta-analyses conducted up to 2015 found significant reductions in infection and/or mortality rates when HD GLN as alanyl-L-glutamine dipeptide (DIPEP) and/or Se (as selenite) were administered to the critically ill[2]. However, following publication of larger, negative RCT [3,4,5], later meta- analyses have concluded that HD Se, or GLN, do not improve clinical outcomes in critical care[6]. Consequently, current evidence does not appear to support the concept of pharmaconutrition and clinical guidelines from the major professional societies do not advocate HD nutrient therapy ([7,8]).

So, is this the end of the era of pharmaconutrition in the critically ill? NOT NECESSARILY!

BACKGROUND

The immune-focused physiological status of the body favours breakdown of structural protein rather than increased use of exogenous nitrogen sources. L-Glutamine (GLN), regarded as 'conditionally essential', is the most abundant amino acid (AA) in the bloodstream. As a key respiratory substrate for rapidly dividing cells such as enterocytes, GLN increases phagocytic activities and plays a major role in providing energy for immune cells. It is also a precursor of ARG through the citrulline-arginine pathway. In sepsis, plasma AA levels decrease due to synthesis of immune related proteins and production of glucose through gluconeogenesis in the liver. Plasma ARG levels decrease as the AA is utilised for conversion into nitric oxide (NO) and for participation in the urea cycle to detoxify ammonia released from metabolism of other AA.

The sulphur-containing amino acids (SCAA) and their major metabolites have a pivotal role on cellular antioxidant systems and attenuate proinflammatory symptoms. In a very elegant research presented at Parenteral and Enteral Nutrition Society of Asia PENSA 2018, Kwang Suk Ko at Ewha Womans University, Korea [9] added SCAA to prohibitin1- deficient macrophages followed by lipopolysaccharide (LPS) activation. Prohibitin1 (a mitochondrial chaperone and hepatic tumour suppressor gene) aggravated the inflammatory responses of macrophages, whereas SCAA attenuated those adverse effects compared to controls. As GLN and SCAA are substrates for the body's major antioxidant, Glutathione (GSH), these data provide increasing evidence that supplementation could be helpful to septic patients through this synergistic relationship, that needs further exploration.

GLUTAMINE AND INFLAMMATION

GLN is important for intestinal metabolism, especially following stress, and GLN diets improve intestinal morphology and function. As a result, GLN has long been studied as a promising agent to preserve intestinal function and recovery during injury or stress. Although the mechanism by which GLN exerts its beneficial effects is not fully understood, it appears to be correlated with the improvement of gut barrier function, oxidant injury, and inhibition of inflammatory processes, such as NF-κB activation and TNF-α production. Many investigators have reported that GLN therapy improves outcomes of experimental colitis models, including the research of Hern Ku Lee and colleagues at Chonbuk National University Medical School, Korea, that provides evidence that GLN can attenuate inflammatory diseases such as sepsis, asthma, late anaphylaxis, dermatitis, and colitis in mice at a dose of 20mg/mouse[10] . They have shown that GLN increases extracellular signal-regulated kinase (ERK) MAPK activity via activation of the pathway involving Ca^{2+}/Ras/c-Raf/MEK (ERK cascade). ERK phosphorylates protein phosphatase MAPK phosphatase-1 (MKP-1) on two carboxyl-terminal serine residues - serine 359 and serine 364, which enhances MKP-1 stabilization, resulting in the early induction of MKP-1 to deactivate cPLA2 either by dephosphorylating p38 mitogen activated protein kinase (MAPK) a major upstream pathway for cPLA2 phosphorylation or by directly dephosphorylating cPLA2 due to enhanced physical interaction between GLN-induced MKP-1 and cPLA2. These data suggest that GLN functions as an endogenous cPLA2 inhibitor via MKP-1 induction, which by reactivation of p38 and cPLA2 results in suppression of many cardinal inflammatory mediators including reactive oxygen species.

GLUTAMINE DEFICIENCY OR HYPOGLUTAMINAEMIA

GLN pioneer, Professor Jan Wernerman, (Karolinska University Hospital, Sweden) has coined the term 'hypo-

glutaminaemia' in place of 'deficiency' to better define the depleted levels of GLN in the critically ill, during periods of systemic inflammation and sepsis (normal plasma GLN value: 420 – 930 μmol/L). The prevalence of hypoglutaminaemia, estimated at 31%-65% of all patients admitted to the ICU[11] has important implications. Certain adverse clinical conditions and symptoms are more frequently associated with low plasma GLN levels and can potentially be regarded as clinical indicators of deficiency. These include severity of illness (APACHE II scores), presence of infections (measured by CRP, IL-6 amongst others), higher age, lower albumin levels and non-elective ICU admissions. GLN levels are significantly lower in non-elective patients with infection (P=0.01)[11] . Low plasma GLN levels have correlated with longer ICU and hospital length of stay (LOS), as well as improved 6-month mortality[12,13] and have been proposed as an independent predictor of mortality [14].

GLUTAMINE SUPPLEMENTATION IN THE CRITICALLY ILL

Historically, the small single-centre, RCT that showed clinical benefit with GLN supplementation, mostly used aseptically prepared solutions of pure L-GLN[15]. Initial meta-analyses, of these trials concluded that HD GLN supplementation led to significant reduction in hospital infections, mortality, ICU and overall hospital LOS. However, whilst the Scandinavian study[16] reported decreased mortality during ICU stay it was not sustained at 6 months. Nevertheless, at discharge, hypoglutaminaemia was not very prevalent and it was not a predictor for unfavourable outcome. In contrast the early research by Griffiths et al did observe decreased mortality at 6 months, but it is notable that restoration of muscle GLN levels took over 6 months[17]. This raises the question whether it would be advantageous to prolong GLN therapy post ICU.

Conversely, high GLN levels from supplementation with DIPEP have been associated with adverse outcomes. Two large multi-centre RCT assessing the efficacy of antioxidant cocktails, including DIPEP plus Se in ventilated ICU patients, failed to reproduce those early positive results. The REDOXS[3] multicentre trial which included 1223 ventilated patients randomised from 40 ICUs showed increased mortality in those receiving HD DIPEP. The MetaPlus trial[4] of 14 ICUs, which randomized 301 ventilated ICU patients to DIPEP -enriched EN versus an isocaloric diet, noted increased 6-month mortality in the GLN DIPEP-supplemented group. So, Why these apparent differences in outcome between the early and later studies?

There is clearly a need to further investigate the many questions that still remain unanswered, but before commencing better designed clinical trials it is time to return to basics and adopt a more pharmaceutical approach. Synthetic pharmaconutrients such as dipeptides must be categorised and investigated as drugs. It is essential to establish the *in vitro* and i*n vivo* stability of these pharmaconutrients, their pharmacology, toxicology and safety from animal models, the preferred method of administration and drug response curves at very high dosages. Drug-drug or drug-nutrient interactions during use must also be determined before proceeding to human pharmacokinetics and pharmacodynamics studies.

In hindsight, these basic pharmaceutical and metabolic protocols were inadequately investigated before initiating past clinical studies, such as the REDOXS, Metaplus or SISPCT trial[3,4,5]. The REDOXS trial also had a randomization problem, where fixed supraphysiological doses of DIPEP were administered to all patients, irrespective of weight, age or sex - a significant proportion of whom did not have hypoglutaminaemia (nor were necessarily 'hyposelenaemic'). The nutrition support regimen was also inadequate: energy intakes of most patients were very low, the study group received much higher protein from an unbalanced AA mixture, which the patient's already compromised livers had to oxidize, whereas N intake was much lower in the controls. It is still not clear what caused the unfavourable outcome for patients in the DIPEP supplemented arm, but the subgroup of North American patients, for which plasma GLN concentrations were available, showed that high plasma concentrations were not the reason. It is noteworthy that both GLN and Alanine (ALA) are involved in gluconeogenesis but to date no-one has reported or commented upon the equally high ALA levels resulting from DIPEP supplementation.

Since the major clinical nutrition societies currently recommend against routine HD supplementation until additional data is available, larger, better designed multicentre trials are needed. Werneman points out that the hypothesis that Gln supplementation could be beneficial for patients with hypoglutaminemia at time of ICU admission has never been properly tested. In spite of a multitude of clinical trails, no study has verified whether or not hypoglutaminaemia was prevalent on admission and no study has verified that supplementation can convert hypoglutaminaemia into normoglutaminaemia. In long stay ICU patients the efflux of GLN from muscle

tissue is still high but this metabolic process appears not to be inhibited by exogenous GLN. A higher plasma GLN concentration may be advantageous for the utilization of GLN in liver and gut. Even though the reported prevalence of high plasma GLN (6.7% to 14%) is lower than the deficiency prevalence, it is becoming increasingly apparent that the association of circulating plasma GLN levels with mortality seems to follow a U-shaped curve[18]. High GLN seems to be more common in liver disease and to correlate with degree of liver failure[16].

Consequently, we must establish the true nature of deficiencies/anaemias of pharmaconutrients, such as GLN or Se, in the critically ill. How, Where and Why does it occur? Do plasma levels and other surrogate markers reflect a true deficiency or 'anaemia'? How different is a nutrient deficiency in a population with naturally low levels versus a 'normal' population? What exactly happens to a high dose of a synthetic DIPEP in a nutrient deficient critically ill patient or one with organ failure, and what happens to the excess pharmaconutrient that is not utilised by a nutritionally replete patient? [19]

IN SUMMARY

Without further safety and efficacy evidence HD pharmaconutrients should not be given to patients who are not adequately fed. On the other hand, supplementation at 'nutritional' dosages to patients with hypoglutaminemia may be beneficial without any safety concerns, when given as a part of a full nutrition support regimen. Until such time that plasma determinations can be performed accurately and routinely at the bedside, attention should be given to identification of at-risk patients[6] (10) and clinicians must rely on clinical indicators to identify those individuals before treatment is implemented.

When quality data have been generated on all these preclinical parameters, then we can conduct clinical research to confirm the validity of hypotheses, more accurately determine indications, optimum posology and develop better guidelines for new clinical investigations into potential benefits of HD pharmaconutrient therapy. Understanding the functions and metabolism of individual pharmaconutrients could promise better prognosis for critically ill, immune compromised patients who are fighting invading organisms trying to overwhelm their normal immune processes.

This is certainly NOT the end of an era but the beginning of a new exciting Era of Pharmaceutical Nutrition.

Conflicts of interest

None.

Financial disclosures

None.

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