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Pharmaconutrition with Antioxidants in the Critically Ill

Is Selenium Monotherapy the Cornerstone of this Strategy?

This article explores the evolving paradigm of pharmaconutrition using antioxidant micronutrients, looking at the available evidence for antioxidant supplementation in the critically ill. In particular it discusses the protective mechanisms of action of selenite in critically ill SIRS patients and how selenium supplementation as a pharmaconutrient can be best applied.

Why are Antioxidants Required in the Critically Ill?

Critical illness is characterised by a significant redox imbalance, which leads to mitochondrial dysfunction, systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndromes (MODS). Although in the last few years there have been important developments in supportive techniques for use in intensive care units (ICUs) around the world, sepsis-related organ dysfunction remains the most common cause of death in the ICU (Galley, 2012). Over the last two decades, many observational studies have evaluated oxidative stress in the critically ill. Oxidative stress is defined as a state in which the levels of toxic reactive oxygen species (ROS) and reactive nitrogen oxide species (RNOS) overcome the endogenous antioxidant defenses of the host. In fact, during critical illness antioxidant capacity is drastically decreased due to an excessive production of ROS and RNOS. ROS activate the nuclear transcription factor kappa B (NF- κ B), which is one of the steps involved in amplifying SIRS (Manzanares and Hardy et al. 2012).

SIRS is associated with redistribution of micronutrients (vitamins and trace elements) from the circulating compartment to the interstitial compartment and different tissues, especially those involved in protein synthesis and immune cell proliferation. Trace elements escape to the interstitial compartment by capillary leakage, which is a distinctive characteristic of SIRS (Manzanares et al. 2009). Furthermore, low levels of trace elements may be explained by several other causes, such as losses through biological fluids and haemodilution, previous insufficient intake, low levels in enteral formulas and parenteral mixtures, and continuous renal replacement therapies (CRRTs) (Hardy et al. 2012). In this scenario, it is most likely that micronutrient status is always compromised during critical illness, despite standard micronutrient dietary intake.

What Does the Most Up-to-Date Evidence Show About Antioxidant Supplementation in the Critically Ill?

In 2005, for the first time, a meta-analysis demonstrated that antioxidants were associated with a significant reduction in ICU mortality (risk ratio [RR], 0.65; 95% confidence interval [CI], 0.44–0.97; $P=0.03$) (Heyland et al. 2005). The authors further demonstrated that daily doses of selenium (higher than 500 μ g) showed a tendency towards a decrease in mortality (RR, 0.52; 95% CI, 0.24–1.14; $P=0.10$). Four years later, the same Canadian group updated these results, showing that antioxidant supplementation was still associated with a significant reduction in mortality (RR, 0.76; 95% CI, 0.64, 0.91; $P=0.002$). Moreover, the specific effects of parenteral selenium on mortality were similar (RR, 0.84; 95% CI, 0.67, 1.05; $P=0.13$).

Most recently, an updated systematic review and metaanalysis, which aggregated 20 trials that had reported mortality as an outcome, concluded that combined antioxidant supplementation was associated with a significant reduction in mortality (RR, 0.82; 95% CI, 0.72–0.93; $P=0.002$) (Manzanares et al. 2012). Supplementation with antioxidant micronutrients showed a significant reduction in duration of mechanical ventilation (weighed mean difference, -0.67 days; 95% CI, -1.22, -0.13; $P=0.02$) and a trend towards a reduction in infections (RR, 0.88; 95% CI, 0.76, 1.02; $P=0.08$). However, it was not possible to demonstrate any significant overall effect on ICU or hospital length of stay (LOS). Of practical interest is the fact that antioxidant micronutrients were associated with a significant reduction in overall mortality among patients with higher risk of death (>10% mortality in control group) (RR, 0.79; 95% CI, 0.68, 0.92; $P=0.003$). This finding supports the notion that patients with more severe insults and higher mitochondrial dysfunction resulting from bioenergetic failure experience the largest depletion of antioxidants (Manzanares et al. 2012). These patients may therefore exhibit a greater clinical improvement with antioxidant supplementation than less sick patients.

When aggregated, selenium supplementation was specifically associated with a trend towards a reduction in mortality (RR, 0.89; 95% CI, 0.77–1.03; $P=0.12$). The seven selenium trials demonstrated a trend towards a reduction in infections (RR, 0.87; 95% CI, 0.74–1.02; $P=0.08$), whereas three of the trials that didn't use selenium demonstrated no effect on infections (RR, 1.10; 95% CI, 0.60–2.04; $P=0.75$). Thus, parenteral selenium monotherapy, administered as a loading dose followed by a continuous infusion, may be strongly recommended to reduce mortality and infections in critically ill SIRS patients (Hardy et al. 2012).

What do We Know About the Protective Mechanisms of Action of Selenite in Critically Ill SIRS Patients?

Although the optimal time to start antioxidant therapy has not yet been established, both experimental and clinical data support the concept that antioxidant micronutrients are more effective when initiated prior to injury or as early as possible after the insult. Selenium is an essential trace element with antioxidant, immunological, and anti-inflammatory properties. Selenium is essential for the activity of selenoenzymes such as

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selenoprotein P1, which may be protective against endothelial oxidant injury, and glutathione peroxidase, which belongs to the body's first line of antioxidant defense. Selenite is able to inhibit the activation of NF- κ B by controlling selenoprotein gene expression and thus down-regulating the synthesis of proinflammatory cytokines.

An intravenous loading dose of selenite given as bolus has a biphasic action, initially as a pro-oxidant and then as an antioxidant (Vincent JL et al. 2009; Manzanares et al. 2009). Furthermore, in a sheep model of severe sepsis, the bolus of sodium selenite was able to improve haemodynamics, delaying arterial hypotension, and improving cardiac index, with delayed hyperlactataemia, and fewer sepsis-induced microvascular alterations (Wang et al. 2010). Various clinical trials have successfully implemented the bolus plus continuous infusion protocol (Angstwurm et al. 2007; Manzanares et al. 2011), showing improvement in relevant clinical outcomes, especially mortality and infectious complications. Conversely, continuous high-dose selenite infusion, without the initial bolus, has been clinically ineffective (Forceville X et al. 2007).

What is the Current Concept of Pharmaconutrition?

The concept of pharmaconutritional supplementation in supraphysiological doses is quite different from the classical nutritional concept of nutrient replacement, which is designed to replenish losses and target restoration of normal function (Berger M 2012). Pharmaconutrition considers pharmaconutrients as drugs or nutraceuticals.

During critical illness, pharmaconutrition with antioxidant trace elements and vitamins, or both, is considered an attractive therapeutic strategy for ICU patients (Manzanares and Heyland 2012). Currently, the concept of pharmaconutrition is quite distinct from the concept of immunonutrition, whereby immune-modulating nutrients such as arginine, glutamine, and ω -3 fatty acids are combined together with macronutrients and are provided in so-called immune-enhancing diets (IEDs) by the enteral route. According to the pharmaconutrition concept, high dose pharmaconutrients should be provided separately from standard enteral or parenteral nutrition regimens (Manzanares and Heyland 2012) to ensure optimum delivery of the pharmaconutrients.

Selenium Supplementation as a Pharmaconutrient for the Critically Ill: When, How and How Much?

There is enough evidence in current literature to consider antioxidant cocktails and/or parenteral selenite supplementation as monotherapy in critically ill SIRS patients. The best antioxidant cocktail approach has not yet been determined. However, we know that initiating high-dose intravenous sodium selenite (1000–2000 μ g as a bolus over 30 minutes to two hours) immediately on admission to the ICU (within the first 24 hours), and thereafter as a continuous infusion at a daily dose between 500–1600 μ g for up to 10 to 14 days, is a novel and successful strategy in the critically ill. This concept of pharmaconutrition, using selenium as monotherapy, is quite distinct from the routine incorporation of selenium (and other micronutrients) in standard parenteral or enteral nutrition. High-dose sodium selenite should be supplemented in the most seriously ill ICU patients, including those with severe sepsis and septic shock. High-risk cardiac surgery patients may also benefit in the near future, but more evidence from on-going clinical trials is awaited before recommendations can be made for this patient population.

What is the Future for Antioxidant Micronutrient Supplementation for Intensive Care?

The largest randomised controlled trial on antioxidants in combination with high-dose glutamine supplementation has been the Reducing Deaths due to Oxidative Stress (REDOXS) Study, which is unpublished; but it seems to have failed to demonstrate any improvement on clinical outcomes in MODS patients. In this multicentre trial, more than 1,200 patients were enrolled to receive intravenous glutamine in combination with enteral or parenteral antioxidant cocktails, including vitamins C (1500 mg), E (500 mg), β -carotene (10 mg), zinc (20 mg), and selenium (300 μ g). Although this strategy was safe, it was unfortunately unable to demonstrate efficacy by improving relevant clinical outcomes, including ICU and 90 day survival, in critically ill SIRS patients.

How can we explain the unexpected REDOXS results regarding antioxidants supplementation? Perhaps the absence of an intravenous bolus of selenite as a loading dose inhibited stimulation of the protective effects of selenium as an anti-inflammatory strategy for ICU patients with organ failure. This could be considered as a methodological weakness. Furthermore, some patients received an insufficient daily dose of intravenous selenium. In fact, according to the recent metaanalysis on antioxidant micronutrients (Manzanares et al. 2012), a daily parenteral dose greater than 500 μ g is necessary for better clinical outcomes. Although some patients in the REDOXS protocol received 800 μ g of selenium, this was administered by either the enteral or the parenteral route, and we do not know enough about the pharmacokinetic profile of enterally administered selenium in SIRS patients. We suspect that enteral absorption in septic shock patients is unpredictable and these doses may have been insufficient.

Among the antioxidant micronutrient strategies, parenteral selenite should be the cornerstone of a pharmaconutrition approach for the critically ill. We believe, there is sufficient evidence to consider initiating high dose intravenous selenium therapy routinely in SIRS patients, immediately on admission to the ICU. Nonetheless, more research is needed to define the true role of pharmaconutrients in the prevention or treatment of cellular and tissue dysfunctions. A research strategy that combines basic investigations into the pharmacokinetic and pharmacodynamic profiles of pharmaconutrients, with well-powered prospective clinical trials for safety and efficacy, will clarify the future of pharmaconutrition in critical care medicine and clinical nutrition. This type of study would be able to further elucidate the best antioxidant micronutrient approach, including safety, tolerability, and feasibility of highdose antioxidants in ICU patients.

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