Commentary

Seleno-enzymes and seleno-compounds: the two faces of selenium

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Published: 13 December 2006
This article is online at http://ccforum.com/content/10/6/180

Critical Care 2006, **10:**180 (doi:10.1186/cc5109)

See related research by Berger *et al*., http://ccforum.com/content/10/5/R153

Abstract

Selenium protects cells and inhibits many inflammatory cell mechanisms through antioxidant seleno-enzymes. Immunity improvement is illustrated by the study of Berger and colleagues, with reduction of nosocomial pneumonia in burnt patients under multitrace-element supplementation. As seleno-compounds (especially sodium selenite) are pro-oxidant, however, administration above 800 μg/day may be dangerous in septic shock. Paradoxically, direct reversible pro-oxidative effects of seleno-compounds may also be beneficial for reduction of inflammation (genomic action, apoptosis), and may even be bactericidal or virucidal. These facts need to be further examined, as well as the possible dramatic drop of plasma selenoprotein P in septic shock and its role in endothelium protection.

Biological and medical advances in the area of selenium provide interest in selenium for both its antioxidant properties through seleno-enzyme incorporation, as illustrated in the previous issue of *Critical Care* [1], and its direct pro-oxidant toxic effect through seleno-compounds.

In intensive care, and especially in septic shock adjunctive therapy, there is a growing interest in the antioxidant role of selenium [2-5]. We know that there is a very low level of selenium in the human (20 mg for the whole body) but that a severe deficiency is lethal [6]. We also know that selenium plays a crucial role in antioxidant defense, as one selenium atom is absolutely required at the active site of all seleno-enzymes in the form of the 21-amino-acid selenocystein [6,7]. Mammals largely use seleno-enzymes for antioxidant purposes, whereas bacteria do not. The seleno-enzymes are ubiquitous in mammal cells and have two main roles. Firstly, the seleno-enzymes protect cell components against oxidation: membranes, enzymes, proteins, and DNA. Secondly, seleno-enzymes inhibit proinflammatory cell metabolisms by reducing the peroxide tone of intracellular water (NF-κB, acid arachidonic and complement cascades, and mitochondria) [6,8]. As a consequence, selenium has been found to improve immunity [6,7]. In septic shock patients there is a dramatic and early decrease of the plasma selenium concentration [9].

In the previous issue of *Critical Care*, Berger and colleagues [1] reported the results of a very interesting aggregative study on a group of 41 severely burnt patients. The authors show a significant reduction of nosocomial pneumonia by intravenous multitrace-element supplements (copper, selenium, and zinc). These results confirm Berger's research on burnt and trauma patients conducted since 1986 [4]. This particular population has lower mortality than septic shock patients [2].

The approach of these studies is to increase the antioxidant defense by supplementing patients with multimicro-nutrients (vitamins and trace elements) when there is a dangerous overproduction of free radicals [4]. In these studies Berger progressively focused on selenium, and increased the amount of selenium supplementation. Berger and colleagues, however, continue to use doses of selenium lower than 1 mg.

For convenience sake, these studies used the easily available pro-oxidative sodium selenite compound, as have most – if not all – other studies in intensive care unit patients. But the question of the compound probably has little importance when administrated at a level close to the nutritional 800 μg/day no-observed-adverse-effect level for selenium [7]. The two meta-analyses [2,3] tend to conclude that there is a mortality decrease in septic shock patients when selenium is administrated at higher doses, but is still less than 1 mg.

There may be another explanation for the efficiency of such high 1 mg selenium doses, especially when administered

NF = nuclear factor.

early. In plasma, selenoprotein P – the main form of plasma selenium – seems to rapidly and dramatically decrease in septic shock patients [10]. This protein has been described to protect the endothelium against oxidative stress related to peroxynitrite in a rat model of diquat intoxication, which may also be the case in septic shock [10-12]. In fact, the liver incorporates selenium and may induce a rapid synthesis of selenoprotein P.

Even though it seems that higher doses of sodium selenite supplementation are more effective in sepsis, we must remember that sodium selenite is a pro-oxidant compound. We must therefore be prudent in administrating sodium selenite, especially intravenously, in oxidative stress related to septic shock or similar syndromes, when there is additional risk of drug interactions [13,14]. In fact, all seleno-compounds are known to be more or less pro-oxidant compounds as selenium belongs to the same column of the periodic table as oxygen [13,15,16]. Acute selenium intoxication leading to shock and acute respiratory distress syndromes may be lethal, similar to arsenic poisoning [17].

Paradoxically, the direct pro-oxidative effect of selenium compounds may be beneficial in septic shock treatment. As previously stated [10], selenium compounds – especially sodium selenite – may have a direct inhibition of NF-κB to DNA binding through a reversible rupture of the disulfide bridge fixation. Selenium compounds may similarly inhibit cellular adhesion and even, at higher concentration, induce a reversible proapoptotic effect, which may help reduce overactivated phagocytic cells [16]. At even higher concentrations, seleno-compounds may be bactericidal or virucidal [15].

Unpublished animal studies support such an interest in cautious use of very high doses of selenium in sepsis [18]. In addition, we can note that the studies on septic shock with the most positive results used a sodium selenite first injection as a bolus, resulting in a transient peak of blood selenite concentration [19,20]. The pro-oxidant effect is most probably transitory due to the rapid incorporation of selenium into the seleno-enzymes, causing an antioxidant action. At least five ongoing randomized monocenter or multicenter studies have differing results, including our *sérenité* study. These studies will certainly help us understand the role of dosage and the method of administration.

Selenoprotein P and selenium compounds, especially sodium selenite, should therefore be further examined for their potential interests in the diagnosis and treatment of septic shock and related syndromes.

Competing interests

XF is the co-inventor of patent FR 98 10889, PCT N° FR 99/02.66 (delivered: US 6,844,012 B1, Au 760 534; EP 1107767), the sole inventor of patent US 60 290973, PCT N° EP 02/05350, and has ownership of the corresponding patents. XF is the sole shareholder of a small start-up named SÉRÉNITE-Forceville.

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