Pharmaconutrition Revisited for Critically Ill COVID-19 Patients

Does selenium have a place?

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The global pandemic of SARS-CoV-2 (COVID-19) provides one of the biggest challenges for critical care medicine. Mortality is much greater in elderly males, many of whom succumb to acute respiratory distress syndrome (ARDS) triggered by the viral infection. With no specific treatment available, the overall intensive care unit (ICU) mortality remains unacceptably high, at greater than 60%, underlining the urgent need for new therapeutic strategies.[1] Poor nutritional status and low selenium (Se) in particular can be a determinant of viral virulence. Many Se pharmaconutrition studies previously demonstrated reduced incidence of ventilator associated pneumonia (VAP), ARDS and mortality in the critically ill. Consequently, we postulate that intravenous Se therapy should be part of the therapeutic fight against COVID-19 in ICU patients with ARDS, and that outcomes could be affected by age, sex, and body weight.

COVID-19 & the inflammatory response

Mortality from the COVID-19 pandemic is over 74% for those patients over 65 years and much higher in 80-year old's, particularly in those with pre-illness comorbidities such as diabetes mellitus, cardiovascular disease, obesity, cancer, and chronic respiratory disease.[2] Moreover, COVID-19 appears to be deadlier in men. Over 60% of fatalities have been males, with a fatality rate of 2.8% in Chinese men compared to 1.7% in women.[2] In England and Wales, the age-standardised mortality rate (ASMR) for males was 65.1 deaths per 100,000 males compared with 43.3 deaths per 100,000 females.[3]

ARDS is a sepsis-related process fueled by a cytokine storm, which is triggered by a viral infection. Excessive lung parenchyma inflammation is responsible for severe, life-threatening hypoxemia requiring mechanical ventilation and prolonged stay in the ICU and hospital.[4, 5] Hypercytokinemic inflammation in COVID-19 patients, as in other viral infections shows a cytokine profile similar to the macrophage activation syndrome characterised by very high levels of proinflammatory cytokines, notably interleukins 6 (IL-6), IL-1 and IL-17 and tumour necrosis factor (TNF-α).[6] The elderly and others with comorbidities have exhibited the most aggressive inflammatory response.

Selenium & viruses

It is well established that poor nutritional status of the host increases pathogenicity of viruses, increasing susceptibility or severity of illness. Oxidative stress and depletion of endogenous antioxidant levels enhance viral replication and the viral RNA mutation rate. Reducing the incidence of severe ARDS, multiorgan failure, and new infectious complications, especially in elderly males where micronutrient deficiencies have been associated with severe adverse events during viral infections is a worthwhile aim.[6] In this clinical scenario, early micronutrient repletion and, specifically, pharmaconutrition with high-dose Se as intravenous sodium selenite, is worthy of re-investigation. Se is an essential trace element for humans, present in selenoproteins as the 21st amino acid selenocysteine. The antioxidant, immunological, and anti-inflammatory properties of Se have made it one of the most extensively studied micronutrients in the critical care setting.[7] The glutathione peroxidase (GPx) family catalyses the interconversion of glutathione (GSH) and its oxidised form, glutathione disulphide (GSSG), facilitating the reduction of various hydroperoxides and oxidised forms of other antioxidants. Inadequate Se status not only compromises GPx status but also cellular and humoral immunity, which are linked to an inflammatory response, involving the production of free radicals and redox control processes.[8] Free radicals increase expression of proinflammatory cytokines, such as IL-6, and TNF-α, through upregulation of nuclear factor–kappa B (NF-κB) activity where the Se status of the host may play a role in viral evolution, which has been associated with sepsis.[9]

Many geographical regions have populations with low Se status, depending on the Se content in soils.[7] In China, seasonal and annual variation in Se-deficient Keshan disease patients has been confirmed as a coxsackievirus.[10] Moreover, there is a higher mortality rate in recently observed Se-deficient Chinese COVID-19 patients and a positive correlation with Se status and the cure rate.[11] This observation supports the results from an earlier volunteer study in UK.[12] Where low Se status may have accelerated viral replication by down-regulating the immune response and increasing the permissiveness of the host for viral replication. We therefore speculate that increasing GPx-3 activity with Se supplementation could improve immune function and downregulate systemic inflammation in COVID-19 patients with positive outcomes.

Selenium pharmaconutrition: evidence & current guidelines

In critically ill patients, low Se status in sepsis negatively correlates with illness severity. In this context, high-dose Se pharmaconutrition has been extensively studied in different ICU patient populations.[7] The majority of randomised clinical trials (RCT) published between the late 1990s and 2015 reported that Se pharmaconutrition with intravenous Se 4+ as sodium selenite/selenious acid was well-tolerated, optimised Se status and enhanced activity of antioxidant selenoenzymes, such as GPx and selenoprotein P (SELENOP). These trials all demonstrated improvement in clinical outcomes, such as overall mortality, reduced incidence of VAP and infectious complications in the critically ill.[7] Subsequently, two larger studies failed to confirm these early results.[13, 14]

Whilst their study protocols have been widely criticised, these results heavily influenced later systematic reviews of Se pharmaconutrition in the critically ill, which concluded no improvement in clinical outcomes.[15] As a result, the latest guidelines from the European Society for Clinical Nutrition and Metabolism (ESPEN) now recommend that antioxidants such as Se should not be administered without proven deficiency.[16] On the other hand, the American Society of Parenteral and Enteral Nutrition (ASPEN)/Society of Critical Care Medicine (S.C.C.M) guidelines still recommend the provision of a combination of antioxidant micronutrients "in safe doses" (i.e. 5-10 times DRI).[17]

Is intravenous Se therapy, worthy of re-investigation in COVID-19 patients, as part of the therapeutic fight against acute respiratory failure in the ICU? Our affirmative answer and working hypothesis is: "*Early interventions with high-dose selenite pharmaconutrition could be effective at reducing the incidence and progression of ARDS, multiorgan failure, and new infectious complications in COVID-19 patients.*"

Selenium pharmacokinetics (PK) & pharmacodynamics (PD)

To test our hypothesis future research needs to treat pharmaconutrients as drugs, not as simple nutrients. Investigations need to be carried out on the pharmacokinetics (PK) and pharmacodynamics (PD) to determine the optimum daily dosage (posology) based on BMI; evaluate any sex differences in metabolism; and investigate any age-related influences on drug efficacy. Classical drug PK take into consideration changes with *Age in adsorption, Distribution, Metabolism and Excretion* (ADME) but this has not been considered in Se supplementation studies.

Critically ill, Se depleted patients may require much higher doses of intravenous sodium selenite/selenious acid to produce beneficial clinical effects in COVID-19 infection. In our earlier PK studies we showed that Se concentration does not normalise until day 10, whereas maximum GPx-3 activity is achieved at day 7, suggesting that high dose supplementation up to 15 µg/kg/d (1000 µg or 12.7 µmol/d) is required to optimise selenoenzymes and antioxidant status by increasing the bioavailability of reduced glutathione.[18]

Posology & BMI

Body mass index (BMI) is an important variable, not considered in earlier studies, all of which used a fixed daily dose of Se irrespective of BMI. This significant posology difference of 60-70% might have affected results of the REducing Deaths due to OXidative Stress (REDOXS) study.[13] Likewise, in the Placebo Controlled Trial of Sodium Selenite and Procalcitonin Guided Antimicrobial Therapy in Severe Sepsis (SISPCT),[14] the actual individual dosage varied from 300 µg/d to 1352 µg/d. This equates to a 4-5-fold difference between patients that could have influenced their outcome. Evidence from Italy suggests that overweight and obese patients have a higher risk of severe clinical symptoms during COVID-19 infection. Busetto *et al.*[19] report that overweight and obese patients, despite their younger age, were more likely to be admitted to ICU. Moreover, they had a higher need for non-invasive ventilation for pneumonia than older normal weight patients.

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How might age & sex differences affect metabolic and clinical responses to Se supplementation?

In the developed world more than 10% of the population is over 65 years, with a male to female ratio of 0.75 and by 2030, one in five people will be classified as 'Old' (75-84 years) or 'Old Old' (85 years+). In recent Brazilian and Iranian investigations,[20, 21] almost half the subjects were >60 years with low Se intakes and Se status well below normal, with female levels significantly lower than males. In Brazil, Iran and several other countries, such as China, New Zealand and USA, there are both Se-rich and Se-poor regions. Consequently, males and females from different regions or countries might have different 'normal' Se values, as has been observed between USA patients and European patients.[24] In a sub-group analysis of data from the REDOXS study, Heyland *et al.*[13] showed that antioxidant (Se) supplementation actually improved 28-day mortality for those under 65 but not for older patients. Age and sex differences are not immediately obvious in the SISPCT[14] study, where the mean age was 65 but the male to female ratio was 0.6, with over 4-fold differences in Se posology.

In Se-deficient male animals the reproductive organs assume greater importance, with the testes, epididymus and sperm taking up a high proportion of the administered Se dose.[22] Conversely, Se-deficient females retain larger amounts of Se in all tissues, except the brain and reproductive organs.[23] Se is essential for spermatogenesis and is present in the capsule surrounding the sperm mitochondria. Consequently, Se status and supplement efficacy is likely influenced by sex linked hormonal patterns. All these factors point to the fact that any future pharmaconutrition therapy should be administered on the basis of the age, sex, weight and/or BMI of the patient.

Future clinical investigations

Clearly age and sex differences have been an 'invisible' confounder in many pharmaconutrition studies. Now, in the COVID-19 era, it is surely not a coincidence that age and sex differences are increasingly being identified as important factors influencing the severity of the response to the virus. In future supplementation studies we should monitor Se status and ADME separately in both males and females after at least 2-3 months follow up. Simultaneous to the new PK/PD studies, we propose that large-scale RCT aimed at addressing the questions of age, sex, BMI and optimum posology need to be designed. Groups of severely ill COVID-19 patients admitted to the ICU will receive an initial loading dose of high dose parenteral sodium selenite, followed by Se pharmaconutrition as soon as possible after admission to the ICU for up to 14 days, with follow up on Se status and outcome measures for up to 100 days.

We believe there is sufficient evidence on the anti-inflammatory, immunological and antioxidant properties of Se that allows us to initiate further in-depth investigations into metabolic and clinical aspects of Se pharmaconutrition as adjuvant therapy aimed at combating this global COVID-19 pandemic.

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