Clinical Infectious Diseases

CORRESPONDENCE

Antioxidant Therapy in Coronavirus Disease 2019: The Crucial Role of Early Treatment and Antioxidant Typology

To the Editor—I read with interest the article by de Alencar et al in which they describe the possible therapeutic effects of N-acetylcysteine (NAC) in patients with severe coronavirus disease 2019 (COVID-19) [1]. Intravenous NAC, a well-known hydrophilic thiol antioxidant, was clinically ineffective compared with placebo. Central problematic aspects of this study are the selection of patients and the type of antioxidant used. The patients selected already had a severe form of COVID-19 with evident pneumonia, a pathological condition conceivably not amenable at that stage to antioxidant treatment. Oxidative stress and lipid oxidation are involved in the pathogenesis of COVID-19–related pulmonary damage. In particular, virus-induced uncontrolled oxidant species generation in monocytes/macrophages results in formation of oxidized phospholipids (Ox-PLs), particularly from lung surfactant, which contains 80%–90% phospholipids including unsaturated phosphatidylcholine as oxidizable substrate [2]. It is relevant that OxPLs can activate the macrophage Toll-like receptor 4 (TLR4) signaling cascade, leading to cytokine overproduction and acute lung injury (ALI) and eventually culminating in acute respiratory distress syndrome (ARDS) [2]. Thus, a fundamental aspect of antioxidant therapy in COVID-19 is the timing of antioxidant administration, namely, antioxidants should be administered early in the course of disease, ideally before pneumonia development, to prevent oxidant-induced OxPLs formation and TLR4 activation.

Regarding the antioxidant used, after intravenous administration, NAC undergoes extensive reaction with plasma and tissue proteins, greatly limiting the amount of circulating free drug and its antioxidant effects [3]. On the other hand, in a more lipophilic liposomal formulation, NAC is superior to conventional NAC, showing a better pharmacokinetic–pharmacodynamic profile [4]. Indeed, there is experimental evidence that liposomal NAC, but not conventional NAC, can afford significant protection against lipopolysaccharide-induced ALI, reaching far higher lung concentrations [5]. Lipophilic antioxidants are relevant since they directly protect lung surfactant and cell membrane phospholipids against oxidative injury. This is the case with vitamin E (V-E), namely, α-tocopherol, the most important lipophilic antioxidant in the lung and an integral constituent of alveolar surfactant [6]. Notably, V-E administration can reportedly attenuate experimentally induced ALI [7] and improve APACHE II (Acute Physiology and Chronic Health Evaluation) score in ARDS patients [8]. V-E acts as an efficient radical scavenger in the lipid phase [9]. As a result, V-E is converted into the radical species α-tocopheroxyl, which may be further oxidized into α-tocopheroxyl quinone or reduced back to V-E by reducing compounds with V-E regeneration [9]. The antioxidant ascorbic acid (AA) can reduce α-tocopheroxyl radicals to V-E undergoing oxidation to dehydroascorbic acid [9]. The latter is, in turn, readily reduced, for example, by dihydrolipoic acid (DHLA) in the couple lipoic acid/DHLA so that the association of V-E, AA, and DHLA is particularly effective against lipid oxidation [9]. α-tocopheroxyl radicals are reduced directly and efficiently to V-E also by the lipophilic antioxidant ubiquinol, but not by thiols [9]. The aforementioned antioxidants may be incorporated into liposomes [4] (Figure 1), in turn, also prepared using plasmalogens, ether phospholipids with antioxidant properties present in lung surfactant [10]. Inhalational administration of liposomal antioxidants expectedly maximizes pulmonary therapeutic effects as occurring with nebulized liposomal antibiotics. Early treatment of COVID-19 with this specific antioxidant therapy warrants further investigation.

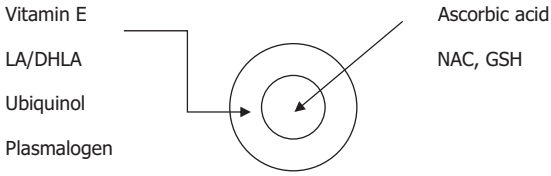

Figure 1. Schematic representation of antioxidants incorporated into phospholipid liposome. The hydrophilic antioxidants ascorbic acid, NAC, and GSH are located in the central hydrophilic liposomal structure (straight arrow), while the lipophilic antioxidants, in particular, vitamin E (α-tocopherol), are located within the peripheral lipophilic phospholipid compartment (rectangular arrow). GSH, whose biosynthesis is boosted by NAC, is a major endogenous antioxidant therapeutically available also in a liposomal formulation. See text for further explanations. Abbreviations: GSH, reduced glutathione; LA/DHLA, lipoic acid/dihydrolipoic acid; NAC, N-acetylcysteine.

Note

Potential conflicts of interest. The author reports no conflicts of interest. The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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