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ORIGINAL ARTICLE

A review of free radicals and antioxidants for critical care nurses

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Summary In the critical care setting, nurses frequently care for patients with acute and chronic diseases that affect multiple body systems. Many of these medical conditions have been associated with an imbalance between oxidizing chemicals called free radicals and antioxidants. Free radical damage is now assumed to be a contributing factor in all major diseases. In order to provide the most current and comprehensive care, critical care nurses need to be well informed about how free radicals cause damage and the antioxidant compounds that neutralize their destructive effects. This article provides an overview of oxygen free radicals and antioxidants and how they impact different clinical illnesses familiar to critical care nurses.

Introduction

The presence of free radicals in biological materials was discovered less than 50 years ago (Droge, 2002). Today, there is a large body of evidence indicating that patients in the intensive care unit (ICU) are exposed to excessive free radicals from drugs, organisms, and other substances that alter cellular reduction—oxidation (redox) balance, and disrupt normal biological functions (Dalton et al., 1999; Lunec et al., 2002; Keher, 1993).

Excess free radicals can result from tissue damage and hypoxia, overexposure to environmental factors (smoking, ultraviolet radiation, and pollutants), a lack of antioxidants, or destruction of free radical scavengers. When the production of damaging free radicals exceeds the capacity of the body's antioxidant defenses to detoxify them, a condition known as oxidative stress occurs. The cellular injury caused by oxidative stress has been linked to over 200 clinical disorders, many of which are seen in ICU patients units (Kohen and Nyska, 2002). This article explains what oxygen free radicals are, the clinical significance of free radicals in the critical care setting, and the benefits of antioxidants.

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Free radicals

When reviewing the literature, nurses will often see a symbolic dot next to a chemical abbreviation such as $^{\bullet}OH$. This dot signifies a free radical. A free radical is any atom that there is at least one unpaired electron in the outermost shell (Gutteridge and Mitchell, 1999). These uncoupled electrons are very reactive with adjacent molecules such as lipids, proteins, and carbohydrates and can cause cellular damage (Kuhn, 2003). Free radicals can also be produced by many cells as a protective mechanism. Neutrophils produce free radicals to attack and destroy pathogens, while the liver uses free radicals for detoxification (Lunec et al., 2002). However, the presence of free radicals within the body can also have a significant role in the development and progression of many disease processes like heart disease, congestive heart failure, hypertension, cerebrovascular accidents, and diabetic complications (Chen et al., 2002).

Any free radical involving oxygen is then referred to as reactive oxygen species (ROS) (McDermott, 2000). The most commonly formed ROS are superoxide anion radical ($O_2^{\bullet -}$) and hydroxyl radical ($^{\bullet}OH$) (Wilson et al., 2001; Kendler, 1995). $O_2^{\bullet -}$ is formed when one electron is added to an oxygen molecule, and is considered the least reactive type of ROS (Kohen and Nyska, 2002). Once $O_2^{\bullet -}$ is produced, it triggers a rapid cascade of events that creates other free radicals, eventually terminating in the formation of H_2O (see Fig. 1). In humans, $O_2^{\bullet -}$ is the most commonly produced free radical. Phagocytic cells such as macrophages and neutrophils are prominent sources of $O_2^{\bullet -}$. In an inflammatory response, these cells generate free radicals that attack invading pathogens such as bacteria. Production of $O_2^{\bullet -}$ by activated phagocytic cells in response to inflammation is one of the most studied free radical-producing systems (Gutteridge and Mitchell, 1999).

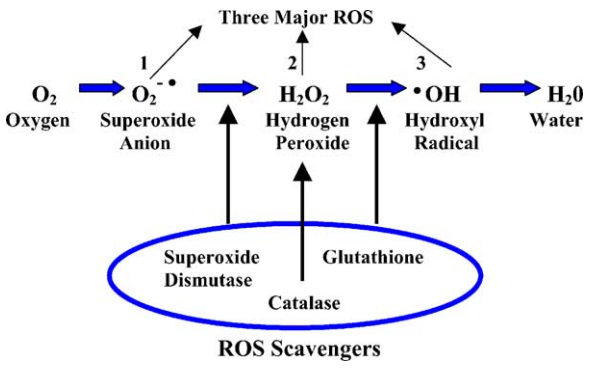

Figure 1. The process of formation of reactive oxygen species (ROS).

Table 1 Dietary antioxidants and enzymes that are part of the oxidant defense mechanism.

Dietary antioxidant	Enzyme
Vitamin C—Ascorbic acid	Catalase
Vitamin E—alpha-tocopherol	Co-Q10
Vitamin A and carotenes	Peroxidases
Ubiquinones and ubiquinol	Superoxide dismutase (SOD)

If oxygen attracts two hydrogen molecules, hydrogen peroxide (H_2O_2) is formed. H_2O_2, though not technically considered an oxygen free radical, is a member of the ROS family and may selectively participate in free radical generation (Kerr et al., 1996). The majority of the H_2O_2 is broken down to oxygen and water by the cellular enzyme catalase. In addition to catalase, the enzyme glutathione peroxidase is responsible for the break down of H_2O_2 and any peroxides that form on lipids within the body (Gutteridge and Mitchell, 1999).

The hydroxyl radical ($^{\bullet}OH$) is the most reactive of the free radical molecules (Droge, 2002). The hydroxyl radical damages cell membranes and lipoproteins by a process called lipid peroxidation. Lipid peroxidative damage to lipids in low-density lipoprotein (LDL) plays an important role in atherosclerosis (Kerr et al., 1996).

Antioxidants

Antioxidants are substances capable of counteracting the damaging effects of oxidation in body tissues. Antioxidants are divided into two classes based on mechanism of action: (1) chain-breaking antioxidants, such as Vitamin E and beta-carotene, ''break the chain'' of free radical formation by donating an electron to stabilize an existing free radical; and (2) preventive antioxidants are enzymes that scavenge initiating radicals before they start an oxidation chain. Antioxidants are found in the drugs and total parenteral nutrition (TPN) we administer to ICU patients that significantly decrease the adverse effects of oxygen free radicals (Kuhn, 2003; Goodyear-Bruch and Pierce, 2002) (see Table 1).

Chain-breaking antioxidants are found in the blood and the fluids of the extracellular space, where preventive antioxidant enzymes are absent or present in very small quantities (McDermott, 2000). These small-molecule antioxidants include both water and lipid-soluble varieties. The lipid-soluble antioxidants are located in the cellular membranes and lipoproteins, whereas the water-soluble antioxidants are present in the aqueous

Table 2 A few diseases associated with oxidative stress.

- Asthma
- Atherosclerosis
- Cerebral vascular accident
- Chronic obstructive pulmonary disease
- Congestive heart failure
- Diabetes
- Hypertension
- Influenza
- Myocardial infarction
- Pneumonia

environments, such as fluids inside cells and in the blood (Clark, 2002).

The antioxidant enzymes inside cells are an important defense against free radicals. The main enzymatic scavengers responsible for the prevention of ROS formation and oxidation are superoxide dismutase (SOD), catalase, and glutathione (see Fig. 1). SOD is found in virtually every oxygen-based organism, and its major function is to catalyze the dismutation of superoxide to hydrogen peroxide. This reaction is generally considered to be the body's primary antioxidant defense because it prevents further generation of free radicals. In humans, the highest levels of SOD are found in the liver, adrenal gland, kidney, and spleen (Halliwell, 1996).

Catalase and glutathione peroxidase work to detoxify oxygen-reactive radicals by catalyzing the formation of H_2O_2 derived from superoxide. The liver, kidney, and red blood cells possess high levels of catalase which helps to detoxify chemicals in the body.

Glutathione also plays an important role in a variety of detoxification processes. Glutathione readily interacts with free radicals, especially the hydroxyl radical, by donating a hydrogen atom. This reaction provides protection by neutralizing reactive hydroxyl radicals that are thought to be a major source of free radical pathology, including cancer (Clark, 2002).

Implications for practice

In the critical care setting, nurses care for patients with a range of acute and chronic illnesses. A large number of these disease processes are linked to the presence of free radicals in the body (see Table 2). Many antioxidants are currently being utilized in combination with traditional medical treatments to reduce the pathological damage created by free radicals in the body. In the future, critical care nurses will provide care that will affect free radical formation with the aim of reducing the length of stay for patients in ICUs.

The naturally occurring molecule Coenzyme Q10 (Co-Q10) was discovered in 1957, and has since been shown to possess powerful antioxidant properties. Specifically, Co-Q10 provides hydrogen atoms to free radicals that attack cell membranes through lipid peroxidation (Thomas et al., 1995). Co-Q10 administration has shown therapeutic benefits in the treatment of hypertension, coronary artery disease, myocardial infarction, congestive heart failure, and cardiomyopathy (Sarter, 2002). A study by Crestanello et al. (2002) has demonstrated that Co-Q10 has a cardioprotective effect on mitochondrial function after myocardial ischemia reperfusion. Currently, there are physicians prescribing intravenous Co-Q10 for post-myocardial infarction patients in critical care settings.

The consumption of alpha-carotene, beta-carotene, and Vitamin C has been shown to be a protective factor against the development of hypertension. These water-soluble antioxidants scavenge free radicals in the bloodstream. Studies have shown that when a patient has a normal to moderate serum level of alpha-carotene and beta-carotene, the systolic blood pressure measurements are lower. Likewise, when the serum Vitamin C level was higher, there was a significant decrease in both systolic and diastolic blood pressures (Chen et al., 2002).

Oxidative stress has been associated with neuronal death in the brain following a cerebral vascular accident (Garcia-Estrada et al., 2003). Maier et al. (2002) said that:

there is a marked increase in free radical production within the first 10—15 min of reperfusion and again at the peak of the inflammatory process. (p. 28)

Acute insults to the brain also trigger an increase in levels of glutamate and other excitotoxic amino acids that produce free radicals (Gilgun-Sherki et al., 2002). Inadequate amounts of scavengers or antioxidants to neutralize the rising number of free radicals results in oxidative stress, which worsens central nervous system damage and produces widespread adverse effects on all body systems. Antioxidant therapy for stroke patients has been suggested as a treatment to prevent further tissue damage by free radicals, and to improve patient survival rates and neurological outcomes (Gilgun-Sherki et al., 2002).

Free radicals also have a significant role in septic shock. In addition to mediating several

cytotoxic processes that contribute to shock, ROS can actually nullify pharmacological treatments administered to stabilize the condition (Salvemini and Cuzzocrea, 2002). Catecholamines such as dopamine and norepinephrine are typically given to shock victims to improve vasomotor tone and hemodynamics. Superoxide interacts with these catecholamines and changes their structure, converting them from vasopressors to compounds called adrenochromes that have no effect on blood pressure. Recent studies have shown these adrenochrome compounds actually exhibit some cardiotoxic properties, which may bring into question the therapeutic benefits of administering exogenous catecholamines to shock victims (Salvemini and Cuzzocrea, 2002). Current research suggests using drugs that mimic superoxide dismutase to reduce catecholamine oxidation and enhance the vasopressor responses of septic shock patients (Salvemini and Cuzzocrea, 2002).

Free radicals are also important in the pathogenesis of several inflammatory diseases of the lungs. In diseases such as ARDS and chronic obstructive pulmonary disease (COPD), inflammatory stimuli trigger the release of free radicals from alveolar macrophages and other cells, which in conjunction with other inflammatory mediators damage surrounding pulmonary tissues (Lang et al., 2002). Free radicals can oxidize surfactant proteins and damage the alveolar—capillary membrane, making the alveoli more permeable and prone to collapse, and providing an environment for the onset of bacterial pneumonia (Lang et al., 2002; Pacht et al., 2003). Pacht et al. (2003) found that ARDS patients given an enteral diet high in antioxidants had a reduction in pulmonary inflammation, thus improving oxygenation to the tissues.

Synthetic antioxidants are now being utilized at the bedside to reduce free radicals by establishing or enhancing effective cellular defense mechanisms. For example, treatment with intravenous *N*-acetylcysteine increased phagocytosis by neutrophils in patients with sepsis or systemic inflammatory response syndrome (Heller et al., 2001). *N*-Acetylcysteine has also been used to reduce oxidative stress in diseases such as acute respiratory distress syndrome (ARDS), human immunodeficiency syndrome, and chronic obstructive pulmonary disease (Goodyear-Bruch and Pierce, 2002; Chang and Crapo, 2002; Kasielski and Nowak, 2001). Probucol, another synthetic antioxidant has been used in coronary angioplasty. In two recent clinical trials, the MultiVitamins and Probucol (MVP) Trial and the Probucol Angioplasty Restenosis Trial (PART), have shown that Probucol significantly reduces the incidence of restenosis after percutaneous coronary angioplasty (Tardiff et al., 2003). Other common drugs, such as beta-antagonists, angiotensin-converting enzyme (ACE) inhibitors, and ''statins'' have exhibited antioxidant properties (Chin et al., 2003; Inoue et al., 2003; On et al., 2002). These and other synthetic antioxidant compounds are at the forefront of free radical and antioxidant research. Clinical research in the future will focus on ways to measure levels of free radical damage at the bedside and methods to deliver the appropriate amount of antioxidant therapy in response to excessive ROS formation (Barclay, 2002).

Conclusion

In practice, critical care nurses could begin applying this knowledge of free radicals by suggesting to other health care professionals' possible antioxidants therapies. For instance, before taking an ICU patient for a contrast CT scan of the head, the nurse could suggest administering intravenous *N*-acetylcysteine to prevent contrast agent-associated nephrotoxicity from free radical formation. Another possibility could be to suggest intravenous Co-Q10 administration to decrease free radicals in myocardial infarction patients.

Free radicals have a significant role in several clinical conditions commonly seen in critical care settings. Unfortunately, few practicing ICU nurses understand what free radicals are, how they are produced, and the impact they can have on patient health. Critical care nurses need to understand on a molecular level what is occurring with their patients' diseases in order to effectively intervene in ways that will provide cellular balance to alleviate and treat those conditions. Thus, knowledge of how free radicals are formed, the scavengers that prevent their overproduction, and interventions to maintain cellular reduction—oxidation balance should be an integral part of the nurse's clinical practice.

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