Nutrition support and antioxidant defenses: a cause for concern?1–3

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Parenteral nutrition support is widely used in patients with gastrointestinal dysfunction to prevent malnutrition-associated morbidity and mortality (1). Although the efficacy of this therapy in many circumstances remains controversial, it is clear that parenteral nutrition is life saving for patients unable to eat or absorb nutrients for prolonged periods. Clinical studies continue to clarify specific nutrient needs for patients receiving intravenous feeding because there is evidence that current formulations may provide insufficient or, in some cases, excessive amounts of certain nutrients (1, 2).

In this issue of the Journal, Pironi et al (3) examined the effects of parenteral nutrition containing a standard soybean oil–based lipid emulsion on lipid peroxidation, systemic antioxidant enzymes, and plasma α-tocopherol and selenium concentrations. Antioxidant status was assessed in 12 clinically stable adult patients with intestinal failure (primarily short gut syndrome) requiring prolonged parenteral nutrition. For 3–7 d/wk, patients received parenteral nutrition containing various amounts of an identical lipid emulsion product. The emulsion provided polyunsaturated fatty acids (PUFAs) in amounts ranging from 12% to 24% of intravenous energy (3 ± SE: 16 ± 2%). All subjects received a standard intravenous infusion of a vitamin mixture providing 11.2 mg all-rac-α-tocopherol/d plus 12.8 mg RRR-α-tocopherol in the lipid emulsion for an average of ≈24 mg/d (3). A selenium-free trace element mixture was also added to the parenteral nutrition solution. All but one subject consumed a free oral diet or small amounts of liquid supplements.

Results showed evidence of peroxidative stress and diminished antioxidant defenses in the plasma of patients receiving parenteral nutrition. Serum malondialdehyde, an index of lipid peroxidation, was 25% higher in patients than in age- and sex-matched control subjects (NS). However, serum malondialdehyde concentrations in patients were 56% higher than those in a separate group of 40 healthy subjects of similar age (P < 0.003). Plasma α-tocopherol concentrations were 44% lower in patients requiring parenteral nutrition than in control subjects. Plasma selenium concentrations were markedly lower in patients requiring parenteral nutrition than in control subjects. Plasma selenium concentrations were 50% lower in the parenteral nutrition patients than in control subjects, which correlated with significantly decreased plasma and erythrocyte selenium-dependent glutathione peroxidase (Se-GSHPx) activities. Erythrocyte superoxide dismutase (SOD) activity was significantly higher in patients than in control subjects. No patient had clinical signs or symptoms of vitamin E or selenium deficiency (3).

A peroxidative effect of intravenous PUFAs was suggested by the significant positive correlation between serum malondialdehyde and the daily PUFA load. Furthermore, serum malondialdehyde was negatively associated with plasma α-tocopherol values. The degree of plasma antioxidant depletion was significantly associated with the daily or weekly PUFA loads. In multiple regression analysis, the peroxidative effects of PUFA infusion (increased malondialdehyde concentrations) were dependent only on plasma α-tocopherol status (3).

Weaknesses of the study by Pironi et al (3) include the one-time determination of circulating nutrient and antioxidant concentrations and the lack of information on food intake or oral multivitamin-mineral use by the patients and control subjects. Also, it is unknown whether insufficient provision of antioxidant nutrients directly caused increased lipid peroxidation, whether oxidant-mediated stress due to underlying illness or other factors depleted antioxidant nutrient concentrations, or whether both of these situations occurred. Nonetheless, the study is important because it provides new evidence that vitamin E and selenium nutriture may be compromised in adults receiving parenteral nutrition. The vitamin E provided parenterally was not sufficient to prevent increased lipid peroxidation, and plasma α-tocopherol concentrations appeared to decline as the duration of intravenous feeding increased (3). The amount of α-tocopherol contained in the daily intravenous multivitamin supplement (11.2 mg) met the amount recommended in the most recent formal guidelines for intravenous vitamin therapy (10 mg) published by the American Medical Association Nutrition Advisory Group > 2 decades ago (4). Also, the intravenous α-tocopherol dose per gram of PUFA exceeded the value of 0.4 mg vitamin E/g PUFA recommended for healthy subjects consuming oral diets (5).

The authors did not provide intravenous selenium, and plasma concentrations were markedly lower in patients requiring parenteral nutrition than in control subjects. Plasma selenium concentrations were insufficient to maintain the antioxidant enzyme Se-GSHPx at concentrations similar to those of healthy control subjects. Of note, there is no current consensus on guidelines for parenteral use of selenium. The actual requirements for α-tocopherol and selenium in patients requiring parenteral nutrition

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remain unknown (6). Thus, additional clinical investigations to determine changes in antioxidant status and indexes of oxidative stress over time in patients requiring parenteral nutrition are indicated. Such studies should be performed in clinically stable patients and also during acute catabolic illnesses, such as infection or inflammation, which are associated with oxidant-mediated tissue injury and decreased antioxidant capacity.

The concept that lipid emulsions alone or complete parenteral nutrition solutions are potential sources of oxidative stress is supported by several other investigations (7–12). Soy-based standard lipid emulsions used in parenteral nutrition support largely contain unsaturated fatty acids with a high linoleic acid (18:2n-6) content. Van Gossum et al (7) showed that patients receiving parenteral nutrition had lower plasma α-tocopherol and normal selenium concentrations compared with control subjects. Furthermore, short-term infusion of lipid emulsion alone significantly increased lipid peroxidation in both parenteral nutrition patients and healthy subjects as measured by breath-pentane output (7). The easily peroxidized unsaturated fatty acids composing conventional lipid emulsions are possible sources of reactive peroxides capable of initiating in vivo peroxidative processes (7, 8). During standard storage conditions, 10% lipid emulsions used in parenteral feeding of premature infants were found to contain significant amounts of the oxidative products pentane and malondialdehyde (8). Administration of these lipid emulsions increased breath-pentane output by ~10-fold in premature infants, which then returned to baseline within hours of discontinuing the infusion (8). Another group showed that potentially harmful lipid peroxides are generated after daylight exposure of standard lipid emulsions that are contained in all-in-one admixture bags (9). Additional studies also showed the presence of reactive lipid hydroperoxides in 20% lipid emulsion solutions that were maintained under standard storage conditions (10, 11).

In addition to oxidation of the lipid component, other evidence suggests that solutions containing only amino acids and micronutrients may undergo photodestruction with ambient light exposure, producing hydrogen peroxide (12). When infused into animals, the photooxidized solutions depleted plasma antioxidants such as glutathione and induced hepatic injury (13). Our recent study in adults undergoing bone marrow transplantation suggests that standard lipid-containing parenteral nutrition does not support plasma vitamin E or glutathione concentrations over time (14). Patients receiving standard solutions showed significantly lower plasma α-tocopherol concentrations and tended to have lower plasma glutathione concentrations than patients given hydration and micronutrients alone. This effect occurred despite administration of conventional amounts of intravenous all-rac-α-tocopherol (10 mg/d), selenium, and other micronutrients in both groups (14). Thus, potential causes of oxidative stress in parenteral nutrition–dependent patients may include oxidative products present in standard solutions, an inadequate supply of nutrient antioxidants, or both. Evaluation of the specific components of parenteral nutrition solutions and delivery methods that may contribute to oxidative stress in the clinical setting are needed. Investigations in patients receiving parenteral formulas containing increased amounts of nutrient antioxidants (eg, α-tocopherol and selenium) or modifications in lipid components indicated.

The available data point to an important concern in the administration of parenteral nutrition, in addition to the well-documented infectious and metabolic complications of this therapy. Oxidative tissue damage undoubtedly contributes to acute and chronic disease processes in many patients receiving parenteral nutrition (15). It is unclear whether the apparent oxidative stress associated with parenteral nutrition contributes to patient morbidity. In a recent study, infusion of a soybean oil–based lipid emulsion increased plasma indexes of lipid peroxidation with a concomitant decrease in plasma glutathione status in healthy volunteers (16). Inhibition of insulin-mediated glucose uptake in these subjects appeared to be due, in part, to oxidative stress (16). Decreased tissue glucose uptake mediated by oxidative stress may potentially exacerbate hyperglycemia in some patients receiving parenteral nutrition and increase the risk of infection.

The current shortage of intravenous vitamin products in the United States has resulted in elimination or decreased provision of essential micronutrients in many patients receiving parenteral feeding (17). In light of the study by Pironi et al (3) and other published reports, increased clinical and biochemical monitoring for deficiency of α-tocopherol, selenium, and other micronutrients in parenteral nutrition–dependent patients may be prudent.

REFERENCES

15. McKenzie SJ, Baker MS, Buffington GD, Doe WF. Evidence of oxidant-
