Admixture of a Multivitamin Preparation to Parenteral Nutrition: The Major Contributor to In Vitro Generation of Peroxides

Jean-Claude Lavoie, MSc*; Sylvie Bélanger, MD‡; Monica Spalinger, Pharm*; and Philippe Chessex, MD*‡

ABSTRACT. *Background.* **Peroxides have been reported to contaminate lipid emulsions and amino acid solutions used in total parenteral nutrition (TPN). This is particularly disturbing in newborn infants who are prone to several diseases related to immature defense mechanisms against oxidative challenges. It is not clear whether the antioxidants in multivitamins help protect parenteral nutrients against the hazards of oxidation.**

Objective. **To evaluate the role of a multivitamin preparation (MVI) on the actual peroxide load received by patients on TPN.**

Methodology. **The generation of peroxides in parenteral nutrition was tested first using test solutions. We compared the relative contribution of commercially available amino acid solutions, a lipid emulsion, and MVI on the level of peroxides in clinically relevant TPN solutions. Second, we measured the level of peroxides actually infused at the bedside. In both circumstances, the effects of time and light exposure were isolated. The level of peroxides was determined by a colorimetric technique and expressed as μM equivalents tert-butyl hydroperoxide (μM = TBH).**

Results. **Even when protected from light, the addition of MVI produced a 10-fold increase in peroxides (mean ± SEM, n = 3, 19 ± 4 to 189 ± 8 μM = TBH at 4 h) in the fat-free TPN solution and a fourfold increase (64 ± 6 to 244 ± 8 μM = TBH at 4 h) in the lipid-containing TPN solution. A dose–response relationship was found between the concentration of MVI and peroxide levels. The effect of light was the strongest in the presence of multivitamins. The amino acid solutions had a relative inhibitory effect on the generation of peroxides by MVI, which varied (from 54 ± 1% to 72 ± 1%) all according to the amino acid blend. In parenterally fed premature infants, protecting the intravenous set from light decreased the load of infused peroxides (146 ± 15 vs 215 ± 24 μM = TBH).**

Conclusions. **The lipid emulsion had a significant but minor additive effect compared with the multivitamin preparation, which was the major contributor to the generation of peroxides. Protection from photooxidation is not sufficient to prevent peroxidation of TPN solutions. Contrary to what one would expect, increasing the concentration of MVI will lead to a greater generation of peroxides, suggesting that the essential antioxidants in MVI do not have antiperoxide properties.** *Pediatrics* **1997;99(3). URL: http://www.pediatrics.org/cgi/content/full/99/3/e6;** *amino acids, antioxidants, detergents, lipids, newborn infants, oxidation, parenteral nutrition.*

Isolated constituents of total parenteral nutrition (TPN) represent a potential source of oxidants. Because lipids infused with TPN solutions are contaminated by peroxides,[1,2] these emulsions are often believed to be the major source of oxidants in solutions of parenteral alimentation. However, other nutrients can promote peroxidation such as amino acids,[3,4] vitamins,[5,6] trace metals,[7] and additives used for stability.[8] But the total peroxide load received by patients on TPN has not been clearly established.

Peroxides are products of oxidation, but they can also become highly reactive oxygen species in the presence of trace metals. Increasing evidence indicates that these sources of oxidants disrupt cell membrane integrity and mediate tissue injury.[9–11] Furthermore, the oxidation can cause changes in the quality of solutions,[12] as well as loss of potency of parenteral nutrients, because the concentrations of several vitamins and amino acids decrease in TPN solutions exposed to light.[12] In the face of immature antioxidant defenses, infused peroxides have the potential to cause an oxidative challenge with general effects or local repercussions at the site of infusion. This is supported by the demonstration that the infusion of an antiperoxide such as bisulfite was associated in parenterally fed infants with a drop in urinary malondialdehyde,[8] a marker of peroxidation[13]. At the site of infusion, tert-butyl hydroperoxide (TBH) induced an oxidative response in endothelial cells characterized by modifications in prostaglandin and glutathione productions.[14]

Multivitamin preparations contain several antioxidants such as ascorbate, tocopherol, vitamin A, mannitol, butylhydroxytoluene. Therefore, one would expect the multivitamins to help protect parenteral nutrients against the hazards of oxidation. This is supported by the observation that ascorbate hinders the generation of peroxides in a lipid emulsion.[15] These antioxidants act as chain-breaking agents by scavenging peroxyl radicals and reactive oxygen species. Multivitamin preparations also contain molecules associated with the generation of peroxides, such as riboflavin[16] and detergents.[17] It is not clear whether multivitamins have antiperoxide properties.

The aim of our study was to evaluate the role of a multivitamin preparation on the actual peroxide load received by patients on TPN.

METHODS

The peroxide-generating capacity of parenteral nutrition was tested first on the bench by comparing the relative contribution of amino acids, lipids, and the multivitamin preparation, as well as by comparing different commercially available amino acid preparations. Second, it was also tested at the bedside.

Test Solutions

The generation of peroxides was compared between different TPN preparations left at darkness or at daylight for 6 h. The tested solutions contained clinically relevant concentrations of individual parenteral nutrients delivered to newborn infants: (*a*) fat-free and vitamin-free parenteral nutrition (PN) = 2.5% (w/v) amino acids (Travasol 10% Blend C; Clintec Canada, Mississauga, Ontario, Canada) plus 10% (w/v) dextrose plus standard electrolytes and trace elements (Micro + 6 Pediatric, Sabex International, Montreal, Quebec, Canada); (*b*) PN + LIPIDS = the same as in *a*, to which the lipid emulsion Intralipid-10% (Pharmacia Inc, Mississauga, Ontario, Canada) was added to obtain a final 5.5% (v/v) concentration; (*c*) PN + multivitamin preparation (MVI) = the same as in *a*, to which the multivitamin preparation MVI Pediatric (Rhône Poulenc Rorer, Montreal, Quebec, Canada) was added to obtain a final 1% (v/v) concentration; (*d*) PN + LIPIDS + MVI = the same as in *b*, to which the multivitamin preparation MVI Pediatric was added to obtain a final 1% (v/v) concentration. All these solutions were prepared in water to obtain a constant concentration of nutrients. Furthermore, a dose–response relationship was sought between MVI in water and peroxides after 3 h of exposure to daylight.

As bags of TPN are changed daily, the effect of a 24-h exposure to daylight was sought in the following preparations, characterized by varying amino acid contents in the face of a constant MVI concentration (1%) relative to the final volume: 100% PN; 50% PN + 49% H_2O + 1% MVI; 25% PN + 74% H_2O + 1% MVI; 15% PN + 84% H_2O + 1% MVI; 99% H_2O + 1% MVI.

Commercially available 10% (w/v) amino acid solutions provided us with the opportunity to isolate the effects of amino acid blends as well as bisulfite and cysteine hydrochloride, both known for their antioxidant properties[8,18] on peroxide generation. The level of peroxidation was compared after 18 h of light exposure under the same experimental conditions as described above for the 25% PN + 74% H_2O + 1% MVI preparation. The following amino acid solutions were analyzed. Blend C: Travasol 10% Blend C in glass, (Clintec Canada), which contains 300 mg/L bisulfite, but no cysteine; TIV: Travasol 10% Blend C in Viaflex, (Clintec Canada), which has the same amino acid blend but contains no bisulfite and no cysteine; Primene: Primene 10% (Clintec Canada), which has a different amino acid blend and no bisulfite, but 2460 mg/L cysteine hydrochloride; Aminosyn: Aminosyn PF (Abbott Laboratories, Montreal, Quebec, Canada) contains <300 mg/L bisulfite to which cysteine hydrochloride was added at either 0 mg/L or 500 mg/L as the maximum recommended by the manufacturer; Trophamine: Trophamine 10% (McGaw Inc, Irvine, California) contains <500 mg/L bisulfite and <240 mg/L cysteine hydrochloride.

At the Bedside

To verify that the findings in the test solutions were of relevance to patient care, we sought to confirm the presence of peroxides in TPN solutions actually delivered to preterm infants. The effect of protecting the parenteral solution from photooxidation during the transit from the bag to the patient was tested on the peroxide content. The concentrations of amino acid (Blend C) and dextrose were ordered by the attending physician; all solutions were supplemented with standard electrolytes, trace elements (Micro + Pediatric), and 2.5 mL/d multivitamin preparation (MVI Pediatric). According to routine procedures, all bags containing TPN solutions hang at the bedside, protected from light by an opaque plastic cover that is open toward the bottom. Twenty-two hours after infusing fat-free TPN preparations, a sample was taken simultaneously from the bag and from the extension set (Baxter, Toronto, Ontario, Canada) at the closest sampling site to the

infant. This procedure was performed in two groups of infants: (*1*) those fitted with the unprotected extension set according to routine procedures, and (*2*) those with the same tubing but protected from light with a custom-made opaque plastic sleeve extending from the TPN bag to the infusion pump and from that device to the patient. To ensure similar transit time and experimental conditions in both groups, patients were selected so that the infusion rates were comparable (between 4 and 7 mL/h) and MVI concentrations within a range of 1% to 2.5% (v/v) of final solution.

To quantify hydroperoxides in the TPN solutions, the ferrous oxidation/xylenol orange technique was used as described previously.[19] All reagents were purchased from Aldrich Chemical Company (Milwaukee, Wisconsin). At low pH, Fe^{2+} is oxidized in the presence of hydroperoxides; the formed Fe^{3+} reacts with xylenol orange to produce a chromophore that absorbs at 560 nm linearly with the concentration of a wide range of hydroperoxides.[8] In the present study, 22.5 mM H_2SO_4, 90 μM xylenol orange, 225 μM $FeCl_2$, and 3.6 mM BHT were added to 100 μL of sample, for a total volume of 1 mL. The absorbance was read (Beckman spectrophotometer DU-6) after 30 min incubation at room temperature. Intra- and interassay coefficients of variation were 4% and 5%, respectively. Hydroperoxides were expressed in μM equivalents of TBH (μM = TBH). The level of detection within a 95% confidence limit was 2.7 μM = TBH. To confirm that the solutions did generate peroxides, they were also tested after exposure to the following antiperoxides: 50 U/mL catalase (Sigma Chemical Co, St Louis, Missouri) or 1 mM bisulfite (Fisher Scientific Ltd, Montreal, Quebec, Canada).

Statistics

The data are presented as the mean ± SEM. Unless otherwise stated, measurements were performed in triplicate. The effects of nutrients, daylight, and duration of exposure were isolated in a 4 × 2 × 2 × 2 (time × LIPID × MVI × light) multifactorial ANOVA. The effect of bisulfite was isolated by comparing Blend C vs TIV. The effects of cysteine and amino acid blends were isolated in a 2 × 2 × 2 multifactorial ANOVA (Blend C ± 500 mg/L cysteine hydrochloride vs Aminosyn ± 500 mg/L cysteine hydrochloride). At the bedside, the effect of daylight on peroxidation was isolated by ANOVA. The level of significance was set at P <.05.

RESULTS

Hydroperoxides were detected in newly open bottles of Intralipid-10% (134 ± 16 μM = TBH, n = 6) in the freshly prepared PN solution (16 ± 5 μM = TBH) as well as in newly reconstituted 5-mL vials of MVI (3280 ± 110 μM = TBH). However, the actual peroxide load measured in TPN solutions (Figs 1, 2) reflected the dilution of the original constituents.

Figure 1 presents the variation over time in peroxide contents of solutions without MVI. It appears that the addition of the lipid emulsion at a final concentration of 5.5% (v/v) resulted in a threefold higher peroxide content (P < .001), which remained constant over time. Overall, exposure to daylight had no effect ($F_{(1,64)}$ = 0) on the solutions devoid of MVI. From Figure 2, it appears that immediately on preparation of the solutions, the addition of multivitamins resulted in a significantly higher initial peroxide content compared with PN (16 ± 5 vs 66 ± 5 μM = TBH, n = 6) and to PN + LIPID (83 ± 3 vs 126 ± 6 μM = TBH, n = 6). In the presence of MVI, the peroxide content rose significantly over time (P < .001), and the exposure to daylight had a rapid and dramatic effect on stimulating peroxide generation (P < .001). From Figures 1 and 2, it appears that the presence of lipids had only an additive effect to that of MVI; the lipid emulsion did not potentiate the generation of peroxides induced by MVI.

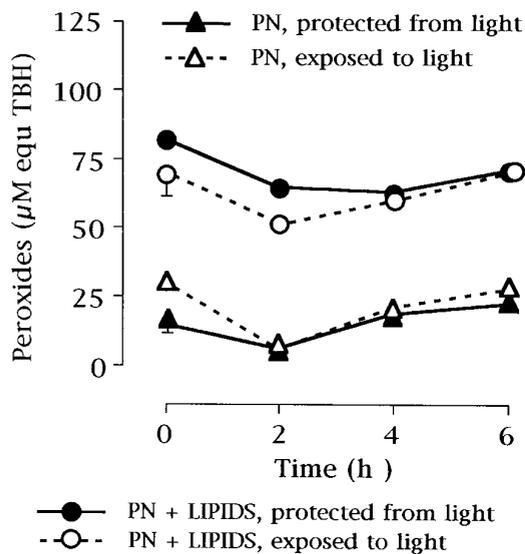Three hours after exposure to light, the addition of

Fig 1. Influence of a lipid emulsion and daylight on peroxide levels in freshly prepared solutions of PN devoid of multivitamins (PN and PN + LIPID). The data represent the mean ± SEM, n = 3; the variations are not depicted because of their small size relative to the symbols. There was a significant difference ($P <$ .001) between PN and PN + LIPID on peroxide content, whereas daylight had no effect ($F_{(1,64)} = 0$).

catalase to the PN + LIPID + MVI solution produced a 88% drop in peroxides, confirming that H_2O_2 was the main source of peroxides. Bisulfite produced a 100% drop in peroxides.

The dose–response relationship in Fig 3 underlines the direct effect of MVI content on peroxide generation in the presence of light. It is worth noting that the peroxide content, measured at an MVI concentration of 1% (v/v), corresponds to what was documented in Figure 2. From Fig 4, it appears that con-
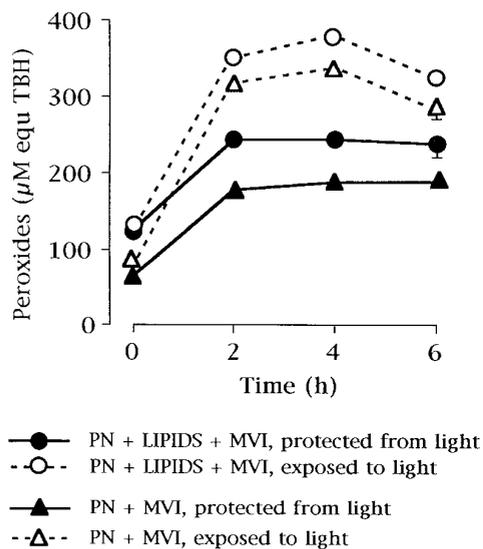

Fig 2. Influence of a lipid emulsion and daylight on peroxide levels in freshly prepared solutions of parenteral nutrition containing multivitamins (PN + MVI and PN + LIPID + MVI). The data represent the mean ± SEM, n = 3; the variations are not depicted because of their small size relative to the symbols. The peroxide content rose significantly over time ($P <$ .001), and exposure to daylight had a significant effect on peroxide generation ($P <$ .001).
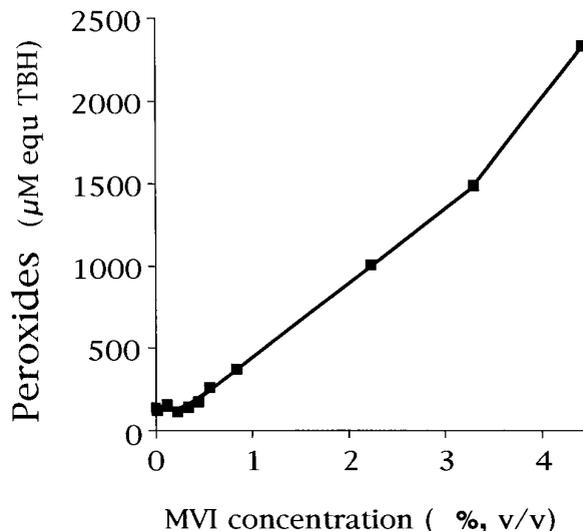

Fig 3. Dose–response relationship between peroxide content and MVI admixture in PN in water after 3 h of exposure to daylight.
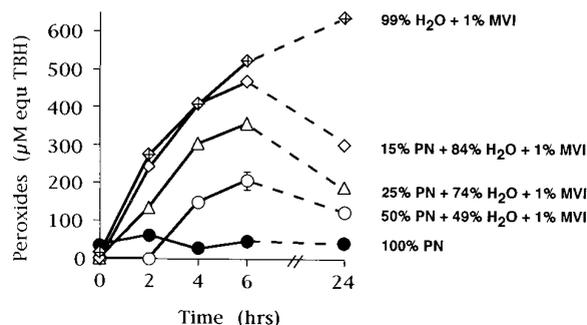

Fig 4. Influence of a 24-h exposure to daylight on peroxide content in preparations with varying amino acid content and constant MVI concentration (1%) relative to the final volume. The data represent the mean ± SEM, n = 3; the variations are not depicted because of their small size relative to the symbols. Despite a constant MVI content, peroxide generation was inhibited by increasing amino acid concentrations, suggesting a protective effect.

trary to MVI, the amino acid solution had a protective effect, because a lower amino acid concentration resulted in a significant increase in peroxides in the face of a constant MVI concentration.

The protective effect of different commercially available amino acid solutions is presented in the Table and expressed as a percentage inhibition of peroxide generation by MVI. The comparison between Blend C and TIV revealed that bisulfite is not accountable for the protective effect of the amino acid solutions. The addition of 500 mg/L cysteine hydrochloride to Aminosyn and Blend C showed a specific effect related to the amino acid solution; the interaction was significant ($P <$ .01). The addition of

TABLE. Percent of Inhibition of Peroxide Generation by MVI

Travasol TIV	67.3 ± 0.6
Travasol Blend C	64.5 ± 0.3
Aminosyn PF	53.5 ± 0.7
Aminosyn PF + cysteine	58.5 ± 2.0
Trophamine	71.6 ± 0.9
Primene	60.3 ± 0.8

Abbreviation: MVI, multivitamin preparation.
Mean ± SEM (n = 3).

cysteine hydrochloride to Aminosyn produced an increase of 5% in the antiperoxide property ($P < .05$) of the final solution; in Blend C, the addition of cysteine hydrochloride diminished by 6% ($P < .01$) the protective capacity of the solution.

The peroxide concentrations measured in actual TPN solutions being delivered to premature infants were similar to those reproduced on the bench (Fig 5). The difference between sampling sites showed that the transit through the extension set was associated with a higher peroxide concentration ($P < .01$). The rate of increase in the level of peroxides was higher in the group exposed to light, as documented by the statistically significant interaction ($P < .05$) between the effects of light and sampling sites. There was no difference in the infusion rates (4.9 mL/h ± 0.1 mL/h vs 5.2 mL/h ± .3 mL/h) or the MVI concentrations (1.9% ± 0.2% vs 1.8% ± .2%) between the two groups of six patients each (weight: 975 g ± 63 g vs 937 g ± 55 g).

DISCUSSION

The important findings of this study are that the multivitamin preparation is the major contributor to *in vitro* peroxidation and that commercially available amino acid preparations offer some degree of protection in the final solution. Our measurements were validated previously by recovery of externally added peroxides such as TBH, H_2O_2, and cumen peroxide,[8] and furthermore, we found in Intralipid-10% peroxide levels that were in the same range as those reported for the 10% lipid emulsion Liposyn[1] despite differing analytical techniques. This is further supported by the drop in peroxide content after catalase or bisulfite admixture.

The generation of peroxides in MVI could be related to photooxidation in the presence of riboflavin and amino acids such as tryptophan, tyrosine, methionine, cysteine, and phenylalanine.[6] However, MVI was found to generate peroxides even in the absence of amino acid admixture (Figs 3, 4). Therefore, other constituents of MVI, such as detergents, might account for the spontaneous photooxidation

(Figs 3, 4). Indeed, the multivitamin preparation contains polysorbate 80 and polysorbate 20 at concentrations of 1% (w/v) and .02%, respectively. Both of these nonionic detergents are highly susceptible to peroxidation by photooxidation, even at concentrations as low as .1%.[17,20] These detergents are the same as those that were implicated, at 10-fold higher concentrations, in an unusual fatal syndrome among premature infants, characterized by unexplained clinical deterioration.[21,22] Additional information is needed to verify the clinical impact of these detergents in multivitamin preparations.

The dose–response relationship (Fig 3) underscores the potential risk of inadvertently infusing higher concentrations of peroxides than those reported in this study during the weaning of intravenous alimentation. Indeed, if the volume of administered MVI is kept constant while the total volume of fluids to be infused is decreased, the patients will receive concentrations of MVI that can reach >5% during the weaning process, with dramatic effects on peroxide concentrations.

The magnitude of peroxides infused with the studied solutions corresponds to H_2O_2 released during phagocytosis by 10 000 human neutrophils per mL over 24 h.[23,24] In red cells, an organic peroxide stimulates proteolysis at concentrations lower than those in the studied solutions, whereas 200 μM H_2O_2 had no such effect.[25] Therefore, infused peroxides are potentially cytotoxic under conditions of weak peroxidase activity, as found in the lung and liver of preterm and term neonates.[26] Furthermore, these immature infants receive the highest concentrations of MVI (up to 5% v/v) when compared with adolescents and adults (0.1% v/v). Although newborn infants are at greater risk of being unable to counter effectively an oxidative challenge such as that represented by TPN, the biological significance of the infused peroxides remains to be proven.

The experimental conditions closely mimic the clinical practice in neonatal units, where the TPN solution can be exposed to light for periods as long as 4 h during its transit through the tubing from the bag to the infant. Protecting the extension set from light produced a significant ($P < .01$) drop in the amount of peroxides infused in these infants. These data suggest that the use of tubing shielded from light would diminish the oxidant load associated with TPN. The study was not designed to find the best protection from light, but rather to emphasize the magnitude of the phenomenon of photooxidation on MVI under clinical conditions. The group with the tubing shielded from light had a better photoprotection of the bag, because the bottom of its opaque cover was completely closed as opposed to the other group, the bag for which was open toward the bottom, resulting in a higher peroxide concentration (Fig 5). This point stresses the importance of the quality of the shielding from light. The biological significance of protecting the TPN solutions from light has been documented in animals by others researchers, who showed that light exposure was associated with an increase in biliary concentrations of oxidized glutathione and free amino acids.[27]
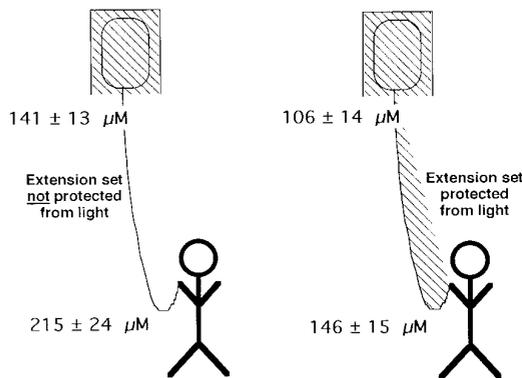

Fig 5. Comparison of peroxide concentrations (μM = TBH) measured in actual fat-free TPN solutions being delivered to premature infants. Values (mean ± SEM, n = 6) represent peroxides sampled in the bag of TPN or in the extension set close to the infant. Two groups of six infants were studied while on comparable TPN regimens; those with extension sets protected from light received a significantly lower infusion of peroxides.

141 ± 13 μM

106 ± 14 μM

Extension set not protected from light

Extension set protected from light

215 ± 24 μM

146 ± 15 μM

The amino acid solutions presented a relative protection against peroxidation. It appears that the inhibition of peroxide generation varied from 54% to 72% (Table). The significant interaction between cysteine and amino acid blends indicates that statistical comparisons between the different solutions were not warranted and suggests that the variation in the protective effect depends above all on differing amino acid blends. The antiperoxide property of these solutions might not be desirable if certain amino acids become oxidized in the process.[16] Indeed, data not presented show that the thiol function of cysteine was lost in the presence of peroxides. This raises the question as to whether the amino acid blend showing the least antiperoxide activity (Table 1) is the one that conserves best its original composition. This point is emphasized further when considering the fall in peroxide concentrations in PN solutions after 6 h (Fig 4). The balance between generation and consumption of peroxides is positive during the first 6 h after preparation. After that time, we presume that the balance changed in favor of the consumption of peroxides during their transformation into free radicals via the Fenton-like reaction[9] induced by trace elements present in the PN solutions. This is supported by the absence of a fall in peroxides in the solution devoid of trace elements (Fig 4). The fact that added cysteine presented a different redox effect in Aminosyn and Blend C might not be solely related to the amino acid blend but also to the level of peroxides, as well as to trace elements and free radicals present in these solutions. In general, we wish to emphasize that an antioxidant can become prooxidant depending on the concentration of peroxides, as documented previously with bisulfite.[8]

In conclusion, a greater effort should be made to decrease the level of peroxides in TPN solutions. Protection from photooxidation is not sufficient to prevent peroxidation of TPN solutions (Figs 2, 5). We caution against choosing an amino acid solution for its antiperoxide properties. Contrary to what one would expect, increasing the concentration of MVI will lead to a greater generation of peroxides, suggesting that the essential antioxidants in MVI do not have antiperoxide properties. It remains to be verified whether the detergents represent a source of peroxides that could be eliminated by separating the multivitamins between the hydrosoluble and liposoluble fractions, the later being infused with the lipids. The biological significance of the infused peroxides remains to be proven.

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