Compatibility and Stability of Additives in Parenteral Nutrition Admixtures

MICHAEL C. ALLWOOD, PHD, AND MELANIE C. J. KEARNEY, PHD

From the Medicines Research Unit, University of Derby, Mickleover, Derby, United Kingdom

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ABSTRACT

The addition of additives (electrolytes, trace elements, and vitamins) to parenteral nutrition (PN) mixtures can lead to precipitation as a result of physical incompatibilities and can lead to chemical degradation of individual ingredients. The most significant cause of precipitation is excessive concentrations of calcium phosphate. The most significant cause of chemical instability is the oxidation of specific vitamins. The factors influencing calcium phosphate solubility include the commercial amino acid source, the calcium and phosphate salts used, temperature, magnesium concentration, and final volume. Precipitation can be avoided by organic phosphates. Trace element precipitation is most commonly caused by the formation of iron phosphate salts or copper cysteinate in cysteine-containing amino acid infusions. The least stable nutrient is ascorbic acid, which reacts with oxygen, and is catalyzed by copper ions. Oxygen originates from PN ingredients, the filling process, air remaining in the bag after filling, and oxygen permeation through the bag wall. Storage in multilayered bags with reduced gas permeability can protect residual ascorbic acid. Other chemical losses are caused by the reduction of thiamine by metabisulfite, and photodegradation of daylight-sensitive vitamins, especially retinol and riboflavin, during administration. *Nutrition* 1998;14:697–706. ©Elsevier Science Inc. 1998

Key words: parenteral nutrition, additives, electrolytes, trace elements, vitamins, precipitation, chemical degradation

INTRODUCTION

The compounding of parenteral nutrition (PN) admixtures in large volume plastic containers ("big bags") leads inevitably to infusions that are less stable than the constituent components. The individual injections used in the compounding of any mixture are manufactured as relatively stable products with shelf-lives measured in years. Stability is maintained by optimizing both the formulation and packaging of the products. Once each injection or infusion has been removed from its original container and mixed with other parenteral ingredients, the chemical stability of the active ingredients and also any excipients will be compromised. In addition, the mixing of various compounds may lead to loss of physical compatibility by formation of new salts of low aqueous solubility compared with constituent chemical components, leading to precipitation.

It is the purpose of this review to consider the possible causes for chemical degradation and physical incompatibility in PN admixtures that involve parenteral additives, and to relate the significance of these changes to clinical consequences.

For the purpose of this review, the parenteral additives reviewed include electrolytes, trace elements, and vitamins. Mechanisms to avoid these unfavorable reactions are considered.

ELECTROLYTES

All PN regimens must contain a range of essential electrolytes, some of which must be included within a particular concentration range (for example potassium and sodium coincident with the clinical condition of the patient), whereas others must be present in amounts at least sufficient to provide a minimum daily requirement (for example calcium, magnesium, and phosphate). Individual patient requirements depend on a number of factors, such as clinical condition, age, renal function, and their level of physical activity. Electrolytes in PN mixtures normally retain their chemical status, although certain electrolytes can cause physical incompatibilities.

The monovalent ions do not pose any significant physical compatibility problems, and high concentrations are generally tolerated in PN mixtures. In contrast, precipitation can derive from di- and trivalent ion interactions, in particular calcium and phosphate. Although, in practice, normal daily requirements for adults can be included in PN mixtures without causing precipitation,

Correspondence to: Professor M. C. Allwood, PhD, Medicines Research Unit, University of Derby, Mickleover, Derby DE3 5GX, UK. E-mail: M.C.Allwood@derby.ac.uk

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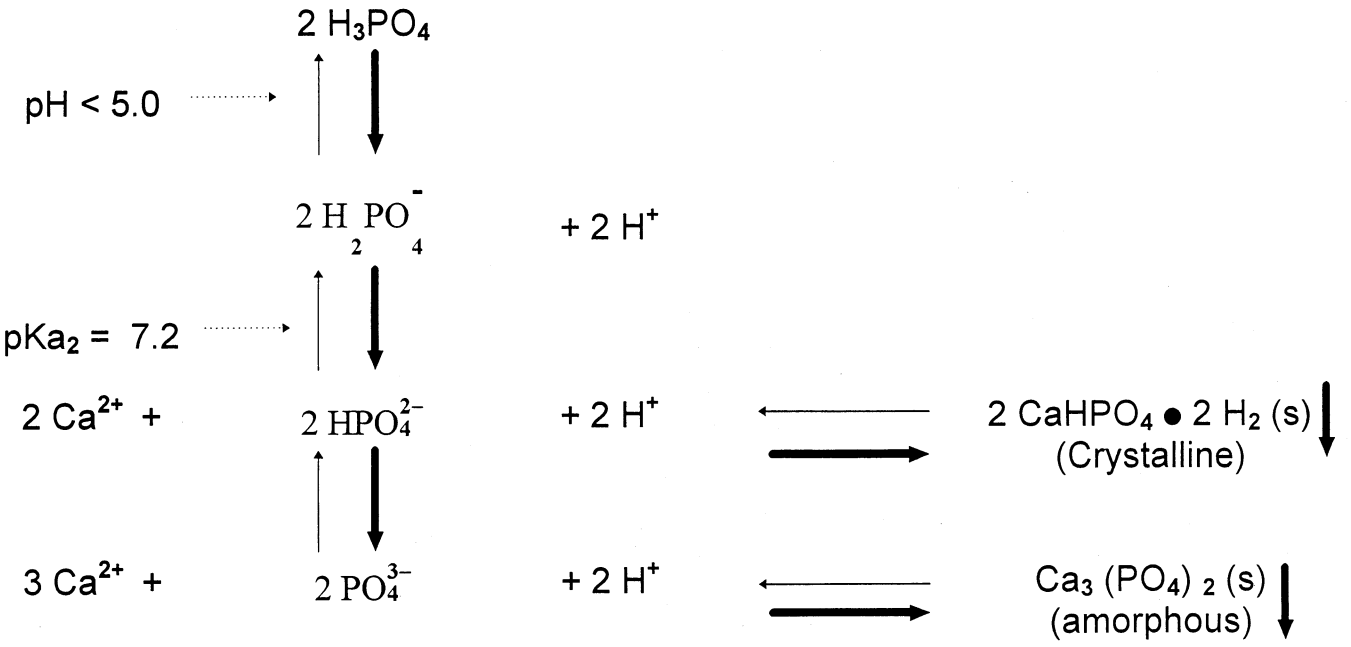

FIG. 1. Speciation of inorganic phosphate in parenteral nutrition mixtures.

physical incompatibilities can arise in attempting to achieve the greater daily needs of children and neonates due to the low final volume (i.e., highly concentrated) typically delivered. An understanding of the causes of calcium phosphate precipitation can lead to compounding strategies that maximize the amounts of calcium and phosphate ions that can be added safely to PN mixtures.

Factors Influencing Calcium Phosphate Compatibility in Total PN Mixtures

In aqueous solutions containing phosphate salts, an equilibrium will be established between the three ionic phosphate species; the trivalent phosphate ion and its monobasic ($H_2PO_4^-$) and dibasic (HPO_4^-) forms (Fig 1). The pKa values for the two equilibria give an indication of the predominant phosphate species at any particular solution pH. The tribasic phosphate species will not normally be present in PN admixtures because of the extreme alkalinity necessary for it to become ionized. Both mono- and dibasic phosphate salts may form a salt with calcium, but the dibasic salt is the least soluble of the two options. The solubility of the monobasic and dibasic calcium salts are 1.8 and 0.03% w/v, respectively.[1] For example, at physiologic pH (7.4), approximately 60% according to calculations based on the Henderson-Hasselbach equation of the phosphate is in the dibasic form. Because the dibasic calcium phosphate salt is poorly soluble, this enhances the probability of calcium phosphate precipitation. By decreasing the pH by 2 U, approximately 95% of the phosphate is in the monobasic form,[1] which is far more soluble. The most important factor, therefore, governing calcium phosphate compatibility in any PN mixture is the final pH of the mixture. This will be determined by range of a factors.

These factors that determine the final pH are, in order of importance:

The commercial source of the amino acid infusion.[2–4] Amino acid infusions from different manufacturers vary in pH between around approximately 5.0 and 7.4. In addition, each amino acid mixture will vary in buffering capacity (titratible acidity).[2] This is largely determined by the concentrations of arginine, histidine, and lysine.[5]

The amino acid concentration in the final mixture.[3,6,7] This will depend on both the amino acid concentration in the original infusion and the total volume of the PN mixture, which results in altering the buffering capacity (increasing the final amino acid concentration enhances buffering capacity and vice versa).

The type and final concentration of phosphate injection. Inorganic phosphate additives are available as a mixture of mono- and dibasic salts with either sodium and potassium as the counter ion, producing formulations that form strong buffers with pH values in the range of 5.0–6.5. This pH depends on the ratio of the two phosphate ions. Alternatively, a monobasic phosphate injection can be used, containing, for example, potassium dihydrogen phosphate. The pH of this injection is approximately 5.0. This monobasic phosphate injection can therefore be used to enhance the amounts of phosphate and calcium that can be added to total parenteral nutrition (TPN) mixtures without causing precipitation,[3,6,8] due to its pH-lowering effect.

The addition of cysteine.[7] Cysteine, in sufficient concentration, can reduce the pH of the final PN mixture.

The final concentration of glucose.[2] Although glucose infusions are acidic, the buffering capacity of the amino acid infusion and phosphate additive will predominate as controllers of final pH.

Many other factors influence the physical compatibility of calcium and phosphate salts in PN mixtures. No single factor can be seen in isolation and the final outcome will be a result of a multifactorial interaction.

The second important factor effecting calcium phosphate solubility is the final concentration of free calcium ion,[1,2,6,8,9] because the formation of the poorly soluble dibasic phosphate salt is dependent on the equilibrium between phosphate and calcium ions. Calcium ion concentration depends on a number of factors:

The calcium salt. Calcium additives are available as inorganic salts (calcium chloride) or organic compounds (calcium gluconate or gluceptate). Calcium chloride reduces the solubility of calcium phosphate complexes in PN mixtures compared with calcium gluconate or gluceptate, because the chloride salt dissociates to a greater extent.[1,9] The two organic salts show similar degrees of dissociation, and there appears, therefore, to be no advantage in usage between these two compounds in PN mixtures.[1] Organic salts should be the preferred source of calcium. Calcium gluconate injection is, however, commonly contaminated with aluminum and a recent study[10] indicates it is contra-indicated for use in neonates and small children.

Temperature. Temperature has a major influence on calcium phosphate solubility, in particular if organic calcium salts are employed. This is because temperature effects the dissociation of the organic calcium salts[1,2,8,11] and possibly the equilibria between the different phosphate species.[2] Raising temperature causes a greater dissociation of calcium gluconate to free calcium. This is significant if temperatures rise from 5 to 37°C. Second, raising the temperature of a mixture may also shift the phosphate equilibrium from mono- to dibasic salt. Both effects increase the likelihood of precipitation.

The commercial amino acid source. Some degree of complexation between calcium and specific amino acids has been reported.[2,9] Computer simulations have suggested the relative degree of complexation with different amino acids. The amino acid most likely to complex with calcium is lysine, although glutamic and aspartic acids, arginine, and histidine also form complexes.[9] The degree of complexation is also pH-dependent.[9] Cysteine, in contrast, shows very low levels of calcium complexation.

The final concentration of magnesium. Magnesium influences the likelihood of precipitation because it forms relatively more soluble and stable salts with phosphate ions.[4] This effect increases with pH. It also depends on the molar ratio of calcium and magnesium. Ratios of magnesium/calcium less than two exert a positive effect on calcium phosphate solubility.[4,9]

Other factors. Other factors have also been reported to influence the final outcome. The order of mixing can affect the final solubility profile of calcium phosphate.[1,4] The phosphate additive should always be added and the mixture thoroughly mixed before adding calcium. An alternative approach has been reported that also enhances calcium and phosphate additions. Kaminski et al.[12] found that mixing the two salts into separate infusions (phosphate into the amino acid, calcium into the glucose) and combining these mixtures slowly reduced the likelihood of precipitation.

Factors such as the time of storage before administration may be significant. Experience indicates that calcium phosphate precipitates do not necessarily form immediately but may take up to 24 h to become evident.[1,6]

Finally, it is worth noting that PN mixtures generally have a greater capacity for phosphate than for calcium ions.[6]

Organic Phosphates

One method of avoiding the risk of calcium phosphate precipitation is to use organic phosphate compounds. The disodium salts of glucose 1-phosphate, glycerophosphate, and arginine glucose 1-phosphate have been employed. These compounds have been reported to be fully compatible in a range of PN mixtures, and to be at least equally bioavailable when compared with inorganic phosphate,[9,13,14] although some dissociation or degradation to release phosphate ions cannot be ignored. Calcium glycerophosphate has also been reported to be effective in providing adequate requirements of the two elements in infants.[15]

The Process of Precipitation

It has been reported that precipitates may form either during the mixing process or after some time has lapsed after compounding, referred to as *time-mediated precipitation.*[9] These variations relate to the chemistry of the system. A precipitate formed during the compounding process due to poor mixing and layering of different ingredients comprises calcium phosphate, whereas the time-mediated precipitate is normally caused by dibasic calcium phosphate crystallization. Although the first type appears as a white flocculent amorphous precipitate, the latter is identified as semitransparent and well-defined crystals, commonly adhering to the sides of the container.[7,9] In any case, precipitates once formed are highly unlikely to redissolve.[16] Formation of the latter may take up to 24–48 h at 37°C,[6] depending on the relative concentrations of calcium and phosphate salts.

Testing for Precipitation

The formation of calcium phosphate precipitates can be identifiable by visual inspection, and this approach has been employed by most investigators. A number of other methods have been applied in different studies to identify, in particular, critical points in the solubility matrix of PN mixtures. These can be categorized as methods to detect particulates or methods to quantify calcium or phosphate solution concentration changes. Methods to detect particulates include light or electron microscopic examination of filter surfaces after filtration of the PN mixture[3,11] for particulate counts. Methods to quantify concentration changes include calcium concentration measurement by atomic absorption spectroscopy, potentiometric titration,[6] or spectrophotometry.[1]

No method provides complete confidence in ensuring detection of all incompatible mixtures. The use of relatively simple methods, such as visual examination with appropriate illumination and background, the data from which are then used to construct solubility diagrams, are probably as reliable as a general screening method as the more technical and time-consuming methods used by some laboratories. Particle counting with laser light extinction can detect particles down to 1.75 μm, as they can be suspended during the analysis with a magnetic stirring bar. Particles have been detected even with time-mediated precipitate formation when sampled at different time intervals. Particle counts, however, will only detect precipitation if the particles are suspended in the mixture, and this may not be the case with time-mediated precipitate formation in which some solid material may adhere to container surfaces. Microscopic examination of filter surfaces following the isolation of particles by filtration of PN mixtures is relatively sensitive but is time-consuming and again depends on particle suspension before filtration. Particle counts will also not differentiate between calcium phosphate microcrystallization and other particles present in the mixture. Filters must also be made transparent and often the particles may coalesce to form a "carpet" on the filter surface, which is difficult to identify. Only electron microscopical x-ray energy dispersive spectroscopy (EDX) analysis, a highly specialized technique, will confirm the presence of calcium and phosphate in isolated precipitates.[17]

Compatibility Assessment of Calcium Phosphate in All-in-One Mixtures

The rate and spectrum of calcium phosphate particulate formation is very different from flexible lipid droplet enlargement (fat emulsion instability). In the case of calcium phosphate particulate formation, calcium phosphate precipitates when formed show dramatic increases in the number and size spectrum, whereas in the case of flexible lipid droplet enlargement, enlargement of fat

globules is slow, such that the number and size gradually increase from one sampling interval to the next. These characteristics, in terms of particle growth, may help discern calcium phosphate from coalesced lipid droplets in these opaque formulations. The technical aspects of this differentiation are difficult and require further study. Precipitation in all-in-one mixtures cannot readily be detected by visual inspection, due to the fat emulsion.[18] Light microscopy has been employed[18] to detect crystalline precipitation, although the limit of detection with regard to particle size is 5 μm. The sensitivity of the microscopic method was not determined. An alternative approach is to evaluate the compatibility of the mixture with the exclusion of the fat emulsion, and test for incompatibility in the normal manner. Because removal of the fat emulsion will reduce the volume and hence increase the concentration of each ingredient, it can be argued that in such an approach the mixture tested is at least as likely to precipitate as the same mixture with fat emulsion. However, this makes the assumption that increasing the concentration of other ingredients does not significantly enhance calcium phosphate solubility. This may not be true for amino acids, for example. It also assumes that the emulsion does not influence calcium phosphate compatibility. The alternative, therefore, is to replace the fat emulsion with an equivalent volume of glucose infusion.

Clinical Effects

The recent US incidences have highlighted the consequences of infusing precipitates such as calcium phosphate.[15] Knowles et al.[19] report a case of pulmonary deposition of calcium phosphate crystals in a patient on home PN. The patient developed diffuse granulomatous interstitial pneumonitis after approximately a 14-d infusion of PN. The cause was directly linked to calcium phosphate deposition in the lung. Calcium phosphate precipitation has also been identified as a cause of blocking in-dwelling catheters through which PN was being administered.[19]

The Federal Drug Administration (FDA) has now recommended that in-line filters should be used in all TPN administration to avoid calcium phosphate precipitates entering the patient.[15] This recommendation applies to non-fat containing and all-in-one PN mixtures.

TRACE ELEMENT INCOMPATIBILITY

A wide range of trace elements are necessary to meet the nutritional needs of patients receiving PN. The list of recognized requirements has grown with our increasing knowledge of micronutrient functions in nutrition. The list includes such elements as selenium, molybdenum, chromium, and bromine, as well as the more obvious iodine, fluorine, manganese, and copper. Daily requirements remain, in many cases, poorly defined, although both the minimum and maximum amounts are defined for most elements, because both clinical evidence of deficiencies and toxic levels have become evident (e.g., manganese). There are two aspects to be considered with regard to the stability of trace elements in PN mixtures. First, assurance is required that each element is chemically stable, and second, that each element is physically compatible with other ingredients. The very low concentrations used in PN mixtures pose analytical challenges to determine both of these aspects. This probably accounts for the fact that there is a sparsity of information on trace element stability and compatibility in PN mixtures.

Investigations into the stability of trace element additives to PN mixtures have, in most studies, relied on analysis of specific trace element concentrations by atomic absorption spectroscopy. Zinc, copper, manganese, and chromium were reported to be stable and compatible in PN mixtures for 48 h at ambient temperature, and after passage through a 0.45 μm in-line filter.[21,22] It was also noted that certain PN ingredients contained copper, zinc, or manganese as contaminants, in some cases significantly contributing to final concentrations in PN mixtures, an observation also reported by Kartinos,[22] who noted that amino acid infusions may contain detectable quantities of iron, cobalt, manganese, molybdenum, fluorine, and iodine. The compatibility of zinc, manganese, copper, chromium, and iodine in TPN mixtures after 24 h of storage at ambient temperature or 4°C has been confirmed (by M.C.A.). In a longer-term storage study, it has been shown that zinc, copper, manganese, and chromium are compatible and stable in PN mixtures containing one particular amino acid source (Synthamin, Baxter, Baxter Health Care, Ltd., Wallingford, UK) for 4 mo at 2–6°C.[24] It was, however, noted that copper showed some evidence of physical incompatibility in Synthamin alone, but not in PN mixtures containing Synthamin, even after only 2 d storage. Copper precipitates have also been recovered from PN mixtures containing Novamine as the amino acid source.[25] It was hypothesized that the precipitate consisted of copper sulfide, due to reaction with cysteine.[26] A more recent study has also noted copper and sulfur ions present on in-line filters after delivery of PN mixtures containing Vamin (Pharmacia & Upjohn Ltd., Milton Keynes, UK) as amino acid source.[27]

Precipitation of iron added to PN mixtures has been reported.[28] This appeared to relate to a specific amino acid infusion used to compound the mixture. It has been reported that iron dextran[28] and ferrous citrate[29] are compatible in PN mixtures, although the study periods were related to infusion times (18–24 h) only.

The stability of selenium has also received some attention since Levander[30] reported that high concentrations of ascorbic acid reduced the soluble selenite ion to insoluble elemental selenium. This reaction may be further enhanced by the high reduction potential of other cations, such as the cuprous ion. Shils and Levander[31] reported that ascorbic acid 5 g/L induced significant selenite reduction, but McGee et al.[32] noted that PN mixtures containing 1 g/L ascorbic acid did not cause loss of selenium in solution, even after extended periods of storage up to 10 wk. A later report indicated that reduction of selenite was only detected if the pH of the TPN mixture was ≤ 5.0. In mixtures with pH < 5.0 ascorbic acid at concentrations as low as 100 mg/L could cause selenite reduction to elemental selenium.[32] It would therefore appear that reduction of selenite to free selenium is not likely to occur in PN mixtures, provided the pH remains > 5.0. Allwood and Greenwood[17] reported evidence of selenium precipitation in PN mixtures containing ascorbic acid, after deliberately reducing the pH to < 5.0, using EDX to analyze filters for precipitated selenium after filtration of stored PN mixtures.

Other potential losses of trace elements, including, for example, reduction of iodide to iodine, have not been reported in practice, although Allwood and Greenwood[17] reported that calcium phosphate precipitates in TPN mixtures also contained evidence of other phosphate salts, including iron and manganese.

SUMMARY OF PHYSICAL INCOMPATIBILITY

The risk of calcium phosphate precipitation is the major problem regarding the addition of electrolytes and trace elements to PN mixtures. The mechanisms and consequences are now well recognized. Clear strategies are available to avoid this physical incompatibility. The most promising development is the availability of organic phosphate injections that provide a means of avoiding any risk associated with calcium phosphate precipitation. Our limited knowledge of trace element stability in PN mixtures suggests that incompatibilities are generally avoided in compounded mixtures, and that extended shelf-lives can be assigned to many mixtures containing trace elements. However, until further evidence is available, caution is necessary when extending shelf-lives of untested PN mixtures, in particular those with high levels of sulfhydryl-containing amino acids.

VITAMIN STABILITY

Vitamins are commonly believed to be among the least stable ingredients in PN mixtures, and it is generally recommended that vitamins be added immediately before commencing infusion or that infusion should be commenced within 24–48 h of addition. This constraint poses severe limitations on the ability of compounding units to provide aseptically prepared complete PN mixtures. A careful consideration of the stability of vitamins is crucial to the operation of safe and effective compounding services. Stability must be considered in the context of both storage after compounding and during administration, because some vitamins can undergo degradation during administration. With the increasing demand for extended storage of complete PN mixtures, especially for home patients, investigation of vitamin stability during storage has become an important development in contributing to improving the quality of patient care.

Various vitamins are known to be degraded under particular conditions and in the presence of specific PN ingredients. The major physico-chemical considerations are exposure to light, the type of plastic used to manufacture the PN container and infusion equipment, and storage temperature. The chemical parameters of concern relate to the oxidation or reduction of particular vitamins.

Photodegradation of Vitamins

Vitamins most sensitive to photolysis are retinol (vitamin A) and riboflavin (B_2). The nature of the light is extremely important, because it is exclusively the ultraviolet (UV) component that causes chemical photolysis of vitamins.[34,35] Most artificial light sources, including fluorescent light, contain insignificant emissions in the UV range. It is therefore only daylight exposure that causes serious photolytic losses in practice. Photolysis during storage should be readily avoidable.

Plastic Interactions

The vitamin most liable to bind with plastics is retinol. However, only the acetate ester form has been shown to exhibit sorption to polyvinyl chloride (PVC) bags and administration sets.[36]

Chemical Degradation

Chemical degradation is the most important cause of vitamin losses in PN mixtures. Although many vitamins are likely to degrade eventually after addition to TPN mixtures, two particular reactions are of major concern: the oxidation of ascorbic acid and the reduction of thiamine, being the most readily oxidized and reduced vitamins, respectively.

The stability of all vitamins added to TPN mixtures will be considered, both during storage and administration.

FAT SOLUBLE VITAMINS

Retinol

Multivitamin additives intended for PN may contain either the acetate or palmitate ester of retinol. The former compound is commonly used in formulations originating from the USA.

The stability of retinol in PN mixtures during storage has been widely reported. Allwood[35] has shown that retinol (palmitate) is stable in two-in-one mixtures for at least 28 d during storage at 5°C. Billion-Rey et al.[37] reported that retinol (palmitate) was stable for 20 d in all-in-one PN mixtures stored at 4°C, although degradation was observed in some PN mixtures containing trace elements, depending on the amino acid source.

Retinol is the most light sensitive of the vitamins. Exposure of PN mixtures in bags to daylight can show up to 90% loss in 2–4 h, whereas direct sunlight will cause even more rapid degradation.[35–38] Photolysis proceeds both in the bag and during passage through the administration set.

A light-protecting overwrap to the container and the use of special light-protecting administration sets is therefore commonly recommended,[40] unless the patient is being fed in a position away from strong daylight or at night.[36] Administration in a room with only artificial lighting will lead to minimum degradation. It should also be noted that fat emulsion will protect retinol from photolysis,[32,41] both in the big bags and during infusion, although direct sunlight may penetrate the emulsion sufficiently to cause some degradation during administration.

Sorption of retinol has been reported,[39,42] and has also lead to clinical manifestations of vitamin deficiency in long-term PN feeding.[39] It was shown that substantial amounts of retinol (acetate) in PN mixtures prepared in glass bottles was lost by absorption to the administration set during simulated infusion.[31,39] In contrast, other studies have been unable to confirm retinol binding to plastic bags or sets.[36,37] Further investigations have confirmed that sorption to PVC depends on the ester used. Whereas the acetate ester (used in most US-manufactured products) binds strongly to PVC bags and administration sets, with losses up to 90% being reported,[39] the palmitate ester commonly used by European manufacturers shows no evidence of binding to plastics used to store and administer PN, in either two-in-one[35,43] or three-in-one[37,44] TPN mixtures.

Tocopherol

All fat emulsions contain some tocopherol, although it will be present as a mixture of isomers, some of which are more biologically active than others.[45] However, the proportions of the isomers vary widely, both between batches of the same product, and between products.[42,44]

Tocopherol appears to be relatively stable in PN mixtures. Billion-Rey et al.[37] reported that this vitamin was stable for 20 d at 4°C, with or without fat emulsion. Dahl et al.[35] reported that total tocopherol in all-in-one PN mixtures was stable for 6 d at 2–8°C and during simulated infusion over 24 h in normal room illumination conditions. However, the relative proportions of the different isomers was not assessed.

Kishi et al.[46] reported that tocopherol was stable during simulated infusion in PN mixtures, both with and without light-protective measures. McGee et al.[32] monitored the stability of α-tocopherol (5 IU in a 2.5-L mixture) in PN mixtures exposed to fluorescent light at room temperature in the bag and during simulated infusion through in-line filters. No significant losses were reported. No losses were reported by Dahl et al.[35] during simulated infusion in fat emulsion. Kishi et al.[46] reported similar results after 24-h storage, although McKenna and Bieri[47] reported a 10% loss during infusion. Billion-Rey et al.[37] reported that tocopherol was stable during exposure to sunlight for up to 8 h. In contrast, Gillis et al.[48] reported that only 63% of the added α-tocopherol was delivered during administration of the PN mixture (monitored using a radioactively labeled vitamin source). Drott et al.[49] also reported some loss during simulated infusion, amounting to approximately 10% during 20 h of administration. The role of light (the nature of which was not described) in this reported tocopherol loss was not clear, as the vitamins were added to the fat emulsion, which was then infused into the same line with mixing only during delivery.

It should also be noted that some multivitamin additives contain tocopherol as the acetate whereas others contain tocopherol base. It is not clear whether this difference has any significance regarding delivery.

Ergocalciferol

Information on the stability of ergocalciferol in PN mixtures during storage is sparse. The stability of ergocalciferol during administration from PN mixtures has been investigated. Gillis et al.[48] reported that average losses amounting to 32% were recorded during simulated infusion from PN mixtures without fat emulsion. Dahl et al.[35] reported that no losses occurred during simulated infusion in fat emulsion. Indirect data from bioavailability studies in children suggest that ergocalciferol delivery from PN mixtures is at least sufficient to maintain vitamin D status.[50,51]

Phylloquinone

Commercially available fat emulsions contain some phylloquinone. Lennon et al.[52] report, for example, that one product contained between approximately 30–60 μg/dL, the quantity being proportional to fat concentration. The concentration is also fairly consistent between batches of fat emulsion. In contrast, other products contain substantially less phylloquinone. This is due to the type of vegetable oils used.[52]

Phylloquinone has been reported by Billion-Rey et al.[37] to be stable in PN mixtures, with or without fat emulsion, stored in ethylene vinyl acetate (EVA) bags, for 20 d at 4°C.

Phylloquinone losses of between 5 and 17% were reported during simulated infusion over 24 h in an all-in-one TPN mixture exposed to indirect daylight or fluorescent light.[53] Billion-Rey et al.[37] indicated that greater degradation occurred during simulated infusion in sunlight, amounting to at least 50% losses over a 12-h period, even in all-in-one mixtures.

Phytomenadione

Phytomenadione was reported to be stable for at least 10 d after addition to all-in-one PN mixtures, although light protection may be indicated following a reported 6–8.5% degradation after a 4.5-h exposure to artificial daylight.[55]

WATER-SOLUBLE VITAMINS

Riboflavin

Riboflavin has been reported to be stable for at least 4 d in all-in-one PN mixtures stored at 2–8°C,[35] and for 48 h at 5°C or ambient temperature in a range of PN mixtures.[54] Kearney et al.[54] reported that riboflavin is relatively stable (> 80% remaining) after 8 wk of storage at 5°C in two-in-one PN mixtures containing different amino acid infusions.

Riboflavin is degraded by exposure to daylight,[56] although it is less sensitive than retinol. Chen et al.[56] reported total degradation of riboflavin after an 8-h exposure to direct sunlight and 47% loss during exposure to indirect daylight. In contrast, the vitamin was not degraded by exposure to fluorescent light. Losses of riboflavin from all-in-one PN mixtures during simulated infusion over 24 h can amount to 10–20% during indirect daylight exposure.[40] Provided direct exposure to sunlight is avoided, light protection during administration is therefore unnecessary to protect riboflavin.

Riboflavin has been reported to accelerate the photodegradation of certain amino acids.[57] Enhanced degradation of methionine, tryptophan, proline, and tyrosine accelerated in the presence of riboflavin was reported during simulated infusion over a 24-h period. The conditions involved extended exposure to intense phototherapy illumination. Riboflavin concentrations decreased by approximately 50% after 24 h of exposure to phototherapy light.

Pyridoxine

Pyridoxine has been reported to be stable for 4 d at 20°C in an all-in-one PN mixture.[35] Kearney et al.[54] reported that pyridoxine was relatively stable (< 25% degradation) in a range of two-in-one PN mixtures for 8 wk at 5°C.

Direct sunlight causes degradation of pyridoxine. Chen et al.[56] reported almost 90% losses after 8 h of exposure to sunlight, although pyridoxine was stable during exposure to indirect daylight or fluorescent light.

Nicotinamide, Biotin, Pantothenate, and Cyanocobalamin

Although there is virtually no information on the stability of vitamins nicotinamide, biotin, pantothenate, and cyanocobalamin in PN mixtures, Dahl et al.[35] reported that these vitamins were all stable in an all-in-one PN mixture for 4 d at 2–8°C.

Ascorbic Acid

Ascorbic acid is the least stable of all the vitamins added to TPN mixtures. The mechanism of degradation is oxidation, and the compound readily reacts with oxygen. The degradation pathway was described by Tolbert and Ward,[58] and is summarized in Figure 2. The first stage of the reaction, to dehydroascorbic acid (DHA), is reversible. It is also important to note that DHA is biologically active, with biological activity similar to that of ascorbic acid. The second and later stages are not reversible,

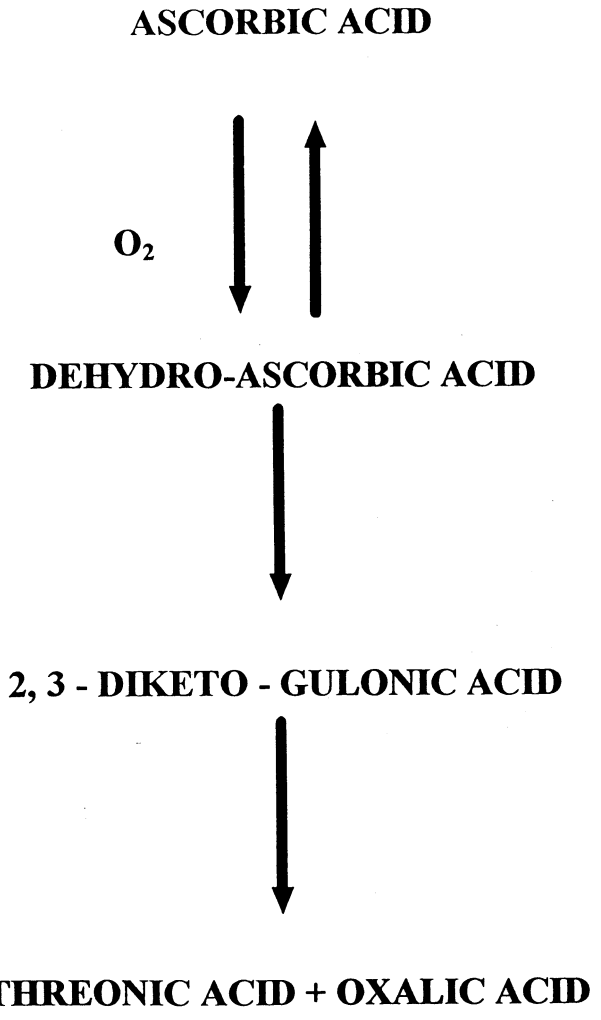

FIG. 2. Ascorbic acid degradation pathway.

leading to loss of biological activity. The reaction rates are governed by temperature and are accelerated rapidly by catalysts, especially copper ions, but also to a lesser extent by ferric, zinc, and manganese ions.[59]

The total quantity of ascorbic acid lost during storage depends on the amount of oxygen present.[60] This oxygen originates from a number of sources, including the infusions and additives (but excluding amino acid and fat emulsion, which are either packed under vacuum or are nitrogen-overlaid), aeration during fluid transfer into the bag, any residual headspace in the bag after filling and sealing, and permeation through the bag wall during storage. Rates of oxygen transmission of plastic film used to fabricate PN bags have been reported as follows (conditions = 100% oxygen, 1 atmosphere, RH; conditions = 50% side one, 90% side two):[61]

1. EVA: Approximately 1000 mL $\cdot$ $(m^2)^{-1}$ $\cdot$ 24 h^{-1}
2. Multilayered bags (composition commonly consists of a triple layer of EVA/ethyl vinyl alcohol [EVOH]): Approximately 10 mL $\cdot$ $(m^2)^{-1}$ $\cdot$ 24 h^{-1}

Ascorbic acid degradation in PN mixtures during storage in big bags and during administration has been widely reported and there is general agreement that ascorbic acid is the least stable component in any PN mixture. Most studies have measured ascorbate only, and have not reported DHA concentrations. West et al.[62] reported rapid degradation of ascorbic acid in two-in-one PN mixtures, with > 80% loss after 24 h at 25°C in one mixture. These authors also highlighted the importance of air causing the greatest and most rapid losses in PN mixtures. Nordfjeld et al.[44] described the degradation of ascorbate in two-in-one PN mixtures with trace elements in PVC bags. The vitamin source was either MVI-12 or Soluvit and the initial concentrations were 30 and 9 mg/L respectively. Concentrations of ascorbate in MVI-12 were reduced by 50%, in 2–4 hours at 24°C, or 8 h at 4°C.

Allwood[63] reported ascorbate degradation in a range of two-in-one PN mixtures in PVC bags stored at 5°C. The multivitamin source was Multibionta, which contains 500 mg ascorbic acid. Losses of ascorbate without trace elements accumulated to a maximum of 20% after 3 d, 30% after 7 d, and greater than 90% after 28 d. Losses, however, were influenced to some extent by the amino acid source. In the presence of trace elements, losses were greater, with up to 80% loss after 3 d, and complete disappearance by 28 d, in all mixtures tested.

In a later study,[60] it was reported that degradation was determined by the amount of oxygen present, and rates of degradation were greatly enhanced in the presence of copper. Degradation during storage at 5°C in two-in-one PN mixtures in PVC bags containing Multibionta as the vitamin source showed losses of 30–40% in 1 d, 60% in 7 d, and 95% in 28 d. Losses during simulated infusion of a two-in-one TPN mixture with trace elements amounted to approximately 30% in 3 h, after which degradation proceeded more slowly. DHA concentrations were also measured during simulated infusion, never apparently rising above 5 μg/mL (equivalent to only approximately 2–3% of ascorbic acid added).

Dahl et al.[35] also determined the degradation of combined total ascorbate (ascorbate + DHA) in all-in-one PN mixtures, the vitamin source being Soluvit N (Pharmacia Upjohn Ltd.) (which contains 100 mg ascorbic acid), but only one-half vial per bag. Losses amounted to approximately 40% in 24 h and 60% in 4 d at 2–8°C in EVA bags. However, the DHA levels contributed more than half of this total. Degradation during simulated infusion over 24 h was also monitored. This amounted to an additional 15–20% total ascorbate/DHA.

Proot et al.[64] examined ascorbic acid and DHA concentrations in an all-in-one PN mixture stored in a variety of containers. The vitamin additive was Cernevit (Baxter Health Care, Ltd.) (containing 125 mg ascorbic acid). DHA levels present during storage were always substantial and often greater than ascorbate concentrations during 7 d of storage at 2–4°C. The authors conclude that a 7-d shelf-life is acceptable, although the effect of the container remained unclear.

Smith et al.[65] examined ascorbic acid degradation (100 mg/PN mixture) in a variety of PN mixtures containing trace elements, with or without fat emulsion. Stability was monitored over a 48-h period at 25°C. Losses accumulated to between 10 and 80%, depending on the amino acid used and the type of container. They reported also that no losses were recorded at 5°C.

Dahl et al.[53] determined the degradation of ascorbic acid (including DHA) in fat emulsion during infusion. The vitamin source, Soluvit N, was added to fat emulsion before administration. Recovery from the infusate fell to approximately 70% after 8 h and to approximately 50% after 24 h.

It should also be noted from this summary that levels of DHA reported in different PN mixtures during storage appear to vary widely, although the reasons are not immediately apparent.

Allwood[43] investigated the causes of ascorbic acid degradation in PN mixtures. Results confirmed the importance of copper as a catalyst for oxidation of ascorbate. The quantities of ascorbate degraded directly correlated with the amount of oxygen present in the solution. Removal of oxygen prevented significant degradation. It was estimated that the oxygen present in infusions and additives, together with the oxygenation of solutions during compounding, would account for between 30 and 50 mg ascorbic acid degradation. This loss would occur within 2–6 h of compounding, although the rate of degradation was reduced in cysteine-containing amino acid infusions. A secondary degradation would then commence due to the permeability of EVA for oxygen. This could account for another 5–10 mg/d. The importance of removing all air from the bag before sealing to minimize ascorbic acid losses was emphasized. Recent studies have shown that this secondary stage of ascorbic acid degradation can be largely avoided if multilayered bags replace the more oxygen-permeable EVA bag.[66] PN mixtures with or without fat emulsion stored in multilayered bags retained up to 80% of added ascorbic acid after 3 mo storage from the vitamin source Multibionta. In EVA bags, the same mixtures showed complete loss of ascorbic acid after 4–5 d. Additional losses will also occur during administration, due to reaction with air (oxygen) present in the administration set.

The final stage of the ascorbate degradation pathway results in oxalic acid, a potentially toxic compound. Although little is known about its possible toxic effects, Das Gupta[67] reported evidence for calcium oxalate precipitation in a PN mixture during administration. Perhaps the recommendation to separate vitamin and trace element additives by administration on alternative days requires careful consideration.[68]

In summary, ascorbic acid is the least stable vitamin, degrading by direct reaction with oxygen, which originates from infusions containing dissolved air such as glucose, and additives; by aeration of infusions during transfer from bag or bottle to PN bag; by residual air in the compounded bag after sealing; and by transmission through the bag wall. Degradation is accelerated by trace elements, especially copper, but this effect is reduced by cysteine. Removal of oxygen will stabilize ascorbic acid in TPN mixtures.

The key nutritional point, however, is that the amount of ascorbic acid delivered to the patient depends on the amount of oxygen, and is unrelated to the concentration of ascorbic acid added to the bag.[60] The oxygen present in any compounded bag will depend on PN mixture composition, but estimates suggest that typically 10–50 mg can be degraded by reaction with residual oxygen. The possible formation of oxalic acid as the final degradation product and subsequent formation of calcium oxalate precipitate requires further investigation.

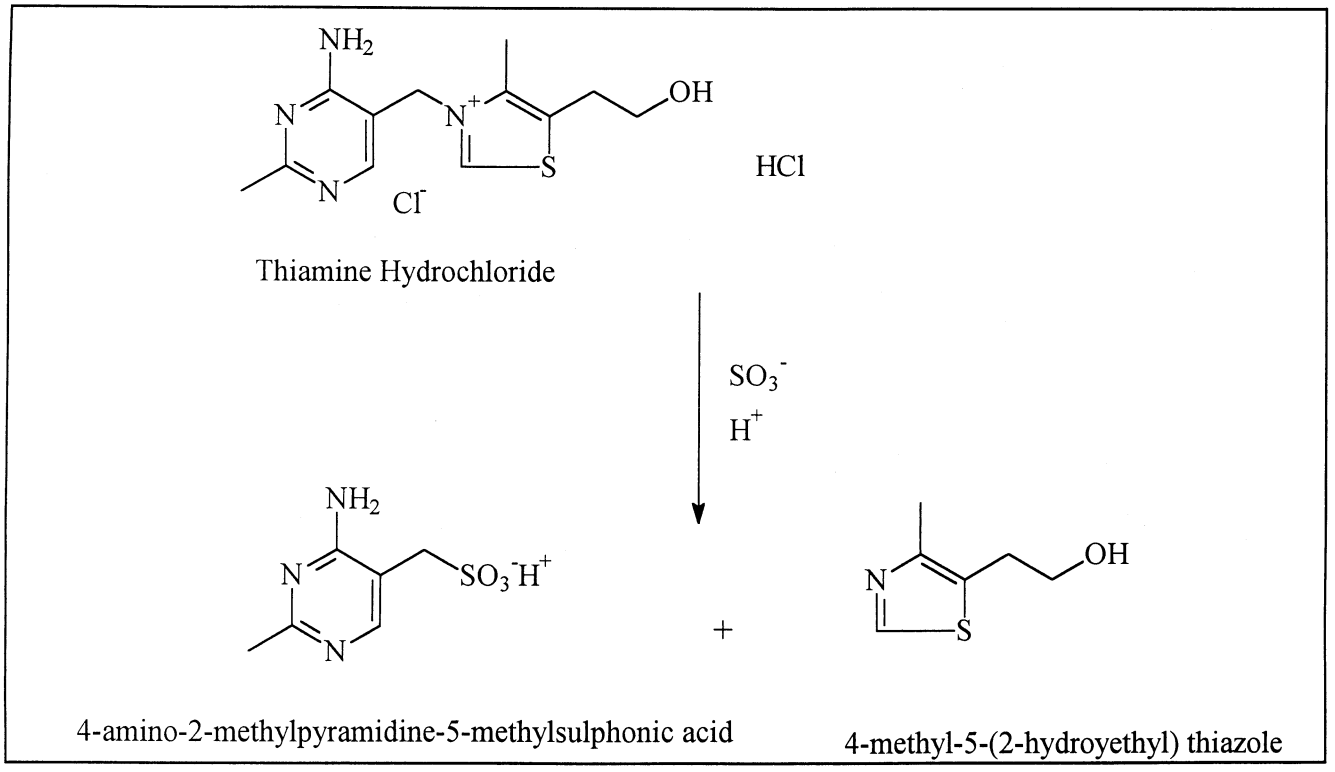

FIG. 3. Thiamine degradation pathway.

Thiamine

Thiamine is degraded by a number of mechanisms.[69] The compound is increasingly unstable as the pH rises and is decomposed by oxidizing or reducing agents. The predominant cause of degradation in TPN mixtures is by reduction, caused in particular by sodium metabisulfite, used as an antioxidant in some commercial amino acid infusions.[70] The route of degradation is summarized in Figure 3.[69] Sulfite cleaves the molecule into pyrimidine and thiazole moieties. The rate of this cleavage increases with increased pH to a maximum rate of pH 6.[70]

The degradation of thiamine in TPN mixtures has been widely investigated. Early work by Scheiner et al.[70] indicated that losses of thiamine were relatively rapid after addition to amino acid infusions containing bisulfite, with almost complete loss recorded after 24 h at ambient temperature. Allwood[63] reported that thiamine (50 mg/bag, Multibionta) was relatively stable during storage in two-in-one PN mixtures, using amino acid infusions with or without metabisulfite. Greater than 75% remaining after 28 d of storage at 5°C, although degradation was slightly greater in PN mixtures containing metabisulfite.

It has been suggested, however, that, after dilution of metabisulfite-containing amino acid infusions in PN mixtures, the degradation of thiamine becomes relatively unimportant. For example, Bowman et al.[71] reported that thiamine in PN mixtures was stable for 22 h at 30°C. It was assumed that dilution of metabisulfite below 4.8 mmol was sufficient to prevent thiamine reduction.

Schmutz et al.[55] investigated the effect of fat emulsion, amino acid, container, and temperature on the stability of thiamine. Losses were greatest when Freamine III (contains 9.6 mmol/L bisulfite nominal) was used as the amino acid source. Only 25% remained after 48 h of storage at 25°C. PN mixtures containing Travasol (Baxter Health Care, Inc., Deerfield, IL, USA), which nominally contained 3 mmol/L bisulfite, showed losses of up to 25% after 48 h at 25°C. In contrast, thiamine was stable in PN mixtures containing amino acid infusions that did not contain bisulfite. A further study confirmed that bisulfite at concentrations above 1 mmol/L caused thiamine degradation.[64]

Because thiamine degradation in PN mixtures is a result of a chemical reaction with metabisulfite, the rates of degradation will depend on metabisulfite concentration. As metabisulfite is added as an antioxidant, some variable losses of this reducing agent can be expected during manufacture of the amino acid infusion. In addition, losses can also occur during PN mixture storage after compounding by reaction with oxygen. This will in turn depend on the amount of oxygen in the bag and on the oxygen permeability of the bag wall. Consequently, degradation of thiamine in stored PN mixtures will depend on a number of factors and predicting losses is, therefore, difficult. For example, recent work in our laboratory indicate that thiamine is stable in PN mixtures for periods in excess of 28 d in mixtures without metabisulfite.[54] Other reducing agents used in amino acid infusions as reducing agents, such as malic acid, do not degrade thiamine. In contrast, degradation in mixtures formulated using Freamine III 8.5% show approximately 50% loss in 5–7 d and greater than 90% loss in some mixtures after 21 d.[72] Because degradation is first order with respect to metabisulphite, degradation rate is independent of thiamine concentration.

Chen et al.[56] noted a 26% loss of thiamine in PN mixtures after 8 h of exposure to sunlight, but no significant losses after exposure to indirect daylight or fluorescent light. Thiamine in TPN is not degraded by exposure to phototherapy light,[55] fluorescent, or

indirect daylight, but exhibits approximately 26% degradation after 8 h of exposure to direct daylight.[56]

As acute thiamine deficiency caused by failure to include multivitamin additives in PN has been shown to be fatal,[73] it is important to ensure that patients receive adequate amounts.

Folic Acid

Folic acid is included in many multivitamin preparations designed for PN addition. An alternative form is folic acid injection. The pH of this product is in the range of 8–11 to ensure folic acid remains in solution. The compound will precipitate, especially in solutions below pH 4.5–5.[74]

Early reports suggested that folic acid was unstable in PN mixtures stored in plastic (PVC) bags, leading to losses of between 2 and 33% after 42 d of storage at ambient temperature.[75] It was suggested that losses were due to absorption to the PVC bag. Later studies suggest that folic acid in PN mixtures is compatible with plastic bags and sets.[76]

Nordfjeld et al.[44] reported very poor stability of folic acid after addition to two-in-one TPN mixtures, with losses of at least 75% after 24 h of storage. Degradation was even greater if exposed to light (although the nature of this light was not described). In contrast, in another report folic acid was shown to be relatively stable in many PN mixtures. Barker et al.[74] reported that folic acid in a range of complete PN mixtures was relatively stable when stored at 4°C. Losses generally amounted to not more than 10% after 14 d of storage. However, whereas Nordfjeld et al.[44] tested two multivitamin preparations containing folic acid (400 μg/vial), Barker et al.[74] used folic acid injection to supplement the low folic acid content of a multivitamin additive (Solivito, Pharmacia Upjohn, Ltd.) to increase final concentrations to between 0.40 and 0.566 mg/L.

Folic acid has also been shown to be stable in all-in-one mixtures for 4 d at 4°C or at ambient temperature.[77] Chen et al.[56] reported that folic acid in PN mixtures was stable for 8 h of exposure to either florescent light, indirect, or direct daylight.

Louie and Stennet[77] investigated the stability of folic acid in amino acid dextrose mixtures under light (fluorescent illumination) and dark conditions, at 2–8°C or ambient temperature, and reported that the compound was stable for 48 h under any combination of these conditions.

Finally, there is evidence to suggest that certain B vitamins may cause folic acid degradation.[78]

The conflicts in published results make it difficult to reach firm conclusions. Results obtained in our laboratory have indicated that folic acid is stable in a range of two-in-one PN mixtures tested in multilayered bags, with greater than 80% remaining after 2 mo of storage (M.C. Allwood and M.C.J. Kearny, unpublished data).

SUMMARY

Common practice is to avoid adding vitamins to PN mixtures until immediately before administration, in which case the addition is commonly made by ward staff at the bedside, without pharmaceutic control. The least stable vitamin is undoubtedly ascorbic acid, and losses during administration can be substantial, although these can, to some extent, be predicted by our knowledge of the mechanisms involved in ascorbate oxidation. Because degradation is directly related to oxygen content of compounded PN mixtures, the use of the multilayered reduced-gas-permeable bag can prevent substantial ascorbate losses during storage. Paradoxically, the presence of ascorbic acid then enhances the overall stability of the PN mixture by creating a highly reduced chemical environment. Two other important mechanisms lead to vitamin losses. Thiamine reduction can be rapid in PN mixtures containing metabisulfite, but this stabilizer is now absent from most amino acid infusions. Photodegradation, especially of retinol, can be prevented during storage and controlled during administration by minimizing exposure to daylight. All-in-one mixtures protect photo sensitive ingredients to all light except direct sunlight. Retinol absorption to plastic bags and administration equipment can be prevented by using the palmitate ester.

REFERENCES

1. Dunham B, Marcuard S, Khazaine PG, Meade G, Craft T, Nichols K. The solubility of calcium and phosphorus in neonatal total parenteral nutrition solutions. JPEN 1991;15:608
2. Henry RS, Jurgens RW, Stugeon R, Athaniker N, Welco A, van Leuvan M. Compatibility of calcium chloride and calcium gluconate with sodium phosphate in a mixed TPN solution. Am J Hosp Pharm 1980;37:673
3. Poole RL, Rupp CA, Kerner JA. Calcium and phosphorus in neonatal parenteral nutrition solutions. JPEN 1983;7:358
4. Schuetz DH, King JC. Compatibility and stability of electrolytes, vitamins and antibiotics in combination with 8% amino acid solution. Am J Hosp Pharm 1978;35:33
5. Driscoll DF, Newton DW, Bistrian BR. Precipitation of calcium phosphate from parenteral nutrient fluids. Am J Hosp Pharm 1994; 51:2834
6. Allwood MC. The compatibility of calcium phosphate in paediatric TPN infusions. J Clin Pharm Ther 1987;12:293
7. Lenz GJ, Mikrut BA. Calcium and phosphate solutions in neonatal parenteral nutrient solutions containing Aminosyn-PF or Trophamine. Am J Hosp Pharm 1988;45:2367
8. Eggert ID, Rusho WJ, Mackey MW, Chan GM. Calcium and phosphorus compatibility in parenteral nutrition solutions for neonates. Am J Hosp Pharm 1982;39:49
9. Jimenez-Torres NV, Ronchera-Oms CL. Calcium and phosphate in all-in-one mixtures. In: *Proceedings 9th Congress ESPEN*. Barcelona Basel: Karger, 1987:204
10. Bishop NJ, Morley R, Day JP, Lucas A. Aluminum neurotoxicity in preterm infants receiving intravenous-feeding solutions. N Engl J Med 1997;336:1557
11. Fitzgerald AK, Mackey MV. Calcium and phosphate solubility in neonatal parenteral nutrient solutions containing aminosyn PF. Am J Hosp Pharm 1987;44:1396
12. Kaminski MV, Harris DF, Collins CF, Sommers GA. Electrolyte compatibility in a synthetic amino acid hyperalimantation solution. Am J Hosp Pharm 1974;1:244
13. Jimenez-Torres NV, Juan Colomer J, Ronchera-Oms CL, et al. Aporte de glucosa-l-fosfato en nutricion parenteral total protocolizada. Nutr Hosp 1989;4:264
14. Ronchera-Oms CL, Jimenez-Torres NV, Peidro J. Stability of parenteral nutrition admixtures containing organic phosphates. Clin Nutr 1995;14:373
15. Hanning RM, Atkinson SA, Whyte RK. Efficacy of calcium glycerophosphate vs conventional mineral salts for total parenteral nutrition in low-birth-weight infants: a randomized clinical trial. Am J Clin Nutr 1991;54:903
16. Food and Drug Administration. Safety alert: hazards of precipitation associated with parenteral nutrition. Am J Hosp Pharm 1994;51:1427
17. Allwood MC, Greenwood M. Assessment of trace element compatibility in total parenteral nutrition infusions. Pharm Weekbl (Sci) 1992;14:321
18. Koorenhof MJC, Timmer JG. Stability of total parenteral nutrition supplied as "all-in-one" for children with chemotherapy-linked hyperhydration. Pharm Weekbl (Sci) 1992;14:50
19. Knowles JB, Cusson G, Smith M, Sitrin MD. Pulmonary deposition of calcium phosphate crystals as a complication of home total parenteral nutrition. JPEN 1989;13:209
20. Stennet DJ, Gerwick WH, Egging PK, Christensen JM. Precipitate analysis from an in-dwelling total parenteral nutrition catheter. JPEN 1988;12:88
21. Shearer CA, Bozian RC. The availability of trace elements in intra-

venous hyperalimentation solutions. Drug Intell Clin Pharm 1977;11: 465
22. Kartinos NJ. Trace element formulations in intravenous feeding. In: Johnson IDA, ed. *Advances in parenteral nutrition*. Lancaster: MTP Press, 1978:233
23. Boddapati S, Yang K, Murty R. Intravenous solution compatibility and filter-retention characteristics of trace element preparations. Am J Hosp Pharm 1981;38:1731
24. Allwood MC. The compatibility of four trace elements in total parenteral nutrition infusions. Int J Pharmaceutics 1983;16:57
25. Bates CG, Greiner G, Gegenheimer A. Precipitate in admixtures of new amino acid injection. Am J Hosp Pharm 1984;41:1316
26. Chatterji DC, Kapoor J. Precipitate in admixtures of new amino acid injection, reply. Am J Hosp Pharm 1984;41:1316
27. Hinchliffe L, Allwood MC. SEM-EDX Assessment of in-line filters following administration of paediatric TPN mixtures. NTPNG Symposium 1994, Proceedings, 1994:3
28. Wan KK, Tsallas G. Dilute iron dextran formulation for addition to parenteral nutrient solutions. Am J Hosp Pharm 1980;37:206
29. Sayers MH, Johnson DK, Schumann LA, Ivey MF, Young JH, Finch CA. Supplementation of total parenteral nitrition solutions with ferrous citrate. JPEN 1983;7:117
30. Levander OA. Considerations in the design of selenium bioavailability studies. Fed Proc 1983;42:1721
31. Shils ME, Levander OA. Selenium stability in TPN solutions. Am J Clin Nutr 1982;35:829
32. McGee CD, Mascarwnhas MG, Ostro MJ, Rasallas G, Jeejeebhoy K. Selenium and vitamin E stability on parenteral solutions. JPEN 1985; 5:568
33. Ganther HE, Kraus RJ. Chemical stability of selenious acid in total parenteral nutrition solutions containing ascorbic acid. JPEN 1989;13: 185
34. Allwood MC, Plane JH. The wavelength-dependent degradation of vitamin A exposed to ultraviolet light. Int J Pharmaceutics 1986;31:1
35. Dahl GB, Jeppson RI, Tengborn HJ. Vitamin stability in a TPN mixture stored in an EVA plastic bag. J Clin Hosp Pharm 1986;11:271
36. Allwood MC. Stability of vitamins in TPN solutions stored in 3 litre bags. Brit J Intraven Ther 1982;3:22
37. Billion-Rey F, Guillaumont M, Frederich A, Aulanger G. Stability of fat-soluble vitamins A (retinol palmitate), E (tocopherol acetate) and K1 (phylloquinone) in total parenteral nutrition at home. JPEN 1993; 17:56
38. Shenai JP, Stahlman MT, Chytil F. Vitamin A delivery from parenteral alimentation solution. J Ped 1989;99:661
39. Howard L, Ohu R, Feman S, Mintz H, Ovesen L, Wolf B. Vitamin A deficiency from long-term parenteral nutrition. Ann Int Med 1980;93: 576
40. Kirk B. The evaluation of a new light-protecting set. Br J Paren Ther 1985;4:146
41. Smith JL, Canham JE, Wells PA. Effect of phototherapy light, sodium bisulfite, and pH on vitamin stability in total parenteral nutrition admixtures. JPEN 1988;12:394
42. Moorhatch P, Chiou WL. Interactions between drugs and plastic intravenous fluid bags. Part 1: sorption studies on 17 drugs. Am J Hosp Pharm 1974;31:72
43. Allwood MC. Compatibility and stability of TPN mixtures in big bags. J Clin Pharm Therap 1984;9:181
44. Nordfjeld K, Pederson JL, Rasmussen M, Jensen VG. Storage of mixtures for parenteral nutrition III. Stability of vitamins in TPN mixtures. J Clin Hosp Pharm 1984;9:293
45. Gutcher GR, Lax AA, Farrell PM. Tocopherol isomers in intravenous lipid emulsions and resultant plasma concentrations. JPEN 1984;8:269
46. Kishi HK, Yamaji A, Kataoka K, et al. Vitamin A and E requirements during total parenteral nutrition. JPEN 1981;5:420
47. McKenna MC, Bieri JC. Loss off vitamin A from total parenteral nutrition solutions. Federation Proc 1980;39:561
48. Gillis J, Jones G, Penchardz P. Delivery of vitamins A, D and E in total parenteral nutrition solutions. JPEN 1983;7:11
49. Drott P, Meurling S, Meurling L. Clinical adsorption and photodegradation of the fat soluble vitamins A and E. Clin Nutr 1991;10:348
50. Hariz MB, De Potter S, Corriol O, et al. Home parenteral nutrition in children: bioavailability of vitamins in binary mixtures for 8 days. Clin Nutr 1993;12:147
51. Davis AT, Franz FP, Coutney DA, Ullrey DE, Scholten DJ, Dean RE. Plasma vitamin and mineral status in home parenteral nutrition patients. JPEN 1987;11:480
52. Lennon C, Davidson KW, Sadowski JA, Mason JB. The vitamin K content of intravenous lipid emulsions. JPEN 1993;17:142
53. Dahl GB, Svensson L, Kinnander NJG, Zander M, Bergstrom UK. Stability of vitamins in soybean oil fat emulsion under conditions simulating intravenous feeding of neonates and children. JPEN 1994; 18:234
54. Kearney MCJ, Martin H, Allwood MC, Hardy G. Stability of vitamins in TPN mixtures after prolonged storage. In: *BAPEN conference proceedings 1994*. Birmingham
55. Schmutz CW, Martinelli E, Muhlebach S. Stability of vitamin K assessed by HPLC in total parenteral nutrition. Clin Nutr 1992; 12(suppl):169
56. Chen MF, Boyce W, Triplett L. Stability of B vitamins in mixed parenteral nutrition solution. JPEN 1983;7:462
57. Bhatia J, Stegink LD, Ziegler EE. Riboflavin enhances photo-oxidation of amino acids under simulated clinical conditions. JPEN 1983; 7:277
58. Tolbert BM, Ward JB. Dehydroascorbic acid. In: *Advances in chemical series*. Washington: American Chemical Society, 1982;200:101
59. Davies MB, Austin J, Partridge DA. *Vitamin C: its chemistry and biochemistry*. Letchworth: Royal Society of Chemistry Paperback, 1991:130
60. Allwood MC. Factors influencing the stability of ascorbic acid in total parenteral nutrition infusions. J Clin Hosp Pharm 1984;9:75
61. Hardy G, Mari G. The stability of TPN solutions in a new plastic container. Clin Nutr 1988;7(suppl):75
62. West KR, Sansom LN, Cosh DG, Thomas MP. Some aspects of the stability of parenteral nutrition solutions. Pharma Acta Helv 1976; 51:19
63. Allwood MC. Stability of vitamins in total parenteral nutrition solutions stored in three litre bags. Brit J Int Ther 1982;1:22
64. Proot P, De Pourco L, Raymakers AA. Stability of ascorbic acid in a standard total parenteral nutrition mixture. Clin Nutr 1994;13:273
65. Smith JL, Canham JE, Kirkland WD, Wells PA. Effect of Intralipid, amino acids, container, temperature and duration of storage on vitamin stability in total parenteral nutrition admixtures. JPEN 1988;12: 478
66. Allwood MC, Brown PE, Ghedini C, Hardy G. The stability of ascorbic acid in TPN mixtures stored in a multilayered bag. Clin Nutr 1992;11:284
67. Das Gupta V. Stability of vitamins in total parenteral nutrient solutions. Am J Hos Pharm 1986;43:2132
68. Allwood MC. Stability of vitamins in total parenteral nutrient solutions. Am J Hosp Pharm 1986;43:2138
69. Williams RR, Spies TD. *Vitamin B1 and its use in medicine*. New York: The Macmillan Company New York, Macmillan Medical Monographs, 1938
70. Scheiner JM, Araujo MM, DeRitter E. Thiamine destruction by sodium bisulphite in infusion solutions. Am J Hosp Pharm 1981;38:1911
71. Bowman B, Nguyen P. Stability of thiamine in parenteral nutrition solutions. JPEN 1983;7:567
72. Kearney MCJ, Allwood MC, Hardy G. The stability of thiamine in TPN mixtures stored in EVA and multilayered bags. Clin Nutr 1995; 14:295
73. Anon. Deaths associated with thiamine deficient parenteral nutrition. MMWR 1989;38:43
74. Barker A, Hebron BS, Beck PR, Ellis B. Folic acid and total parenteral nutrition. JPEN 1984;8:3
75. Almodovar MJ, Hernandez Jaras MV, Leon-Sanz M, et al. Estabilidad del acido folico y vitamina B_{12} en NTP. Nutr Hosp 1991;6:249
76. Lee DR, Ware I. Survival of folic acid in TPN solutions. Br J Int Ther 1980;1:13
77. Louie N, Stennett DJ. Stability of folic acid in 25% dextrose 3.5% amino acids and multi-vitamin solution. JPEN 1984;8:421
78. Biamonte AR, Schneller GH. A study of folic acid stability in solutions of the B complex vitamins. J Am Pharmacol Assoc (Sci ed) 1951;40:313