International Journal of Pharmaceutics, 81 (1992) 1–20

IJP 02697

Invited Review

Chemical stability of total parenteral nutrition mixtures

R.J. Manning and C. Washington

Department of Pharmaceutical Sciences, University of Nottingham, University Park, Nottingham NG7 2RD (U.K.)

(Received 9 September 1991)
(Accepted 1 October 1991)

Key words: Stability; Parenteral nutrition; Amino acid; Vitamin; Electrolyte; Trace element; Glucose

Summary

Total parenteral nutrition mixtures are complex multicomponent systems which have considerable potential for reaction between the various nutrients present. The article discusses the factors affecting the chemical stability of materials commonly added to total parenteral nutrition mixtures. This includes the stability of amino acids, vitamins, trace elements, and calcium phosphate compatibility. The stability of a range of the more common drug additives is also examined. This review complements an earlier article (*Int. J. Pharm.*, 66 (1990) 1–21) which discussed the physical emulsion stability of TPN mixtures.

Introduction

Malnutrition is a common problem in hospitals. Indeed, one study has shown that as many as 50% of patients in surgical wards are undernourished at some stage (Hill et al., 1977). These patients are more likely to suffer complications, are more susceptible to infections, have increased post-operative mortality and generally have a longer hospital stay. Therefore, methods of providing nutritional support are important. Parenteral nutrition is an accepted method for prevention or correction of malnutrition in patients whose gastro-intestinal tract is not functioning adequately to provide the body with the necessary nutrients. Total parenteral nutrition (TPN) provides the body with all the nutrients it needs, nitrogen, energy and micronutrients, as an intravenous infusion.

Nitrogen is derived from L-amino acids, and the amino acid solutions used in TPN generally contain all the essential and many non-essential amino acids used in protein synthesis. Non-protein energy requirements from TPN come from two sources: carbohydrates and lipids. Carbohydrates are normally administered in the form of glucose (dextrose) because it is inexpensive and easily monitored in the blood, and also because this is the form in which most dietary carbohydrate reaches the body's tissues. Fat emulsions, e.g. Intralipid, are the most common source of lipid calories and essential fatty acids in TPN, and are emulsions of soybean oil with egg yolk

Correspondence: C. Washington, Department of Pharmaceutical Sciences, University of Nottingham, University Park, Nottingham NG7 2RD, U.K.

phospholipid emulsifiers. Micronutrients provided by TPN include vitamins and trace elements, and electrolytes are also included.

TPN mixtures thus contain amino acids, glucose, fat, electrolytes, trace elements, vitamins and water. They are often given as an all-in-one admixture, in which everything is mixed together before administration. However, due to concern over the compatibility and stability of fat emulsions in all-in-one admixtures (Washington, 1990), the lipid can also be separated from the other components and co-administered, so that mixing occurs on entry to the body. TPN preparations have a complex composition and this increases the potential for component incompatibilities. These incompatibilities can either cause chemical instability (i.e. that of the added nutrients) or physical instability (i.e. flocculation or coalescence of the emulsion).

Chemical instability involves the irreversible degradation of a component such that the chemical integrity and potency of the active ingredient are no longer within the specified limits, while physical instability produces a change in appearance, palatability, uniformity, gas production, dissolution or suspendibility of the lipid emulsion. This review will be concerned with the compatibility problems in terms of chemical stability rather than physical, which has already been extensively reviewed. Chemical instability is normally due to chemical reactions among the TPN constituents, and these include hydrolysis, molecular complexation, oxidation, reduction, photolysis, and racemization. These reactions are affected by the surrounding conditions such as pH and temperature; for example, a 10°C rise in temperature increases the rate of many reactions several times.

In general, a component of a TPN admixture is considered chemically stable over a given period if it decomposes by less than 10% under the specified conditions. The chemical stability of amino acids, vitamins, electrolytes, trace elements and glucose will each be examined in turn, and the effects that the surrounding conditions have on chemical stability will also be considered. The chemical stability of some widely used drugs will also be reviewed.

Amino Acids

Amino acids are an important component of TPN mixtures and are used by the body for synthesising proteins. A number of different amino acid solutions are available. All contain the eight essential amino acids (isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan and valine), but differ in their content of non-essential amino acids. These include histidine (essential in infants and uraemic patients), cysteine, taurine and tyrosine (which may be essential in premature infants), alanine, arginine, proline, serine, glycine, aspartic and glutamic acids, and glutamine. None of the solutions mentioned below contain taurine or glutamine, and only Vamin contains aspartic and glutamic acids. Each amino acid solution also differs in pH, electrolyte content and osmolarity.

Mixed amino acid and dextrose solutions were found to be stable for 12 weeks at 4°C (Laegler et al., 1974). These workers used 4.25% FreAmine (which contains all the afore-mentioned amino acids except tyrosine) in 25% dextrose solution with sodium bisulphite as an antioxidant, and stored samples in evacuated sterile containers with no additives at temperatures of 4, 25 and 37°C for 12 weeks. As the temperature increased, amino acid degradation was enhanced and only the samples stored at 4°C showed no deterioration after 12 weeks. Decomposition occurred with time due to the Maillard reaction (which is an interaction between organonitrogenous agents and dextrose causing darkening of solutions and will be considered later). This group therefore concluded that amino acids retain their chemical integrity for at least 12 weeks under refrigeration. They also suggested that microbial contamination was probably a limiting factor in storage, and that solutions should be administered as soon as possible after compounding, even if refrigerated.

However, this study did not analyse the stability of cysteine, arginine or tryptophan (which is the most labile amino acid). These amino acids, if degraded by mechanisms other than the Maillard reaction, may further reduce the storage life. The stability of FreAmine over a 2 week period was also investigated by Jurgens et al. (1981), and all

the amino acids were included in the analysis except for cysteine. They found that there was a small decrease in tryptophan concentration, which was more pronounced at room temperature than at 4°C (94.1 and 97.5% of the initial concentration, respectively). The changes in other amino acid concentrations were within experimental variation. Hence, they concluded that amino acid solutions remained stable for up to 2 weeks at either room temperature or 4°C, but that storage at 4°C was better for tryptophan stability and also retarded growth of micro-organisms introduced by accidental contamination. This supports work carried out by Rowlands et al. (1973).

There are several reasons for tryptophan instability. It has been shown to undergo a light-catalysed reaction to indigo carmine, which is coloured (Kleinman et al., 1973). Storage of solutions of essential amino acids in clear glass vials for 6 months at room temperature resulted in solution darkening. Similar storage in amber vials resulted in retention of 96% of the original tryptophan concentration and prevented the solution darkening as in the clear vials. This led to the conclusion that tryptophan decays on exposure to light. The other essential amino acids were found to be unaffected by light. Thus, all manufacturers recommend that their amino acid solutions be protected from light prior to use (Kerner, 1983). Tryptophan also decomposes in the presence of sodium bisulphite, which is an anti-oxidant used in many amino acid solutions. A tryptophan reduction of 20% was seen at a sodium bisulphite concentration of 0.1% (Kleinman et al., 1973). The products formed during the reaction were not identified.

The stability of Travasol (which contains all amino acids except cysteine) in TPN mixtures containing hydrochloric acid (HCl) was investigated by Mirtallo et al. (1981). The concentration of proline and histidine had declined by 24 h after HCl addition, and this phenomenon was dependent on HCl concentration. There was no apparent reduction in concentration of other amino acids after 24 h except for tryptophan, whose levels decreased over time independently of HCl concentration. It has been shown that added acid is available from TPN solutions and therefore could be used in treating severe metabolic acidosis of TPN patients. However, HCl addition reduces pH and therefore should be carried out with caution because pH can affect other amino acids, e.g. tyrosine may precipitate at pH below 3.0, and emulsion stability may be altered.

No significant decreases in amino acid concentrations in mixtures using Aminosyn (which lacks cysteine) were found after 30 days of storage under refrigeration (Parr et al., 1985). TPN mixtures stored at room temperature had a faster rate of amino acid degradation over 30 days, but only arginine and methionine showed significant reductions in concentration (8.2 and 10.2%, respectively).

Synthamin, which does not contain serine, was found to be stable for 2 months in a TPN mixture stored at 4°C (Nordfjeld et al., 1983). After 6 months, only tyrosine, lysine and histidine retained more than 90% of their original concentrations. The greatest degradation was seen with alanine, proline, methionine, glycine, arginine (more than 20% loss) and threonine (more than 25% loss). Tryptophan was one of the more stable amino acids with a reduction of 13%, despite bisulphite being present. The authors considered three explanations for the degradation of the amino acids. The first was oxidation as the PVC bag was permeable to oxygen. However, tryptophan is the most sensitive amino acid to oxygenation and was not degraded. The second, loss due to the Maillard reaction, was not feasible as this reaction does not occur to a great extent at 4°C. The third explanation was that an amino group was released. This would result in raised ammonia levels, which were not shown using their method.

Jeppsson and Tengborn (1987) studied the amino acid solution Vamin (which contains all the essential amino acids) and no reduction in concentration of any amino acid was observed after 4 weeks of refrigeration followed by 24 h at room temperature to simulate hospital use. Cysteine, however, was not analysed, as losses of 33% were seen at time zero. Interestingly, tryptophan levels increased by up to 34%, but this was not explained.

Cysteine is not often included in amino acid solutions for TPN because of its stability problems (Bjelton and Fransson, 1990). The cysteine content of a solution decreases significantly in the presence of oxygen and/or glucose because it forms derivatives such as cystine and D-glucocysteine. However, results suggest that cysteine is available for metabolic processes from these derivatives. An alternative to cysteine in TPN may be OTCA, a cysteine analogue, which is stable in solution and can be metabolised in the body to yield cysteine. It has also been proposed that the sulphydryl group of cysteine may react with copper to form a precipitate (Bates et al., 1984) thus reducing stability, but data as to whether the presence of sodium bisulphite may prevent this reaction are not available.

Glutamine is also unstable and so is not included in amino acid solutions. Recently, the importance of this amino acid has been recognized and new methods for its administration are being investigated. Two possibilities are to administer it as a dipeptide or as acetylated glutamine, which are both chemically stable and biologically available (Clark, 1990).

Photo-oxidation of amino acids, which could occur in neonates receiving phototherapy (which involves high-intensity light) to enhance bilirubin metabolism, has been recognised for some time. The most susceptible amino acids are cystine, histidine, methionine, tryptophan and tyrosine. In amino acid solutions containing vitamins and 10% dextrose, histidine, methionine and tryptophan concentrations decreased by 22, 40 and 44%, respectively, after 24 h light exposure (Bhatia et al., 1980). Concentrations of tryptophan also decreased when vitamins were not present. In a more recent investigation (Bhatia et al., 1983), the study was improved in that the conditions more closely simulated those occurring during neonatal therapy in terms of the length and type of tubing, solution containers, flow rates and intensity of photo-irradiation (unlike the initial study which had more intense radiation, short tubing and no flow). The results showed that photo-oxidation of glycine and leucine, but not that of tryptophan occurred to some extent in the absence of riboflavin over 24 h (although the decreases could be due partly or totally to absorption by the tubing), but that riboflavin, when present, significantly enhanced decreases in concentrations of methionine, proline, tryptophan and tyrosine. Although the losses of amino acids are probably not nutritionally important, the photo-oxidation products are largely unknown and may be toxic. Further investigations are needed in order to identify these products formed in clinical situations and until then it may be sensible to protect amino acid solutions containing vitamins from strong light. More recently, the use of oxygen-impermeable multilaminate bags appears to reduce amino-acid decomposition, and it is likely that many of the photochemical decomposition paths are oxygen dependent.

Vitamins

The major constraint on storage time of TPN solutions is the instability of certain vitamins. There are 13 vitamins in total, divided into six groups; A, B, C, D, E and K. To date, not all of these vitamins have been studied in great detail with respect to chemical stability, even though they are present in commercial vitamin preparations. Vitamin stability may be affected by various factors of the TPN mixture itself, such as pH, electrolytes, trace elements and other vitamins; and environmental conditions including temperature, storage time and light exposure. Some vitamins may also be lost from the TPN mixture through adsorption and/or absorption by the plastic bag in which it is contained.

As several vitamins are light sensitive, manufacturers recommend that TPN solutions be protected from light to retard their degradation. An ultraviolet light protective bag also prevents photo-oxidation of certain amino acids and the light catalysed destruction of tryptophan. It should be noted that the information available on vitamin stability is often conflicting and in some cases, has been based on unsatisfactory experiments where large doses of vitamins were tested under various conditions over several weeks without suitable controls for comparison.

Vitamin A – retinol

Vitamin A is rapidly degraded by UV light, whether it be high-intensity UV light (bilirubin light) used in phototherapy, or sunlight (Allwood and Plane, 1986; Allwood, 1990). Artificial light usually contains very little UV and so will not cause degradation. Kishi et al. (1981) found that after 3 h of direct sunlight only about half of the original vitamin A content remained. More recently, Allwood (1990) stated that more than 90% of the vitamin A content was likely to be lost after just 1–2 h of exposure. However, in mixtures containing Intralipid, vitamin A losses due to photo-degradation are greatly reduced (Smith et al., 1984, 1988a), probably due to the opacity of Intralipid admixtures.

Vitamin A is not affected by sodium bisulphite at concentrations less than 3 mM. At a concentration of 3 mM in admixtures containing Intralipid, a 50% loss of vitamin A occurred after 48 h whereas in admixtures without Intralipid, the losses were smaller (Smith et al., 1988a). No satisfactory explanation was given.

Poor delivery of vitamin A as retinyl acetate has been repeatedly demonstrated from TPN mixtures (Chiou and Moorhatch, 1973). The vitamin A losses from glass bottles vary between 40 and 80%, depending on storage conditions and the duration of infusion (Hartline and Zachman, 1976; McKenna and Bieri, 1980; Shenai et al., 1981). Protection from light had little effect and retinol was successfully and repeatedly extracted from the PVC tubing. No sorption to glass bottles was found and the conclusion was reached that adsorption to the PVC was the major source of vitamin A loss, and that vitamin A addition to TPN should be increased 3–4-fold to compensate for the losses.

The effect of storage in PVC bags was studied by Gillis et al. (1983), who showed mean effluent recoveries of radiolabelled vitamin A from a simulated TPN solution to be 31% after 24 h. The results demonstrated negligible vitamin A concentrations in the effluent after 1–1.5 h of infusion with concentrations reaching a steady state of delivery after 2–3 h. Moorhatch and Chiou (1974) also demonstrated a sustained reduction in unbound retinyl acetate over 24 h, with losses of up to 75% in PVC bags at room temperature and with light protection. Sorption was increased in the presence of dextrose, normal saline, increased temperature and time, by enhancing diffusion. This latter finding led to the conclusion that absorption rather than adsorption was the major cause for the vitamin A loss.

Adsorption, where the solute interacts with the PVC surface, occurs rapidly so that equilibrium would be quickly reached. Absorption into the PVC matrix results in a strong physicochemical interaction such as Van der Waals or hydrogen bonding (which is favoured by the chemical properties of vitamin A). It continues over time without reaching binding site saturation or equilibrium, and as a consequence larger amounts of vitamin can be removed, with the rate of diffusion from solution into the plastic matrix being the rate-limiting factor.

More recent studies, however, have suggested that the sorption process may in fact be saturable (Riggle and Brandt, 1986; Henton and Merritt, 1990). Henton and Merritt (1990) observed that as concentrations of vitamin A increased, less overall vitamin loss occurred. This led to the conclusion that the vitamin was binding to non-specific binding sites on the tubing which were saturable. In the study by Riggle and Brandt (1986), the vitamin A content in intravenous tubing was observed to be reduced by 88% over a period of 5 h, and this uptake by tubing binding sites was found to be saturable. Hence, in a clinical situation using both bag and i.v. tubing, a reduction of only 26–67% of vitamin A occurred, provided the apparatus was kept in dim light to prevent loss by photo-oxidation. When not protected from light, 77–98% of vitamin A was lost, and this reduction occurred quickly inferring photodecomposition. The authors concluded that between 20 and 70% of the vitamin A was lost due to adherence and absorption to both the administration set and tubing; this is unlikely due to the relative rates of these competing processes, which suggests that photodecomposition will always be more important. One interesting possibility is that the absorbed vitamin may be more photochemically stable than that in solution, since the photo-

chemistry of most organic molecules is environment-sensitive, and may be related to the diffusion rate of oxygen in the plastic.

Vitamin A has been shown to have a greater availability from polyolefin than polyvinyl chloride tubing under varying conditions of vitamin A concentration, temperature and flow rate (Henton and Merritt, 1990). Vitamin A recovery after 24 h ranged from 47 to 87% with polyolefin and from 19 to 74% with polyvinyl chloride, with the poorest recovery being at a temperature of 37°C.

Intralipid has a protective action on vitamin A degradation. When kept in Intralipid, about 90% of the initial retinol content remained after 24 h compared to only 20% in a TPN mixture without lipid (Greene et al., 1987). This was attributed to the fact that lipid soluble vitamins are incorporated into the oil phase of lipid emulsions and hence are protected against losses due to light or adherence to plastic infusion sets. Smith et al. (1988b) showed that vitamin A was stable in glass bottles and admixtures containing Intralipid, but that levels were lower without Intralipid and in plastic bags, especially in mixtures without Intralipid where reductions of 35 and 60% were seen after 48 h at 5 and 25°C, respectively. They proposed that the protection of vitamin A by Intralipid was due either to the two competing for binding sites on the plastic or to the vitamin dissolving in the lipid droplets rendering them unable to bind to the plastic.

Tests have been performed on a relatively recent multivitamin preparation, Berocca PN, which instead of retinyl acetate contains retinyl palmitate as a source of vitamin A. Gutcher et al. (1984) showed that retinyl palmitate was more stable than retinyl acetate and was not absorbed by PVC, and should therefore be used in multivitamin preparations. Dahl et al. (1986) also found that retinyl palmitate losses were negligible. In contrast, Martens (1988) discovered a 20% loss in retinyl palmitate after 24 h in a lipid-containing TPN mixture exposed to light. Further studies are therefore necessary before retinyl palmitate stability can be proven.

Significant losses of vitamin A may therefore occur during TPN delivery, the loss being related to storage time, temperature, infusion time and type of administration equipment used, and further vitamin destruction may occur if solutions are exposed to UV light (Niemiec and Walker, 1983). Manufacturers already include an excess of 25–30% vitamin A above the labelled content in their vitamin solutions. Nevertheless, vitamin A status should be monitored during long TPN courses and vitamin A-depleted patients could be supplemented by i.m. or oral routes instead.

Vitamin B group

Thiamine (B1)

Thiamine is partly degraded by direct sunlight (26% loss over 8 h), but not by indirect sunlight or fluorescent light (Chen et al., 1983). Phototherapy light also has no effect (Smith et al., 1988a).

Thiamine instability in the presence of reducing agents, e.g. sodium bisulphite, has been recognised for a long time as they are thought to enhance hydrolytic cleavage. However, in complete TPN mixtures, any reducing agents present in amino acid solutions are highly dilute, so that this reaction is probably of little importance (Niemiec and Vanderveen, 1984; Allwood, 1990). Ascorbic acid will also act as a reducing agent, but there is no evidence to suggest that thiamine is degraded by this mechanism (Allwood, 1990).

Scheiner et al. (1981) observed that the rate of thiamine degradation increased with increasing pH and increasing temperature (at pH 6.5 and room temperature, there was almost complete loss after 24 h). The extent of loss also depended on storage time and the multivitamin preparation used. Thiamine loss was still substantial under refrigeration and normal conditions of administration. However, the concentrations of sodium bisulphite used in this study were much higher than those found in normal TPN mixtures, as the vitamin source was mixed directly into the amino acid solutions. Therefore, the actual loss of thiamine in standard TPN solutions may be smaller than that found by Scheiner et al. (1981).

In a similar experiment, the direct addition of multivitamin solutions to Travasol 10% solution containing 0.1% bisulphite led to a thiamine loss of 40% after 22 h at 31°C (Bowman and Nguyen,

1983). In contrast, when they added the multivitamins to a TPN solution containing 4.25% amino acids, 25% dextrose and electrolytes, where the sulphite was diluted by the mixture volume to approx. 0.05% and the pH buffered, thiamine was found to be stable for 22 h. More recent studies agree with these findings. Smith et al. (1988b) observed that thiamine was stable in all TPN admixtures at 5°C independent of the amino acid solution used, and in all at 25°C except for that containing Freamine III when only 25% remained after 48 h. This was attributed to the fact that Freamine III had the highest bisulphite concentration and also a pH of 6.4. Dahl et al. (1986) also found that no loss of thiamine occurred after 24 h of simulated infusion, but the amino acid solution used did not contain bisulphite.

Addition of Intralipid was not found to influence thiamine degradation by sodium bisulphite (Smith et al., 1988a). Thiamine levels decreased as bisulphite concentration increased at pH 5.5, but at higher pH values, the levels remained unchanged.

Until further studies are undertaken, it is advisable to monitor patients on TPN who are predisposed to thiamine deficiency and alternative methods for thiamine supplementation should be considered (Niemiec and Vanderveen, 1984). The problems associated with vitamin A and thiamine have been made more severe by the recent reduction in concentration of these vitamins in multivitamin preparations as a result of the new recommended dietary allowances.

Riboflavin (B2)

Riboflavin is degraded by light. A study in 1983 by Chen et al. showed that indirect and direct sunlight destroyed 47 and 100% of riboflavin, respectively, in 8 h, but that riboflavin was stable against fluorescent light. On exposure of TPN admixtures to phototherapy light, a loss of riboflavin was again seen (Smith et al., 1984, 1988a). When Intralipid was included, so making the mixture opaque, there was less decomposition. Both experiments also demonstrated that riboflavin was not affected by sodium bisulphite.

Riboflavin has been found to decrease in concentration by 40% after 8 h and 55% after 24 h when stored in 3 l bags, and by a further 2% on passage through the administration set (Allwood, 1984a). In contrast, riboflavin in TPN mixtures has been reported to be stable under varying conditions of temperature, light, storage time, storage container and amino acid solution (Dahl et al., 1986; Smith et al., 1988b). This could be due to the protective effect of the Intralipid in the TPN admixtures.

Niacin (nicotinic acid)

Niacin is known to be unstable in the presence of oxidising agents. It is reported to be stable for 8 h under different conditions of light (Chen et al., 1983). Dahl et al. (1986) found niacin to be stable for 96 h in the dark at 2–8°C. Niacin was stable under all conditions tested in TPN solutions (Martens, 1988).

Pyridoxine (B6)

Although pyridoxine is light sensitive, it undergoes less degradation than vitamin A or riboflavin (Allwood, 1984a). In fact, pyridoxine is unaffected by all forms of light except for direct sunlight, where it is reduced by 86% after 8 h exposure (Chen et al., 1983). It has also been claimed to be incompatible with iron salts and oxidising agents (Phillips and Odgers, 1986).

Cyanocobalamin (B12)

Vitamin B12 undergoes rapid degradation by ascorbic acid (Schuetz and King, 1978). Thiamine also accelerates its degradation (DeRitter, 1982). Cyanocobalamin is reported to be unstable in the presence of light, although this has yet to be proven. However, it has been found to be stable in TPN mixtures for 96 h at 2–8°C with light protection (Dahl et al., 1986).

Biotin

Biotin is stable for 96 h at 2–8°C when light protected (Dahl et al., 1986). DeRitter (1982) also claimed that biotin was stable in typical TPN systems.

Pantothenate

Pantothenate was found to be stable for 96 h when refrigerated and protected from light. (Dahl

et al., 1986). It is stated to be most stable between pH 6 and 7 (DeRitter, 1982).

Folic acid

There are conflicting data as to the stability of folic acid in TPN because it is difficult to analyse and possesses a limited and pH-dependent solubility. Folic acid is stable under fluorescent light, direct and indirect sunlight for 8 h (Chen et al., 1983) and phototherapy light for 48 h (Smith et al., 1988a). However, it does undergo oxidative cleavage when exposed to light and this is significantly enhanced in the presence of riboflavin, more so at pH 4 than pH 6.5 (Scheindlin et al., 1952). Folic acid is also stable in the presence of sodium bisulphite, at concentrations of 0–10 mM (Smith et al., 1988a). In contrast, an earlier report by the same group found that folate concentration decreased significantly at sodium bisulphite concentrations of 10 mM. Folic acid is decomposed by ascorbic acid, but at pH 6.5, only 20% is lost in 4 weeks (Scheindlin and Griffith, 1951) and the significance of this in practice is uncertain. Folic acid is stated to lose less than 10% of its activity after 24 h in a dilute solution with vitamins B and C (Niemiec and Vanderveen, 1984). Precipitation of folic acid may occur when high concentrations of calcium ions are present (Allwood, 1984a).

Folic acid (or folate in its salt form) has been reported to be stable at 4 and 25°C in TPN solutions containing other vitamins for at least 1 week when protected from light (Barker et al., 1984). However, at pH below 5.0, folic acid precipitated from solution, but, as most TPNs have a pH of between 5 and 6, this is unlikely to occur in practice. Caution should be taken when adding large amounts of dextrose, as this lowers pH, and the authors therefore recommended that dextrose concentrations above 20% should not be included in TPNs used for folic acid delivery. Intralipid was found to cause an increase in folate concentration, but this was not satisfactorily explained, and may be related to assay difficulties. No adsorption of folate onto the plastic of the container or administration set was noted (Lee et al., 1980). Barker and co-workers (1984) concluded that provided the acidity of the TPN mixture stayed above pH 5, folic acid would remain stable in solution at the concentrations usually used for TPN and that all the folic acid would be delivered to the patient. However, the common dose of 0.2 mg daily was inadequate to meet the requirements of most patients.

In contrast, Nordfjeld et al. (1984) claimed that folic acid degraded with a half-life of 2.7 h in a TPN mixture which was stored at room temperature and in daylight, of 5.4 h at 24°C and in the dark and 24 h when stored at 4°C and protected from light. They attributed the rapid loss of folic acid to the presence of trace elements, but the low pH of the solutions could equally have been responsible (Gupta et al., 1986).

Folic acid was stable for 48 h at all concentrations between 0.25 and 1.0 mg/l whether kept at room or refrigeration temperatures, in the light or dark (Louie and Stennett, 1984). However, no electrolytes or trace elements were added to the admixtures (which contained dextrose, amino acids and multivitamin solution) as they were thought to complex the folic acid. Folacin stability was not affected by Intralipid, temperature, storage container, amino acid solution or storage time (Smith et al., 1988b).

Vitamin C – ascorbic acid

Ascorbic acid is the least stable vitamin in TPN mixtures and is incompatible with many drugs, degrades and darkens on exposure to light of all kinds and is rapidly oxidised in air and alkaline media. The most important mechanism of degradation is that of oxidation to inactive products. The amount of ascorbic acid degraded depends on the dissolved oxygen content of the TPN mixture, the amount of residual air in the bag after filling, the permeability of the plastic to oxygen and storage time (Allwood, 1984b). Glass bottles are not permeable to oxygen and thus oxidation is reduced (Smith et al., 1988b). Degradation also occurs as the TPN solution passes through the administration set due to the presence of air, and this can cause a further 20–30 mg loss of ascorbic acid (Allwood, 1990).

Trace elements catalyse the oxidation reaction, in particular copper, but also iron and zinc (manganese and magnesium have little effect). In the presence of copper, degradation of ascorbic acid occurs until dissolved oxygen is depleted, and 150–200 mg will be lost within 2–4 h. In the absence of copper, only 20–30 mg of ascorbic acid was found to be degraded within 24 h (Allwood, 1984b). Cysteine however, chelates heavy metals such as copper and so reduces the rate of ascorbate degradation. Hence, amino acid solutions containing cysteine help to minimise ascorbic acid loss.

Ascorbic acid degrades according to first-order kinetics and its half-life increases significantly when protected from light or stored at 4°C rather than at room temperature (Nordfjeld et al., 1984). These findings were supported by a study which showed that ascorbic acid was stable at 5°C but not at 25°C (Smith et al., 1988b) and by the investigation of Dahl et al. (1986) who found that, when stored in EVA plastic bags, vitamin C levels dropped to about 50% after 96 h of storage in the dark at 2–8°C, or after 24 h of simulated infusion. However, protection did not significantly affect the rate of decomposition.

Loss of vitamin C also increases with pH, and hence when mixed with amino acid solutions of high pH, such as Novamine, it degrades more rapidly. Interestingly, bisulphite at 3 mM seems to provide some protection from the time-related degradation at higher pH values (Smith et al., 1988a). Intralipid has no effect on vitamin C stability (Smith et al., 1988a,b).

The inclusion of large excesses of ascorbic acid in TPN to compensate for degradation losses may result in significant amounts of oxalic acid (a decomposition product of ascorbic acid) being formed, which is a cause for concern as it can react with calcium ions, forming calcium oxalate which then precipitates out of solution (Gupta et al., 1986) as well as itself being toxic. The formation of a precipitate will depend on the amount of ascorbic acid in solution, its rate of degradation, calcium concentration, pH and amino acid profile of the solution. It may therefore be advisable to avoid coadministering vitamins and divalent ions by adding them to TPN mixtures on alternate days (Allwood, 1984b; Clark, 1990). In general, TPN mixtures containing vitamin C should be administered rapidly after preparation.

Vitamin D – calciferol

Vitamin D is light sensitive and decomposes in air. Total delivery of vitamin D over 24 h from a simulated TPN mixture was only 68% (Gillis et al., 1983) due to sorption to the PVC bag and tubing, although most loss occurred in the tubing. Due to the method used in this study, light degradation of vitamin D was prevented, and all the loss was attributed to sorption.

Vitamin E – α-tocopherol acetate

This vitamin is stable in phototherapy light (Smith et al., 1988a) and fluorescent light (McGee et al., 1985), but sensitive to UV light (DeRitter, 1982). Gillis et al. (1983) showed a vitamin E delivery of 64% from a TPN solution, implying that it, like the other fat-soluble vitamins, undergoes sorption to the plastic, particularly in the tubing. However, in a later study, no significant losses were found to occur on delivery to patients, implying that no sorption to the PVC bag, administration set or filter took place (McGee et al., 1985). Several studies have shown vitamin E to be stable under a wide range of conditions (Kishi et al., 1981; McGee et al., 1985; Dahl et al., 1986; Martens, 1988; Smith et al., 1988b).

Vitamin K – phytonadione

There is a lack of published data concerning the stability of phytonadione in TPN solutions. It is thought to be light sensitive (Longe, 1974; DeRitter, 1982) and a 10–15% loss was shown to occur over 24 h on exposure to sunlight or fluorescent light (Niemiec and Vanderveen, 1984). Ascorbic acid may enhance degradation (Schuetz and King, 1978).

The degradation of some vitamins can be reduced by covering the TPN solution with a UV protective bag to protect it from light. Nevertheless, manufacturers recommend administration of the TPN solution within 48 h of vitamin addition.

Vitamin B12, K and possibly folic acid are advised to be administered by alternative routes such as i.m. to avoid potential interactions until further information is available. Long-term TPN patients should be monitored periodically for vitamin A, thiamine and ascorbic acid as they have poor availability from TPN solutions.

Electrolytes

The body needs six major electrolytes; sodium, potassium, magnesium, calcium, phosphate and chlorine, and these therefore have to be provided by TPN. Monovalent inorganic ions such as sodium, potassium and chloride pose few problems of stability, but divalent ions such as calcium, phosphate and magnesium have the potential to form precipitates.

On addition to TPN solutions, sodium bicarbonate forms CO_2 and bicarbonate ions. This reaction is enhanced by the acidic pH of the solution and the buffering action of the amino acids. Insoluble carbonate salts may then form with the calcium and magnesium ions present in solution. To avoid this, salts of acetate (which is a physiological precursor to bicarbonate and is both soluble and stable in TPN solutions) can be used for pH adjustment. Care must be taken to avoid adding all cations as chloride salts as this may cause hyperchloraemic acidosis. A fraction are normally administered as acetate salts, and the acetate to chlorine ratio is adjusted to 1:1. Excess acetate salts may, however, cause hypochloraemic metabolic alkalosis.

The most important compatability problem with TPN mixtures is the interaction between calcium and phosphate ions (Scheutz and King, 1978; Mikrut, 1987). TPN mixtures for neonatal use are particularly susceptible to this incompatibility as they require large amounts of calcium and phosphate for bone mineralization, and the higher the concentration of these salts, the more likely is precipitate formation. Calcium phosphate precipitates primarily in the form of dibasic calcium phosphate ($CaHPO_4$) which is less soluble than the monobasic form ($Ca(H_2PO_4)_2$) in aqueous media.

The solubility of calcium and phosphate in TPN mixtures depends on pH; infusion time (since slightly supersaturated solutions may be metastable); temperature; calcium, phosphate and amino acid concentration; type of amino acid solution used; dextrose concentration; contact with i.v. fat emulsion; order of calcium and phosphate addition and cysteine addition. The presence of magnesium in solution may also affect the interaction of calcium and phosphate by competing with the calcium for phosphate and thus reducing precipitation (Arnold, 1990). Of these, pH is the most critical factor affecting solubility and therefore plays a major role in the stability of TPN infusions.

pH

Phosphate exists mainly as monobasic and dibasic forms with the ratio between the two depending on pH. As the pH of the solution increases, there is more dibasic phosphate to bind with free calcium (Fitzgerald and MacKay, 1987). The pH of a TPN mixture is determined mainly by the concentration and titratable acidity of the amino acid product used. Titratable acidity is measured by the amount of sodium hydroxide needed to neutralise the buffering capacity of a solution to an endpoint pH. It is partly related to the amount of acetic acid used to adjust product pH and also to the buffering properties of the amino acids. Hence, the choice of amino acid product may affect the amount of calcium and phosphate that can be administered. This was highlighted in 1982 by Eggert et al., who showed that a solution of Aminosyn 2% and dextrose 20% had a pH of 5.1 and could incorporate 40 mM calcium and 15 mM phosphate without precipitation. In contrast, Freamine III 2% and dextrose 20% had a pH of 6.4 and produced a precipitate at the same concentrations of calcium and phosphate. Any addition that results in an increase in pH may reduce the solubility of calcium phosphate. It should be borne in mind that trace element preparations often have an acidic pH, although the amounts added are small.

Infusion time

Precipitation may not necessarily occur immediately after electrolyte addition but can take place 12 h or more later in the container, tubing, filter or catheter. Precipitate formation increases with standing time or slow infusion rates (Henry et al., 1980; Eggert et al., 1982; Robinson and Wright, 1982). These effects are probably due to slow crystallization from supersaturated solutions; the low concentration of suspended particulates in infusion solutions provides few nuclei for crystallization.

Temperature

As the temperature increases, the soluble calcium salt becomes more dissociated, rendering more calcium ions available to complex with phosphate (Eggert et al., 1982; Fitzgerald and MacKay, 1986). Similarly, calcium phosphate becomes less soluble as temperature increases (Henry et al., 1980). This effect is essentially a problem with calcium gluconate use rather than chloride as the latter is fully ionised in solution, whilst gluconate is only partly dissociated (Allwood, 1987). An increase in precipitation due to a rise in temperature may be a particular cause of catheter obstruction. One study found that at 5°C and room temperature (26°C) there was no precipitation, but at body temperature (37°C) crystals of calcium phosphate appeared (Robinson and Wright, 1982). Hence, the raised temperature where the catheter enters the body may cause precipitation which could either block the catheter or pass into the patient. Babies in incubators or neonatal units have an even greater risk of precipitation occurring due to the warm environmental temperatures.

Amino acid concentration

Increases in amino acid concentration cause a decrease in the pH of the solution, thus increasing calcium and phosphate solubility and therefore stability. Also, since the amino acid product provides an intrinsic buffering system to the TPN mixture (Sturgeon et al., 1980), formulations with high concentrations of amino acids have a greater buffering capacity, so show less of an increase in pH when phosphate is added and therefore a higher tolerance for calcium addition (Lenz and Mikrut, 1988). TPN mixtures containing amino acid concentrations below 2.5% are especially prone to precipitation (Knight et al., 1980; Eggert et al., 1982) due to the reduced buffering capacity. Amino acids in solution at midrange pH exist as ionic species which form soluble complexes with calcium and phosphate, thus decreasing the free ions available for interaction and increasing stability. These complexes dissociate to varying degrees depending on the physiochemical nature of the complex formed (Henry et al., 1980).

Salt form

Greater concentrations of calcium gluconate can be mixed with sodium phosphate in TPN solutions before precipitation occurs than is possible with calcium chloride (Henry et al., 1980; Allwood, 1987; Arnold, 1990). This is because calcium gluconate dissociates much less in water than calcium chloride. Calcium chloride is almost completely dissociated, so precipitation with phosphate occurs at lower salt concentrations than with calcium gluconate. Therefore, unless fluid intake is severely restricted, calcium gluconate should be used rather than chloride. Allwood (1987) found that a phosphate buffer (Addiphos) which contains both sodium and potassium salts could accommodate greater quantities of both calcium and phosphate before precipitation than using potassium dihydrogen phosphate as a source of phosphate. Although the single salt prevented precipitation, the final pH was relatively low (4.8–5.0) and this could be irritant to the patient. Potassium dihydrogen phosphate (where HPO_4^- is predominant) is in its turn better than mixed potassium phosphate solutions for providing calcium and phosphate stability. Therefore, a phosphate buffer should be used in preference to a single salt (Addiphos is the only buffered product currently available). More recent information suggests that organic phosphates, such as glucose phosphate, may be beneficial and reduce precipitation problems.

Dextrose concentration

As dextrose concentration increases, the solubility of calcium and phosphate becomes greater (Henry et al., 1980; Eggert et al., 1982; Lenz and Mikrut, 1988). This is probably due to the slight decrease in solution pH, however, the concentration of dextrose itself seems unlikely to be a major factor in calcium and phosphate compatibility.

Fat emulsions

In general, fat emulsion causes a rise in pH, which may allow calcium phosphate crystals to form and be infused or block the catheter. It was therefore proposed that lipid emulsion should not be infused in the same line as a TPN solution which has a calcium and phosphate content bordering on the precipitation curve for that solution (Eggert et al., 1987). Fat emulsions are often omitted from paediatric TPN solutions because of the high levels of divalent cations which destabilize the emulsion, even though the amino acids improve the stability by their effects on the interdroplet potentials (Washington et al., 1991).

Order of electrolyte addition

It is fairly obvious that the calcium and phosphate should be mixed into the TPN solution when most of the other components have already been added (Kaminski et al., 1974; Kobayashi and King, 1977). A recommended order is: glucose and amino acids first, then phosphates, mix well, and finally fat emulsion. Diluting the phosphate in this manner thus avoids high local concentrations of phosphate and immediate precipitation by calcium.

Calcium and phosphate concentrations

The higher the concentrations of calcium and phosphate salts added, the more likely precipitation is to occur. It has been found that small reductions in phosphate content can allow high calcium concentrations to be incorporated (Allwood, 1987).

Cysteine addition

Cysteine hydrochloride, which is present in some amino acid preparations, has been found to influence calcium and phosphate solubility (Fitzgerald and MacKay, 1986; Lenz and Mikrut, 1988). Addition of 40 mg of cysteine hydrochloride per g of protein decreased solution pH, making calcium and phosphate more soluble and allowing greater incorporation of both salts into the solution. Whether the inclusion of cysteine in certain amino acid products plays a major role in reducing their pH has not yet been determined, and it is unclear whether the stabilizing effect is due to cysteine itself or just the pH change it causes.

Trace Elements

Trace elements are important components of TPN solutions. 15 elements are known to have major physiological roles; however, eight trace elements are generally accepted as essential dietary components because they have deficiency states associated with them (Shenkin et al., 1987). These are zinc, copper, selenium, chromium, iron, manganese, molybdenum and iodine. The stability of multiple trace element solutions containing zinc, copper, manganese and chromium has been demonstrated several times. These elements were found to be stable in TPN for at least 24 h at 4°C (for admixtures containing amino acids and vitamins), and for 48 h at 25°C for those without amino acids and vitamins, whether as individual or multiple trace element solutions (Boddapati et al., 1981). Allwood (1983) supported these findings when he showed that these four elements in the form of MTE-4 were soluble and stable in TPN for at least 1 month. Zinc concentrations were approx. 6% lower than expected, but were still within acceptable range and no interaction between the elements was noted. Similar studies showed that zinc and chromium were stable for 60 days under refrigeration (Tsallas, 1984) and trace elements remained stable for 6 months when kept in a TPN mixture at 4°C (Nordfjeld et al., 1983). No sorption of trace elements to glass or

plastic containers, tubing or filters has been detected during infusions (Shearer and Bozian, 1977; Boddapati et al., 1981; Tsallas, 1982). Chelating agents such as EDTA, which are present as stabilizers in some calcium gluconate injections, chelate heavy metals and so may bind or precipitate trace elements out of solution (Tsallas, 1982). Calcium and phosphate concentration and solubility are also important as precipitation of these two electrolytes can cause coprecipitation of manganese (Schaible and Bandemer, 1942; Leach, 1984).

Iron can be precipitated as iron phosphate in admixtures containing Synthamin (Allwood, 1984a). Alternative ways in which iron can be added to TPN mixtures are as iron dextran or ferrous citrate. Iron dextran is stable in mixtures after 18 h at room temperature (Wan and Tsallas, 1980) but no information is available on the effects of temperature, pH, light and storage time.

Selenium is not always used in TPN and, therefore, is added as a single entity when needed. When given as sodium selenite (a salt of selenious acid) in TPN mixtures containing trace elements and multivitamins (MVI), it was reduced to elemental selenium, which being insoluble precipitated out of solution over 24 h. This was attributed to MVI and the presence of copper ions which accelerate the reduction. MVI-12 (a different vitamin solution) induced little precipitation. Ascorbic acid at concentrations above 1000 mg/l can also induce significant losses of selenium (Shils and Levander, 1982). However, the reduction was pH dependent and in buffered solutions of pH 5 or more, ascorbic acid did not reduce selenite. A later report found that in complete TPN formulae (with Berocca PN as the vitamin source), little or no reduction of selenite to selenium by ascorbic acid occurred after 24 h at 25°C (Ganther and Kraus, 1989), and it was therefore concluded that the amino acids in the TPN were preventing the reduction by their buffering effects, and so reduction to selenium was not a likely problem in TPN solutions near neutral pH. A recent study suggested that amino acids can form complexes with selenium compounds and thus prevent reduction (Postaire and Anglade, 1990). Selenium as selenious acid was found to be stable at room temperature when exposed to fluorescent light for 24 h and for 10 weeks when kept under refrigeration. No significant losses to the PVC bag, administration set or filter were found (McGee et al., 1985). Sodium selenate and selenomethionine are both chemically stable in TPN solutions (Levander, 1984).

Trace element stability is also affected by amino acids. Several amino acids chelate with trace elements which may then precipitate or react with glucose to form Maillard products more rapidly than with amino acids alone (Phillips and Odgers, 1986). Until this has been verified, it is therefore recommended to add trace elements just prior to administration of the TPN mixture.

Glucose

Glucose is the second largest component after water of a TPN solution. There is only one major problem associated with glucose in that glucose and amino acid solution combinations cannot be stored for long periods of time due to the Maillard reaction. This results in a darkening or 'caramelisation' of the mixture which occurs slowly at room temperature and increases as the temperature rises. The reaction begins when the reducing sugar reacts with an amino group of a free amino acid and ends with the formation of complex polymers (Phillips and Odgers, 1986). Glucose remained stable with no loss in concentration for 4 weeks (Jeppsson and Tengborn, 1987) and 6 months (Nordfjeld et al., 1983) when kept under refrigeration. It should also be noted that glucose breaks down on autoclaving, with a considerable reduction in pH.

Drug Stability

Drug administration in TPN solutions is particularly useful in patients with limited venous access or fluid restriction. Nevertheless, addition of drugs should be undertaken with caution unless data are available to show chemical stability and compatibility with TPN mixtures. As the range of drugs available is so large, this review

only covers the most commonly administered drugs.

Insulin

Insulin adsorbs to PVC bags and administration sets causing a 10–55% loss (Hirsch et al., 1977). It is also adsorbed to polyolefin bottles, although to a lesser extent, and this adsorption can reach saturation at high levels of insulin (Hirsch et al., 1981). Hence, the concentration of insulin affects the amount of loss. Adsorption to filters is another problem (Butler et al., 1980; Wingert and Levin, 1981). Weber et al. (1977) found that dextrose/amino acid mixtures failed to deliver more than about 45% of added insulin and that this loss was reduced on the addition of albumin or electrolytes and vitamins. More recently, Marcuard et al. (1990) showed that insulin availability could be higher than previously suggested, with as much as 90–95% delivery. They stated that insulin recovery may be affected by the amino acid solution used, but was independent of lipid addition. Very little binding to ethylene vinyl acetate bags was found.

Antibiotics

None of the major antibiotics are sorbed to PVC (Kowaluk et al., 1981, 1982, 1983). All antibiotics studied appear to be stable in TPN solutions at 4°C for 24 h (Feigin et al., 1973; Reed et al., 1979). The following results are regarding stability at room temperature.

Penicillins

Early studies showed ampicillin to be unstable (Gallelli et al., 1969; Feigin et al., 1973) and sensitive to electrolyte addition (Schuetz and King, 1978). Feigin et al. (1973) also found that the addition of heparin or hydrocortisone improved ampicillin stability. Results of a later study suggested that no ampicillin loss occurred over 24 h (Fox et al., 1988). There are conflicting data as to the stability of carbenicillin and methicillin and also to that of ticarcillin, mezlocillin and piperacillin. These last three have been found to be stable for 24 h and unaffected by dextrose or amino acid concentrations (Perry et al., 1987), but reduced by more than 25% after the same time period in another study (Fox et al., 1988). Penicillin G is stable for 24 h in TPN admixtures (Reed et al., 1979; Fox et al., 1988).

Aminoglycosides

Gentamicin, tobramycin and clindamycin are stable in TPN mixtures at room temperature for 24 h (Feigin et al., 1973; Reed et al., 1979; Fox et al., 1988). Clindamycin has been shown to remain stable for 1 month at 4°C in the dark and 8 weeks at −10°C in both glass and PVC containers (Porter et al., 1983). Kanamycin was found to decrease in amount by 36–52% after 24 h (Feigin et al., 1973).

Cephalosporins

Fox et al. (1988) studied a range of cephalosporins, and found all to be stable for 24 h.

Mixing antibiotics, even those that are stable, should be performed with care as results have shown a loss of stability (greater than 10%) for all 'stable' antibiotics when gentamycin, for example, is also added to the admixture (Fox et al., 1988).

H_2 antagonists

Cimetidine is stable over a wide range of conditions and mixtures. All concentrations studied were stable for 24 h at room temperature (Tsallas and Allen, 1982; Baptista et al., 1985). Cano et al. (1987) observed that cimetidine was stable for at least 72 h in TPN mixtures and Yuhas et al. (1981) found it to be stable for at least 7 days at room temperature. Walker et al. (1981) showed the stability of cimetidine to be maintained for 30 days when frozen and at least 8 days following thawing at 4°C. This procedure is not recommended for mixtures containing fat emulsions.

Ranitidine is less stable than cimetidine in TPN mixtures. It has been found to be stable at room temperature for 12 h (Cano et al., 1988), 24 h (Bullock et al., 1985) and up to 48 h (Walker and Bayliff, 1985). The latter two studies found reductions of about 10% at 48 h whereas Cano et al. found more than 20% loss after 24 h. McElroy

et al. (1989) showed ranitidine to be stable for 72 h if refrigerated.

Famotidine is considered as stable as cimetidine with studies showing stability in TPN admixtures at room temperature for 48 h (Bullock et al., 1989) and up to 72 h (Montoro et al., 1989). Bullock et al. (1989) also demonstrated that refrigerated famotidine remained stable for 7 days and that amino acid concentrations were not affected by famotidine addition.

Cytotoxics

Some sorption of cytarabine to filters occurs (Ennis et al., 1983) but none to glass or PVC over 24 h (Benvenuto et al., 1981). At a concentration of 50 μg/ml, cytarabine is stable for at least 48 h at 8 and 25°C in commonly used paediatric TPN solutions (Quock and Sakai, 1985).

5-Fluorouracil is not sorbed to PVC (Driessen et al., 1978; Kowaluk et al., 1981, 1982), but is adsorbed to glass (Driessen et al., 1978; Benvenuto et al., 1981). The latter study found a decrease of 10% after 7 h. In a TPN mixture, 5-fluorouracil suffered no loss in concentration after 48 h at room temperature and in ambient light whether in glass or plastic containers (Hardin et al., 1982).

Methotrexate is sorbed neither to glass nor PVC in 24 h (Benvenuto et al., 1981), but does undergo photodegradation in dilute solutions (Chatterji and Gallelli, 1978; Bosanquet, 1989). This degradation is catalysed by sodium bicarbonate. In short-term exposure to light, e.g. 4 h, no significant loss is seen (Dyvik et al., 1986). No data in TPN admixtures are available.

Anticoagulants

Heparin sodium is not adsorbed to glass containers (Joy et al., 1979) or to in-line filters (Butler et al., 1980). Heparin activity was retained for 24 h at 25°C in TPN solutions but decreased significantly after that (Matthews, 1982). More recent work (Johnson et al., 1990) has demonstrated that heparin contributes to destabilization of fat emulsions, and so should be included in TPN mixtures only with the greatest caution.

Warfarin sodium absorbs to PVC (Moorhatch and Chiou, 1974; Kowaluk et al., 1981; Illum and Bundgaard, 1982) and sorption increases in the presence of dextrose. Unionized warfarin is absorbed more readily than the ionized form, and hence a low pH increases sorption. No sorption to polypropylene bags occurs (Illum and Bundgaard, 1982). Information regarding TPN stability of warfarin is not available.

Aminophylline

Aminophylline is not sorbed to PVC bags, administration sets (Kowaluk et al., 1981, 1982) or filters (Boddapati et al., 1982). It is stable in TPN mixtures for at least 24 h at both 25 and 4°C (Kirk and Sprake, 1982; Niemiec et al., 1983). However, aminophylline addition has caused precipitation of calcium and phosphate in some TPNs (Kirkpatrick et al., 1989).

Morphine

No significant sorption of morphine to PVC occurred after 1 week (Kowaluk et al., 1981, 1982; Macias et al., 1985). Macias et al. (1985) also showed that morphine was stable in TPN for 36 h at 21.5°C without light protection.

Diazepam

Diazepam is absorbed into PVC containers (Kowaluk et al., 1981, 1982; Illum and Bundgaard, 1982) in its unionized state. This sorption can be reduced by lowering temperature or storage time or increasing flow rate or surface-area-to-volume ratio (Kowaluk et al., 1983). Alternatively, polyolefin or glass bottles and polyolefin tubing can be used to avoid sorption altogether.

Digoxin

Digoxin is not retained by in-line filters (Rusmin et al., 1977; Stiles and Allen, 1979). It has been shown to be available from TPN solutions (Fagerman and Dean, 1981) and stable in TPN for up to 96 h when stored at 4°C in plastic bags (Blackstone et al., 1980).

Metoclopramide

Metoclopramide is stable for 72 h at 25°C at 5 and 20 mg doses in TPN admixtures containing

dextrose, amino acids and electrolytes (Pesko et al., 1988). In the absence of electrolytes, only the 20 mg addition suffered no loss in 72 h, whereas the 5 mg dose decreased by 10% after 48 h.

New Materials

A number of new materials are being investigated as possible nutritional supplements, and may find wider use in the coming decade. Materials such as dipeptide nitrogen sources, carnitine, and glucose phosphates are under extensive study, but little is known about their stability in many cases. Probably the most extensively investigated material is glucose 1-phosphate, which has been shown to be compatible with higher concentrations of calcium (as chloride or gluconate) than inorganic phosphates, and the pH of these regimens is closer to neutrality. Hence, high levels of calcium and phosphate can be incorporated into TPNs with or without lipid (Hardy and Davies, 1987; Hardy and Jimenez Torres, 1987).

Conclusions

Problems can be encountered with the chemical stability of many of the components making up TPN mixtures. Many TPN admixtures used in the studies considered do not include fat emulsion and many do not contain vitamins. Some mixtures merely consisted of amino acids and dextrose. This causes problems in analysing the material, and relating findings to TPN solutions used clinically. More studies are therefore needed to verify the results already obtained from research. Further investigations into all-in-one mixtures including lipid are required as little is known about chemical stability of electrolytes, vitamins and trace elements in these systems. Additionally, the conflicting findings of many workers suggest that stability is dependent on minor variations in mixture composition, and, therefore, that it may not be straightforward to extrapolate from older studies to current practise.

Until further research is performed, it is advisable to administer the TPN mixture as soon as possible after formulation (preferably within the first 24 h), if many of the problems due to chemical instability are to be minimised. In particular, vitamin and drug addition to TPN mixtures should always be undertaken with care unless chemical stability and compatibility have been proven.

References

Allwood, M.C., The compatibility of four trace elements in total parenteral nutrition infusions. *Int. J. Pharm.*, 16 (1983) 57–63.

Allwood, M.C., Compatibility and stability of TPN mixtures in big bags. *J. Clin. Hosp. Pharm.*, 9 (1984a) 181–198.

Allwood, M.C., Factors influencing the stability of ascorbic acid in total parenteral nutrition infusions. *J. Clin. Hosp. Pharm.*, 9 (1984b) 75–85.

Allwood, M.C., The compatibility of calcium phosphate in paediatric TPN infusions. *J. Clin. Pharm. Ther.*, 12 (1987) 293–301.

Allwood, M.C., The stability of vitamins in all-in-one TPN. *All-in-One Soc. Newslett.*, November (1990) 1–3.

Allwood, M.C. and Plane, J.H., The wavelength-dependent degradation of vitamin A exposed to ultraviolet irradiation *Int. J. Pharm.*, 31 (1986) 1–7.

Arnold, W.C., Parenteral nutrition and fluid and electrolyte therapy. *Pediatr. Clin. North Am.*, 37 (1990) 449–461.

Baptista, R.J., Palombo, J.D., Tahan, S.R., Valicenti, A.J., Bistrian, B.R., Arkin, C.F. and Blackburn, G.L., Stability of cimetidine hydrochloride in a total nutrient admixture. *Am. J. Hosp. Pharm.*, 42 (1985) 2208–2210.

Barker, A., Hebron, B.S., Beck, P.R. and Ellis, B., Folic acid and total parenteral nutrition. *J. Parenter. Enteral Nutr.*, 8 (1984) 3–8.

Bates, C.G., Greiner, G. and Gegenheimer, A., Precipitate in admixtures of new amino acid injection. *Am. J. Hosp. Pharm.*, 41 (1984) 1312.

Benvenuto, J.A., Anderson, R.W., Kerkof, K., Smith, R.G. and Loo, T.L., Stability and compatibility of antitumour agents in glass and plastic containers. *Am. J. Hosp. Pharm.*, 38 (1981) 1914–1918.

Bhatia, J., Mims, L.C. and Roesel, R.A., The effect of phototherapy on amino acid solutions containing multivitamins. *J. Pediatr.*, 96 (1980) 284–286.

Bhatia, J., Stegink, L.D. and Ziegler, E.E., Riboflavin enhances photo-oxidation of amino acids under simulated clinical conditions. *J. Parenter. Enteral Nutr.*, 7 (1983) 277–279.

Bjelton, L. and Fransson, G.B., Availability of cysteine and of L-2-oxo-thiazolidine-4-carboxylic acid as a source of cysteine in intravenous solution. *J. Parenter. Enteral Nutr.*, 14 (1990) 177–182.

Blackstone, M., Lee, P. and Reynolds, E., Use of digoxin in total parenteral nutrition fluids. Paper presented to 15th

Annual ASHP Midyear Clinical Meeting, San Francisco, CA, 7 December 1980.

Boddapati, S., Yang, K. and Murty, R., Intravenous solution compatibility and filter retention characteristics of trace element preparations. *Am. J. Hosp. Pharm.*, 38 (1981) 1731–1736.

Boddapati, S., Yang, K. and Murty, R., Physicochemical properties of aminophylline-dextrose injection admixtures. *Am. J. Hosp. Pharm.*, 39 (1982) 108–112.

Bosanquet, A.G., Stability of solutions of antineoplastic agents during preparation and storage for in vitro assays. III: Antimetabolites, tubulin-binding agents, platinum drugs, amsacrine, L-asparaginase, interferons, steroids and other miscellaneous antitumour agents. *Cancer Chemother. Pharmacol.*, 23 (1989) 197–207.

Bowman, B.B. and Nguyen, P., Stability of thiamin in parenteral nutrition solutions. *J. Parenter. Enteral Nutr.*, 7 (1983) 567–568.

Bullock, L., Fitzgerald, J.F., Glick, M.R., Parks, R.B., Schnabel, J.G. and Hancock, B.G., Stability of famotidine 20 and 40 mg/l and amino acids in total parenteral nutrient solutions. *Am. J. Hosp. Pharm.*, 46 (1989) 2321–2325.

Bullock, L., Parks, R.B., Lampasona, V. and Mullins, R.E., Stability of ranitidine hydrochloride and amino acids in parenteral nutrient solutions. *Am. J. Hosp. Pharm.*, 42 (1985) 2683–2687.

Butler, L.D., Munson, J.M. and DeLuca, P.P., Effect of inline filtration on the potency of low-dose drugs. *Am. J. Hosp. Pharm.*, 37 (1980) 935–941.

Cano, S.M., Montoro, J.B. and Pastor, C., Stability of cimetidine in total parenteral nutrition. *J. Clin. Nutr. Gastroenterol.*, 2 (1987) 40–43.

Cano, S.M., Montoro, J.B., Pastor, C., Pou, L. and Sabin, P., Stability of ranitidine hydrochloride in total nutrient admixtures. *Am. J. Hosp. Pharm.*, 45 (1988) 1100–1102.

Chatterji, D.C. and Gallelli, J.F., Thermal and photolytic decomposition of methotrexate in aqueous solutions. *J. Pharm. Sci.*, 67 (1978) 526–531.

Chen, M.F., Boyce, H.W. and Triplett, L., Stability of the B vitamins in mixed parenteral nutrition solution. *J. Parenter. Enteral Nutr.* 7 (1983) 462–464.

Chiou, W.L. and Moorhatch, P.A., Interaction between vitamin A and plastic intravenous fluid bags. *J. Am. Med. Assoc.*, 223 (1973) 328.

Clark, C.M., Adult total parenteral nutrition – an update. *Pharm. J.* (Hosp. Suppl.), September 8 (1990) 12–15.

Dahl, G.B., Jeppsson, R.I. and Tengborn, H.J., Vitamin stability in a TPN mixture stored in an EVA plastic bag. *J. Clin. Hosp. Pharm.*, 11 (1986) 271–279.

DeRitter, E., Vitamins in pharmaceutical formulations. *J. Pharm. Sci.*, 71 (1982) 1073–1096.

Driessen, O., De Vos, D. and Timmermans, P.J.A., Adsorption of fluorouracil on glass surfaces. *J. Pharm. Sci.*, 67 (1978) 1494–1495.

Dyvik, O., Grislingaas, A.L. and Tonnesen, H.H., Methotrexate in infusion solutions – a stability test for hospital pharmacy. *J. Clin. Hosp. Pharm.*, 11 (1986) 343–348.

Eggert, L.D., Rusho, W.J., MacKay, M.W. and Chan, G.M., Calcium and phosphorus compatibility in parenteral nutrition solutions for neonates. *Am. J. Hosp. Pharm.*, 39 (1982) 49–53.

Ennis, C.E., Merritt, R.J. and Nett, O.N., In vitro study of inline filtration of medications commonly administered to pediatric cancer patients. *J. Parenter. Enteral Nutr.*, 7 (1983) 156–158.

Fagerman, K.E. and Dean, R.E., Daily digoxin administration in parenteral nutrition solution. *Am. J. Hosp. Pharm.*, 38 (1981) 1955.

Feigin, R.D., Moss, K.S. and Shackleford, P.G., Antibiotic stability in solutions used for intravenous nutrition and fluid therapy. *Pediatrics*, 51 (1973) 1016–1026.

Fitzgerald, K.A. and MacKay, M.W., Calcium and phosphate solubility in neonatal parenteral nutrient solutions containing Aminosyn PF. *Am. J. Hosp. Pharm.*, 44 (1987) 1396–1400.

Fox, A.S., Boyer, K.M. and Sweeney, H.M., Antibiotic stability in a pediatric parenteral alimentation solution. *J. Pediatr.*, 112 (1988) 813–817.

Gallelli, J.F., MacLowry, J.D. and Skolaut, M.W., Stability of antibiotics in parenteral solution. *Am. J. Hosp. Pharm.*, 26 (1969) 630.

Ganther, H.E. and Kraus, R.J., Chemical stability of selenious acid in total parenteral nutrition solutions containing ascorbic acid. *J. Parenter. Enteral Nutr.*, 13 (1989) 185–188.

Gillis, J., Jones, G. and Pencharz, P., Delivery of vitamins A, D and E in total parenteral nutrition solutions. *J. Parenter. Enteral Nutr.*, 7 (1983) 11–14.

Greene, H.L., Phillips, B.L. and Franck, L., Persistently low blood retinol levels during and after parenteral feeding of very low birth weight infants: Examination of losses into intravenous administration sets and a method of prevention by addition to a lipid emulsion. *Pediatrics*, 79 (1987) 894–900.

Gupta, V.D., Allwood, M.C. and Louie, N., Stability of vitamins in total parenteral nutrient solutions. *Am. J. Hosp. Pharm.*, 43 (1986) 2132–2143.

Gutcher, G.R., Lax, A.A. and Farrell, P.M., Vitamin A losses to plastic intravenous infusion devices and an improved method of delivery. *Am. J. Clin. Nutr.*, 40 (1984) 8–13.

Hardin, T.C., Clibon, U., Page, C.P. and Cruz, A.B., Compatibility of 5-fluorouracil and total parenteral nutrition solutions. *J. Parenter. Enteral Nutr.*, 6 (1982) 163–165.

Hardy, G. and Davies, C., Stability of TPN mixtures incorporating glucose 1 phosphate (Abstr. P50). *Clin. Nutr.*, 6 (1987) S79.

Hardy, G. and Jimenez Torres, N.V., Glucose-1-phosphate in parenteral nutrition. *Pharm. J.*, 239 (1987) 641–642 (letter).

Hartline, J.V. and Zachman, R.D., Vitamin A delivery in total parenteral nutrition solution. *Pediatrics*, 58 (1976) 448–451.

Henry, R.S., Jurgens, R.W. Jr, Sturgeon, R., Athanikar, N., Welco, A. and Van Leuven, M., Compatibility of calcium chloride and calcium gluconate with sodium phosphate in a mixed TPN solution. *Am. J. Hosp. Pharm.*, 37 (1980) 673–674.

Henton, D.H. and Merritt, R.J., Vitamin A sorption to polyvinyl and polyolefin intravenous tubing. *J. Parenter. Enteral Nutr.*, 14 (1990) 79–81.

Hill, G.L., Pickford, L., Young, G.A., Schorah, C.J., Blackett, R.L., Burkinshaw, L., Warren, J.V. and Morgan, D.B., Malnutrition in surgical patients: an unrecognised problem. *Lancet*, i (1977) 689.

Hirsch, J.I., Fratkin, M.J., Wood, J.H. and Thomas, R.B., Clinical significance of insulin adsorption by polyvinyl chloride infusion systems. *Am. J. Hosp. Pharm.*, 34 (1977) 583–588.

Hirsch, J.I., Wood, J.H. and Thomas, R.B., Insulin adsorption to polyolefin infusion bottles and polyvinyl chloride administration sets. *Am. J. Hosp. Pharm.*, 38 (1981) 995–997.

Illum, L. and Bundgaard, H., Sorption of drugs by plastic infusion bags. *Int. J. Pharm.*, 10 (1982) 339–351.

Jeppsson, R.I. and Tengborn, H.J., One week's stability of TPN mixtures in plastic bags. *Clin. Nutr.*, 6 (1987) 155–160.

Johnson, O.L., Washington, C., Davis, S.S. and Schaupp, K., Flocculation of fat emulsions in total parenteral feeding mixtures by heparin. *Clin. Nutr.*, 9 (1990) 29–30.

Joy, R.T., Hyneck, M.L., Berardi, R.R. and Ho, N.F.H., Effect of pH on the stability of heparin in 5% dextrose solutions. *Am. J. Hosp. Pharm.*, 36 (1979) 618–621.

Jurgens, J.W. Jr., Henry, R.S. and Welco, A., Amino acid stability in a mixed parenteral nutrition solution. *Am. J. Hosp. Pharm.*, 38 (1981) 1358–1359.

Kaminski, M.V. Jr., Harris, D.F., Collin, C.F. and Sommers, G.A., Electrolyte compatibility in a synthetic amino acid hyperalimentation solution. *Am. J. Hosp. Pharm.*, 31 (1974) 244–246.

Kerner, J.A., Jr, *Manual of Pediatric Parenteral Nutrition*, Wiley, New York, 1983.

Kirk, B. and Sprake, J.M., Stability of aminophylline. *Br. J. Intravenous Ther.*, 3 (1982) 4–8.

Kirkpatrick, A.E., Holcombe, B.J. and Sawyer, W.T., Effect of retrograde aminophylline administration on calcium and phosphate solubility in neonatal total parenteral nutrient solutions. *Am. J. Hosp. Pharm.*, 46 (1989) 2496–2500.

Kishi, H., Yamaji, A., Kataoka, K., Fujii, Y., Nishikawa, K., Ohnishi, N., Hiraoka, E., Okada, A. and Kim, C.W., Vitamin A and E requirements during total parenteral nutrition. *J. Parenter. Enteral Nutr.*, 5 (1981) 420–423.

Kleinman, L.M., Tangrea, J.A., Gallelli, J.F., Brown, J.H. and Gross, E., Stability of solutions of essential amino acids. *Am. J. Hosp. Pharm.*, 30 (1973) 1054–1057.

Knight, P.J., Buchanan, S. and Clatworthy, H.W., Jr, Calcium and phosphate requirements of preterm infants who require prolonged hyperalimentation. *J. Am. Med. Assoc.*, 243 (1980) 1244–1246.

Kobayashi, N.H. and King, J.C., Compatibility of common additives in protein hydrolysate/dextrose solutions. *Am. J. Hosp. Pharm.*, 34 (1977) 589–594.

Kowaluk, E.A., Roberts, M.S., Blackburn, H.D. and Polack, A.E., Interaction between drugs and polyvinyl chloride infusion bags. *Am. J. Hosp. Pharm.*, 38 (1981) 1308–1314.

Kowaluk, E.A., Roberts, M.S. and Polack, A.E., Interactions between drugs and intravenous delivery systems. *Am. J. Hosp. Pharm.*, 39 (1982) 460–467.

Kowaluk, E.A., Roberts, M.S. and Polack, A.E., Factors affecting the availability of diazepam stored in plastic bags and administered through intravenous sets. *Am. J. Hosp. Pharm.*, 40 (1983) 417–423.

Lacgeler, W.L., Tio, J.M. and Blake, M.I., Stability of certain amino acids in a parenteral nutrition solution. *Am. J. Hosp. Pharm.*, 31 (1974) 776–779.

Leach, R.M., Manganese in enteral and parenteral nutrition. *Bull. N.Y. Acad. Med.*, 60 (1984) 172–176.

Lee, D.R., Ware, I. and Winsley, B.E., Survival of folic acid in TPN solutions. *Br. J. Intravenous Ther.*, 1 (1980) 13–15.

Lenz, G.T. and Mikrut, B.A., Calcium and phosphate solubility in neonatal parenteral nutrient solutions containing Aminosyn-PF or TrophAmine. *Am. J. Hosp. Pharm.*, 45 (1988) 2367–2371.

Levander, O.A., Importance of selenium in total parenteral nutrition. *Bull. N.Y. Acad. Med.*, 60 (1984) 144–155.

Longe, R.L., Stability of phytonadione in hyperalimentation fluids. *Am. J. Hosp. Pharm.*, 31 (1974) 1039.

Louie, N. and Stennett, D.J., Stability of folic acid in 25% dextrose, 3.5% amino acids, and multivitamin solution. *J. Parenter. Enteral Nutr.*, 8 (1984) 421–426.

McElroy, B., Wiggins, D. and Hardy, G., Stability of ranitidine-containing all-in-one (A-I-O) parenteral nutrition mixtures (abs. P61). *Clin. Nutr.*, 8 (1989) S88.

McGee, C.D., Masarenhas, M.G., Ostro, M.J., Tsallas, G. and Jeejeebhoy, K.N., Selenium and vitamin E stability in parenteral solutions. *J. Parenter. Enteral Nutr.*, 9 (1985) 568–570.

Macias, J.M., Martin, W.J. and Lloyd, C.W., Stability of morphine sulfate and meperidine hydrochloride in a parenteral nutrient formulation. *Am. J. Hosp. Pharm.*, 42 (1985) 1087–1094.

McKenna, M.C. and Bieri, J.G., Loss of vitamin A from total parenteral nutrition (TPN) solutions. *Fed. Proc.*, Abstr. 1561, 39 (1980) 561.

Marcuard, S.P., Dunham, B., Hobbs, A. and Caro, J.F., Availability of insulin from total parenteral nutrition solutions. *J. Parenter. Enteral Nutr.*, 14 (1990) 262–264.

Martens, H.J.M., Stability of vitamins in TPN (Abstr. P48). *Clin. Nutr.*, 7 (1988) S74.

Matthews, H., Heparin anticoagulant activity in intravenous fluids utilising a chromogenic substrate assay method. *Aust. J. Hosp. Pharm.*, 12 (1982) S17–S22.

Mikrut, B.A., Calcium and phosphate solubility in neonatal parenteral nutrient solutions containing Aminosyn PF and TrophAmine. *Am. J. Hosp. Pharm.*, 44 (1987) 2702–2704, letter.

Mirtallo, J.M., Rogers, K.R., Johnson, J.A., Fabri, P.J. and Schneider, P.J., Stability of amino acids and the availability of acid in total parenteral nutrition solutions containing hydrochloric acid. *Am. J. Hosp. Pharm.*, 38 (1981) 1729–1731.

Mirtallo, J.M. and Oh, T., A key to the literature of total parenteral nutrition: update 1987. *Drug Intell. Clin. Pharm.*, 21 (1987) 594–606.

Montoro, J.B., Pou, L., Salvador, P., Pastor, C. and Cano, S.M., Stability of famotidine 20 and 40 mg/l in total nutrient admixtures. *Am. J. Hosp. Pharm.*, 46 (1989) 2329–2332.

Moorhatch, P.A. and Chiou, W.L., Interactions between drugs and plastic intravenous fluid bags. 1: Sorption studies on 17 drugs. *Am. J. Hosp. Pharm.*, 31 (1974) 72–78.

Niemiec, P.W., Jr and Vanderveen, T.W., Compatibility considerations in parenteral nutrient solutions. *Am. J. Hosp. Pharm.*, 41 (1984) 893–911.

Niemiec, P.W., Jr and Walker, J.Z., Vitamin A availability from parenteral nutrition delivery systems. *Nutr. Support Serv.*, 3 (1983) 53–56.

Niemiec, P.W., Jr, Vanderveen, T.W., Hohenwarter, M.W. and Gadsden, R.H. Sr., Stability of aminophylline injection in three parenteral nutrient solutions. *Am. J. Hosp. Pharm.*, 40 (1983) 428–432.

Nordfjeld, K., Rasmussen, M. and Jenson, V.G., Storage of mixtures for total parenteral nutrition – long term stability of a total parenteral nutrition mixture. *J. Clin. Hosp. Pharm.*, 8 (1983) 265–274.

Nordfjeld, K., Lang Pedersen, J., Rasmussen, M. and Gauno Jensen, V., Storage of mixtures for total parenteral nutrition. III. Stability of vitamins in TPN mixtures. *J. Clin. Hosp. Pharm.*, 9 (1984) 293–301.

Parr, M.D., Bertch, K.E. and Rapp, R.P., Amino acid stability and microbial growth in total parenteral nutrient solutions. *Am. J. Hosp. Pharm.*, 42 (1985) 2688–2691.

Perry, M., Khalidi, N. and Sanders, C.A., Stability of penicillins in total parenteral nutrient solution. *Am. J. Hosp. Pharm.*, 44 (1987) 1625–1628.

Pesko, L.J., Arend, K.A., Hagman, D.E., Physical compatibility and stability of metaclopramide injection. *Parenterals*, 5 (1988) 1–3, 6–8.

Phillips, G.D. and Odgers, C.L., *Parenteral and Enteral Nutrition; A Practical Guide*, 3rd Edn, Churchill Livingstone, London, 1986.

Porter, W.R., Johnson, C.A., Cohon, M.S. and Gillespie, W., Compatibility and stability of clindamycin phosphate with intravenous fluids. *Am. J. Hosp. Pharm.*, 40 (1983) 91–94.

Postaire, E. and Anglade, P., Selenium stability in total parenteral nutrition solutions (letter). *J. Parenter. Enteral Nutr.*, 14 (1990) 223–224.

Quock, J.R. and Sakai, R.I., Stability of cytarabine in a parenteral nutrient solution. *Am. J. Hosp. Pharm.*, 42 (1985) 592–594.

Reed, M.D., Perry, E.B., Fennell, S.J., Brissie, E.O. and Ball, W.D., Antibiotic compatibility and stability in a parenteral nutrition solution. *Chemotherapy*, 25 (1979) 336–345.

Riggle, M.A. and Brandt, R.B., Decrease of available vitamin A in parenteral nutrition solutions. *J. Parenter. Enteral Nutr.*, 10 (1986) 388–392.

Robinson, L.A. and Wright, B.T., Central venous catheter occlusion caused by body-heat-mediated calcium phosphate precipitation. *Am. J. Hosp. Pharm.*, 39 (1982) 120–121.

Rowlands, D.A., Wilkinson, W.R. and Yoshimura, N., Storage stability of mixed hyperalimentation solutions. *Am. J. Hosp. Pharm.*, 30 (1973) 436–438.

Rusmin, S., Welton, S. and DeLuca, P., Effect of inline filtration on the potency of drugs administered intravenously. *Am. J. Hosp. Pharm.*, 34 (1977) 1071–1074.

Schaible, P.J. and Bandemer, S.A., The effect of mineral supplements on the availability of manganese. *Poultry Sci.*, 21 (1942) 8–14.

Scheindlin, S. and Griffith, I., The action of ascorbic acid on folic acid. *Am. J. Pharm.*, 123 (1951) 78–86.

Scheindlin, S., Lee, A. and Griffith, I., The action of riboflavin on folic acid. *J. Am. Pharm. Assoc.*, 41 (1952) 420–427.

Scheiner, J.M., Araujo, M.M. and DeRitter, E., Thiamine destruction by sodium bisulphite in infusion solutions. *Am. J. Hosp. Pharm.*, 38 (1981) 1911–1913.

Schuetz, D.H. and King, J.C., Compatibility and stability of electrolytes, vitamins and antibiotics in combination with 8% amino acids solution. *Am. J. Hosp. Pharm.*, 35 (1978) 33–44.

Shearer, C.A. and Bozian, R.C., The availability of trace elements in intravenous hyperalimentation solutions. *Drug Intell. Clin. Pharm.*, 11 (1977) 465–471.

Shenai, J.P., Stahlman, M.T. and Chytil, F., Vitamin A delivery from parenteral alimentation solution. *J. Pediatr.*, 99 (1981) 661–663.

Shenkin, A., Fraser, W.D., McLelland, A.J.D., Fell, G.S. and Garden, O.J., Maintenance of vitamin and trace element status in intravenous nutrition using a complete nutritive mixture. *J. Parenter. Enteral Nutr.*, 11 (1987) 238–242.

Shils, M.E. and Levander, O.A., Selenium stability in TPN solutions. *Am. J. Clin. Nutr.*, 35 (1982) 829.

Smith, J.L., Canham, J.E., Kirkland, W.D. and Wells, P.A., Effect of Intralipid, amino acids, container, temperature, and duration of storage on vitamin stability in total parenteral nutrition admixtures. *J. Parenter. Enteral Nutr.*, 12 (1988b) 478–483.

Smith, J.L., Canham, J.E. and Wells, P.A., Effect of sodium bisulfite and light on vitamin stability in a TPN admixture. *Am. J. Clin. Nutr.*, 39 (1984) 674.

Smith, J.L., Canham, J.E. and Wells, P.A., Effect of phototherapy light, sodium bisulfite and pH on vitamin stability in total parenteral nutrition admixtures. *J. Parenter. Enteral Nutr.*, 12 (1988a) 394–402.

Stiles, M.L. and Allen, L.V., Retention of drugs during inline filtration of parenteral solutions. *Infusion*, 3 (1979) 67–69.

Sturgeon, J.R., Athanikar, N.K. and Henry, R.S., Titratable acidities of crystalline amino acid mixtures. *Am. J. Hosp. Pharm.*, 37 (1980) 388–390.

Tsallas, G., Availability and physicochemical stability of zinc and chromium in total parenteral nutrition solutions. *Bull. N.Y. Acad. Med.*, 60 (1984) 125–131.

Tsallas, G. and Allen, L.C., Stability of cimetidine hydrochloride in parenteral nutrition solutions. *Am. J Hosp. Pharm.*, 39 (1982) 484–485.

Walker, S.E. and Bayliff, C.D., Stability of ranitidine hydrochloride in total parenteral nutrient solution. *Am. J. Hosp. Pharm.*, 42 (1985) 590–592.

Walker, S.E., Paton, T.W., Fabian, T.M., Liu, C.C. and Coates, P.E., Stability and sterility of cimetidine admixtures frozen in minibags. *Am. J. Hosp. Pharm.*, 38 (1981) 881–883.

Wan, K.K. and Tsallas, G., Dilute iron dextran formulation for addition to parenteral nutrient solutions. *Am. J. Hosp. Pharm.*, 37 (1980) 206–210.

Washington, C., The stability of intravenous fat emulsions in total parenteral nutrition mixtures. *Int. J. Pharm.*, 66 (1990) 1–21.

Washington, C., Connolly, M.A., Manning, R. and Skerratt, M.C.L., The electrokinetic properties of phospholipid stabilized fat emulsions V. The effect of amino-acids on emulsion stability. *Int. J. Pharm.*, 77 (1991) 57–63.

Weber, S.S., Warren, A.W. and Jackson, E.A., Availability of insulin from parenteral nutrient solutions. *Am. J. Hosp. Pharm.*, 34 (1977) 353–357.

Wingert, T.D. and Levin, S.R., Insulin adsorption to an air-eliminating inline filter. *Am. J. Hosp. Pharm.*, 38 (1981) 382–385.

Yuhas, E.M., Frances, T.L., Mayron, D., Baldinus, J.G. and Rosenberg, H.A., Cimetidine hydrochloride compatibility. II: Room temperature stability in intravenous infusion fluids. *Am. J. Hosp. Pharm.*, 38 (1981) 879–881.