

8. Vitamins

METHODS

Literature Search

Time frame of publication search: 1992–2004; relevant publications from 1984–1992 were considered.

Key Words: parenteral nutrition [MESH] AND vitamins [MESH] with limits (English language, infant, children <18 years).

VITAMINS

Introduction

Parenteral vitamins are usually applied as a mixture of different vitamins. Vitamins pose particular pharmacological problems, when given intravenously, since some may adhere to the tubing and/or be degraded by light. Also stability in regard to admixture and “ingredients” may have an effect. Therefore the actual amount of vitamins delivered to the patient may be much lower than the intended dose, particularly in the case of retinol (vitamin A) and in premature infants who receive solutions with slow infusion rates. The optimal parenteral vitamin requirements for children and neonates have never been determined. While there are several parenteral vitamin preparations for adults and older children, there are just a few multivitamin preparations available for preterm infants and neonates. The available products for infants contain the same relative amount of lipid soluble vitamins despite different pharmacological properties in different preparations (combined water and fat soluble vitamin solution versus only fat soluble vitamin preparation). Adult formulations containing propylene glycol and the polysorbate additives are not recommended for use in infants because of concerns on potential toxicity. There is little data on vitamin needs of children with acute and chronic diseases whose requirements might differ.

Vitamin concentrations in the effluents of the application sets are the result of a complex interaction of several factors, including flow rates, tubing materials and sizes, intensity of light exposition, environmental humidity and temperature as well as the relative content of each vitamin.

Little new data has been published in this area during the last 20 years. Therefore, this chapter cannot provide a fully evidence based recommendation but tries to provide a reasonable framework for the pediatrician who prescribes parenteral vitamins and to point out particular areas of problems. All studies determining vitamin levels during intravenous supply have been undertaken with commercially available mixtures, either given in the

glucose–amino acid solution or in the lipid emulsion. Therefore, current recommendations are based on the composition of specific products.

Given the lack of adequate evidence, it is recommended to maintain, for the time being, parenteral vitamin dosages that have been previously recommended ((1–3) (LOE 4)) and have been used without apparent harmful effects in clinical practice for a number of years, with the exception of thiamine where needs may be higher than previously assumed. (**GOR D**)

Recommendations

- Infants and children receiving PN should receive parenteral vitamins. **GOR D**
- When possible water and lipid soluble vitamins should be added to the lipid emulsion or a mixture containing lipids to increase vitamin stability. **GOR D**
- Intermittent substitution twice or three times a week has not been studied. There is a hypothetical risk of adverse effects by transient high levels. Present recommendations are based on daily infusion. An exception is Vitamin K, which can be given weekly. **GOR D**
- Optimal doses and conditions of infusion for vitamins in infants and children have not been established, therefore, recommendations in Tables 8.1 and 8.2 are based on expert opinion. **GOR D**
- Measurement of vitamin concentrations in individual parenterally fed children may be needed based on clinical indications and in patients on long term parenteral nutrition, but in other patients routine monitoring is not recommended because of lack of evidence on adequate benefits. **GOR D**

Fat Soluble Vitamins

A sufficient supply of vitamins is essential for growth and development. Infants and particularly low birth weight infants have low body stores of vitamins at birth due to a limited transfer of lipid-soluble substrates across the maternal placenta. Therefore, a sufficient supply of vitamins to preterm infants from the first days of life is recommended. The parenteral vitamin supply to preterm infants is extensively exposed to light and oxygen and to the lipophilic surfaces of tubing materials due to the small infusion rates.

TABLE 8.1. Recommended intakes for parenteral supply of lipid soluble vitamins for infants and children (2,24,27,29,43–45)

	Infants (Dose/kg body weight per day)	Children (Dose per day)
Vitamin A (μg)*	150–300	150
Vitamin D (μg)	0.8 (32 IU)	10 (400 IU)
Vitamin E (mg)	2.8–3.5	7
Vitamin K (μg)	10 (recommended, but currently not possible)**	200

*1 μg RE (retinol equivalent) = 1 μg all-trans retinol = 3.33 IU vitamin A.

Vitamin A is most vulnerable to degradation by light emitted near its absorption maximum at wavelengths of 330 to 350 nm, vitamin E at 285 to 305 nm. Red plastic bags offered for protecting the syringes are impervious for wavelengths from 190 to 590 nm and amber light protecting tubing material absorb wavelengths from 290 to 450 nm. The most detrimental factor for vitamins A and E is intensive sunlight, consisting of the whole light-spectrum including the ultraviolet range. In contrast, neon light illuminating the intensive care unit at night is mainly emitting wavelengths in the visible part of the light spectrum, and the phototherapy lamp used emits mainly wavelengths of 400 and 450 to 460 nm, respectively. Both light sources have little degrading effect on vitamin A.

Losses to tubing and light degradation depend on whether vitamins are given with a lipid emulsion or in the glucose amino acid mixture and vary for different lipid soluble vitamins.

Vitamin A

Vitamin A plays an essential role in normal differentiation and maintenance of epithelial cells and adequate immune function. Prophylactic supplementation of vitamin A was reported to protect against bronchopulmonary dysplasia and to reduce the requirement for oxygen support ((4) (LOE 3); (5) (LOE 2)).

The adequate supply of vitamin A for premature neonates remains controversial. The “adequate” concentration of plasma vitamin A in very low birth weight infants is not known. Serum concentrations below 200 $\mu\text{g}/\text{L}$ (0.7 $\mu\text{mol}/\text{L}$) have been considered to indicate deficiency in premature infants and concentrations below 100 $\mu\text{g}/\text{L}$ (0.35 $\mu\text{mol}/\text{L}$) indicate severe deficiency and depleted liver stores. The range of normal values for children older than 6 months of age (including adults) is 300–800 $\mu\text{g}/\text{L}$. Both the plasma retinol binding protein (RBP) response ((6) (LOE 3); (7) (LOE 3)) and the relative rise in serum retinol concentration (8) following intramuscular (I.M.) vitamin A administration have been described as useful tests to assess functional vitamin A status.

TABLE 8.2. Recommended intakes for parenteral supply of water soluble vitamins for infants and children (2,30,33,38)

	Infants (Dose/kg body weight per day)	Children (Dose per day)
Ascorbic acid (mg)	15–25	80
Thiamine (mg)	0.35–0.50	1.2
Riboflavin (mg)	0.15–0.2	1.4
Pyridoxine (mg)	0.15–0.2	1.0
Niacin (mg)	4.0–6.8	17
B12 (μg)	0.3	1
Pantothenic acid (mg)	1.0–2.0	5
Biotin (μg)	5.0–8.0	20
Folic acid (μg)	56	140

Delivery of vitamin A is complicated by substantial photo-degradation and adsorptive loss when given in combination with the water soluble vitamins as part of the glucose-amino acid infusion. Loss to tubing also depends on the tubing material. Alternative methods of delivery have been proposed to ensure the application of reproducible amounts of vitamin A to premature neonates by using shorter IV tubing and a shorter infusion time with reduced duration of exposure to light and tubing material or by supplying the more stable vitamin A ester retinyl palmitate or the multivitamin solution with the lipid emulsion ((9–11) (LOE 2)).

The total delivery of retinol from parenteral infusions has been consistently reported to be below 40% of the intended dose (9,12,13). Contradictory results have been reported by different authors on the effects of light protection on vitamin A release under “ambient light conditions” that were usually not specified or quantified in the published studies. Thus, light protection should only be considered for protection of retinol exposed to strong direct day light. Under artificial lighting conditions, the use of light protecting tubing materials will have only a marginal influence on retinol delivery compared to the amounts lost by extensive adsorption onto the tubing.

Retinyl palmitate in the lipid emulsion provides reproducible amounts delivered during the infusion period, indicating that it is a stable ester of vitamin A and that it is further protected by the lipid emulsion, presumably because lipid droplets disperse the light and thus protect the vitamin. The major proportion of retinol losses is due to adsorption onto the tubing materials within the first hour of infusion, whereas retinyl palmitate tends to adsorb to tubing material to a lesser extent. A smaller surface of tubing and less passage time of the infusion through the tubing provide improved delivery. However, the available “micro tubing” made of polyurethane are more prone to adsorb lipophilic substances than standard PE tubing (14). PE and PVC tubing materials seem to have comparable adsorption behaviors. Supplying vitamin A in a lipid emulsion is the most feasible way to reduce losses.

In infants an intravenous vitamin A supply of about 920 IU/kg per day together with the water soluble

mixture or 230–500 IU/kg per day with the lipid emulsion are often used. Since losses are quite variable and losses are higher in the water soluble mixture, the amount delivered to the patient may be estimated to be approx. 300 to 400 IU/kg per day for both options. Supplementing vitamin A as retinyl palmitate (1000 IU/d Vitamin A) in premature infants for 28 days in addition to parenteral nutrition (400 IU/day) and enteral supply (1500 IU/day) led to significantly higher serum levels than at birth but with a wide range of variation. 32% still had levels below 20 µg/dL ((15) (LOE 3)).

Vitamin A supplementation for preventing morbidity and mortality in very low birth weight infants. Level 1 evidence exists only for VLBW infant with gestational age <32 weeks or birth weight <1500 g. A Cochrane review (16) found an association of vitamin A supply and a reduction in death or oxygen requirement at one month of age and of oxygen requirement of survivors at 36 weeks post-menstrual age, with this latter outcome being confined to infants with a birth weight <1000 g.

Five eligible trials supplemented vitamin A intramuscularly soon after birth over the next 28 days in various doses of 4000–5000 IU three times a week to 2000 IU every other day. One study supplemented vitamin A as retinyl palmitate in lipid emulsion at approx. 700 RE/kg per day for the first two weeks and 600–700 RE/kg per day for the next two weeks. Control and study infants also received “Standard” vitamin A. The conclusion of the review was that whether clinicians decide to use repeat intramuscular doses of vitamin A to prevent chronic lung disease may depend upon local incidence of this outcome and the value attached to achieving a modest reduction in this outcome balanced against the lack of other proven benefits and the acceptability of the treatment. The benefits, in terms of vitamin A status, safety and acceptability of delivering vitamin in an intravenous emulsion compared with repeated intramuscular injection should be assessed in a further trial.

The NICHD trial necessitates 12 intramuscular injections with 5000 IU (17). Compared with this regimen, once-per week (15 000 IU) worsened, and a higher dose (10,000 IU 3x per week) did not reduce vitamin A deficiency (serum retinol <20 µg/dL, RBP <2.5 mg/dL, and/or RDR >10%) (18).

Conclusion: Vitamin A delivery is improved by the infusion of retinyl palmitate with lipids, but light protecting tubing provides only a marginal benefit.

Dosage recommendations for parenteral vitamin supplementations for premature infants are based on clinical studies measuring vitamin levels during supplementation. Most of these studies were done with the water soluble solution containing water and lipid soluble vitamins. The true needs of the infants are not known. The LOE in I.M. high dosages imply that higher levels of substitution may be warranted in this patient population.

Vitamin E

Vitamin E is a lipid-soluble antioxidant, protecting cell membrane polyunsaturated fatty acids from free radical oxidative damage. Appreciable prenatal vitamin E accretion occurs only in the third trimester of pregnancy with increasing fetal lipid stores. The dietary requirements of a-tocopherol are dependent on the amount of PUFA in the diet. Early vitamin E administration to preterm infants was reported to reduce the severity of retinopathy of prematurity ((19) (LOE 2); (20) (LOE 2)) and incidence and severity of intracranial hemorrhage ((21) (LOE 2); (22)). a-tocopherol tends to adsorb to some extent onto tubing materials, which can be prevented by application with the fat emulsion or by use of a vitamin E ester ((9, 11) (LOE 2); (23) (LOE 2)). Vitamin E is little affected by exposure to light. Light protection of the infusion devices is therefore not necessary to protect vitamin E. Since vitamin E stores are very low at birth in premature infants and these infants are at increased risk for oxidative stress, supplying 2.8–3.5 IU/kg per day of vitamin E is probably advisable ((2) (LOE 4); (24) (LOE 4)).

Vitamin E supplementation in preterm infants leading to serum levels >3.5 mg/dl reduced the risk of intracranial haemorrhage but increased the risk of sepsis (25). In very low birth weight infants it increased the risk of sepsis, and reduced the risk of severe retinopathy and blindness among those examined. Evidence does not support the routine use of vitamin E supplementation by intravenous route at high doses, or aiming at serum tocopherol levels greater than 3.5 mg/dl (25). In premature infants, safe blood levels of vitamin E are 1–2 mg/dL (2). For infants and children, recommended blood levels are 0.5–1.5 mg/dL (2). However, since vitamin E is carried in blood by lipoproteins, the ratio between serum vitamin E/total serum lipids should be used to assess vitamin E status (deficiency: serum vitamin E to total lipid ratio <0.8) ((25) (LOE 1–4)).

Vitamin D

In general, Vitamin D maintains calcium and phosphorus homeostasis together with PTH by increasing intestinal absorption of Ca and P, by affecting the renal re-absorption of P, and to a lesser extent Ca, and by modulating turnover of these minerals in bone. However, it is not known whether preterm infants on parenteral nutrition require vitamin D. The parenteral vitamin D requirements might be lower than enteral requirements, since no enteral intake of minerals needs to be facilitated. It has been suggested that as little as 30 IU/kg per day i.v. might be sufficient ((27) (LOE 3)).

Vitamin K

Vitamin K's most important physiologic role is the regulation of the coagulation factors (factors II, VII, IX, X)

via carboxylation of these factors which is vitamin K dependent. Two proteins, involved in coagulation, namely protein C and protein S, are also vitamin K dependent. In addition, vitamin K plays a role in the synthesis of osteocalcin, a marker of bone formation.

It was recommended that for preterm infants the daily dose should be 100 µg phyloquinone/kg per day. Premature infants supplemented with vitamin K (1 mg) intramuscularly, followed by parenteral nutrition with 60 µg/d (<1000 g) and 130 µg/d (>1000 g) had high plasma vitamin K levels compared with those at 40 weeks postconceptual age ((28) (LOE 2)). A parenteral vitamin K supply of 80 µg/kg per day (29) in premature infants might be excessive if combined with an i.m. dosage of 1 mg on day 1, and lower supplies may suffice during the first weeks of life. Current multivitamin preparations contain high amounts of vitamin K which tend to supply 100 µg/kg (10 times higher than recommended enteral intakes), but adverse clinical effects have not been reported.

The suggested daily intake for children is 200 µg per day.

Statement and Recommendations

- Ranges of reasonable parenteral vitamin supply for infants and children are given in table 1. **GOR D**
- There are substantial losses of vitamin A when given with a water soluble solution; therefore parenteral lipid soluble vitamins should be given with the lipid emulsion whenever possible. **GOR D**
- For preterm infants, serum tocopherol levels should be between 1–2 mg/dL, but not exceed 3.5 mg/d. **GOR A**. To properly assess vitamin E status, the ratio between serum vitamin E/total serum lipids should be used.
- A vitamin K supply of 80 µg/kg per day parenterally in premature infants might be excessive if combined with an i.m. dosage of 1 mg on day 1. **LOE 2**
- In exclusively parenterally fed infants Vitamin D supply of 30 IU/kg/d might be sufficient. **GOR D**

Water Soluble Vitamins

Introduction

Current recommendations are expert opinions based on observed biochemical responses to variations in parenteral intake and on comparison with enteral recommendations. Controlled randomized trials investigating the effect of different parenteral vitamin substitution regimens on clinically relevant long term outcome parameters are lacking.

Given the lack of adequate evidence, it is recommended to maintain, for the time being, dosages that have been recommended previously ((1–3) (LOE 4)) and have been used without apparent harmful effects in clinical practice for a number of years. However, in the case of thiamine (vitamin B1), the needs of preterm infants might be higher than previously recommended ((30) (LOE 2)), therefore a higher dosage is recommended (Table 8.2).

Water-soluble vitamins must be administered on a regular basis as they are not stored in significant amounts, except for B₁₂. Excess is excreted by the kidneys and there is little toxicity. Term infants and children appear to adapt to large variations in vitamin intakes because similar blood levels have been measured despite several-fold differences in intake on a body weight basis. By contrast, the finding of marked elevation of some vitamins and low levels of others seen in infants less than 1500 g suggests that this group has less adaptive capacity to high- or low-dose intakes ((31) (LOE 4); (32) (LOE 2)). Therefore, there may be a need to develop specific vitamin preparations for low birthweight infants ((1) (LOE 4); (2) (LOE 4); (33) (LOE 4)).

Vitamin preparations can protect intravenous lipid emulsions from peroxidation. The administration of multivitamins with the intravenous lipid emulsions provides a practical way to reduce peroxidation of the lipid while limiting vitamin loss (34,35).

Vitamin C (ascorbic acid)

L-ascorbic acid is the biologically more active form of the vitamin and it is a cofactor in hydroxylation reactions in many biosynthetic processes, as well as an antioxidant. The classic clinical manifestation of vitamin C deficiency is scurvy. Vitamin C is particularly important in premature infants as it is involved in the catabolism of tyrosine and its deficiency can result in transient tyrosinemia. Due to its rapid renal clearance, toxicity of vitamin C is rare even when doses exceeding the RDA are used. However, very large doses have been associated with uricosuria, hypoglycaemia and hyperoxaluria ((36) (LOE 4)).

The infusion of an average of 48 mg/kg per day of ascorbic acid for 4 weeks to premature infants resulted in plasma concentration that were substantially higher than those detected in term infants or children ((37) (LOE 2)). Therefore, substantially lower doses (15–25 mg/kg per day) have been recommended for parenteral nutrition (33). In premature infants the parenteral administration of 100 mg/kg per day vitamin C for 7 days led to plasma levels twice as high as the level of the umbilical artery ((38) (LOE 2)). However, Friel et al., demonstrated that for most premature infants the recommended daily dosage of 25 mg/kg per day would be adequate ((30) (LOE 2)).

Thiamine (Vitamin B₁)

Thiamine pyrophosphate is involved in carbohydrate metabolism as well as in lipid synthesis. Its requirements depend on carbohydrate intake. Deficiency of thiamine may lead to beriberi with neurologic and cardiovascular symptoms. Thiamine is excreted by the kidneys and toxicity is rarely detected. In parenterally fed infants and children a deficient thiamine supply may lead to severe lactic acidosis and even death within a period of days to weeks (39). In preterm infants a parenteral thiamine intake of 780 µg/kg per day led to 10-fold higher serum levels than in cord blood ((37) (LOE 2)). Consequently, a considerable lower parenteral intake (200–350 µg/kg per day) has been recommended and repeatedly reiterated until Friel et al. challenged this recommendation ((30) (LOE 2)). In their study a mean parenteral and enteral intake of thiamine of 510 µg/kg per day maintained a normal functional thiamine status and levels slightly below cord blood concentrations (30). Therefore, the current parenteral recommendation for preterm infants (200–350 µg/kg per day) might be too low and dosages up to 500 µg/kg per day seem more appropriate, but further information is required.

Riboflavin (Vitamin B₂)

Riboflavin forms flavin adenine dinucleotides and thus participates in energy metabolism. The requirement for riboflavin is associated with protein intake. The adequacy of the riboflavin status can be assessed by measuring plasma concentrations and by the erythrocyte glutathione reductase test (EGRAC). Clinical manifestations of deficiency include hyperemia of mucous membranes, stomatitis, dermatitis and anaemia. Riboflavin is very light sensitive and is rapidly photodegraded in PN solutions.

A recent trial showed tolerance of a combined enteral and parenteral riboflavin intake up to 624 µg/kg per day in preterm infants (30), however, parenteral riboflavin dosages above 281–500 µg/kg per day were repeatedly shown to exceed requirements ((11) (LOE 2); (40) (LOE 2); (41) (LOE 2); (42) (LOE 4)). Therefore, the recommended dosage of 0.15–0.2 mg/kg per day to preterm infants remains unchanged. As suggested by Greene et al (2), the recommended dosage of 1.4 mg riboflavin per day for term infants and children is more than necessary, but due to the lack of toxicity and studies of actual requirements, this suggested dosage remains unchanged.

Loss of riboflavin through photo-degradation can be very high (65%) and can be halved by adding the water soluble vitamin solution to the lipid solution, and further reduced by using dark tubing (34). Data on the signs and symptoms of riboflavin toxicity in infants and children is insufficient. The precise requirement of riboflavin in parenterally fed infants and children has not yet been defined. In very low birth weight infants, the current

practice of riboflavin supply leads to elevated plasma levels after birth.

Pyridoxine (Vitamin B₆)

Pyridoxine, pyridoxal and pyridoxamine are the three natural pyridines and their phosphorylated forms are involved in metabolism of amino acids, prostaglandins and carbohydrates as well as the development of the immune system and neurologic function. Pyridoxine deficiency presents with hypochromic anemia and neurologic symptoms.

The optimal parenteral pyridoxine intake in infants and children has not been defined. In a recent trial, a considerably higher intake ((30) (LOE 2)) than the previously recommended intake ((33) (LOE 4)) was tolerated in preterm infants. However, this recent data does not justify altering current recommendations.

Cobalamin (Vitamin B₁₂)

Vitamin B₁₂ is an organometallic complex. It participates in metabolic reactions involving the synthesis of DNA nucleotides. A supply of 0.6 µg/kg per day has led to elevated serum levels ((37) (LOE 2)). The adequacy of current recommendations remains to be confirmed.

Niacin

Niacin is essential for the synthesis of nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate which serve as cofactors for electron transport and energy metabolism. Niacin deficiency results in pellagra characterized as cutaneous, gastrointestinal and neurologic symptoms. No new studies are available. Adequacy of current recommendations needs to be confirmed in ELBW infants.

Pantothenic Acid

Pantothenic acid is a precursor of coenzyme A and thus involved in many reactions of energy metabolism. No new studies are available. Adequacy of current recommendations needs to be confirmed in ELBW infants.

Biotin

Long term parenteral nutrition free of biotin together with long-term use of broad spectrum antibiotics leads to a clinical syndrome of lethargy, hypotonia, irritability, alopecia and dermatitis. Adequacy of current recommendations needs to be confirmed.

Folic Acid

Folic acid is needed in the biosynthesis of purines and pyrimidines, in the metabolism of some amino acids, and

Recommendations

- Ranges of reasonable parenteral vitamin supply for infants and children are given in table 2.
- GOR D**
- Water-soluble vitamins should be administered regularly to parenterally fed patients, preferably on a daily basis. When feasible, vitamin preparations should be added to the lipid emulsion.
- GOR D**

in the catabolism of histidine. The adequacy of current recommendations needs to be confirmed.

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