

## ORIGINAL COMMUNICATION

# Losses of vitamin A and E in parenteral nutrition suitable for premature infants

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**Objective:** To assess the bioavailability of vitamins A and E administered parenterally with either water-soluble or lipid-soluble preparations.

**Study design:** A water soluble preparation (MVI Pediatric<sup>®</sup>) administered with a glucose–amino acid solution and a lipid soluble preparation (Vitalipid N Infant<sup>®</sup>) infused with a lipid emulsion were subjected to phototherapy light, different flow rates, light protection, different tubing materials and tubing sizes, and concentrations in the effluents were determined.

**Results:** Recovery of retinol in glucose-amino acid solution was poor under all conditions (16–30% without; 21–42% with light protection tubing) and increased to 61% with polyethylene and to 44% with polyurethane tubings. Polyurethane tubings with reduced volume improved retinol delivery to 56%. Retinylpalmitate (Vitalipid) losses were low, with recovery of 86 and 77% with and without light protection, respectively. Recoveries of  $\alpha$ -tocopherylacetate in GLUC-AA were 103–107% without and 94–102% with light protection and of  $\alpha$ -tocopherol in LIPID 89% without and 85% with light protection.

**Conclusions:** Parenteral vitamin A delivery is improved by the infusion of retinylpalmitate with lipids. Light protecting tubings provide only a marginal benefit with artificial light and none with phototherapy light. Polyethylene and polyvinylchloride tubings adsorb less retinol than polyurethane tubings. Small tubing diameters resulting in higher flow rates enhance retinol delivery.

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**Keywords:** parenteral nutrition; vitamin A; vitamin E; tubing material

### Introduction

Vitamins A and E are degraded by exposure to oxygen and light (Allwood, 1982). Marked losses of parenterally administered vitamin A, and also to a lesser extent vitamin E, have been reported (Allwood, 1982; Drott *et al*, 1991; Gillis *et al*, 1983; Greene *et al*, 1987; Gutcher *et al*, 1984; Henton *et al*, 1990; Inder *et al*, 1995; Riggle & Brandt, 1986; Shenai *et al*, 1981; Thomas *et al*, 1991; Allwood & Plane, 1986). We hypothesized that vitamin delivery to premature neonates is particularly critical, because they receive small volumes of infusate administered continuously at low flow rates, which

results in a high exposure of the solution to light and to the surface of the tubing material. In this patient group an adequate supply of vitamins A and E is of great relevance, since they have low body stores at birth (Brandt *et al*, 1978; Dju *et al*, 1952), high needs for growth and development and a poor antioxidant defense system. Administration of vitamins A and E to very premature infants has been associated with lower incidence and less severity of bronchopulmonary dysplasia, retinopathy of prematurity and intracranial hemorrhage (Johnson *et al*, 1989, 1995; Papagaroufalos *et al*, 1991; Shenai *et al*, 1987; Speer *et al*, 1984).

Data on the delivery of vitamins A and E during total parenteral nutrition in adults and infants have been reported (Drott *et al*, 1991; Gillis *et al*, 1983; Greene *et al*, 1987; Gutcher *et al*, 1984; Henton *et al*, 1990; Riggle & Brandt, 1986; Shenai *et al*, 1981, 1982; Thomas *et al*, 1991; Allwood & Plane, 1986; Dahl *et al*, 1986, 1994), but only one study investigated the supply of these two vitamins to premature infants under the particular conditions of a neonatal intensive care unit (Inder *et al*, 1995). Variation of experimental

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conditions such as the use of different tubing materials, humidity and the elevated temperature in an incubator may substantially influence the delivery of vitamins A and E to the recipient infant (Autian, 1963). MVI pediatric<sup>®</sup> and Vitalipid N Infant<sup>®</sup> are the two most commonly used products for supplying fat soluble vitamins in neonatal parenteral nutrition. Vitamin A is in the form of retinal (vitamin alcohol) in MVI and retinal palmitate (a retinyl ester) in Vitalipid. We tested the delivery of a multivitamin preparation (MVI Pediatric<sup>®</sup>, Astra, Westborough, USA) supplied with a glucose–amino acid infusion and of a soybean-oil based preparation containing only the lipid-soluble vitamins (Vitalipid N Infant<sup>®</sup>, Pharmacia & Upjohn, now Fresenius Kabi), added to a lipid emulsion. The two infusion solutions were submitted to different experimental conditions using delivery systems with and without light protection, different flow rates, blue/green light of 420–550 nm wavelength used for phototherapy and different tubing lengths and plastic materials.

### Material and methods

Standardized infusion solutions were prepared (Table 1) with a composition and dose as used in our neonatal care unit for a hypothetical parenterally fed premature newborn weighing 1 kg. The water soluble vitamin preparation was given in the recommended dose of 2 ml/kg, but the recommended dose of the lipid preparation varies between 1 and 4 ml/kg. We elected an equal volume dose of 2 ml/kg since this is given at our intensive care unit and was currently evaluated in clinical study (data submitted for publication). The glucose-amino acid solution (GLU/AA) and the lipid emulsion were freshly mixed in a brown glass bottle. Aliquots of 40 and 17 ml, respectively, were drawn into syringes (perfusor syringe Plastipak<sup>®</sup>, 50 ml, Becton Dickinson, Heidelberg, Germany or perfusor syringe, 25 ml, Braun, Melsungen, Germany), with an additional volume of 3 ml to fill the tubing. The syringes were fixed in syringe pumps (Perfusomat Secura<sup>®</sup>, Braun, Melsungen, Germany), arranged at an angle of 90° to the outside window of the room. The tubings led into an incubator (Inkubator 8000<sup>®</sup>, Dräger Werk AG,

Lübeck, Germany), placed in parallel to an outside window at a distance of 1–1.5 m. Incubator conditions were held at 85–100% humidity and a constant temperature of 37°C. At night, the room was illuminated by neon light. Each experimental variant was performed in duplicate. Before starting the experiments, the baseline vitamin concentrations was measured in an aliquot of the mixed solution. All further determined concentrations are expressed as a percentage of this baseline value. At intervals of 0.5–6 h, aliquots of the effluents at the end of the tubings were collected in the incubator in amber glass vials closed with a teflon coated cap.

### Experiment 1. Effect of light exposure

The influence of day light and different flow rates was studied over 24 h. Under light protected conditions, syringes were covered with red plastic bags designed for light protection of infusates (Pharmacia-Upjohn, Erlangen, Germany) and were connected to a 1.2 µm particle filter (MX 1483, Medex Medical, Ratingen, Germany) followed by an amber colored tubing made of PVC (OP SE, Becton Dickinson, Heidelberg, Germany, length 150 cm, volume 1.5 ml) and a sterile 0.2 µm filter (MX 1480, Medex Medical, Ratingen, Germany), which could not be used with the lipid emulsions. In infusion sets without light protection, the syringes were not covered and the tubing consisted of clear polyethylene (Original Perfusorleitung Luer Lock, Braun, Melsungen, Germany, 150 cm, 1.8 ml). The GLU/AA-solution was pumped at two different flow rates of 1.6 ml/h providing 40 ml/24 h and of 3.3 ml/h, providing 80 ml/24 h, respectively, with the total daily volume divided into two syringes and a change after 12 h. The syringe pumps for the lipid emulsion were set to deliver 0.7 ml/h. All experiments were started at 9 am. The illumination at the site of the infusion pump and the tubing material was 1000–1600 lx during a sunny day in summer and 200–600 lx at night under the artificial lighting conditions of the intensive care unit (measured with a Lux Digital Tester, Beha, Munich, Germany).

### Experiment 2. Phototherapy

A phototherapy lamp (Phototherapielampe 800, Heraeus Instruments, Hanau, Germany) was placed over the incubator at the usual distance of 40 cm above the infusion tubing. The infusion apparatus and all other conditions were equal to the first experiment with a flow rate of 3.3 ml/h for the

**Table 1** Admixtures investigated in the stability studies

Glucose amino acid solution (GLU/AA solution)		Lipid emulsion	
Glucose 10%	53 ml	Intralipid 20% <sup>®a</sup>	15 ml
Aminoacids 10% <sup>a</sup>	20 ml	Vitalipid N Infant <sup>®a</sup>	2 ml
Calcium 10% <sup>b</sup>	5 ml	Total	17 ml
MVI pediatric <sup>®c</sup>	2 ml		
Total	80 ml		
Containing:		Containing:	
Vitamin A (alcohol)	920 IU	Vitamin A (palmitate)	460 IU
Vitamin E (acetate)	2.8 IU	Vitamin E (alcohol)	1.4 IU

<sup>a</sup>Aminopaed<sup>®</sup>, Pharmacia & Upjohn, Erlangen, Germany.

<sup>b</sup>Novartis, Nürnberg, Germany.

<sup>c</sup>Astra, Westborough (MA), USA.

**Table 2** Calculated amounts of vitamins received by the hypothetical infant

Glucose amino acid solution (GLU/AA solution)		Lipid-emulsion	
Vitamin A (alcohol)	147–386 IU	Vitamin A (palmitate)	345–409 IU
Vitamin E (acetate)	2.8 IU	Vitamin E (alcohol)	1.2–1.3 IU

GLU/AA-solution and of 0.7 ml/h for the lipid emulsion. The experiment was run for 12 h from 9 pm to 9 am. Light intensity of the phototherapy lamp was 9000–11 000 lx, with emitted wavelengths at 410 and 450–460 nm (manufacturer's specification).

### Experiment 3. Tubing material

The following tubings were connected to the infusion set described in the first two experiments: the reference polyethylene (PE) tubing used in experiments 1 and 2, a yellow PE tubing providing light protection (150 cm, 1.8 ml); a polyurethane (PU) tubing (MX 448-HL, 150 cm, 1.3 ml); another polyurethane tubing with a smaller diameter (MX 595-LR, 150 cm, 0.9 ml); and a short polyurethane tubing (SX 562836, 60 cm, 0.5 ml; all from Medex Medical, Ratingen, Germany). The syringes were covered with aluminum foil, and the tubing sets remained unprotected. As a reference without light exposition, another 1.3 ml polyurethane tubing was wrapped up with aluminum foil. The syringe pumps were set to deliver 3.3 ml/h. The intensity of daylight was quite weak with values of approximately 1000 lx. The experiment began at 10 am and lasted 12 h.

### Vitamin analysis

Two aliquots from each sample were taken and diluted immediately after collection with isopropanol (Licrosolv, Merck, Darmstadt, Germany) containing 1.25 g/l butylhydroxytoluene (Fluka, Neu-Ulm, Germany); samples of the GLU/AA-solution were diluted 1:1, samples of the lipid emulsion 1:10 (vol/vol). The vials were stored at  $-80^{\circ}\text{C}$  until analysis, but not longer than 1 month, which does not affect levels of retinol, alpha-tocopherol and carotenoids (Brown Thomas *et al*, 1998). Concentrations of retinol, retinylpalmitate, tocopherols and  $\alpha$ -tocopherylacetate were determined by reversed-phase high performance liquid chromatography (HPLC). The chromatographic system consisted of an Intelligent Pump L6200, an UV-vis Detector L 4250, a Fluorescence Spectrophotometer F 1050, an Autosampler AS 2000 and a Chromatointegrator D-2500 (all Merck-Hitachi, Darmstadt, Germany). Fat-soluble vitamins were separated with a Licrospher 100 RP<sub>18</sub> 5  $\mu\text{m}$  240 $\times$ 5 mm column (Merck, Darmstadt, Germany). Elution was performed by methanol:acetonitrile:ethylacetate 125:68:7, buffered by 0.5 g ammoniumacetate and 0.5 ml triethylamine per litre. The flow rate was set at 1.75 ml/min, rising to 2.5 ml/min at 7 min. The total run-time was 20 min. Temperature was held constant at  $30^{\circ}\text{C}$ . The wavelength of the UV-vis-detector was adjusted to 325 nm, switched to 292 at 2.8 min and set back to 325 nm after 7.5 min. The excitation and emission wavelengths of the fluorescence detector were adjusted to 295 and 330 nm, respectively. The injection volume was 20  $\mu\text{l}$ . Coefficients of variation determined by 10 consecutive analyses of one sample were 6% for retinol, 2.9% for  $\alpha$ -tocopherylacetate,

3.0% for  $\delta$ -tocopherol, 3.2% for  $\gamma$ -tocopherol, 3.4% for  $\alpha$ -tocopherol and 4.8% for retinylpalmitate (Göbel *et al*, 1997).

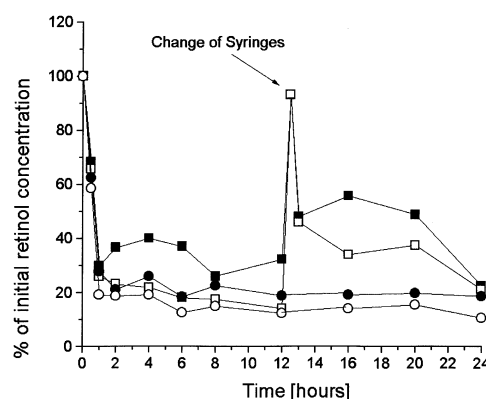
Mean concentrations of vitamins delivered by each infusion set were calculated for each collection interval. The totally infused doses over 24 and 12 h, respectively, were determined by computing the areas under the curve and compared with the amount initially added to the infusate.

## Results

### Experiment 1

The concentrations of retinol in the GLU/AA-solution (Figure 1) decreased markedly to 19–30% of the initial values within the first hour of infusion, apparently due to extensive adsorption onto the tubings. With light protection at the higher flow rate, the adsorption period was followed by a period of desorption. After changing the syringes, the same pattern of ad- and desorption repeated again, but delivering higher concentrations of vitamin A than in the first 12 h of the experiment. In contrast, the amounts delivered by the non-protected application set and administered with half the flow rate, respectively, decreased also within the first hour of the experiment, but then remained constant at between 10 and 23% of the initial concentrations.

The total amounts of retinol recovered at the end of the tubing system over the 24 h time period were 42% of the intended doses (Table 2) with and 30% without light protection at the higher flow rate. Without a change of syringes at 1.6 ml/h flow rate, the total deliveries during 24 h were 21% of the intended doses with and 16% without light protection. As a consequence, using amber light protection tubings provided only a slightly higher benefit of 12% at 3.3 ml/h and of 5% at half the flow rate, respectively, during 24 h. Doubling the flow rate and changing the syringes provided approximately twice the delivered amounts over a day.



**Figure 1** Retinol delivered by the GLU/AA-solution under routine conditions using volumes of 2 $\times$ 40 ml with (solid square) and without (open square) light protection changing the perfusor syringes after 12 h of infusion and 40 ml with (solid circle) and without (open circle) light-protection over a 24 h time period.

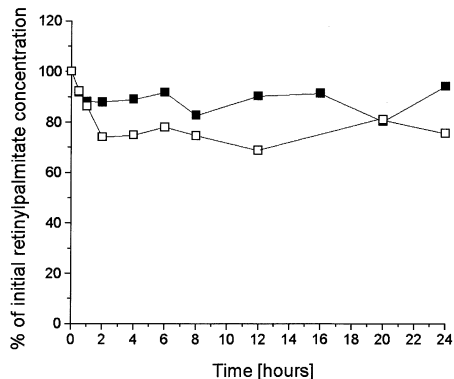
The concentration of was quite stable during the 24 h infusion period with recovery rates between 83 and 114% as seen in Figure 2. No benefit could be attributed to light protection.

In the lipid-emulsion, the delivered concentrations of retinylpalmitate were in the range of 80–94% of the intended doses with and of 69–92% without light protection (Figure 2). The total vitamin A release of the infusion devices during the 24 h time period was 86% with and 77% without light protection.

The delivered amounts of  $\alpha$ -tocopherol were 79–91% of the initial values with protected infusion sets and 80–100% without light protection. Total delivery over 24 h was 85% with compared to 89% without light protection.  $\gamma$ - and  $\delta$ -tocopherols were slightly more stable than  $\alpha$ -tocopherol.

### Experiment 2

Exposed to phototherapy light, the retinol concentrations applied with the GLU/AA-solution decreased significantly to 32% of the initial concentrations within the first hour of the experiment, and remained constant thereafter between 23 and 31%. The total delivery amounted to 34% of the prescribed dose during the 12 h infusion period and was not influenced by the light protection. The concentrations of  $\alpha$ -tocopherylacetate in the GLU/AA-solution attained values of 92–100% of the initial amounts during the 12 h infusion period. The cumulative infused doses were 98 with and 97% without light protection. Concentrations of retinylpalmitate in the lipid emulsion decreased slightly to 86% (covered) and 90% (unprotected) within the first 2 h of experiment. During the 12 h time period, the total delivery amounted to 90% of the intended doses with and 89% without light protection. There was also a slight decrease of  $\alpha$ -tocopherol concentrations during the first hour of infusion to 87–86% of baseline with and without light protection, whereas the effluent contents remained relatively constant thereafter between



**Figure 2** Retinylpalmitate delivered by the LIPID emulsion solution under routine conditions unit using volumes of 17 ml with (solid square) and without (open square) light protection over a 24 h time period.

85 and 96% of the initial concentrations. The total delivered amounts provided 92% of the intended doses; again, no difference in delivery could be measured comparing light protected and uncovered infusion devices.

### Experiment 3

As already observed in experiments 1 and 2, retinol concentrations in the GLU/AA-solution decreased markedly to 50–70% within the first hour of the experiment, but then remained rather constant until the end of the infusion period.

Comparing the two infusion systems with and without light-protection, the amber colored PE tubing delivered 64% of the intended dose during the 12 h infusion period in contrast to the reference PE tubing providing 61% of the initial concentrations. The aluminum-wrapped PU tubing released a total of 41% of the prescribed dose during the experiment, compared to 44% delivered by the non-protected PU tubing. A shorter transit time of the vitamin solutions reduced the time of light exposition and a smaller tubing surface might reduce vitamin A adsorption onto the tubing material. While the transit time of solutes was 33 min in the reference PE tubing, it was reduced to only 24, 16 and 9 min, respectively, in the different PU tubings with smaller diameters. With increasing volumes and diameters the corresponding surfaces of the PE tubing were 29 and 25 m<sup>2</sup> and of the PU tubings 21 and 10 m<sup>2</sup>, respectively. The total delivery of retinol was 61% of the prescribed dose with the reference PE tubing, 44% with the 1.3 ml PU tubing, 43% with the 0.9 ml and 56% with the 0.5 ml volume tubing. Less retinol was lost over the 12 h time period via the PE tubings, irrespective of their greater surface area and their longer transit time, than with the thinner or shorter polyurethane tubing material.

The concentrations of  $\alpha$ -tocopherylacetate measured in the effluents of the PU tubings also decreased markedly within the first 2 h of the experiment compared to the PE tubings. After approximately 4 h of infusion the end concentrations by the PU tubings approached the concentrations of the PE tubings. The total delivered amounts of the PE tubing were 97%, compared to 92% by the 1.3 ml, 95% by the 0.9 ml and 94% by the short 0.5 ml PU tubings. Light protection using yellow light-protected tubings showed little or no effect (94% of dose compared to 97% with the reference PE tubing). Wrapping PU tubings with aluminum foil provided 95% of the intended doses in comparison to 92% without light protection.

### Discussion

Vitamin concentrations in the effluents of the application sets are the results of a complex interaction of several factors, including tubing materials and sizes, intensity of light exposition, environmental humidity and temperature as well as the chosen concentrations of fat-soluble vitamins (Autian,

1963). The total delivery of retinol from parenteral infusates has been consistently reported to be below 40% of the intended doses (Gillis *et al*, 1983; Greene *et al*, 1987; Gutcher *et al*, 1984; Inder *et al*, 1995; Riggle & Brandt, 1986; Shenai *et al*, 1981; Thomas *et al*, 1991). In our experiments, we used perfusor syringes instead of plastic bags that have a much higher absorptive surface. The delivered amounts of retinol during the infusion period were in the range of 16–64% of prescribed doses and higher than most of the results reported before, particularly in the lipid emulsion. Only Henton *et al* (1990) achieved higher final retinol concentrations of 45–87% of initial amounts after 24 h. They minimized environmental diffusion of water vapor and oxygen concentrations by leading the tubing systems through a tempered water bath, which appears not to be suitable for routine use in a neonatal intensive care unit. Most authors showed a marked decrease of retinol concentrations of the infusate within the first few hours; thereafter, retinol concentrations remained relatively constant until the end of the experiments (Drott *et al*, 1991; Gillis *et al*, 1983; Greene *et al*, 1987; Gutcher *et al*, 1984; Riggle & Brandt, 1986; Shenai *et al*, 1981; Thomas *et al*, 1991; Allwood & Plane, 1986).

The recovery of  $\alpha$ -tocopherylacetate during a 24 h infusion period has been reported in the range of 60–100% of the intended concentrations (Gillis *et al*, 1983; Inder *et al*, 1995; Thomas *et al*, 1991; Shenai *et al*, 1982) our recoveries of  $\alpha$ -tocopherylacetate (92–107% of the initial values) are in the upper range of the reported results. Although  $\alpha$ -tocopherylacetate was claimed not to adsorb onto the plastic infusion bags (Moorhatch & Chiou, 1974), several authors identified a substantial adsorption onto the tubing material within the first hour of infusion (Gillis *et al*, 1983; Inder *et al*, 1995; Thomas *et al*, 1991; Shenai *et al*, 1982). Using syringes instead of plastic bags in our experiments may contribute to lesser amounts adsorbed onto the smaller surface of the application devices.

In studies using a lipid soluble preparation with retinyl-palmitate and  $\alpha$ -tocopherol, the concentrations of retinyl-palmitate delivered after 24 h were 50–100% (Drott *et al*, 1991; Dahl *et al*, 1986, 1994), which are comparable to our results of 76–94%. The reported final  $\alpha$ -tocopherol concentrations after 24 h were in the range of 70–105% of the intended doses (Drott *et al*, 1991; Dahl *et al*, 1986, 1994). Again, the concentrations we measured (85–94%) were within this range. We conclude from these results, that administering the vitamins A and E in a lipid emulsion will provide more consistent and reproducible amounts of both vitamins delivered at the end of the application devices. This leads to significantly better vitamin levels in premature infants (Baeckert *et al*, 1988).

#### **Influence of flow rate**

The vitamins supplied to very prematurely born infants are extensively exposed to light and oxygen and to the lipophilic surfaces of tubing materials due to the small volumes of

infusate administered at low flow rates. Therefore, these infants have a much higher risk of vitamin A losses from the infusion supplied during a 24 h period compared to more mature neonates, in whom usually much higher flow rates and hence less exposure to the tubing surface occurs. In our first experiment, an increase of 12% retinol release during the 12 h time period was achieved by doubling the flow rate and by using PVC light protection tubings. Using PE tubings increased the delivered amount by just 4% for the 12 h infusion period compared to the lower flow rate. Varying the flow rate had little effect for  $\alpha$ -tocopheryl acetate, the delivered concentrations at the higher and the lower flow rate differing only marginally by 2–4%.

In previous experiments performed by Riggle and Brandt (1986), a 7.5-fold increase of the flow rate and the use of PVC tubings also improved the delivered retinol concentration from 33 to 74% of baseline concentrations. Henton & Merritt (1990) found an approximately 25% increase of concentrations in the effluent delivered over 24 h by raising the flow rate 2.5-fold and using PVC tubings, but there was no improvement with polyolefin tubing material.

#### **Influence of light protection**

Vitamin A is most vulnerable to degradation by light emitted near its absorption maximum at wavelengths of 330–350 nm (Allwood & Plane, 1986), vitamin E at 285 to 305 nm (Drott *et al*, 1991). According to the manufacturer's information, the red plastic bags used 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 450–460 nm, respectively. Both light sources have little degradative effect on vitamin A (Allwood, 1982).

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. In our experiments with exposure of the infusion devices to strong daylight in summer, the use of amber light protection tubings of PVC provided retinol concentrations that were higher by some 5–22% of the initial concentrations than the amounts delivered without light protection. The use of different tubing materials in the trial with and without light protection may also have contributed to this difference.

In contrast, we found no effect of light protection tubings under phototherapy conditions. During the third experiment, the delivered retinol concentrations were higher than in the first trial, because daylight was less intensive. In this experiment comparing the same tubing materials, the

use of light protection showed only a marginal benefit of 3% for PE and none for PU tubing material. Thus, light protection should only be considered for protection of retinol exposed to strong direct daylight. Under artificial lighting conditions the use of light-protecting tubing materials will have only a marginal influence to retinol delivery compared to the amounts lost by extensive adsorption onto the tubings.

In contrast to vitamin A applied with the GLU/AA-solution, retinylpalmitate in the lipid emulsion provided nearly quantitative and reproducible amounts delivered during the infusion period, indicating that it is a stable ester of vitamin A (Gutcher *et al*, 1984) and that it is further protected by the lipid emulsion. Exposed to intensive day light, light protection showed only a marginal benefit of 9% during the infusion period and none exposed to phototherapy light, presumably because lipid droplets disperse the light and thus protect the vitamin. Weighing higher costs against the marginal effect, the use of light protection tubings appears dispensable with the vitamins supplied in the lipid emulsion.

Vitamin E, applied as the ester with the GLU/AA-solution or as the alcohol with the lipid emulsion, is little affected by the exposition to light. Light protection of the infusion devices is therefore not necessary for vitamin E.

#### **Influence of tubing material and tubing sizes on adsorption**

The major part of retinol losses is due to adsorption onto the tubing materials within the first hour of infusion. A smaller surface of tubing and less passage time of the infusate through the tubing provides an improved delivery, but the available 'micro tubings' made of polyurethane are more prone to adsorb lipophilic substances than standard PE tubings. PE and PVC tubing materials seem to have comparable adsorption behaviors.

Dividing the infusion solutions into two portions, as done in the first experiment, leads to a lesser decrease of retinol concentration in the effluent from the second portion. Provided that light exposition has only a marginal effect, this seems to be due to saturation effects of the tubing material. Repeated use of tubings over several days or flushing of the tubings by an initial dose of vitamin solution (similar to the use of albumin before applying expensive protein preparations) may provide higher deliveries of retinol. Protecting the vitamins by applying them together with a lipid emulsion or by using esters instead of the free alcohol would be another way to minimize adsorption.

Our studies show that  $\alpha$ -tocopherol applied with the lipid emulsion and  $\alpha$ -tocopheryl acetate infused with the GLU/AA-solution are quite stable when exposed to light and are only slightly adsorbed onto tubing materials. In contrast, retinol delivery during strong daylight is slightly better using amber tubing material, but there is no appreciable improvement under artificial light. Phototherapy light

is less damaging than daylight. PVC tubings show little retinol adsorption but contain high amounts of highly soluble plasticisers such as diethylhexylphthalate and stabilizers such as stearates or urea derivatives (40–60% of total PVC weight), which may be deposited in the recipient organism (Göbel *et al*, 1997). The potential biological effects are little evaluated in small preterm infants. Therefore, we favor PE tubing materials, which also show less absorption of lipophilic vitamins. A simple way to minimize adsorption of retinol in infusion solution to the tubing materials is the reduction of tubing surface and transit time. Applying vitamins protected by a lipid emulsion from adsorption and light degradation provides quantitative and reproducible vitamin A delivery to the premature neonate.

Dosage recommendations for parenteral vitamin supplementation 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 (MVI<sup>®</sup>). The true needs of the infants are not known. We have chosen an isovolumetric approach in our experimental design, since the amount of lipid-soluble vitamins in the water soluble solution is calculated with a significant loss in mind, whereas the losses in lipid solution are supposed to be low. As we and other studies have shown, losses of vitamin A and E are quite different and formulations with vitamin A and E in unchanged ratios but different solutions might cause problems. Our hypothetical infant might receive adequate amounts of vitamin A with the lipid solution but will probably receive little vitamin E. Increasing the dosage to 4 ml/kg body weight will supplement enough vitamin E but lead to a vitamin A levels above recommended levels. These factors need to be considered when formulating new parenteral vitamin solutions. Infusion of vitamins in a lipid emulsion protects from light degradation tubing adsorption and provides quantitative and reproducible amounts of vitamin A delivered to the premature neonate.

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