International Journal of Pharmaceutics, 68 (1991) 277–280

 0378-5173/91/$03.50
ADONIS 037851739100097R

IJP 02287

Lipid emulsion content and vitamin A stability in TPN admixtures

D.P. Bluhm [1], R.S. Summers [1], M.M.J. Lowes [2] and H.H. Dürrheim [2]

[1] *School of Pharmacy, Faculty of Medicine, Medical University of Southern Africa, Medunsa (Republic of South Africa) and* [2] *Pretoria College of Pharmacy, University of Pretoria, Pretoria 0001 (Republic of South Africa)*

(Received 6 June 1990)
(Modified version received 12 August 1990)
(Accepted 20 August 1990)

Key words: TPN; Vitamin A; Fat emulsion; Photodegradation

Summary

Vitamin A stability in TPN regimens may be influenced by the different lipid content in lipid, 3-in-1 and aqueous admixtures. In this study vitamin A losses were investigated by HPLC, in a paediatric lipid emulsion, a paediatric 3-in-1 admixture, an adult aqueous glucose/amino acid admixture and an adult 3-in-1 admixture. The admixtures were stored in PVC containers under typical storage and administration conditions. Pharmaceutically significant vitamin A losses under storage conditions occurred only from the paediatric 3-in-1 admixture. These losses could have been caused by the presence of trace elements from Ped-el®. On exposure to ward light and temperature, the only admixture with a $t_{90\%}$ less than 24 h was the adult aqueous admixture. Under these conditions there was an inverse linear correlation between fat content and vitamin A loss. Fat emulsions in TPN afford protection from light to vitamin A. Hence, the vitamin should be added to lipid emulsions where possible.

Introduction

The stability of vitamin A in total parenteral nutrition (TPN) has been shown to be affected adversely by light (Allwood, 1982a). On exposure to fluorescent light the rate of loss was lower in whole milk than in skim milk (Gaylord et al., 1986), which indicates that the fat content of the carrier system may influence the effect of light on the stability of the vitamin.

It has also been suggested that the phospholipid emulsifier in the fat emulsion Intralipid® prevents the absorption of drugs into PVC containers by adsorbing on to the surface of the plastic and altering its surface properties (Washington and Briggs, 1988).

In TPN vitamin A is commonly administered in a lipid emulsion. The vitamin is also administered in aqueous glucose/amino acid regimens and in 3-in-1 admixtures. The stability of vitamin A might therefore be affected by the different lipid content of the various admixtures.

The purpose of this study was to determine the effect of varying lipid content on:
(a) Vitamin A stability in TPN admixtures stored in PVC bags at 2–8 °C in the dark;
(b) Stability of the vitamin in TPN admixtures stored in PVC bags at 30 °C and exposed to ward light, i.e. actual conditions in paediatric wards in our teaching hospital.

The loss of vitamin A in a paediatric lipid emulsion was used as a baseline and was com-

Correspondence: D.P. Bluhm, Medical University of Southern Africa, PO Box 218, Medunsa 0204, Republic of South Africa.

pared with losses from a paediatric 3-in-1 admixture, an adult aqueous glucose/amino acid mixture and an adult 3-in-1 regimen.

Materials and Methods

Vitamin A stability was determined in four admixture systems, the composition of which is shown in Table 1.

The admixtures were stored for 21 days at 2–8 °C in PVC bags, protected from light (Expt A), and for 72 h at 30 °C exposed to ward light (Expt B).

Sampling

Samples for high-performance liquid chromatography (HPLC) analysis were taken immediately and again after 24, 48 and 72 h and at weekly intervals for 3 weeks. Sampling was performed with a hypodermic needle attached to a 10 ml plastic syringe. Samples were protected from exposure to daylight at all times.

TABLE 1

Composition of Admixtures 1–4

Preparation	Quantity (ml)			
	1 Paediatric lipid	2 Paediatric 3-in-1	3 Adult aqueous	4 Adult 3-in-1
Intralipid® 10%	300	120	–	–
Intralipid® 20%	–	–	–	500
Vamin® glucose	–	180	1000	1000
Glucose 50%	–	–	1000	1000
Soluvit® [a]	7.5	3	–	–
Vitalipid® Infant	15	6	–	–
Pancebrin®	–	–	10	10
Ped-el®	–	24	–	–
Addamel®	–	–	10	10
Total volume	315	330	2020	2520
Vitamin A (μg/ml)	4.762	1.818	7.426	5.952
10% fat emulsion content as percentage of total volume	95.2	36.4	0	39.7

[a] Soluvit® was reconstituted with Intralipid® 10%.

Assay of TPN admixtures

Vitamin A palmitate content was analysed by reverse-phase HPLC, based on the method described by Herslöf and Dahl (1982).

Analysis of results

All information was analysed using a Statgraphics software package.

The Student's t-test statistic was applied to the data to determine the significance of the difference between the means of vitamin A stability in Admixture 1 and the other admixtures.

Calculation of pharmaceutical significance

Trissel (1988) stated the standard for the acceptance for ingredients of intravenous admixtures as decomposition of 10% or less within 24 h in an admixture stored under the specified conditions. Therefore, vitamin A losses exceeding 10% were regarded as being pharmaceutically significant. The time period for vitamin A loss to 90% ($t_{90\%}$) was calculated using the first-order rate constant (k). A plot of the logarithm of the amount of drug remaining as a function of time is linear if the decomposition follows first-order kinetics (Florence and Attwood, 1981).

Regression analysis of the data was performed to determine the linearity of the curves. The measure of the goodness of fit to the linear model is the Pearson correlation coefficient (r). The accuracy parameter for r is: $r > 0.95$. In the instances where the rate of loss of vitamin A did not comply with a first-order process loss was plotted against time and $t_{90\%}$ was taken from the relevant graph.

The first-order rate constant may be obtained from the slope of the plot (slope $= -k$). $t_{90\%}$ is calculated from the equation:

$$\frac{\ln(y\text{-intercept}/90)}{k\,(\text{rate constant})}$$

Results

The results of regression analysis of the data showed that the rate of vitamin A loss followed a first-order process in the paediatric (Admixture 2)

and adult 3-in-1 (Admixture 4) admixtures under controlled storage conditions (Expt A). It could not be established whether the loss from Admixture 1 followed a first-order process or not as the changes over the period of the experiment were so low. Therefore, $t_{90\%}$ for vitamin A in Admixtures 1 and 3 was read from the relevant graphs. Under ward conditions over 72 h (Expt B), the vitamin A loss from Admixture 4 could not be established as a first-order process either, so in this case too $t_{90\%}$ was read from the graph.

Experiment A (2–8 °C in the dark)

Vitamin A loss as a function of Intralipid® content A linear relationship between Intralipid® content and loss of vitamin A in TPN admixtures stored at 2–8 °C in the dark could not be demonstrated ($r = -0.35$). Vitamin A loss after 21 days was higher from Admixture 3 which contained no Intralipid® than from Admixture 4 with 39.7% Intralipid® (15.2 and 10.3% losses, respectively) and significantly lower than from the paediatric 3-in-1 admixture (2) with 36.4% Intralipid®.

Pharmaceutical significance of vitamin A losses from Admixtures 1–4 stored at 2–8 °C in the dark The time period for loss of vitamin A to 90% is presented in Table 2.

The only admixture with a pharmaceutically significant loss of vitamin A over a period of 72 h was Admixture 2. The greater than 10% loss over 24 h is not pharmaceutically acceptable. Clinically, a single reduction of daily dose of this magnitude is not likely to prejudice patients, but it is not advisable to add vitamin A to this admixture before storage.

Vitamin A losses from the other admixtures were not pharmaceutically significant up to 21, 12.2 and 20.5 days (Admixtures 1, 3 and 4, respectively) when stored at 2–8 °C in the dark, which indicates that vitamin A may be added to these admixtures prepared for weekends provided they are stored in the refrigerator before use.

TABLE 2

Time period for loss of vitamin A to 90% for Admixtures 1–4 in Experiments A and B

Expt	1 Paed. lipid	2 Paed. 3-in-1	3 Adult AQ.	4 Adult 3-in-1
A	> 21 days [a]	23.1 h [b]	12.2 days [a]	20.5 days [b]
B	> 72 h [a]	30.0 h [b]	11.0 h [a]	48.0 h [a]

[a] Values were taken from the relevant graphs.
[b] Values were calculated using the rate constant (k).

Experiment B (30 °C and ward lighting)

Vitamin A loss as a function of Intralipid® content The plot of vitamin A loss against Intralipid® content in this instance was linear ($r = -0.92$). After 72 h vitamin A loss in Admixture 1 was 6%, in Admixture 4, 13%, in Admixture 2, 24% and in Admixture 3, 36%.

Pharmaceutical significance of vitamin A losses from Admixtures 1–4 stored at 30 °C and exposed to ward lighting Values for $t_{90\%}$ are presented in Table 2. Only the adult aqueous admixture (3) demonstrated a $t_{90\%}$ of less than 24 h, which implies that of the four admixtures tested only this one exhibited pharmaceutically significant losses of vitamin A over the usual period of administration.

Discussion

Admixture 1 (paediatric emulsion) was the most stable admixture in terms of vitamin A losses. It had the highest lipid content, but no additional amino acids, electrolytes or trace elements, all of which have been implicated in vitamin A loss from TPN admixtures (Allwood, 1982b).

The results of the second part of the study, under ward conditions, confirm the work of Gaylord et al. (1986) which showed that vitamin A (from Vitalipid® Infant) was more stable in a fat emulsion (Intralipid®) than in a 3-in-1 mixture (Intralipid® mixed with Vamin® glucose). Additionally, vitamin A (from Pancebrin®) was more stable (up to 72 h after admixing) in an adult 3-in-1 admixture with 500 ml Intralipid® than in an aqueous glucose/amino admixture which contained no fat.

We conclude that:

(1) Vitamin A palmitate from Vitalipid® Infant is not absorbed into PVC from a lipid emulsion (Intralipid®).

(2) There was no correlation between extent of vitamin A loss and Intralipid® content in the admixtures tested, when stored at 2–8°C in the dark.

(3) TPN admixtures which contain vitamin A and trace elements should not be stored for longer than 7 days at 2–8°C. The commercial source of the trace elements may be an important factor which requires further investigation.

(4) The use of a fat emulsion (Intralipid®) in a TPN regimen affords protection to vitamin A from light. We therefore recommend that vitamin A is added to lipid emulsions where possible, despite the fact that vitamins in Pancebrin® are dispersed in an aqueous solution which is compatible with aqueous admixtures.

Acknowledgement

We acknowledge with thanks the contribution of Colleen Mitchell, who typed the original manuscript.

References

Allwood, M.C., The influence of light on vitamin A degradation during administration. *Clin. Nutr.*, 1 (1982a) 63–70.

Allwood, M.C., Stability of vitamins in TPN solutions stored in 3L bags. *Br. J. Intravenous Ther.*, 3 (1982b) 22–26.

Florence, A.T. and Attwood, D., *Physicochemical Principles of Pharmacy*, MacMillan, London, 1981, p. 456.

Gaylord, A.M., Warthesen, J.J. and Smith, D.E., Influence of milk fat, milk solids, and light intensity on the light stability of vitamin A and riboflavin in low fat milk. *J. Dairy Sci.*, 69 (1986) 2779–2784.

Herslöf, B. and Dahl, G., *Technical Report* 82.98.038, Kabi-Vitrum AB, 1982.

Trissel, L.A., *ASHP Handbook on Injectable Drugs*, 5th Edn, American Society of Hospital Pharmacists, Bethesda, 1988, p. vii.

Washington, C. and Briggs, C.J., Reduction of absorption of drugs into TPN plastic containers by phospholipids and fat emulsions. *Int. J. Pharm.*, 48 (1988) 133–139.