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The compatability of four trace elements in total parenteral nutrition infusions

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Summary

Injection MTE-4 contains zinc (10 mg), copper (4 mg), manganese (1 mg) and chromium (40 μg). After addition to Synthamin-containing TPN regimens in 3 litre bags, there was no evidence for precipitation of any of the four elements after storage at 2–6°C for periods up to 4 months. The concentration of zinc, manganese and copper were measured after 24 h storage. Only zinc showed a lower than expected result, although the differences were small (about 6%) and probably due to inherent dilution and other errors difficult to control in the experimental design. This assessment is supported by the lack of evidence for precipitation of zinc. Elements in MTE-4 were not precipitated in Synthamin 17 for at least 2 days, although after longer periods copper residues were evident. Zinc precipitates were also recovered after long-term storage.

Introduction

Trace elements are an important ingredient of total parenteral nutrition (TPN). If a 3 litre bag system is in operation, these trace elements are added to the various infusions combined in the large infusion container. Only one trace element injection, suitable for administration to adults, is available commercially in the U.K. Addamel (Kabi Vitrum, London) contains 6 trace elements, the four cations being iron (50 μmol), zinc (20 μmol), manganese (40 μmol) and copper (5 μmol). However, there is considerable controversy over the daily needs of patients receiving TPN. The American Medical Association has published guidelines for daily requirements of zinc, manganese, copper and chromium and recommended appropriate salts for each element (Journal of the American Medical Association, 1979). The recommended

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requirements were 10 mg (153 μmol) zinc, 1 mg (18.2 μmol) manganese, 4 mg (6.3 μmol) copper and 40 μg (0.08 μmol) chromium. These differ significantly from the contents of Addamel ampoules.

Because of the complex nature of combined TPN solutions, incompatibility between one or more components of a 3 litre bag regime are not uncommon and yet may be difficult to predict. For instance, regimes containing one particular amino acid infusion will show precipitation if excess ($>$ 20 mg/l) zinc is present (Earnshaw, 1981). The addition of Addamel to Synthamin-containing solutions may lead to the formation of a precipitate. Such reactions have been detected by observation. Only by careful measurement of solutions for losses can such reactions be fully recognized and quantified. Boddapati et al. (1981) have reported a careful study in which the concentrations of different trace elements have been measured using a very sensitive and quantifiable technique. It was shown that the addition of trace elements in amounts recommended by the American Medical Association (AMA) to various infusion fluids did not lead to detectable loss of any element from solution, after storage for up to 72 h at 5°C.

The present report concerns the addition of the AMA recommended formulation of trace elements to a Synthamin-containing TPN regime typical of those currently used in the U.K. and to Synthamin alone. Evidence for compatability was sought by examination of the fluids after storage for periods upto 4 months, for evidence of precipitation or loss of each element from solution.

Materials and Methods

Chemicals, materials and equipment used were:

Synthamin 17: Solution A; Dextrose 50% w/v (Viaflex); Dextrose 20% w/v (Viaflex); 3 litre Parenteral Nutrition container, 6 lead set and 150 ml Viaflex Containers (empty) supplied by Travenol Laboratories, Thetford, Norfolk. 10 ml vials MTE-4 (Lypho-Med, Chicago, IL, U.S.A.) supplied by Travenol Laboratories containing: zinc 1.0 mg/ml (giving 4 μg/ml in 2.5 litres), copper 0.4 mg/ml (giving 1.6 μg/ml in 2.5 litres), manganese 0.1 mg/ml (giving 0.4 μg/ml in 2.5 litres), and chromium 4 mg/ml (giving 0.016 μg/ml in 2.5 litres).

Vials containing individual elements were also used. Water — freshly distilled, stored in plastic containers. Strong potassium chloride solution BP 1973, 1.5 g in 10 ml ampoules (20 mmol potassium) (Antigen, Roscrea, Ireland). Calcium Gluconate Injection BP 10% w/v 2.23 mmol calcium in 10 ml ampoules (Evans Medical, Speke, Liverpool). 6 N sulphuric acid (concentrated H_2SO_4, Analar (BDH, Poole, Dorset), diluted with freshly distilled water).

Containers for storing solutions for analysis, 30 ml Universal containers, (Sterilin, Teddington, Middlesex). Filters — 0.45 μm filters, Millipore cellulose acetate membranes, 47 mm diameter. (Millipore (U.K.), Abbey Road, London); — 0.8 μm filters, Nucleopore Polycarbonate Membranes (acid-resistant), 47 mm diameter (Sterilin). Filtration equipment: all-glass 47 mm filter unit (Millipore).

Atomic absorption (A.A.) spectrometer, Model 157 (Instrumentation Laboratory,

TABLE 1

CONDITIONS FOR A.A. ANALYSIS OF EACH ELEMENT

	Measured at: (nm)	Sensitivity (μg/ml)	Linear range	Max. conc. in 2.5 litres (μg/μl)
Zinc	213.9	0.02	up to 5 μg/ml	5.2
Copper	324.7	0.04	up to 4 μg/ml	1.6
Manganese	279.5	0.03	up to 3 μg/ml	0.8
Chromium	357.9	0.05	up to 5 μg/ml	0.016

Wilmington, MA, U.S.A.). Single element hollow cathode lamps for zinc, copper, manganese and chromium (Cathodeon, Cambridge). Conditions for A.A. analysis of each element are shown in Table 1.

Attempts were made to measure chromium in TPN solutions using an atomization furnace (Instrumentation Laboratory Model 555).

Disposable plastic containers and pipettes were used whenever possible. 3 litre bag regimens contained:

Synthamin 17	1000 ml
Solution A	500 ml
Dextrose 50%	500 ml
Dextrose 20%	500 ml

All manipulations in preparing solutions for storage were conducted under aseptic conditions using aseptic technique.

The examination of 3 litre bag regimes and Synthamin for precipitation after long-term storage

Three litre bags TPN regimes were prepared as described.

The MTE-4 injection (10 ml) was injected into the bag via the additive port. It was injected into the final 20% dextrose solution, being added while the solution continued to run into the bag. The bag was then shaken thoroughly, any excess air was removed from the bag, the line sealed off, and each filled bag placed in a black plastic bag. These were stored at 2–6°C. A control bag containing no MTE-4 was also prepared.

The contents of one vial of MTE-4 was added to one bottle of Synthamin 17 by syringe through the additive port. The vacuum in the bottle was not released. The bottle was shaken thoroughly, replaced into its box and refrigerated.

Bags and bottles containing MTE-4 were each prepared in duplicate.

Preparation of samples for analysis

0.8 μm polycarbonate filters were used. Each filter was washed with 50 ml freshly distilled water. The total contents were filtered by vacuum. The filter was washed with about 500 ml freshly distilled water. The filter was then placed in a 30 ml pyrex tube and 10 ml 6 N sulphuric acid added. Tubes were stored for at least 30 min and shaken regularly. The solution was then transferred to a 50 ml volumetric flask, together with the washings, and the volume made up to 50 ml with freshly distilled water. Solutions were transferred to universal containers and analyzed within 24 h.

Synthamin 17 solutions stored after the additions of MTE-4 were treated in a similar manner. Before filtration, bottles were examined under natural and polarized light. The aluminium ring was removed, the rubber bung taken out and the contents poured directly onto the pre-washed filter.

To determine the concentration of each element remaining in solution after storage in the 3 litre bag regimen or Synthamin 17 for 24 h at 2–6°C

TPN solutions were prepared in 3 litre capacity bags, but without the addition of the trace element injections. Three bags were filled, the first bag without further addition. To the second bag was added 20 mmol potassium (as potassium chloride) and to the third bag was added 10 mmol calcium (as calcium gluconate). After thorough mixing, 100 ml aliquots were transferred, using a 50 ml plastic disposable syringe, to 150 ml empty Viaflex containers. 100 ml aliquots of Synthamin 17 were also injected into empty Viaflex containers. Five bags were filled from each solution. 0.4 ml of MTE-4 injection was added to each solution. The procedure was repeated for each individual trace element injection. A TPN solution stored in a polypropylene flask was used as a negative (no trace element added) control. Trace elements were also added to 20% dextrose in polypropylene flasks. All solutions were stored at 2–6°C for 24 h.

At least 10 ml was removed from each container by syringe and filtered through a water-washed Swinnex filter unit (Millipore) fitted with a 0.45 μm cellulose acetate membrane filter. 10 ml of the filtrate was diluted to 50 ml with freshly distilled water and transferred to polycarbonate universal containers. The standard was prepared as follows: MTE-4 0.08 ml; Solution A 4 ml; dextrose 20% 16 ml; water to 100 ml.

All solutions were assayed for individual trace elements by atomic absorption spectrophotometry.

Results

Visual examination

(a) 3 litre bags and bottles. There was no evidence for the presence of a precipitate in any of the solutions, according to visual examination under natural or polarised light.

(b) Examination of membrane filter after filtration of each solution and washing of the filter with water. Observation of filters was carried out. No obvious deposits were noted except in the following instances:

bag content filters, 4 month storage — a faint blue deposit was noted on the filter. This was partially removed in acid;

Synthamin 17 filters, 2 month storage — one filter showed the faint blue; 4 month storage, both filters showed the blue deposit.

Analysis of acid extracts of filters by atomic absorption spectrophotometry

The results are summarized in Table 2.

Zinc was not detected in any samples except in Synthamin 17 injection after 4 months storage. Both bottles contained deposited zinc although only very small amounts were evident. This extract contained about 0.1 μg/ml. No precipitated copper was isolated from bags. However, copper was evident in extracts from the filters taken after filtration of some samples of Synthamin 17. This was detected after 7 days storage and increased until the 4 month stored Synthamin 17 extract contained about 0.20 μg/ml. No evidence of precipitation of manganese or chromium was found in either TPN regimens in bags or Synthamin 17.

The concentrations of elements in bags was measured after 4 months storage. In no instance was there a significant reduction in concentration (chromium concentrations could not be measured using the atomization furnace because of excessive interference by other components of the solution).

Analysis of TPN solutions and Synthamin for trace elements after 24 h storage at 2–6°C

The results are summarized in Table 3. (Some minor differences were observed in spectrophotometer response between aqueous standards and standards in dextrose. It was therefore decided to use a standard prepared in the presence of the equivalent quantity of dextrose. 1 : 5 dilution of 20% dextrose-containing solutions was required to prevent flame interference.)

Concentrations of zinc found in 20% dextrose or Synthamin 17 were as expected,

TABLE 2

THE PRESENCE OF TRACE ELEMENTS ON THE FILTER AFTER FILTRATION OF TPN REGIMENS IN 3 LITRE BAGS AND SYNTHAMIN 17

Storage period	Element							
	Zinc		Copper		Manganese		Chromium	
	Bag	Synthamin	Bag	Synthamin	Bag	Synthamin	Bag	Synthamin
1 day	–	–	–	–	–	–	–	–
2 days	–	–	–	–	–	–	–	–
7 days	–	–	–	+	–	–	–	–
1 month	–	–	–	+	–	–	–	–
2 months	–	–	–	+	–	–	–	–
4 months	–	+	–	+	–	–	–	–
4 months storage — concentration in solution = % of Control	98%		98%		101%			

— = trace element absent in filter acid extract; + = trace element present in filter acid extract.

TABLE 3

TRACE ELEMENT CONTENT OF INFUSIONS AFTER STORAGE FOR 24 h AT 2–6°C

Solution	Zinc concentration (μg/ml)			Manganese concentration (μg/ml)			Copper concentration (μg/ml)		
	Theoretical	Added as zinc injection	Added as MTE-4	Theoretical	Added as manganese injection	Added as MTE-4	Theoretical	Added as copper injection	Added as MTE-4
20% Dextrose	4.00		4.16	0.40		0.39	1.60		1.50
Synthamin 17	4.00	3.96	3.92	0.40	0.38	0.36	1.60	1.65	1.55
TPN regime	5.00 *	4.65	4.70	0.84 *	0.80	0.75	1.60	1.55	1.60
TPN regime + K^+	5.00	4.70	4.65	0.84	0.80	0.80	1.60	1.55	1.55
TPN regime + Ca^{2+}	5.00	4.70	4.75	0.84	0.85	0.80	1.60	1.65	1.60
	Mean (TPN) = 4.69. S.D. = 0.04			Mean (TPN) = 0.80 S.D. = 0.03			Mean = 1.60 μg/ml. S.D. = 0.05		

* Solution A contains zinc (2.62 mg) and manganese (1.10 mg).

within acceptable experimental error. The content of zinc recovered from TPN solutions were all very similar, any differences being insignificant ($\ngtr \bar{x} \pm 2$ S.D.) although rather lower than the expected content. The mean concentration was about 6% lower than expected. A similar result was obtained in the control, indicating that the container was not affecting the result. No differences were apparent between zinc injection and MTE-4, or between the different TPN regimes.

The concentrations of manganese in 20% dextrose and Synthamin 17 were as expected. TPN regimes contained about 0.8 μg/ml, which was 5% lower than expected. However, there were no significant differences between the control, and any of the TPN regimes, either for manganese injection or MTE-4.

The copper contents of all solutions were within acceptable limits of the expected levels.

It proved impossible to measure chromium in TPN regimens because of excessive interference.

Discussion

This study was designed to determine if four trace elements (available as Injection MTE-4) were soluble in TPN regimes mixed and stored in 3 litre bags or Synthamin. After 24 h storage, TPN solutions contained expected concentrations of manganese and copper, although the zinc concentrations were in all instances slightly (about 6%) lower than the standard. Because of the low concentrations present, chromium could not be measured. There was no evidence for interaction between the elements in MTE-4.

The examination for any precipitate from the total bag contents of TPN regimens did not show any evidence for precipitation of zinc, or any other element examined. It is therefore concluded that zinc, manganese, copper and chromium, added as Injection MTE-4, are stable and soluble in TPN regimes for periods of at least one month. There was no evidence for precipitation of the four elements in Synthamin 17, except after storage for 7 days, when copper was detectable as a precipitate after filtration. Such precipitates were not detectable by visual examination. The conclusions are in agreement with those of Boddapati et al. (1981).

References

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