Evaluation of the trace metal supplements for a synthetic low lactose diet

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SUMMARY A trace element supplement used with a synthetic low lactose milk (Galactomins 17 and 18) has been evaluated by means of metabolic balance studies in 4 infants with disaccharide intolerances. The supplement was considered satisfactory for iron and manganese but increases in its zinc and copper content are probably necessary to ensure adequate retentions of these metals.

Diets used in the management of infants with inborn errors of metabolism or dietary intolerances may have an inadequate essential trace element content.¹⁻³ This deficiency may be quantitative in as much as these micronutrients are lost during manufacture of the diet, or it may be a qualitative defect resulting from postulated interactions between these elements and other inorganic and organic dietary constituents which reduce intestinal absorption of the trace metals.⁴

These effects cannot be predicted and our earlier studies have shown that even though the resultant trace metal intake of children on a mineral supplemented synthetic diet may meet standard recommendations, further modifications are necessary to achieve reliable net absorption and retention of some essential elements.¹⁻³

In this study the trace element supplement for

synthetic low lactose milks (Galactomins 17 and 18, Cow and Gate Ltd) has been assessed. There are three similar Galactomin products which are derived from demineralised casein and which are prepared according to a formula elaborated in this department.⁵ They are used in the management of dietary lactose intolerances (Galactomins 17, 18, and 19) and of inborn errors of galactose metabolism (Galactomins 17 and 18). They contain no sucrose and are suitable also for the management of combined sucrose and lactose intolerance; however, the commercially available mineral and vitamin supplement for use with Galactomins (supplementary mineral and vitamin tablets Cow and Gate Ltd) contains sucrose and is not recommended for use in the management of combined disaccharide intolerances. We have used in this study, therefore, the glucose trace element mixture (Table 1) which

Table 1 *Details of the patients and their diets*

Case	Sex	Birthweight (kg)	Age (months)	Weight		Length		Duration on diet (months)	Diet	Clinical features
				kg	Centile	cm	Centile			
1	F	3.26	5	6.0	10	63	25	2	Galactomin 17, 1 g GTE. Ketovite† tablets + liquid. Robinson Baby Rice	Protracted diarrhoea, cows' milk protein intolerance
2	F	2.98	3	4.4	3	56	<10	2	Galactomin 17, 1 g GTE. Gastrocaloreen,* Ketovite† tablets + liquid	Necrotising enterocolitis, total colectomy, ileo-rectal anastomosis
3	M	3.27	3	5.0	10	59.5	25	1.5	Galactomin 17, 2 g GTE. Gastrocaloreen.* Ketovite† tablets + liquid	Diaphragmatic hernia, intestinal malrotation
4	M	3.04	8.5	5.6	<3	62	<3	3	Galactomin 18, 1 g GTE. Gastrocaloreen.* Ketovite† tablets + liquid	Failure to thrive, fundoplication of hiatus hernia. Intravenous feeding, with symptomatic copper and zinc deficiency at one time

*Scientific Hospital Supplies Ltd (Liverpool, UK).

†Paines and Byrne Ltd (Greenford UK).

GTE—glucose trace element mixture 1 g of which provides Fe, 71.7 µmol; Cu, 8.03 µmol; Zn, 14.7 µmol; Mn, 8.43 µmol; I, 0.48 µmol; Co, 0.19 µmol; Mo, 0.12 µmol; Al, 0.04 µmol.

is used routinely as a supplement to these diets at The Hospital for Sick Children, London.

Patients and methods

Four children aged between 3 and 8 months with disaccharide intolerance were studied. All had been born at term and all became symptomatic during the first 2 weeks. Their clinical features are summarised in Table 1. Only Case 2 was showing catch-up growth, the other children were growing but the centiles of their weights and lengths were falling. All were receiving a Galactomin preparation made up in tap water according to the manufacturer's recommendations; extra calories, vitamins, and mineral supplements were provided for all 4 patients as indicated (Table 1).

Three-day metabolic balance studies were performed on each child, and they all had been on the same dietary intake for a week before the study. None of the children had any intercurrent infection during the run-in and balance periods. The collection of duplicate and reject diets, faeces, and urine, and the analytical procedures have been described previously.¹ Analyses were performed for macronutrients (N, P, Ca, Mg, Na, and K) and for Fe, Zn, Cu, and Mn. Analyses of replicate (5 or 7) samples of dietary, urinary, and faecal homogenates indicated intrabatch and interbatch variations (SD) of $\pm 2.3\%$ and $\pm 3.4\%$ respectively. Accuracy was assessed additionally by determining the recoveries, at analysis, of trace metals which had been added in known amounts to the homogenates to increase the latter's content of these elements by about 25, 50, and 100%. The mean recovery for all elements was $98.5 \pm 2.8\%$. The elemental composition of six separate batches of Galactomin 17 and Galactomin 18 was assessed in triplicate using the same techniques because the trace metal content of these unsupplemented powders was not known. Reference values for the balance studies were derived from concurrent and earlier departmental metabolic studies on infants.¹ The intakes and retentions of the four trace metals were compared with the reference values using the Mann-Whitney rank test.

Results

The mineral compositions of the Galactomin powders are shown in Table 2, although there was some variation between the types of product which exceeded that which could be attributed to analytical variation, this was not statistically significant. The mean values for daily intake, excretion, and retention of the minerals by the children are shown

Table 2 *Analysed mineral composition of Galactomin powder (units/kg $\pm$ SD)*

	Galactomin 17 (n=6)	Galactomin 18 (n=6)
Ca (mmol)	144 $\pm$ 24	174 $\pm$ 13
Mg (mmol)	15.9 $\pm$ 3.3	18.3 $\pm$ 0.9
Zn (μ mol)	126 $\pm$ 17	151 $\pm$ 22
Cu (μ mol)	11.4 $\pm$ 1.6	11.4 $\pm$ 2.0
Fe (μ mol)	130.8 $\pm$ 2.8	141.4 $\pm$ 21.4
Mn (μ mol)	20.9 $\pm$ 2.0	22.7 $\pm$ 0.5

in Table 3. Net absorption is not shown because contamination of the urine with faecal fluid produced an overestimate of the urinary excretion of the micronutrients and of their net absorption. However, subsequent analysis of bag collections from the 2 boys confirmed a negligible loss of trace metals in the urine. It should be emphasised that net retention is really the maximum apparent retention; actual retention is less than this owing to additional losses of the elements in hair, skin, and sweat which were not measured in this study.

The net intake of Ca, Mg, N, and P exceeded the reference values and all the patients were in positive balance for these elements as well as for Na and K even though the intakes of these were lower than the reference values.

All 4 patients were in positive balance for manganese. The intake of this cation was greater than that of the reference group ($P < 0.01$) but the net retention was not significantly different. Similarly, the intakes of iron and copper were greater ($P \leq 0.05$) than those of the healthy children but their net retentions were not significantly different. However, 1 child (Case 2) was in net negative balance for iron, and 2 (Cases 1 and 2) exhibited net loss of copper. The intake of zinc by the study group was similar to the reference values but 3 of the patients (Cases 1, 3, and 4) were in net negative balance for this nutrient ($P < 0.05$). Allowing for analytical variation all the negative balances would remain so, with the exception of the copper balance of Case 2 who could have had a marginally positive net retention.

Discussion

In this study the positive retentions of the macronutrients suggest that the intakes of these elements were adequate and that no amendment of their level of supplementation is indicated. Nevertheless, only one infant was showing evidence of catch-up growth whereas the other 3 were not gaining weight normally, although their energy intake was adequate for their expected weight. During new tissue synthesis there is an increased requirement for zinc⁶ and although this has not been established for

Table 3 *Metabolic balances: intake and retention of elements (units/kg per day) of children receiving Galactomin products*

		Intake	Total excretion	Apparent retention
Calcium (mmol)	1	2.96	1.97	0.99
	2	4.24	2.87	1.38
	3	2.68	1.19	1.49
	4	3.51	2.32	1.19
Healthy (n=7)	Median	1.42	0.75	0.49
	Range	1.02—3.24	0.18—1.34	0.32—3.07
Magnesium (μmol)	1	410	270	140
	2	735	550	185
	3	484	382	102
	4	594	391	203
Healthy (n=7)	Median	370	243	91
	Range	177—539	144—473	14—193
Iron (μmol)	1	14.37	12.24	2.13
	2	17.87	19.77	-1.89
	3	22.21	20.27	1.94
	4	17.14	10.83	6.31
Healthy (n=6)	Median	6.9	6.06	1.08
	Range	3.46—21.5	1.2—18.7	0.73—2.75
Zinc (μmol)	1	5.33	6.09	-0.76
	2	7.06	4.39	2.67
	3	6.83	8.35	-1.52
	4	6.44	8.91	-2.47
Healthy (n=7)	Median	5.00	4.11	0.89
	Range	3.04—7.31	-1.30—7.71	-0.41—2.83
Copper (μmol)	1	1.34	1.69	-0.35
	2	1.45	1.56	-0.11
	3	2.13	1.37	0.76
	4	1.59	1.22	0.37
Healthy (n=7)	Median	0.42	0.38	0.03
	Range	0.41—1.56	0.23—1.21	-0.25—0.38
Manganese (μmol)	1	2.14	1.89	0.25
	2	2.65	2.64	0.01
	3	3.17	2.83	0.34
	4	2.45	2.18	0.27
Healthy (n=7)	Median	0.58	0.55	0.09
	Range	0—1.69	-0.07—1.53	-0.07—0.3
Sodium (mmol)	2	1.81	1.02	0.79
	3	1.25	1.26	-0.01
	4	1.76	0.18	1.58
	Median	2.82	2.33	0.49
Healthy (n=6)	Range	0.38—5.14	0.60—3.79	-0.22—1.35
Potassium (mmol)	2	2.57	0.86	1.71
	3	1.61	0.89	0.72
	4	2.22	1.13	1.09
	Median	2.66	1.81	0.95
Healthy (n=6)	Range	1.75—3.73	1.06—2.77	0.01—0.99
Nitrogen (mmol)	1	38.4	28.0	10.4
	2	48.0	20.0	28.0
	3	48.4	28.4	20.0
	4	55.2	28.1	27.1
Healthy (n=6)	Median	27.6	18.0	11.4
	Range	16.1—40.4	12.1—27.7	-2.6—12.7
Phosphorous (mmol)	1	2.13	1.99	0.14
	2	2.30	0.90	1.4
	3	2.22	1.11	1.11
	4	2.86	1.53	1.33
Healthy (n=6)	Median	2.25	1.44	0.74
	Range	0.63—2.82	0.23—2.22	0.40—0.85

Conversion: SI to traditional units—Zn: 1 μmol=65.4 ug; Cu: 1 μmol=63.5 ug; Mn: 1 μmol=54.9 ug; Fe: 1 μmol=55.9 ug; Ca: 1 mmol=40.1 mg; Mg: 1 mmol=24.3 mg; N: 1 mmol=14 mg; P: 1 mmol=31 mg; Na: 1 mmol=23.0 mg; K: 1 mmol=39.1 mg.

copper, inadequate intakes both of zinc⁶ and copper⁷ can impair recovery during the renutrition of malnourished children.

It is possible, though this study does not attempt to substantiate it, that inadequate intake of trace elements may have been contributing to the poor weight gain seen in 3 of these infants and that some

modification of the trace mineral intake is needed. If one uses the mean trace element content of the Galactamins, as determined in our analyses, to calculate the powder's contribution to our patients' intake of micronutrients, it is seen that they would have provided ((median and range)/kg bodyweight per day); Fe, 3.36 (2.86–4.04) μmol; Cu, 0.29

(0.25–0.33) μmol ; Zn, 3.24 (2.75–4.31) μmol ; and Mn, 0.54 (0.46–0.65) μmol . For Fe, Cu, and Mn these amounts were less than 20% of the total supplemented daily intake whereas that for zinc was about half. Baby Rice and Caloreen made a negligible contribution to the daily intake of the trace metals most of which was provided therefore by the glucose trace element supplement, the adequacy of which can be assessed from the balance studies.

All 4 children were in positive balance for Mn and 3 had net retention of Fe. The single negative balance for Fe occurred in the one child (Case 2) who was thriving and, in view of her high intake of Fe, we interpret the net loss of this element as being consistent with adequate nutrition and with homeostatic loss of the element by the intestine.⁸

All 3 children who were failing to gain weight normally were in negative balance for Zn and 2 had net loss of Cu; for the reasons discussed below, we think that the intake of these two metals was inadequate. In an evaluation of the trace metal supplementation of a diet based on comminuted chicken,³ we found that infants whose mean daily intakes of Zn (5.97 $\mu\text{mol/kg}$) and Cu (1.73 $\mu\text{mol/kg}$) were similar to those of the children in this study required further supplementation to achieve reliably positive balances even though all these intakes were similar to, or in excess of, those seen in healthy infants.

The negative balances in our studies were all due to net intestinal loss of zinc and copper and we suspect that this is indicative of a reduced availability of the metals for intestinal absorption from the diet.^{4,9} There are many possible reasons for this reduced bioavailability but they are unpredictable; a possible exception to this is that the inorganic iron content of a diet can reduce the intestinal absorption of zinc.¹⁰ It is possible that the high iron content of the supplemented Galactomin preparation may be interfering with the intestinal uptake and transfer of zinc and copper, and that a suitable modification would be to reduce the intake of iron rather than to increase that of zinc and copper. However, because the extent and mechanisms of inter-element interactions have not been elucidated, the latter modification seems more appropriate at present. Since no other recommendations are available to assist in designing these amendments of the supplement, we have been obliged to use the albeit unreliable regression equations of the retentions of each trace element against its intake to judge intakes which might achieve net retentions comparable to those seen in the healthy reference group. This approach results in 'ideal intakes' of Zn and Cu of 8.7 and 1.94 $\mu\text{mol/kg}$ per day respectively, for Fe and Mn, intakes of 14.9 and 1.6 $\mu\text{mol/kg}$ per day should be sufficient. The Galactomin powders alone

would, on the basis of our analyses, daily provide Fe 3.4 $\mu\text{mol/kg}$, Cu 0.2 $\mu\text{mol/kg}$, Mn 0.6 $\mu\text{mol/kg}$, and Zn 3.4 $\mu\text{mol/kg}$. The necessary supplement should provide, therefore, at least Fe 11.5, Cu 1.74, Mn 1.0, and Zn 5.3 $\mu\text{mol/kg}$ per day. It would be more convenient if the trace element supplement could be incorporated in the Galactomin powders, provided this is compatible with a suitable shelf-life. Ironically, if the infants had been able to have the mineral and vitamin supplement which is commercially available, their intakes of Fe and Zn would have been adequate but the suggested intakes of Cu and Mn would not have been met.

Our findings stress some important points in relation to foods prepared for therapeutic purposes which are also applicable to other synthetic foods. During their manufacture a variety of substances are inevitably removed from the native product (for example cows' milk). The manufacturer faces a dilemma in knowing which essential nutrients should be replaced, and he has to take into account also their availability. Balance-type studies, despite their difficulties and disadvantages, do provide an ethically acceptable method for assessing such products.¹¹ Nutritional guidelines for the composition of artificial feeds have been published recently¹² but guidelines for trace elements other than iron are not included.

For infants aged up to 6 months, and between 6 and 12 months recommended dietary allowances have been given for iron and zinc as have safe and adequate ranges of intake for copper, manganese, chromium, selenium, and molybdenum,¹³ but this helpful information cannot take into account bioavailability or the increased metabolic requirement for trace elements during recovery from disease. There are wide differences at present in the composition of milk substitutes.¹⁴ There is a need for manufacturers to assess the adequacy of the trace elements in their products by means of clinical studies, and attention to quality control is essential so that similar concentrations of trace elements occur in different batches of a product. Such arguments would apply not only to infant feeds but to any products marketed as providing complete nutrition in the form of parenteral and enteral feeds for adults.

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Fifty years ago

The treatment of rhinitis due to the Klebs-Loeffler bacillus

J D'EWART (Manchester)

Dr D'Ewart reported 31 cases of nasal virulent Klebs-Loeffler bacillus treated by a weekly x-ray dose of one-third pastille. An aurist reported few cases as clinical diphtheria, several showed inflammatory conditions. The majority gave no ocular evidence. Twelve cases were cured by one treatment, 9 by two. Three required six, and one eight. If discharge was present the x-ray dose cleared it speedily. Attention was drawn to the variations in obtaining negative swabs at weekly intervals. Even after 5 or 6 negative results further positive ones were obtained. It was suggested that the Klebs-Loeffler bacillus persisted in the accessory sinuses. Only three references to x-ray treatment could be found.

Proceedings of the sixth annual general meeting of the BPA. *Archives of Disease in Childhood* 1933; **8**: 365.

(Ewart was a fever hospital doctor, so not a member of the British Paediatric Association! Nasal diphtheria was common on the wards when I was a house physician nearly 50 years ago. PRE).

Intra-peritoneal therapy

L THATCHER (Edinburgh)

Dr Thatcher regarded the following as the essential points to be observed for the safe administration of fluids into the peritoneal sac—(1) The nature of the fluid used; 6% solution of glucose in normal saline is the most satisfactory. (2) This fluid must be injected slowly, at least 45 minutes for the volume used; this being 6–7 ounces as a general rule. (3) The fluid must be kept at or about body temperature all the time; a simple apparatus for maintaining it during the process of administration was described. Charts were shown to demonstrate the value of this therapy in the starvation of acute congenital hypertrophy of the pylorus; in acute infections of the alimentary tract; and in severe dyspepsia, especially that associated with intolerance for carbohydrates.

Proceedings of the sixth annual general meeting of the BPA. *Archives of Disease in Childhood* 1933; **8**: 362.

(Intraperitoneal treatment was used because in those days babies' veins were thought to be too small for infusion. Within the year Donald Bateman returned from the USA, designed the 'Bateman needle' which was a double cannula, and peritoneal infusion went out of fashion. Bateman, a man of originality and vigour, was killed in the 1939–45 war. PRE).