

Clinical trial of a milk formula for infants of low birth weight

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Summary

An infant milk formula specially designed to meet the specific needs of the small premature infant was compared with a modified infant milk formula in common use.

Healthy infants of very low birth weight were fed with either the specially designed infant milk formula or the standard modified infant milk formula.

No statistically significant differences between the two groups of infants were found, although the weight gain, skinfold thickness, serum total protein, albumin and calcium values were marginally better at 28 days in the group fed with the specially designed formula.

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The small premature baby fed on pooled human milk or various standard formulas not only fails to achieve intra-uterine growth rates,^{1,2} but may develop overt or subclinical nutritional deficiencies³ such as demineralization of the skeleton.⁴

An infant milk formula, Alprem*, which has been designed to meet the specific nutritional needs of the small premature infant, was developed by the Scientific and Marketing Development Section of the Infant Food and Dietetic Products Division, Nestlé, Vevey, Switzerland.

This study was undertaken to evaluate this formula clinically.

Patients and methods

Healthy Coloured infants with a birth weight of 1 500 g or less were assessed. They had either been born at Tygerberg Hospital or had been admitted to the hospital soon after birth. Informed consent was obtained from the mothers for admission to the trial.

The infants were fed with either Alprem or a modified infant milk formula in common use, Nan. Breast milk was not available for the study. Infants were randomly allocated to the two groups, the feeding regimens being similar in all respects except the type of milk product used.

Clinical examination took place on admission to the trial. The gestational age of each infant was estimated according to the Dubowitz method.⁵ Those infants with a gestational age of more than 34 weeks were evaluated according to the growth charts compiled by Jaroszewicz *et al.*⁶ These charts, compiled for Coloured infants, are not reliable for the evaluation of infants

with a gestational age of less than 34 weeks, for whom the growth charts of Gairdner and Pearson⁷ were used.

A Berkel baby scale (accurate to 2 g) was used to weigh the babies daily throughout the trial. An accurate measuring device was used to determine crown-to-heel length on the 1st day of life and at weekly intervals thereafter. A metal measuring tape was used to measure the head circumference after birth and at weekly intervals thereafter.

Skinfold thickness was measured with a Harpenden caliper over the triceps area midway between the acromion and olecranon processes. The mean of three measurements was used.

Blood for biochemical and haematological studies was collected by venepuncture from each infant on entry to the trial and fortnightly thereafter. Urine samples for a 24-hour period were collected on the 1st day of life and at 2-weekly intervals for osmolality estimations. Blood and urine were analysed in the biochemistry and haematological departments of Tygerberg Hospital according to accepted methods of laboratory practice.

The infants were evaluated daily. Weight gain, volume of feeds taken, number and consistency of the stools and the physical well-being of the infant were assessed. Infants were excluded from the trial if they had a serious illness or whenever illness necessitated discontinuation of enteral feeds.

Descriptive statistics were used to assess the data and to study the distributions of the 73 continuous variables measured. The means and standard deviations of the important variables were obtained, together with the approximate probabilities of exceeding the calculated values in the Student's *t* test (with the Welsh modification) whenever the standard deviation of the two samples was different.

Chi-square tests were applied to assess the presence or absence of conjunctivitis, respiratory distress syndrome, other respiratory diseases and jaundice.

Results

The two groups of infants were comparable as regards gestational age, birth weight and sex (Table I).

The Alprem group initially consisted of 35 infants; 21 infants were available for assessment at 28 days, and 7 at 42 days. The

TABLE I. CLINICAL CHARACTERISTICS OF THE STUDY GROUPS*

	Alprem group	Nan group	P
Initial No. of infants	35	30†	
Gestational age (wks)	33,84 ± 1,282	33,86 ± 0,784	0,95
Sex ratio (F:M)	20:15	21:9	0,29
Birth weight (g)	1 365 ± 152	1 321 ± 156	0,37
Small for gestational age	35	25	

*Results expressed as mean ± SD where appropriate.

†N = 25 for gestational age and small for gestational age categories.

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*Since the study on this product was carried out, the formulation has been improved. New trials on the revised formula are being undertaken.

Nan group initially consisted of 30 infants; 20 were assessed at 28 days and 11 at 42 days.

The slight advantage of the Alprem group of infants over the Nan group as regards weight gain, growth in length, increase in skinfold thickness and head circumference at 28 days, and increase in serum total protein, albumin, calcium and magnesium values at 42 days, was not statistically significant.

The volume of formula feed consumed by the infants throughout the trial was monitored very closely and found to be in accordance with that of the feeding regimen.

The stools of both groups were normal in consistency and number. No clinical signs of lactose intolerance were observed.

Urine collection for the 24-hour periods proved to be difficult, especially in the females. It must therefore be assumed that in some instances urine was lost by leakage, and that not all specimens were truly 24-hour specimens.

The complications encountered in the two groups of infants necessitating exclusion from the trial were gastro-enteritis, pneumonia, septicaemia, necrotizing enterocolitis and exchange transfusions (Table II). A comparison of the two groups showed no significant differences in the complications arising during the first 28 days of the trial ($\chi^2_{5df} = 5.58; P = 0.35$).

TABLE II. COMPLICATIONS NECESSITATING EXCLUSION FROM THE TRIAL BEFORE 28 DAYS

	Alprem group (N = 35)	Nan group (N = 30)
Gastro-enteritis	8	4
Exchange transfusion	1	0
Septicaemia	2	4
Necrotizing enterocolitis	3	0
Pneumonia	0	2

TABLE III. MINOR COMPLICATIONS

	Alprem group (N = 35)	Nan group (N = 30)	P
Conjunctivitis	1	7	0,01
Respiratory disease	0	2	0,1
RDS — mild	3	3	0,3
Jaundice	11	3	0,03

RDS = respiratory distress syndrome.

Minor complications did not warrant exclusion from the trial (Table III).

The majority of infants attained the Tygerberg Hospital discharge weight of 2300 g after 28 days, leaving only a few infants in each group for assessment at 42 days.

Discussion

There are two schools of thought about the optimal nutrition of the small premature infant. One group claims that the aim should be to achieve postnatal growth rates similar to those of the fetus which reaches full term.⁸ The other group believes that to achieve this goal excessive demands will be made on the immature gut and the other organs. They are apprehensive of the metabolic consequences and are satisfied with a somewhat slower growth rate.^{2,9,10}

The infant formula Alprem was designed to be more suited to the needs of the small premature infant and not necessarily to achieve intra-uterine growth rates. The formula provides approximately 3 g protein per kg bodyweight. This is in agreement with the amount calculated by Fomon *et al.*³ to be necessary for the optimal growth of small premature infants. The renal and metabolic capacities of the infants in the present study were not exceeded. Serum urea and CO₂ content values were normal after 28 days and 42 days of formula feeding, as were the serum protein and albumin values.

The carbohydrates contained in Alprem are lactose and glucose. Limited lactose intake is thought to be desirable in the small premature infant who has retarded lactase development,^{11,12} while glucose is readily absorbed and provides immediate energy.¹³ The calcium content of Alprem (67 mg/100 kcal) has been increased to provide more calcium than is presently available in infant formula milk feeds. This amount is inadequate to ensure sufficient retention of Ca⁺⁺ according to Fomon *et al.*, who have calculated that 132 mg/100 kcal Ca⁺⁺ needs to be absorbed.³ However, the serum Ca⁺⁺ levels of the infants in the trial were found to be normal.

Phosphate-deficiency rickets has been reported in small premature infants fed exclusively on human milk.¹⁴ The Alprem formula has a higher phosphate content than human milk and provides 40 mg/100 kcal phosphate, which is substantially less than the approximate 70 mg/100 kcal required for optimal growth and retention.¹⁵

No statistically significant differences were found between the serum sodium levels of the two groups, which were normal at 28 and 42 days. Balance studies have shown that small premature infants need 3 mmol sodium/kg/d.¹⁶ The sodium level in Alprem is approximately 11 mmol/l or 2,2 mmol/kg/d when fed at 200 ml/kg/d. The sodium level in Nan is 7 mmol/l or 1,4 mmol/kg/d when fed at 200 ml/kg/d.

The mean daily weight gain was 18 g for the Alprem study group and 17 g for the Nan study group, which is less than the intra-uterine growth rate — estimated to be approximately 30 g/d during the last 3 months of pregnancy.³

Initially it was planned to select infants whose weights were appropriate to their gestational age. Unfortunately this was not found to be possible, and all healthy infants of very low birth weight who could be fed enterally within a few days after birth were entered into the trial. Eventually all of them were found to be small for gestational age (Table I). The fact that all the infants in the trial were small for dates may be due to a natural selection of relatively more mature infants for the study group, the relatively more mature infants being less liable to develop those complications that preclude oral feeding.

No statistically significant differences in the many variables studied were found between the two groups, although weight gain, skinfold thickness and serum protein, albumin and calcium values were initially marginally better in the study group fed with the special formula.

Conclusion

Optimal feeding of the low-birth-weight infant should support an acceptable rate of growth without imposing excessive metabolic stress. From the study results it can be concluded that no undue metabolic stress was imposed on the infants in the study groups.

Initially the Alprem study group had a slight growth advantage and compared favourably with infants fed the standard modified infant formula. This initial advantage, however, was no longer apparent at 42 days. Intra-uterine growth rates could not be achieved.

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Early introduction of milk feeds in acute infantile gastro-enteritis

A controlled study

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Summary

A blind controlled trial was performed to test the hypothesis that early introduction of full-strength cow's milk (FCM) during an attack of acute infantile gastro-enteritis does not prolong the course of the illness. A total of 74 children matched for age was admitted to the trial, which compared the effect of FCM with that of graduated milk (the strength of which was gradually increased). Thirteen children (17,5%) were withdrawn because of lactose malabsorption; of those remaining, 29 were given FCM and 32 graduated milk. The mean duration of diarrhoea was 2,62 days for those on FCM and 2,64 days for those given graduated milk ($P=0,71$, not significant). Early introduction of FCM therefore does not prolong the course of acute infantile gastro-enteritis. Because of the prevalence of malnutrition in South Africa the practice of giving clear fluids or diluted milk during an attack of gastro-enteritis is unnecessary and dangerous.

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That milk feeds are responsible for prolonging the course of acute infantile gastro-enteritis is a widely held belief. This view is prevalent not only among the lay public but also among the medical fraternity. The occurrence of temporary lactose malabsorption in some patients with alleviation of symptoms on withdrawal of milk feeds is no doubt partly responsible for this belief. The increase in the volume and frequency of stools due to early feeding is also partly responsible. It has led to the widespread practice of stopping all milk feeds during an attack of acute gastro-enteritis and to the reintroduction of milk in gradually increasing concentrations once the stools have returned to normal.^{1,2} This practice is probably without risk in a well-nourished population. We have, however, seen many cases of iatrogenic kwashiorkor due to milk feeds being stopped following an attack of acute gastro-enteritis in the Black and Coloured populations that we serve. On questioning, the mothers frequently say that they substituted weak tea for milk on their doctor's advice and never reintroduced milk. The doctors were reinforcing the lay belief that milk causes diarrhoea.

In our gastro-enteritis unit it is routine practice in patients with acute gastro-enteritis requiring intravenous rehydration to stop all oral feeds overnight and to reintroduce full-strength cow's milk (FCM) the next day. Usually half the fluid requirements are given intravenously and half orally for 24 hours and then the total requirement is given orally. If the diarrhoea persists for more than 2 days the stools are tested for lactose by the standard Clinitest method; if the test is positive a change is made to a lactose-free formula. Our impression was that our patients were not prejudiced by this routine; recent trials from Britain³ and Australia⁴ have supported this. In view of the vital importance of maintaining adequate nutrition in our population, we decided to conduct a prospective trial to test the hypothesis