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ORIGINAL CONTRIBUTION

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Magnesium balance studies in premature and term infants

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Summary *Background:* The knowledge of magnesium requirements of premature infants is still very limited, although it is essential for the optimal composition of suitable formulas.

Aim of the study: The study concept was 1) to assess physiological magnesium balance data of healthy term infants and longitudinal results from formula-fed premature infants and 2) to deduce conclusions on the magnesium content of the formulas.

Methods: Premature infants (n=14, birth weight ≤ 1500 g, gestational age ≤ 32 weeks) were studied in conventional balance trials with 1) a semi-elemental diet (A), 2) preterm infant formula (B), and 3) infant formula (C). In addition, healthy term formula-fed (n=11, D) and breast-fed (n=14, E) infants were investigated. Analysis was performed by flame atomic absorption spectroscopy.

Results: The median magnesium intake ranged between 4.84 mg/kg x d^{-1} (breast-fed infants) and 16.33 mg/kg x d^{-1} (premature infants). The term breast-fed infants retained nearly as much magnesium as term formula-fed infants (3.37 vs. 3.97 mg/kg x d^{-1}), due to a low percental fecal and urinary excretion. A higher magnesium retention was observed in the premature group: A: 7.97 mg/kg x d^{-1}, B: 5.3 mg/kg x d^{-1}, 3.) C: 5.54 mg/kg x d^{-1}.

Conclusion: In view of the high percental magnesium retention in formula-fed premature infants, excessive supply should be avoided. The long-term effects of lower intakes have to be monitored.

Key words Premature infants – magnesium – balance studies – human milk – formula

Introduction

Human milk is regarded as the optimal source of nutrients for the healthy young infant and it is believed that adequate quantities of minerals and trace elements are absorbed and retained. However, the utilization of nutrients from cow's milk formula and other infant diets by premature and term infants is still under investigation [1]. The knowledge of magnesium absorption in infancy is very limited. This applies especially to the needs of very low birth weight premature infants.

The magnesium concentration of breast milk ranges between 25 and 45 mg/l, the longitudinal variation during lactation is small [2–5]. The magnesium concentration of infant formulas usually exceeds that of human milk by far and an upper limit of 120 mg/l has been recommended [6]. Since gestational and post-natal age may affect magnesium metabolism, its long-term assessment in the very low birth weight premature infant is important. Comparative investigations of the magnesium metabolism in healthy term infants are also essential to gain basic knowledge for the nutritive management of premature infants in the period following discharge.

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Table 1 Infants and formulas studied – anthropometric data, nutrition (median, range)

	Premature infants (n=18)			Term infants (n=25)	
Group	A	B	C	D	E
Nutrition	diet, semi-elemental ⧫	preterm infant formula □	infant formula ■	infant formula ○	human milk ●
Mg (mg/l) analyzed	95.6 (51.6–120.8) ■ □ ○ ●	58.8 (30.5–69) ⧫ ■ ○ ●	54.9 (17.6–96.8) ⧫ □ ○ ●	50.2 (19.6–63.6) ⧫ □ ■ ●	28.6 (21.2–44)* ⧫ □ ■ ○
Infants studied	n=14	n=14	n=14	n=11	n=14
Age at study, weeks	7.6 (3.3–11.4)	10.6 (5.7–13)	15.9 (10.4–17.9) 3.3 (2–4.9) **	3.4 (2.6–4.3)	3.6 (2.6–4.7)
Birth weight, kg	0.91 (0.59–1.49)			3.40 (2.63–4.30)	3.70 (2.83–4.40)
Study weight, kg	1.57 (1.25–2.14)	1.99 (1.63- 2.51)	3.00 (2.56–4.07) ○ ●	3.78 (3.12–5.2) ● ■	4.57 (2.98–5.36) ■ ○
Weight gain g/kg x d^{-1}	14 (8.6–23.5)	13.6 (9.6–18.6)	9.6 (5.35–11.7) Δ	9.2 (5.6–20.1) Δ	7.4 (3.3–19.5) Δ

* total: 248 specimens, ≥ 15 samples of the individual mother; ** premature infants corrected for gestational age, age in weeks; ⧫ ■ ○ ● $p < 0.05$, Δ $p > 0.05$ Mann Whitney U-Test, Kruskal-Wallis-ANOVA

Methods

Premature infants were investigated twice in 72 hour balance studies on the neonatal ward and once, in addition to term infants, at home. Details of the participants are given in Table 1. The investigation was approved by the institutional ethics committee and performed in accordance with the ethical standard in the Declaration of Helsinki from 1964. Informed consent was obtained from the parents of the participants before their inclusion in the study.

The intake was measured by bottle weighing (accuracy of scales ± 1 g) or test-weighing (breast-feeding, accuracy of scales ± 5 g, Seca & Halke, Hamburg). Specimens were collected daily (infant formula, n = 178) or at each breast-feeding (n = 248). Human milk was collected with electric breast pumps (Medela mini electric, Medela, Eching) or manual expression pumps (Ruska, Hanover). Samples from the fore and hind milk of the left or right side, respectively, were subsequently pooled. The formula-fed infants received ready-to-feed formulas in order to avoid contamination through the water used for preparation.

Premature infants with a gestational age ≤ 32 weeks and a birth weight ≤ 1500 g, adequate for the respective gestational age, were nourished in accordance with the nutritional concept used in the clinic. They were consecutively fed a semi-elemental diet (Alfaré®, Nestlé, Munich), preterm infant formula (Prematil with Milupan®, Milupa, Friedrichsdorf/Ts) and infant formula (PreAptamil with Milupan®, Milupa, Friedrichsdorf/Ts). The compositions are given in Table 2. Healthy term infants received either human milk or infant formula. Additional intake by tea or routine supplementation by drugs was analyzed and added. It comprised ≤ 5 % of the total magnesium intake.

Infant- or pediatric-sized 24-hour collection bags (Hollister Inc., Ballina, Ireland) were used for urinary collection and changed every 24 hours. Feces were sampled with nappy inserts (Blümia, Moltex Baby-Hygiene GmbH & Co, Mayen). The stool collection period was defined by the appearance of two doses of carmine red given 72 h apart. All specimens were stored at –20 °C until analysis. The balance method used has been applied in earlier trace element studies [7] and was adapted to the materials presently available.

Table 2 Formula composition, macronutrients and minerals – product information at time of study

Nutrient	Semi-elemental diet*⧫	Preterm infant formula*⧫⧫	Infant formula* ⧫⧫⧫
Enery kcal/100 ml	66.9	71.2	67
Protein g/100 ml	2.2	2.0	1.5
Carbohydrates g/100 ml	7.2	7.7	7.2
Fat g/100 ml	3.2	3.5	3.6
Sodium mg/100 ml	40	30	23
Chloride mg/100ml	70	40	53
Potassium mg/100ml	87	75	75
Calcium mg/100ml	55	70	60
Phosphorus mg/100ml	33	42	31
Magnesium mg/100ml	9.7	6.0	5.2

⧫ Alfaré®, Nestlé, Germany; ⧫⧫ Prematil and ⧫⧫⧫PreAptamil with Milupan®, Milupa Co., Friedrichsdorf, Germany; *note: Actual composition of all formulas may have changed.

Table 3 Magnesium intake, excretion and retention in premature and term infants

		Premature infants			Term infants	
Nutrition	Mg	diet, semi-elemental ⧫	preterm infant formula □	infant formula ■	infant formula ○	human milk ●
Intake	mg/kg x d^{-1}	16.3 (11.9–19.7) □■○●	9.9 (8.9–13.6) ⧫■○●	11.6 (8.6–4.1) ⧫□○●	9.4 (6.4–12.7) ⧫□■●	4.8 (2.9–5.8) ⧫□■○
Urinary excretion	◣ mg/kg x d^{-1}	2.2 (0.1–6.6)	0.9 (0–2.4)	2.6 (0.8–4.5)	1.3 (0.2–2.8)	0.4 (0.2–2.1)
	% of intake	14.1 %	9.7 %	25 %	19.3 %	9 %
Fecal excretion	◣ mg/kg x d^{-1}	4.5 (2.7–14.7)	4.0 (1.9–6.2)	2.7 (1.1–5.9)	3.7(2.2–6.4)	0.9 (0–1.7)
	% of intake	29.2 %	35.2 %	25.2 %	42.5 %	17.6 %
Retention	◣ mg/kg x d^{-1}	7.9 (–1.5 to 12.7) □○●	5.3(3.4–9) ⧫○●	5.5 (2.5–9.9) ○●	3.9 (1.1–6.3) ⧫□■	3.4 (0.6–4.7) ⧫□■
	% of intake	55.9 %	53.4 %	48.9 %	41.3 %	66.5 %

◣ balance data: Median and range; ⧫ □ ■ ○ ● $p < 0.05$, Mann Whitney U-Test, Kruskal-Wallis-ANOVA

Milk, most of the drugs and fecal samples were lyophilized and ashed with nitric acid according to Tölg [8], urinary samples and tea were analyzed directly. Flame atomic absorption spectrometry (Beckmann AAS 1272. Berghof GmbH, Eningen) was used for analysis.

Reference materials for the assessment of analytical precision were milk powder A 11: n = 9; 1.11 ± 0.03 mg/g (International Atomic Energy Agency, Vienna, assigned value 1.1 (1.02–1.18) mg/g and milk powder NBS 1549: 1.13 ± 0.10 mg/g (National Institute of Standards, NIST, Gaithersburg, assigned value 1.2 ± 0.03 mg/g). Accuracy was checked by the use of pool samples: 1) formula: 50.84 ± 3.0 mg/l (cv 5.9 %), 2) infant urine: 22.9 mg/l ± 0.78 (cv 3.41 %), and 3) infant feces: 3.94 ± 0.31 mg/g (cv 7.87 %). Routine analysis of blank probes did not render any indication of contamination.

Blood specimens were collected with routine methods of venipuncture used in pediatrics. Magnesium in plasma was analyzed with an automatic analyzer Hitachi 911 by photometric measurement via the decrease in the xylidyl blue absorbance (Boehringer / Roche Diagnostics GmbH, Mannheim, Germany).

Statistical evaluation was performed with non-parametric tests (Kruskal Wallis ANOVA, Mann Whitney U-Test, Wilcoxon test, Spearman's rank correlation) using the program Statistica 5.0 (Stat Soft Incorp., Tulsa, USA). The threshold of significance was set to $p < 0.05$ and a descriptive presentation based on median and range was used for the balance trials.

Results

Premature infants, corrected for gestational age, investigated parallel to term infants did not achieve comparable weights at the times of study ($p < 0.05$). However, the weight of term formula-fed infants was also lower than the weight of the breast-fed group ($p < 0.05$). The weight gains (g/kg x d^{-1}) in the three groups, corrected for gestational age, did not differ in the 3rd to 5th weeks of life (C, D, E, Table 1).

The magnesium concentration of the preterm infant formula differed significantly from that observed in infant formula. However, an overlap of range was observed (Table 1). The variances of the magnesium concentration in the same formula were mainly attributable to the differing batches. All formula-fed infants had higher magnesium intakes than breast-fed infants (Table 3). The highest magnesium intake was observed initially in the premature infants fed semi-elemental diet ($p < 0.05$, Table 3).

In repeated balances in premature infants one child showed longitudinal characteristics in his balance: He showed the highest retention in two periods and the second highest retention in one period by diminishing percental urinary excretion. Only one balance rendered a negative result (Fig. 1), caused by increased fecal and urinary magnesium excretion. The patient, however, did not show compensatory retention during the next periods.

Fecal excretion exceeded urinary excretion in all groups (Table 3). The highest percental fecal and renal excretion were observed in infants fed infant formulas. The median retention was 41.3 % (formula-fed infants) to 66 % (breast-fed infants) of the intake. The latter was the result of a reduced percental urinary and fecal excretion in these infants. The highest absolute retention was observed in premature infants fed semi-elemental diets (Table 3, $p < 0.05$).

The magnesium plasma concentration in premature infants fed infant formula exceeded the results of the other groups investigated (Table 4, $p < 0.05$).

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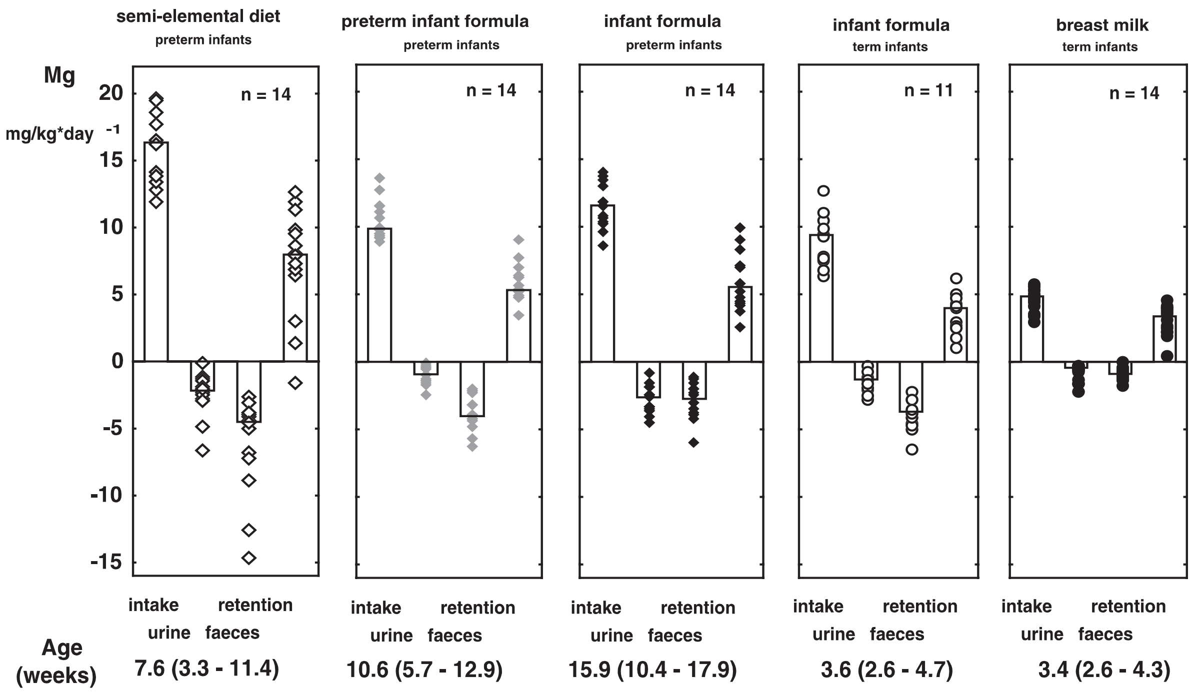

Fig. 1 Magnesium balance studies in premature and term infants. Age of premature infants fed infant formula, corrected for gestational age: 3.3 (2–4.9) weeks; conversion factor for magnesium: mg x 41.2 = µmol; ▭ Median, ⧫ □ ■ ○ ● results of individual infants

Discussion

The adequate intake of minerals is essential for the term newborn infant. Providing the optimal amount of these nutrients to orally fed very low birth weight (VLBW) infants during the period of very rapid catch-up growth remains a challenge. The breast milk concentration is often used as a "golden standard" for nutritive requirements of healthy term infants [1], but this is not unequivocally applicable in the nutrition of premature infants.

The magnesium concentration observed in human milk ranged from 21.2 to 44.0 mg/l (Table 1), which was in accordance with preceding investigations [2–4]. The formulas contained 50 to 96 mg magnesium/l (Table 1), which was within the range recommended by the European Community (30–112 mg/l, [9]) and data published in the literature [1]. In contrast, the recommendations of the Nutrition Committee of the Canadian Pediatric Society [10] are based on the opinion that the magnesium requirement of premature infants is similar to that of term infants fed human milk.

The composition of the formula used (Table 2) may be of importance for the effect of some dietary constituents on magnesium absorption. Neither the absolute nor the percental retention were compromised in infants fed semi-elemental diet (Table 3). Studies in suckling rat pups showed that magnesium has a high bioavailability from infant diets ranging between 51 % and 92 %. Moderate differences in their composition with regard to the source of proteins (casein, soy protein, whey/casein protein) or carbohydrates

Table 4 Magnesium plasma concentration (median, range)

	Premature infants			Term infants	
nutrition	semi-elemental diet ⧫	preterm infant formula	infant formula ■	infant formula ○	human milk ●
Mg	18.9	—	21.9	18.7	19.9
mg/L	(17–22.8) ■	—	(18.2–23.6) ⧫○●	(17–21.4) ■	(16.5–23.6) ■
n=	11	—	11	9	14

⧫ ■ ○ ● $p < 0.05$ Wilcoxon – Test, Kruskal-Wallis-ANOVA, U-Test Mann Whitney (lactose, glucose polymer, corn syrup solids) did not affect bioavailability significantly [11].

Seventy-two hour balance studies have been established as a method for the assessment of magnesium balances in premature infants during the last three decades [12, 13]. In view of a predominantly positive magnesium retention throughout the study, balance trials confirm a sufficient magnesium supply of the premature infants studied (Fig. 1). Despite the low magnesium retention in three premature infants in the first collecting period, no compensatory retention was observed in the next period. The plasma and urinary concentrations in these patients rendered normal results; fecal magnesium, however, was elevated.

The magnesium retention of premature infants in the present study exceeded that of term infants in all of the investigation periods. In addition, it was greater than the daily intrauterine retention rate (2.69 mg/kg body weight) assumed by Atkinson et al. [14]. This is suggestive of an increased demand during the first months of life. In term infants, however, a magnesium retention comparable to formula-fed infants receiving twice the intake was observed in breast-fed infants (Table 3). In view of sufficient retention, it has been assumed that magnesium supplements are not needed for LBW infants fed human milk ([15], Table 3). Studies in formula-fed LBW infants indicate that, despite lower percental absorption compared with human milk, intrauterine estimates for magnesium accretion are surpassed. The effect of this greater intake and retention is unknown.

Similar calcium, phosphorus and magnesium absorptions were assessed in small- and in appropriate-for-gestational-age VLBW infants [13]. It has been shown, however, that deficits may occur at the currently recommended intakes of 10 mg magnesium/kg x day^{-1} for VLBW infants with calcium and phosphorurs intakes allowing retentions equivalent to uterine accretions [16]. The authors recommended magnesium intakes approaching 20 mg/kg x day^{-1}. Lapillonne et al. observed an average intake of 8 mg magnesium/kg x day^{-1} and an average retention of 3 mg magnesium/kg x day^{-1} (45 % of the intake, [17]).

The initial growth rate of premature infants exceeds that of term infants in correspondence to the high magnesium retention observed in this group. Though this may be suggestive of magnesium retention being related to the growth rate, statistical analysis rendered no correlation of these parameters except for the term formula-fed infant group.

Previous magnesium balance studies in premature infants indicated a magnesium resorption over 50 % from human milk and milk-based formulas [12–21]. Absorption has been studied directly in VLBW infants by the use of two stable magnesium isotopes, ^{25}Mg and ^{26}Mg [18]. This was supplied by human milk and a human milk fortifier containing protein, calcium, phosphorus, magnesium and vitamin D. The infants absorbed 86 % to 89 %, respectively, of the magnesium given.

The present study showed that breast-fed infants maintain a magnesium retention equivalent to that of term formula-fed infants, despite lower intakes. An upper limit of magnesium concentration in formulas equivalent to the concentration in cow's milk (120 mg/l) has been recommended [6]. This is supported by the actual results since the increased retention observed in premature infants was accompanied by elevated magnesium concentrations in plasma compared to healthy term breast-fed and formula-fed infants. Low urinary excretion in breast-fed infants may serve as an adaptive mechanism, plasma levels of the respective infants were comparable to the formula-fed term group.

Conclusion

Milk-based infant formulas containing 50 to 100 mg magnesium/l supply sufficient amounts of magnesium for the growing premature infant. The results rendered no support for magnesium concentrations exceeding this range. Investigations in the post-discharge period suggest that unsupplemented human milk may not cover the needs of the very low birth weight premature infant. Premature infants fed unsupplemented human milk or formulas with low magnesium concentrations should be monitored carefully.

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