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Safety of a Triple-chamber Bag Parenteral Nutrition in Children Ages up to 24 Months: An Observational Study

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ABSTRACT

Objectives: Hypermagnesemia has been reported in preterm neonates treated with commercial pediatric triple-chamber bag (3CB) parenteral nutrition (PN). This postmarketing study was requested by the European Medicines Agency to assess the safety of a 3CB PN product in full-term neonates and children up to 24 months of age.

Methods: This prospective, multicenter, observational study enrolled hospitalized, full-term, newborn infants and children up to 24 months of age receiving >70% of nutrition as PN and requiring ≥50% of nutrition as PN for ≥5 days. All patients received 3CB PN during the study for ≤15 days. The primary outcome was serum magnesium, summarized by age group (0–1, >1–12, and >12–24 months). Secondary outcomes were nutritional intake and adverse events (AEs), including clinically significant abnormal laboratory results and vital signs.

Results: A total of 102 eligible patients were included. Median (interquartile range) parenteral magnesium intake was 0.23 (0.18–0.30) mmol · kg^{-1} · day^{-1}. Mean serum magnesium showed no consistent changes during treatment in any age group. One moderate and 3 mild AEs of hypermagnesemia were reported in 4 patients (3.9%), all ages 0 to 1 month. Other AEs in >2 patients were hypertriglyceridemia (6.9%), laryngitis (3.9%), hyperkalemia, hypokalemia, hyponatremia, hypophosphatemia, and neonatal hypotension (each 2.9%). Other serum electrolytes were stable, and revealed no safety concerns.

Conclusions: Mean serum magnesium levels were not affected by 3CB PN in full-term neonates and children up to 24 months of age. The risk of hypermagnesemia AEs was low when providing median parenteral magnesium of 0.2 to 0.3 mmol · kg^{-1} · day^{-1} in this population.

Key Words: electrolytes, hypermagnesemia, neonates, parenteral nutrition, ready-to-use

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What Is Known

- Parenteral nutrition provides crucial nutritional support for pediatric patients whenever oral or enteral nutrition is not possible, insufficient, or contraindicated.
- Pediatric formulations of commercial triple-chamber bag parenteral nutrition products are designed to meet the specific nutritional requirements of infants and children.
- Cases of hypermagnesemia have been reported in preterm neonates treated with a commercial triple-chamber bag parenteral nutrition.

What Is New

- Commercial pediatric triple-chamber bag parenteral nutrition was well tolerated in full-term neonates and children up to the age of 24 months.
- Mean serum magnesium levels were not affected by up to 15 days of pediatric triple-chamber bag parenteral nutrition.
- Events of hypermagnesemia were infrequent and generally mild, and reported at a similar incidence to other electrolyte imbalances.

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Parenteral nutrition (PN) can be lifesaving for neonates and children who cannot receive adequate oral or enteral nutrition because of intestinal failure or inability to tolerate enteral feeds (1,2). Pediatric patients are especially vulnerable to the energy and protein restriction seen during periods of serious illness. Poor nutritional status in critically ill children is associated with adverse clinical outcomes, such as longer duration of mechanical ventilation, higher risk of hospital-acquired infection, and increased mortality (3,4).

Pediatric PN is formulated to meet the specific nutritional requirements for pediatric growth that are not met with adult PN formulations (2,5). Recent European pediatric PN guidelines state that standard PN solutions should generally be used over individualized PN in most pediatric and newborn patients, including very low-birth-weight infants (6). The French health authority has also recommended using commercial products in preference to compounded PN for pediatric patients to improve treatment quality and safety (7). Ready-to-use, commercial triple-chamber bag (3CB) products provide advantages over compounded PN in terms of reduced risk of bloodstream infections (8,9), safety, and ease of preparation and use (2,10,11). The flexibility of optional components and possible nutrient additions allows tailoring to specific pediatric age groups, including very low-birth-weight infants (5,6,11,12).

The Numeta (Baxter Healthcare Corporation, Deerfield, IL) line of pediatric 3CB products includes formulations designed for preterm neonates (G13%E), full-term neonates and children up to 2 years of age (G16%E), and children from 2 to 18 years old (G19%E). Following reports of hypermagnesemia in preterm neonates treated with the G13%E formulation (13), the product was altered to reduce the magnesium content. Although no cases of hypermagnesemia were identified with the G16%E formulation, the European Medicines Agency requested a study of serum magnesium during treatment with the G16%E formulation in clinical practice (13). Consequently, this observational study was conducted to evaluate the safety of the G16%E 3CB PN formulation when used as approved in full-term neonates and children up to 24 months of age.

METHODS

Study Design

This was a phase IV, prospective, multicenter, uncontrolled, open-label, observational study to assess serum magnesium levels in full-term, newborn infants and children up to 24 months of age receiving pediatric 3CB PN. The study was conducted at 11 sites throughout Belgium, France, and Sweden, where standard-of-care treatment included the monitoring of serum magnesium. The sites included neonatal and pediatric intensive care units, gastroenterological units, and surgical departments.

The study protocol was reviewed and approved by ethics committees. Written informed consent was obtained from the parent(s) or legal representative of each patient before initiation of treatment. The study was registered at the European Union Electronic Register of Post-Authorisation Studies (ENCEPP/SDPP/7113). Data collection occurred from December 2014 to April 2017.

Study Population

Eligible patients included hospitalized, full-term, newborn infants and children up to 24 months of age who were receiving >70% of total nutrition intake as PN at study entry and who were expected to require ≥50% of total nutrition intake as PN for ≥5 days. Infants born prematurely and who presented with a postmenstrual age of ≥37 weeks could also be included.

Patients were ineligible to enter the study if they met any of the following exclusion criteria: life expectancy <6 days; severe illness with foreseeable intercurrent events that could jeopardize the patient's participation; pathologically elevated sodium, potassium, magnesium, calcium, and/or phosphorus concentrations; severe hyperglycemia (≥300 mg/dL); uncorrected metabolic disorders; severe hyperlipidemia; severe disorders of lipid metabolism characterized by hypertriglyceridemia (≥400 mg/dL); and congenital abnormalities of amino acid metabolism. Patients whose requirements could not be met by the pediatric 3CB PN and newborns receiving concomitant ceftriaxone were excluded. There was no restriction on PN received before study entry, and study enrollment did not affect PN prescription.

Target enrollment was 100 patients with a minimum of 20 infants in each age group (0–1, >1–12, and >12–24 months).

Treatment Protocol

All patients were treated with the G16%E formulation of the pediatric 3CB PN (Baxter Healthcare Corporation, Deerfield, IL), approved for full-term newborn infants and children up to 24 months. The product constitutes 3 chambers containing: (chamber A) a pediatric amino acid solution (10% Primene; Baxter Healthcare Corporation) with electrolytes and minerals including magnesium, (chamber B) a glucose solution, and (chamber C) an optional olive and soybean lipid emulsion (diluted 20% ClinOleic; Baxter Healthcare Corporation). Activation of the lipid component was optional and, thus, this pediatric PN solution could be activated as a 2-in-1 binary PN solution (using chambers A and B) or as a 3-in-1 ternary PN solution (using chambers A, B, and C), as shown in Table 1. The binary PN is a 20.6% glucose solution and the ternary PN is a 15.5% glucose solution.

TABLE 1. Nutritional composition of pediatric triple-chamber bag parenteral nutrition G16%E* with and without lipids

Ingredients	Without lipids	With lipids
Volume, mL	376	500
Nutrients, g per 100 mL		
Nitrogen	0.52	0.39
Amino acids	3.5	2.6
Glucose	20.6	15.5
Lipids	NA	3.1
Energy, kcal per 100 mL		
Total energy	96	103
Nonprotein energy	82	93
Glucose energy	82	62
Lipid energy	NA	31
Electrolytes/minerals, mmol per 100 mL		
Magnesium	0.41	0.31
Sodium	3.1	2.4
Potassium	3.0	2.3
Calcium	0.82	0.62
Phosphate†	0.85	0.87
Acetate	3.9	2.9
Malate	1.1	0.9
Chloride	3.7	2.8
pH	5.5	5.5
Osmolarity, mOsm/L	1585	1230

3CB = triple-chamber bag; NA = not applicable; PN = parenteral nutrition.
*The product is also marketed under trade names Numetah G16%E and Numetzah G16%E.
†Includes phosphate from egg phosphatide component of the lipid emulsion.

Dosing was in accordance with local prescribing guidelines and the treating physician's prescription, based on the individual patient's total nutritional needs and non-PN intake. Patients participated in the study for a maximum of 15 days after initiation of treatment.

Outcome Measures

The primary outcome, serum magnesium, was measured using blood samples drawn during routine clinical care before and during pediatric 3CB PN treatment. Whenever possible, samples were collected 2 to 4 hours post PN infusion. If a serum magnesium level was outside the reference range for the study site, the magnesium measurement could be repeated at the discretion of the investigator.

Secondary outcome measures included nutritional intake from all sources (parenteral [3CB and concomitant medications], enteral, and oral) and adverse events (AEs). Abnormal serum magnesium and other laboratory values or vital sign results that were considered by the investigator to be clinically significant were reported as AEs. All assessments were measured and recorded according to standard of care for the site.

Statistical Analysis

All patients with serum magnesium data at baseline and at least 1 posttreatment time point who received pediatric 3CB PN for ≥5 days were included in the primary analysis set. All patients who received at least 1 dose of pediatric 3CB PN were included in the full analysis set. The target sample size of 100 patients was based on the feasibility of enrollment. No formal power calculation was performed as no hypothesis was being tested.

Data were summarized using descriptive statistics. The primary end point, serum magnesium levels, and the corresponding changes from baseline were summarized for each treatment day using the full analysis set and the primary analysis set. Secondary outcomes were summarized using the full analysis set. Outcomes were also presented by age group (0–1, >1–12, and >12–24 months). Missing data were not imputed or replaced.

RESULTS

Demographic and Baseline Clinical Characteristics

A total of 104 patients were enrolled in the study, of whom 2 were screen failures. All 102 eligible patients received pediatric 3CB PN and were included in the full analysis set. Of these, 87 patients (85.3%) completed the study. Six patients were discontinued because of AEs (1 patient each for AEs of catheter site extravasation, phlebitis, hypermagnesemia, sepsis, vena cava thrombosis, and catheter site erythema), 1 patient was discontinued because of missing magnesium level measurements postinfusion, and 8 patients were lost to follow-up. Of the 102 treated patients, 83 patients had baseline and postbaseline serum magnesium data and had received pediatric 3CB PN for ≥5 days, thus meeting the criteria for inclusion in the primary analysis set; the remaining 19 patients did not meet these criteria and were excluded from the primary analysis.

Fifty patients were of ages 0 to 1 month, 31 patients were of ages >1 to 12 months, and 21 patients were of ages >12 to 24 months (Table 2). The most common diagnoses requiring PN were severe enteropathy (20.6%), intestinal atresia (13.7%), infection (5.9%), intestinal obstruction (4.9%), surgery (4.9%), asphyxia (4.9%), respiratory distress (3.9%), diaphragmatic hernia (3.9%), Hirschsprung's disease (3.9%), and omphalocele (2.9%). One quarter of patients had received PN before study entry (3CB PN, 2.0%; individualized PN, 24.5%).

Nutritional Intake

Median (interquartile range [IQR]) pediatric 3CB PN intake was 75.2 (57.3–93.2) $kcal \cdot kg^{-1} \cdot day^{-1}$ (Table 2), increasing from 59.1 (33.2–93.4) $kcal \cdot kg^{-1} \cdot day^{-1}$ on day 1 to 89.4 (59.2–106.1) $kcal \cdot kg^{-1} \cdot day^{-1}$ on day 6 and declining slightly thereafter. Treatment duration in the study ranged from 1 to 15 days, with a median duration of 9 days. Median (IQR) parenteral magnesium intake was 0.23 (0.18–0.30) $mmol \cdot kg^{-1} \cdot day^{-1}$, starting at 0.18 (0.11–0.28) $mmol \cdot kg^{-1} \cdot day^{-1}$ on day 1 and increasing to 0.28 (0.19–0.34) $mmol \cdot kg^{-1} \cdot day^{-1}$ by day 6, then decreasing slightly thereafter. Parenteral magnesium intake was solely from the 3CB PN, except

TABLE 2. Patient characteristics and nutritional intake by age category

Patient characteristics	Age at enrollment			Total
	0 to 1 month	>1 to 12 months	>12 to 24 months	
Number of patients*	50	31	21	102
Sex, male, n (%)	36 (72.0)	18 (58.1)	15 (71.4)	69 (67.6)
Weight, kg, mean ± SD	3.27 ± 0.66	4.68 ± 1.55	9.82 ± 2.33	5.05 ± 2.89
Anthropometric *z* scores, mean ± SD, n				
BMI for age	−0.60 ± 1.27, 43	−1.28 ± 2.82, 29	−0.02 ± 1.55, 18	−0.70 ± 1.98, 90
Weight for length	−0.93 ± 1.34, 40	−1.00 ± 1.59, 28	−0.08 ± 1.49, 18	−0.78 ± 1.48, 86
Weight for age	−0.37 ± 1.45, 50	−2.26 ± 1.73, 31	−0.75 ± 2.02, 21	−1.02 ± 1.85, 102
Pediatric 3CB PN				
Days, median (min–max)	8 (1–15)	10 (2–15)	8 (3– 5)	9 (1–15)
$mL \cdot kg^{-1} \cdot day^{-1}$, median (IQR)	74.2 (59.8–92.3)	78.7 (60.9–95.6)	56.5 (43.8–72.8)	73.3 (56.2–91.7)
$kcal \cdot kg^{-1} \cdot day^{-1}$, median (IQR)	76.3 (60.8–94.4)	81.0 (61.5–96.7)	57.3 (45.1–75.0)	75.2 (57.3–93.2)
Non-PN intake				
$kcal \cdot kg^{-1} \cdot day^{-1}$, median (IQR)	22.1 (13.2–32.8)	13.9 (3.3–30.9)	14.4 (0.0–19.0)	18.3 (7.1–29.8)
Parenteral magnesium intake				
$mmol \cdot kg^{-1} \cdot day^{-1}$, median (IQR)	0.24 (0.18–0.29)	0.24 (0.20–0.32)	0.19 (0.14–0.23)	0.23 (0.18–0.30)

3CB = triple-chamber bag; BMI = body mass index; IQR = interquartile range; PN = parenteral nutrition; SD = standard deviation.
*Full analysis set.

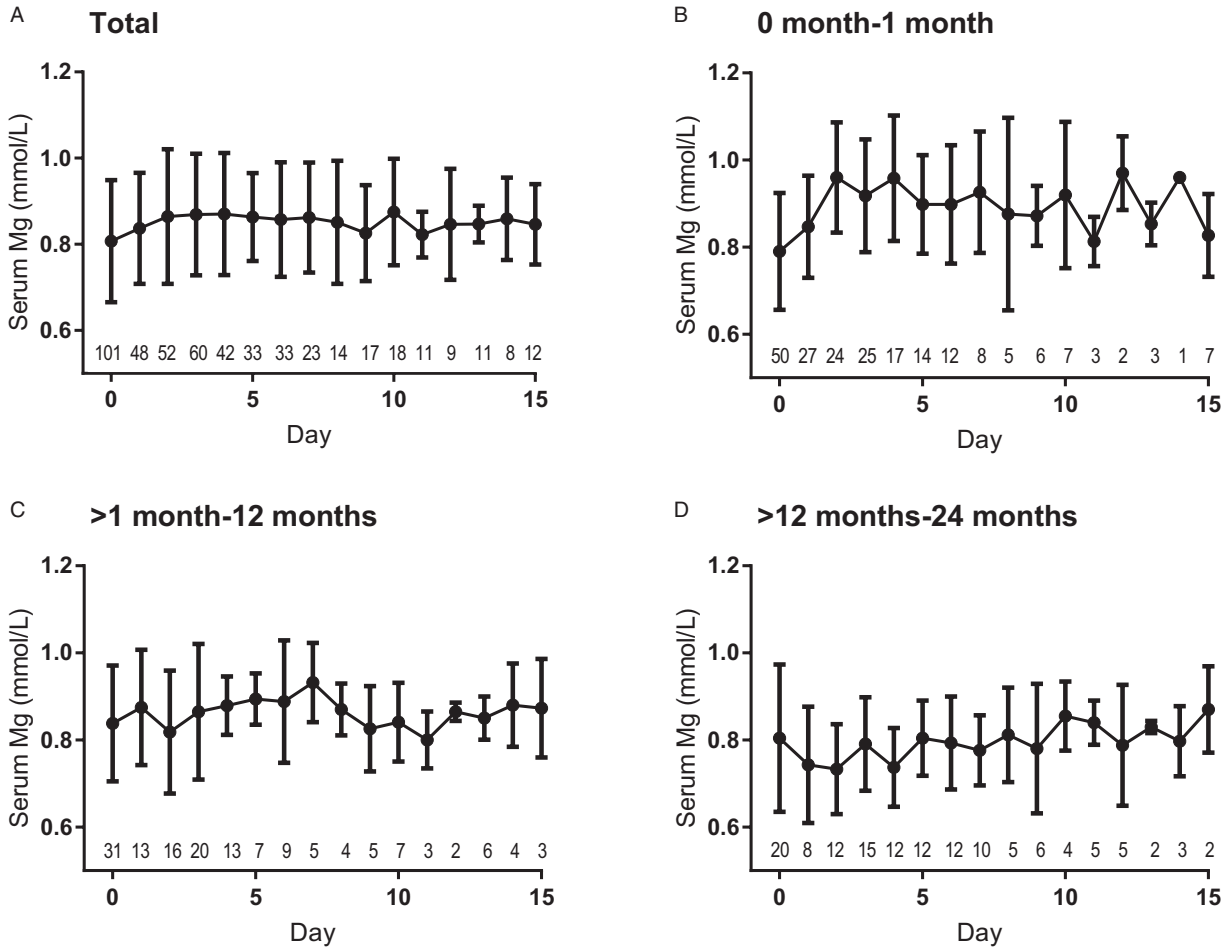

FIGURE 1. Mean serum magnesium during parenteral nutrition by age group. Mean ± standard deviation is presented by treatment day for (A) total full analysis set, (B) patients ages 0 to 1 month, (C) patients ages >1 to 12 months, and (D) patients ages >12 to 24 months. Numbers of patients with data are shown above the *x*-axis for each time point. The baseline serum magnesium value was missing in 1 patient in the >12 to 24 months age category. Normal serum magnesium reference ranges were determined by each site's local laboratory. Lower limits ranged from 0.6 to 0.74 mmol/L and upper limits ranged from 0.95 to 1.3 mmol/L across the sites.

for 2 patients who received some magnesium from another intravenous solution used to compensate for ileostomy losses. The majority of patients (87%) also received nonparenteral food or breast milk. PN accounted for an estimated 79% of median total daily energy intake.

Primary Outcome: Serum Magnesium

Mean serum magnesium levels showed no consistent changes during pediatric 3CB PN treatment in any age group (Fig. 1). Mean ± SD (standard deviation) serum magnesium was 0.81 ± 0.14 mmol/L at baseline (n = 101; baseline value was missing in 1 patient) and 0.85 ± 0.09 mmol/L at day 15 (n = 12), with a mean ± SD change from baseline to day 15 of 0.13 ± 0.17 mmol/L in the full analysis set. Similar results were seen in the primary analysis set.

Adverse Events of Hypermagnesemia and Hypomagnesemia

AEs of hypermagnesemia were reported in 4 of 102 patients (3.9%; Table 3). All 4 patients were of ages 0 to 1 month, constituting 8% of this age group (4 of 50 patients). The AEs of hypermagnesemia were nonserious and considered to be possibly related (2 events) or probably related (2 events) to treatment with pediatric 3CB PN. Parenteral magnesium intake on the day of hypermagnesemia onset was between 0.29 and 0.33 $mmol \cdot kg^{-1} \cdot day^{-1}$ across the 4 patients. The 2 patients with the highest serum magnesium levels received breast milk as well as pediatric 3CB PN without the lipid component; none of the 4 patients received magnesium additions to the PN. Total energy intake on the day of hypermagnesemia onset was between 86.7 and 108.3 $kcal \cdot kg^{-1} \cdot day^{-1}$ in the 4 patients, compared with a median intake of 99.3 $kcal \cdot kg^{-1} \cdot day^{-1}$ in the 0 to 1 month age group. One of the 4 patients was born late preterm at 36 weeks and 6 days of gestation, but was included in the study at 1 day of life after 37 weeks' postmenstrual age and full-term age were reached. The hypermagnesemia AEs were mild in 3 patients, with no accompanying clinical symptoms. In 1 patient, the hypermagnesemia AE was moderate, with accompanying symptoms of muscular weakness. This patient had a medical history of hypotonia as well as hemolytic disease of the newborn, with exchange transfusion for severe hyperbilirubinemia, neonatal anemia,

TABLE 3. Adverse events of hypermagnesemia

Age at baseline (days)	Day of AE	Weight at event (kg)	Serum magnesium (mmol/L)			Severity/ symptoms	Action/outcome	Intake on day of AE		Comments
			Baseline	Maximum	Site reference range			Parenteral Mg (mmol/kg)	Other	
27	Day 6	4.11	0.74	1.05	0.65–1.02	Mild/none	3CB PN interrupted then restarted the next day/unknown	0.30	None	
6	Day 4	3.14	0.73	1.12	0.62–0.91	Mild/none	None/resolved	0.33	None	
11	Day 10	3.1	0.78	1.23	0.65–1.05	Mild/none	PN dose reduced/ resolved	0.33	Breast milk	Born premature
3	Day 4	3.03	0.81	1.27	0.65–1.05	Moderate/ muscle weakness	PN stopped/resolved	0.29	Breast milk	Prior hypotonia, concomitant amikacin

3CB = triple-chamber bag; AE = adverse event; Mg = magnesium; PN = parenteral nutrition.

hypocalcemia, and hypertriglyceridemia (resulting in a reduction in the lipid dosage). The patient was receiving concomitant treatment with amikacin.

There were no AEs of hypomagnesemia.

Other Serum Electrolytes

Mean serum levels of calcium, sodium, potassium, and phosphate during pediatric 3CB PN treatment are shown in Supplemental Figure 1 (Supplemental Digital Content, *http://links.lww.com/MPG/B725*). Serum phosphate levels suggested a gradual increase in each age group (Supplemental Figure 2, Supplemental Digital Content, *http://links.lww.com/MPG/B725*) but patient numbers were low at later time points and no AEs of hyperphosphatemia were reported. The incidence of AEs for elevated electrolyte levels (hyperkalemia, 2.9% of patients; hypercalcemia, 1.0%; hypernatremia, 1.0%) was similar to the incidence of AEs of low electrolyte levels (hypokalemia, 2.9%; hyponatremia, 2.9%; hypophosphatemia, 2.9%; Supplemental Table 1, Supplemental Digital Content, *http://links.lww.com/MPG/B725*).

Safety and Tolerability

Approximately one half of patients (48.0%) experienced AEs. The most common AEs reported in more than 2 patients overall were hypertriglyceridemia (6.9% of patients), hypermagnesemia (3.9%), laryngitis (3.9%), hyperkalemia (2.9%), hypokalemia (2.9%), hyponatremia (2.9%), hypophosphatemia (2.9%), and neonatal hypotension (2.9%). Five patients (4.9%) had cholestasis or transient liver dysfunction; 2 of these patients also had hyperbilirubinemia.

Overall, 11.8% of patients experienced AEs considered by the investigator to be possibly or probably related to the study product, none of which were serious or severe. Seven patients (6.9%) experienced serious AEs (SAEs). There were no deaths during the study.

Body Weight and Vital Signs

Mean body weight increased during pediatric 3CB PN treatment (Supplemental Figure 3, Supplemental Digital Content, *http://links.lww.com/MPG/B725*). No clinically important changes in mean vital signs were observed.

DISCUSSION

This is the first observational study to measure serum magnesium levels during treatment with the G16%E formulation of pediatric 3CB PN in real-world clinical practice. Changes in mean serum magnesium levels during pediatric 3CB PN were small and not clinically relevant. AEs of hypermagnesemia were infrequent and generally mild, and were reported at a similar incidence to other electrolyte imbalances. There were no AEs of hypomagnesemia. One AE of hypermagnesemia in a neonate was considered moderate because of a suspected association with muscular weakness. The patient had hypotonia before treatment and was receiving concomitant amikacin, which may potentiate neuromuscular weakness (14). One of the patients with mild hypermagnesemia was born preterm but was enrolled after 37 weeks postmenstrual age, meeting the inclusion criteria. Prematurity is associated with higher serum magnesium levels (15). This was the only study participant born preterm.

All 4 hypermagnesemia AEs occurred in infants <1 month of age, suggesting this age group may be at higher risk of hypermagnesemia, and thus need close electrolyte monitoring during PN (15). The kidney is an important regulator of magnesium homeostasis, and postnatal renal immaturity increases the risk of hypermagnesemia (16). Clinical symptoms may not manifest unless hypermagnesemia is severe and may not be identified in critically ill children (17).

The treatment regimens in this observational, noninterventional study represent real-world clinical practice across a range of neonatal and pediatric intensive care, pediatric gastroenterological, and pediatric surgical environments. The patient population reflected the full age range for which the pediatric 3CB product is approved, and the variety of diagnoses, which can necessitate PN. The treating physicians were able to adjust the 3CB PN to meet individual patient needs, through dilution, nutrient additions, or the optional lipid component, and make PN dosing adjustments as clinically appropriate. Although treatment duration within the study was limited to 15 days, this reflects the short-term use typical of intensive care situations.

Achieving correct parenteral magnesium intake is essential. Magnesium plays a role in bone development, protein synthesis, energy production, and glycolysis (15). Hypomagnesemia is associated with osteoporosis and, if severe, can cause seizures, drowsiness, and cardiac ventricular fibrillation (18). Hypermagnesemia can cause nausea and vomiting, and in severe cases, generalized weakness, depressed respiration, hypotension, and bradycardia

(17). However, defining hypermagnesemia in pediatric patients is complicated by a lack of well-defined normal reference ranges for serum magnesium (15). In 2012, Colantonio et al presented age-specific pediatric magnesium reference ranges for healthy patients ages 0 to 14 days (0.82–1.62 mmol/L), 15 days to <1 year (0.81–1.27 mmol/L), and 1 to <19 years (0.86–1.17 mmol/L) (19). Applying these proposed reference ranges to the current study would have produced no adverse events of hypermagnesemia in any age group. The magnesium reference ranges used in the present study were determined by the sites' local laboratories, and showed considerable variation in the upper limit from 0.95 to 1.3 mmol/L.

Discrepancies exist between current international guidelines for magnesium intake in pediatric PN (3,20–22) (Supplemental Table 2, Supplemental Digital Content, *http://links.lww.com/MPG/B725*), which reflect uncertainties about ideal pediatric magnesium intake and some probable confusion between lower threshold intake, estimated average requirements, reference nutrient intake, population reference intake, recommended daily allowance, acceptable range of intake, and upper safe level of intake when defining guidelines (23). This probably explains why, in infants ages 0 to 12 months, the 2018 PN guidelines from the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), European Society for Clinical Nutrition and Metabolism (ESPEN), European Society of Paediatric Research (ESPR), and Chinese Society of Parenteral and Enteral Nutrition (CSPEN) recommend 0.1 to 0.2 $mmol \cdot kg^{-1} \cdot day^{-1}$ of magnesium (3), whereas Hartman et al (20) recommend 0.25 to 0.4 $mmol \cdot kg^{-1} \cdot day^{-1}$. Interestingly, the American Society for Parenteral and Enteral Nutrition (ASPEN) recommends 0.15 to 0.25 $mmol \cdot kg^{-1} \cdot day^{-1}$ (21), whereas the American Academy of Pediatrics (AAP) (22) recommends a wide magnesium intake range (0.125–0.5 $mmol \cdot kg^{-1} \cdot day^{-1}$) that encompasses all of these guidelines (3,20,21). In this study, the median (IQR) parenteral magnesium intake was 0.23 (0.18–0.30) $mmol \cdot kg^{-1} \cdot day^{-1}$, starting at 0.18 (0.11–0.28) $mmol \cdot kg^{-1} \cdot day^{-1}$ on day 1 and increasing to 0.28 (0.19–0.34) $mmol \cdot kg^{-1} \cdot day^{-1}$ by day 6. Thus, the safe use of 3CB PN observed in this study suggests that a magnesium intake of 0.2 to 0.3 $mmol \cdot kg^{-1} \cdot day^{-1}$ is probably in the acceptable range of intakes in this patient population ages 0 to 24 months.

Pediatric 3CB PN was well tolerated across all age groups in this study. AEs of elevated serum electrolytes were infrequent, especially for a pediatric population including intensive care patients, and were no more frequent than AEs of low serum electrolytes. Underlying medical conditions were likely contributors to the majority of metabolic AEs.

Limitations of the study were the absence of clinical stability assessment, and the exclusion of patients whose requirements could not be met by the pediatric 3CB PN and patients with severe illness that could jeopardize their participation in the study. This study confirms that clinician judgment remains necessary before any PN prescription and that adequate monitoring is required when providing PN as recommended in the 2018 European guidelines (24). The single-arm study design does limit safety comparisons of the pediatric 3CB PN against other regimens; however, the low rate and mild-to-moderate nature of the hypermagnesemia events supports the favorable safety profile.

CONCLUSIONS

Mean serum magnesium levels were not affected by up to 15 days of pediatric 3CB PN in this study. The risk of hypermagnesemia AEs was low when providing 0.2 to 0.3 $mmol \cdot kg^{-1} \cdot day^{-1}$ of parenteral magnesium in this population of full-term neonates and children up to the age of 24 months. Other serum electrolytes were stable and revealed no safety concerns. The G16%E pediatric 3CB PN is safe and well tolerated in this population but requires appropriate clinical assessment and monitoring as recommended when providing PN. These results should not be extrapolated to patients whose requirements could not be met by this pediatric 3CB PN.

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