Incidence of Hypertriglyceridemia in Critically Ill Neonates Receiving Lipid Injectable Emulsions in Glass Versus Plastic Containers: A Retrospective Analysis

Camilia R. Martin, MD, Gregory J. Dumas, RPh, Claire Shoaie, RD, Zheng Zheng, MPH, Brenda MacKinnon, RN, Issa Al-Aweel, MS, Bruce R. Bistrian, MD, PhD, DeWayne M. Pursley, MD, and David F. Driscoll, PhD

Objective To evaluate plasma clearance of lipid injectable emulsions packaged in either glass or plastic containers in neonates from 2 7-month periods, 1 year apart.

Study design Clinical records from June 1 to December 31, 2003 (glass [G] period) and the same months in 2004 (plastic [P] period) were assessed. Neonates who received lipid injectable emulsions were studied. Lipid container (glass vs plastic) was the independent variable.

Results Of the 197 patients studied, 122 (G, 50/81; P, 72/116) had evaluable triglyceride (TG) levels, for an overall rate of 62%. Only birth weight (G, 1.09 ± 0.32 kg vs P, 1.23 ± .45 kg) and birth length (G, 36.4 ± 3.5 cm vs P, 37.9 ± 3.5 cm) were significantly different between the 2 groups ($P = .047$ and .028, respectively). There were no differences in the day of life on which lipid injection was started, the lipid dose, or the timing of TG measurements. The incidence of hypertriglyceridemia was significantly higher in the P period (G, 3/50 vs P, 19/72; $P = .004$).

Conclusions Administration of the same lipid formulation in plastic bags compared with glass containers is associated with higher rates of hypertriglyceridemia. The poorer clearance of lipids could be due to a higher proportion of large-diameter fat globules in plastic bags compared with those in glass containers. *(J Pediatr 2008;152:232-6)*

The United States Pharmacopeia (USP), which produces official drug standards as monographs and related chapters for all Food and Drug Administration (FDA)-approved drugs, issued a proposed new compendial version of lipid injectable emulsion in 2004 known as Chapter <729>, "Globule Size Distribution in Lipid Injectable Emulsions."[1]* Although the USP has been working on Chapter <729> for more than 15 years, the version published in 2004 included for the first time desirable globule size limits, under the thesis that unstable lipid injectable emulsions forming large-diameter fat globules "must be kept at a minimum to avoid obstruction of the microvasculature, particularly the capillaries of the lungs."[1] The current USP Chapter <729> limits the percentage of fat globules > 5 μm ($PFAT_5$) to < 0.05%, recognizing previous recommendations.[2]

Tolerance of intravenous (IV) lipid emulsions in the newborn is inversely related to maturity and birth weight (BW), with the more immature and smaller neonates at greatest risk for hypertriglyceridemia.[3] In addition, lipid metabolism can be further impaired by acute illness, such as sepsis.[4] This has raised several potential clinical concerns for the preterm neonate receiving IV lipid emulsions, including pulmonary microembolization of fat globules,[5] impaired oxygenation,[6] increased pulmonary vascular resistance,[7] and immunosuppression.[8] Although the risk for many of these clinical complications remains controversial,[9,10] a "black box warning" was issued by the FDA and is provided in the

BL	Birth length	GIR	Glucose infusion rate
BW	Birth weight	IV	Intravenous
DOL	Day of life (from birth)	P	Plastic
EFA	Essential fatty acid	$PFAT_5$	Volume-weighted percent of fat > 5 μm
FDA	Food and Drug Administration	TG	Triglycerides
G	Glass	USP	United States Pharmacopeia
GA	Gestational age		

From the Departments of Neonatology (C.M., Z.Z., B.M., I.A., D.P.), Pharmacy (C.M., B.B., D.P., D.D.), Nutrition Services (C.S.), and Medicine (B.B., D.D.), Beth Israel Deaconess Medical Center, Boston, MA and the Department of Pediatrics (C.M., D.P.), and the Department of Medicine (B.B., D.D), Harvard Medical School, Boston, MA.

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The institutional protocol number for conducting the chart review for this study is 2006-P-000222/1;BIDMC; it was approved on June 14, 2006.

*USP Chapter <729> becomes official on December 1, 2007.

Dr Bistrian is a consultant in parenteral lipids for B. Braun. Dr Driscoll is a consultant and/or researcher in lipids for AstraZeneca, B. Braun, Biolink, and Hospira.

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Reprint requests: Camilia R. Martin, MD, 330 Brookline Avenue, Rose-318, Boston, MA 02215. E-mail: cmartin1@bidmc.harvard.edu.

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manufacturer's package insert of all commercially available formulations;[11,12] this warning is reproduced in Table I (available at www.jpeds.com).

On February 26, 2004, a change in the packaging of Intralipid (Baxter Healthcare Corp, Deerfield, IL; Fresenius Kabi, Uppsala, Sweden) from glass to plastic containers was announced.[13] The product of the other US supplier of lipid emulsion (Liposyn; Abbott Laboratories, North Chicago, IL) is still supplied in glass bottles. A subsequent analysis of these newly introduced lipid emulsions in plastic bags versus those in conventional glass bottles revealed that those packaged in plastic failed to meet the USP Chapter <729> limits for $PFAT_5$, demonstrating on average an approximate 55-fold higher concentration of very large fat globules over that in glass bottles, as shown in Figure 1 (available at www.jpeds.com).[14] To investigate whether these laboratory findings are clinically significant, we reviewed plasma clearance of identical lipid emulsions differing only in terms of the container (glass vs plastic) in neonates from 2 7-month periods, 1 year apart.

METHODS

We performed a retrospective review of the medical records of all neonates receiving lipid injectable emulsions between June 1 and December 31 of 2003 (glass [G] period) and for the same months in 2004 (plastic [P] period). Moreover, during these time periods, the same lipid injectable emulsion product was used, differing only in its container (glass vs plastic) for each period. Data were collected on all eligible patients, including baseline characteristics, clinical variables, and nutritional variables. Baseline characteristics included gestational age in weeks (GA); BW, in kg; birth length (BL), in cm; small for gestational age (SGA) status, defined as a BW < 10th percentile for GA using an updated Babson and Benda fetal-infant growth curve;[15] sex; and race. Clinical variables included 5-minute Apgar score; total bilirubin, in mg/dL; day of life [from birth] (DOL) on which bilirubin level was measured; presence of sepsis or shock; and use of any systemic steroid. Sepsis was defined as having a positive blood culture. Shock was defined as receiving any vasopressor. Nutritional variables included concurrent glucose infusion rate (GIR, in mg/kg/min), DOL on which the lipid was initiated, total lipid dose (in g/kg/day), concurrent enteral fat intake (in g/kg/day), and total fat intake (lipid dose + enteral intake, in g/kg/day).

To be included in the final analysis of hypertriglyceridemia, a patient needed to have a documented serum triglyceride (TG) level in his or her medical record, which, according to institutional clinical protocol, was measured on DOL-4 as the fat dose was titrated toward a goal dose of 3 g/kg/day. Lipid infusions began on the second day of life (DOL) or DOL-2 at 1 g/kg/day and were ramped up to 3 g/kg/day by DOL-6, as shown in Table II (available at www.jpeds.com). At our institution, the upper limit of the normal range for serum TG by our clinical laboratory is 149 mg/dL. Thus, before data analysis, hypertriglyceridemia was defined as any TG level ≥ 150 mg/dL. This definition is consistent with other studies regarding lipid tolerance in neonates.[16] In addition, current pediatric and neonatal clinical recommendations are to maintain TG levels below 150 mg/dL,[10,17-19] even though the precise upper limit for lipid toxicity remains unknown.[10] Therefore, to comply with current clinical recommendations, when the serum TG level is ≥ 150 mg/dL, it is our practice to discontinue the lipid emulsion and follow TG levels until they return to the normal range, at which time the lipid infusion is reinstituted if clinically indicated. In addition to the TG level, the DOL on which the TG level was drawn was also noted.

Student's t test was used, with lipid container (glass vs plastic) as the independent variable against the parametric dependent variables as determined by normality testing (GA, BW, BL, and GIR). For all other nonparametric or categorical dependent variables, Wilcoxon's rank-sum test and the χ^2 test were applied. Fisher's exact test was used to compare the proportions of hypertriglyceridemia between the 2 groups. Finally, logistic regression modeling was used to determine the odds of hypertriglyceridemia while adjusting for any potential confounders, using the Wald approach for a 95% confidence interval. Statistical significance was set at a P value of $< .05$. This study was approved by the Beth Israel Deaconess Medical Center's Institutional Review Board.

RESULTS

Of 197 patients available, a total of 122 (62%) had evaluable TG levels. With respect to the individual groups, 50/81 patients (62%) in the G period (2003) and 72/116 patients (62%) in the P period (2004) had evaluable TG levels. Compared with neonates who had a TG level measured (participants), those neonates who did not have a TG level measured (nonparticipants) were more mature and thus also had greater BW and BL (Table III). In addition, at the time that a TG level should have been drawn, the nonparticipant neonates were receiving a greater amount of enteral feedings, as expressed by a greater enteral fat intake. As a result, their total fat intake was also higher, achieving statistical significance in the G period. Finally, the total bilirubin level for the nonparticipants also was higher in the P period, while approaching statistical significance in the G period.

Among the neonates with an evaluable TG level, the differences in BW (G: 1.09 ± .32 kg vs P: 1.23 ± .45 kg) and BL (G: 36.4 ± 3.5 cm vs P: 37.9 ± 3.5 cm) were statistically significant ($P = .047$ and .028, respectively), and the difference in GA (G: 28.4 ± 2.4 weeks vs P: 29.1 ± 2.3 weeks) approached statistical significance ($P = .096$). There were no differences in the other baseline, clinical, or nutritional variables. In particular, the amount of concurrent IV glucose administration, the day of lipid initiation, the dose of lipid administered, the enteral and total fat intakes, and the DOL of TG measurement were similar. Therefore, the duration of lipid exposure also was similar for both groups, as reflected by no differences in the DOL of initiation of lipid infusion and the DOL of TG measurement.