

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

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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 (PFAT₅) 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

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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		

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 PFAT₅, 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 reinstated 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: $1.09 \pm .32$ kg vs P: $1.23 \pm .45$ 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.

Table III. Baseline and clinical characteristics of infants receiving lipid injectable emulsions in the neonatal intensive care unit

	G period (n = 81)			P period (n = 116)			G vs P, participants only
	Participants	Nonparticipants	P	Participants	Nonparticipants	P	
N (%)	50 (62)	31 (38)		72 (62)	44 (38)		
Baseline characteristics							
GA, weeks, mean (SD)	28.4 (2.4)	31.6 (1.9)	<.0001	29.1 (2.3)	31.2 (2.3)	<.0001	.096
BW, kg, mean (SD)	1.09 (0.32)	1.45 (0.33)	<.0001	1.23 (0.45)	1.51 (0.44)	.0016	.047
Length, cm, mean (SD)	36.4 (3.5)	40 (3.3)	<.0001	37.9 (3.5)	40.5 (2.9)	<.0001	.028
SGA, n (%)	8 (16)	7 (22.6)	.46	9 (12.5)	5 (11.4)	.86	.58
Male, n (%)	24 (48)	15 (48.4)	.97	43 (59.7)	20 (45.5)	.13	.2
Race, n (%)							
White, n (%)	34 (68)	18 (60)	.66	46 (63.9)	32 (74.4)	.77	.96
Black, n (%)	7 (14)	5 (16.7)		10 (13.9)	4 (9.3)		
Asian, n (%)	1 (2)	1 (3.3)		1 (1.4)	0		
Hispanic, n (%)	2 (4)	0 (0)		5 (6.9)	2 (4.7)		
Other, n (%)	6 (12)	6 (20)		10 (13.9)	5 (11.6)		
Clinical variables							
5-min Apgar, median (IQR)	8 (7, 9)	8 (8, 8)	.4	8 (7, 8)	8 (8, 9)	.15	.55
Total bilirubin, g/dL, median (IQR)	4.8 (3, 6.4)	5.4 (4.2, 7.7)	.07	4.7 (3.2, 6.1)	5.5 (4.7, 6.9)	.0095	.65
DOL bilirubin, median (IQR)	5 (4, 6)	5 (5, 5)	.66	5 (4, 6)	5 (5, 5)	.29	.36
Sepsis, n (%)	3 (6)	0	.16	4 (5.6)	1 (2.3)	.4	.92
Shock, n (%)	10 (20)	4 (12.9)	.41	15 (20.8)	6 (13.6)	.33	.91
Steroids, n (%)	1 (2)	0	.43	0	0	.99	.23
Nutritional variables							
GIR, mg/kg/min, mean (SD)	7.1 (1.9)	5.5 (2.2)	.0007	6.8 (2.8)	5.8 (1.9)	.012	.43
Fats							
DOL Intralipid started, median (IQR)	2 (2, 2)	2 (2, 2)	.85	2 (2, 2)	2 (2, 2)	.91	.68
Intralipid, g/kg/day, median (IQR)	1.3 (1.1, 1.5)	1.2 (.7, 1.6)	.18	1.3 (1.2, 1.5)	1.4 (1, 1.6)	.97	.43
Enteral fat intake, g/kg/day, median (IQR)	0 (0, 1.2)	1.9 (.3, 3.6)	.0002	0 (0, .4)	.3 (0, .1)	.0008	.12
Total fat intake, g/kg/day, median (IQR)	1.4 (1.2, 2.7)	3.2 (1.6, 5)	.0074	1.4 (1.2, 2)	1.8 (1.4, 2.4)	.11	.37
Triglyceride level							
DOL TG level, median (IQR)	5 (4, 6)	—	—	5 (4, 6.5)	—	—	.43
TG level, mg/dL, median (IQR)	81.5 (60, 113)	—	—	102.5 (56, 163.5)	—	—	.14
Hypertriglyceridemia (TG ≥ 150 mg/dL), n (%)	3 (6)	—	—	19 (26.4)	—	—	.004

IQR, interquartile range.

Although the median TG level did not differ between the 2 groups, the difference in the incidence of hypertriglyceridemia was statistically significant (G = 3/50 vs P = 19/72) by Fisher's exact test ($P < .004$). These results are summarized in Table III. A plot showing the variability in the measured serum TG levels between the 2 groups for all participating neonates is shown in Figure 2A, and a subplot of only the mean hypertriglyceridemic levels is shown in Figure 2B. These levels were 200 ± 37 mg/dL (range, 179 to 243 mg/dL) in the patients with hypertriglyceridemia in the G period and 233 ± 88 mg/dL (range, 154 to 536 mg/dL) in those patients in the P period. Using logistic modeling with

hypertriglyceridemia as the binary outcome and controlling for GA, BW, SGA, sex, race, DOL of TG measurement, and total fat intake, the adjusted odds of hypertriglyceridemia during the P period remained statistically significant at a point estimate of 5.8 and a 95% Wald confidence interval of 1.5, 22.3 (Table IV).

DISCUSSION

The use of lipid injectable emulsions in neonates, particularly in preterm neonates, is often clinically indicated, serving as an important source of essential fatty acids (EFAs) and calories. Hyperlipidemia is a significant complication of

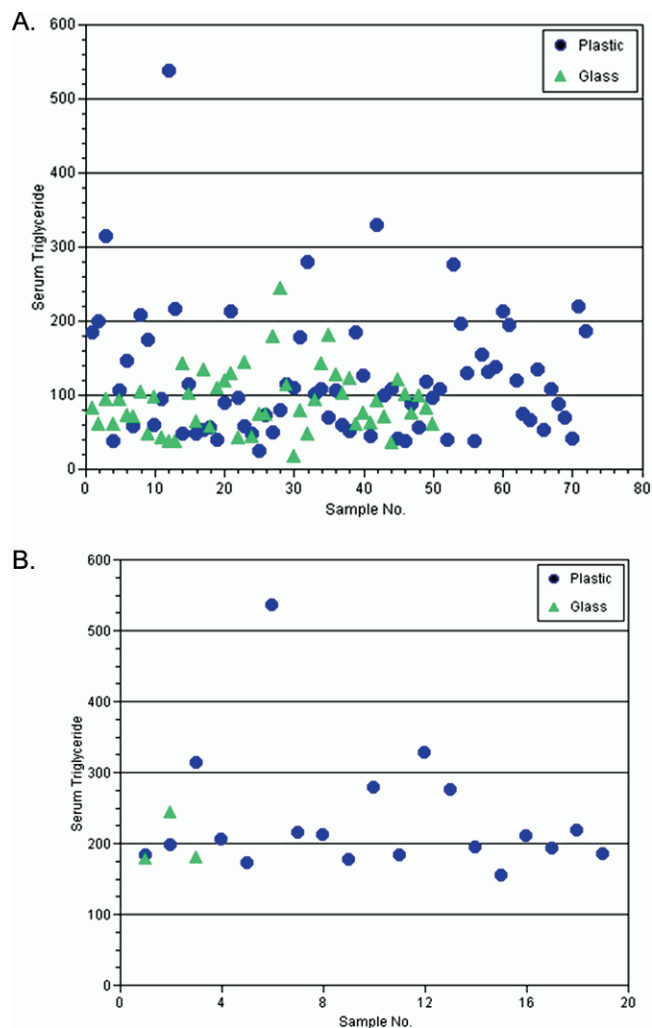


Figure 2. Plots of serum TG levels in mg/dL for (A) all neonates receiving lipid emulsions from plastic containers (n = 72, circles) versus glass containers (n = 50, triangles) and (B) the subset of neonates with hypertriglyceridemia. (Available in color at www.jpeds.com.)

Table IV. Adjusted logistic regression model for the odds of hypertriglyceridemia

Variable	Odds ratio	95% Confidence interval	P
Plastic container	5.8	1.5, 22.3	.01
Gestational age	1.3	0.8, 2	.29
Birth weight	0.4	0.04, 4.3	.46
SGA	1.9	0.4, 10.2	.44
Male	1.4	0.5, 4	.58
White	3	0.9, 10.4	.08
DOL lipid level	0.9	0.4, 2	.71
Total fat intake	1	0.5, 1.9	.97

IV lipid emulsion therapy, and excessive lipid administration resulting in hypertriglyceridemia has significant clinical consequences for the preterm neonate.⁹⁻¹² Nonetheless, lipid injectable emulsions are necessary in all such neonates requir-

ing parenteral nutrition, with a minimum fat intake of 0.5 g/kg/day needed to meet EFA requirements.¹⁹ Preterm neonates are especially susceptible to EFA deficiency due to limited hepatic metabolism (ie, activity of Δ^6 -desaturase enzyme, the rate-limiting enzyme in the conversion of linoleic acid to arachidonic acid and the conversion of alpha-linolenic acid to eicosapentaenoic acid and docosahexaenoic acid), which, without adequate supplementation, may produce visual and cognitive deficits.²⁰ Higher fat intake also is a desirable source of calories to reduce carbohydrate intake in critically ill neonates and prevent attendant complications.

Among the participating neonates receiving lipid injectable emulsions through glass or plastic containers, the data show that neonates receiving IV lipids through plastic bags have a higher incidence of hypertriglyceridemia compared with neonates receiving the same parenteral lipids packaged in conventional glass bottles. These findings are particularly notable considering that the neonates in the G period had a considerably lower BW, yet had a significantly lower incidence of hypertriglyceridemia. These findings are counterintuitive. The neonates in the G period would appear to be predisposed toward being less tolerant of IV lipid administration with respect to plasma clearance,³ yet we have shown that despite the differences in BW and, to a lesser extent, GA, the increased risk of hypertriglyceridemia during the P period persisted even after adjusting for these variables.

Recent work investigating the compliance of plastic-packaged lipids with proposed USP Chapter <729> guidelines showed that they exceed the proposed globule size limits.¹⁴ These findings were subsequently corroborated in 3 additional studies.²¹⁻²³ Another, more extensive investigation confirmed the abnormal globule size profile seen previously in plastic-packaged lipid emulsions from 2 European manufacturers,²¹ but not in another plastic-packaged emulsion from a different manufacturer. This finding suggests that the problem with the plastic bags is likely manufacturer-dependent and not specifically related to plastic containers. To check whether the abnormal globule size distribution specific to one manufacturer of plastic-packaged lipids also had an effect on the stability of commonly prescribed all-in-one or total nutrient admixtures in adult patients (ie, parenteral nutrition admixtures that combine lipids with amino acids, dextrose, electrolytes, vitamins, etc into a single infusion container), another physical stability study was conducted.²² This included a comparison of identical adult total nutrient admixtures intended for patients weighing 40 to 80 kg (in 10-kg increments; 5 formulations, triplicates of each) made from glass-packaged (n = 15) and plastic-packaged (n = 15) lipid injectable emulsions as used in the present study. The results showed that the admixtures made with plastic-packaged lipids had evidence of instability 60% of the time, whereas those made with glass-packaged lipids were 100% stable during the 30-hour test period (ie, no significant increase in PFAT₅ from baseline measurements with all samples < 0.05% and no visual evidence of instability, such as free oil separating from the emulsion).²² Most recently, in an effort to check whether

the abnormal globule size distribution found in the lipids packaged in plastic resulted in less stable emulsions when given by syringe infusion, a simulated neonatal lipid infusion over 24 hours compared the results of glass-packaged (n = 18) and plastic-packaged (n = 18) 20% lipid injectable emulsions.²³ Significant differences in the globule size distribution of the plastic-packaged lipids were seen from the outset, with all samples exceeding proposed USP Chapter <729> limits (PFAT₅: 0.162 ± 0.026%), followed by further deterioration after 24 hours (PFAT₅: 0.328 ± 0.046%). In contrast, the glass-packaged lipids in syringes met the USP Chapter <729> limits for all samples at the beginning (0.006 ± 0.001%) and end (0.013 ± 0.003%) of the study.²³ The larger fat globule sizes found in the plastic-packaged lipid emulsions in these studies might affect the lipid clearance rate by virtue of differential organ clearance related to size²⁴ and/or slower clearance by usual mechanisms related to the total surface area available for enzymatic action.²⁵

In the present study, the data support an association between the lipid emulsion container and hypertriglyceridemia. The fact that patients in the P period had significantly higher serum TG concentrations and higher rates of hypertriglyceridemia even after adjusting for BW and GA implies an exogenous cause. Moreover, because the products used in both periods of the present analysis came from the same manufacturer, the data further suggest the plastic container and its abnormal globule size distribution as the underlying cause of hypertriglyceridemia.

The recent introduction of lipid emulsions in plastic containers from one manufacturer has resulted in a coarser emulsion containing higher concentrations of large-diameter fat globules compared with their similar formulations previously packaged in glass. This, in turn, appears to significantly impair plasma clearance, as reflected in the rate of hypertriglyceridemia compared with that in preterm neonates receiving lipid emulsions packaged in conventional glass containers. Further studies are needed to confirm the current observations; a prospective clinical trial is currently ongoing.²⁶ Nonetheless, caution is advised when administering lipid emulsions packaged in plastic bags currently available in the United States, along with careful monitoring of the neonate's ability to clear TGs from the circulation.

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Table I. “Black box warning” for lipid injectable emulsions^{11,12}

Deaths in premature infants after infusion of intravenous fat emulsion have been reported in the medical literature.^{a,b} Autopsy findings included intravascular fat accumulation in the lungs. Treatment of premature and low birth weight infants with intravenous fat emulsion must be based upon careful benefit-risk assessment. Strict adherence to the recommended total daily dose is mandatory; hourly infusion rate should be as slow as possible in each case and should not in any case exceed 1 g fat/kg in four hours. Premature and small for gestational age infants have poor clearance of intravenous fat emulsion and increased free fatty acid plasma levels following fat emulsion infusion; therefore, serious consideration must be given to administration of less than the maximum recommended doses in these patients in order to decrease the likelihood of intravenous fat overload. The infant’s ability to eliminate the infused fat from the circulation must be carefully monitored (such as serum triglycerides and/or plasma free fatty acid levels). The lipemia must clear between daily infusions.

^aLevene M, Wigglesworth J, Desai R. Pulmonary fat accumulation after Intralipid infusion in the preterm infant. *Lancet* II:1980;815-18.

^bDahms B, Halpin T. Pulmonary artery lipid deposit in newborn infants receiving intravenous lipid infusion. *J Ped* 1980;97:800-05.

Table II. Institutional infusion protocol for lipid injectable emulsions in the neonatal intensive care unit

Age	Lipid dose (g/kg/day) per birth weight group	
	< 1000 g	> 1000 g
DOL-0 or birth	0	0
DOL-1	0	0
DOL-2	1	1
DOL-3	1.5	2
DOL-4	2	3
DOL-5	2.5	3
DOL-6+	3	3

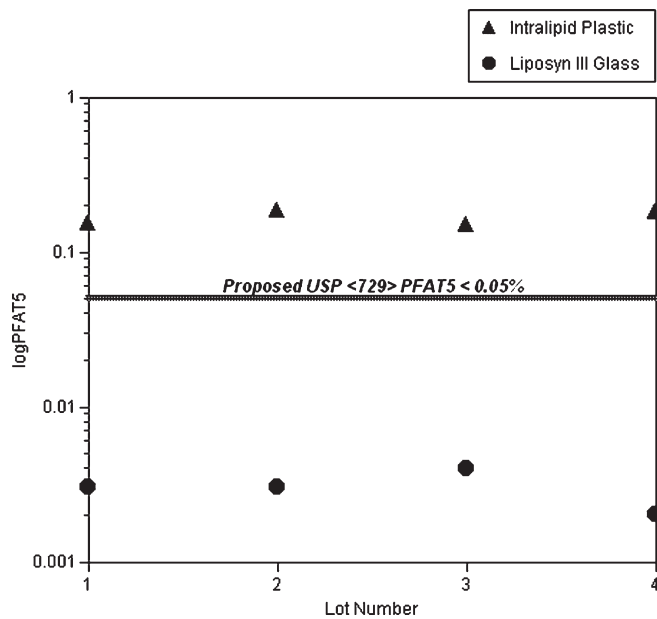


Figure 1. Large-diameter fat globule profiles of US-based manufacturer-produced 20% lipid emulsions packaged in plastic bags versus conventional glass bottles.¹⁴