LIPID METABOLISM OF THE MICROPREMIE

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In the very low-birth weight (VLBW) or extremely low-birth weight (ELBW) infant, who often cannot be fed adequately for days or weeks by the enteral route in the early neonatal period, intravenous (IV) lipid emulsions are important constituents of total parenteral nutrition (TPN). They provide essential fatty acids (FA) and allow increased calorie intake without an excess in glucose intake, which can be associated with an increase in carbon dioxide production. The most representative lipid emulsions currently available contain primarily soybean oil or a mixture of safflower and soybean oil. More recently, a lipid emulsion has been introduced containing a mixture of soybean oil and olive oil. All these lipid emulsions contain mainly long-chain triglycerides (LCT), but lipid emulsions containing medium-chain triglycerides (MCT) are available as a mixture of soybean oil and MCT (i.e., 50% LCT to 50% MCT). Egg yolk phospholipid is the emulsifier usually used in all these emulsions, which are available as either 10% or 20% triglycerides.

The main compounds of representative lipid emulsions are listed in Table 1. It can be seen that the FA composition varies between them, relative to the FA composition of human milk. All LCT emulsions based on soybean or soybean and safflower oil provide a large amount of polyunsaturated FA (e.g., mainly linoleic acid, linolenic acid being less present in the soybean–safflower oil mixture). The olive oil–soybean mixture provides a large amount of oleic acid and far less polyunsaturated FA, which is also the case with the MCT-LCT emulsion.

INTRAVENOUS LIPID EMULSION: METABOLIC FATE OF ITS COMPOUNDS AND CLINICAL CONSEQUENCES

The metabolism of IV lipid emulsion has received considerable consideration in the literature in recent years[4, 13, 14, 15, 66] and these data provide a better understanding on how to estimate their tolerance in the parenterally fed neonate.

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Table 1. COMPARISON OF THE COMPOSITION OF REPRESENTATIVE INTRAVENOUS LIPID EMULSIONS WITH HUMAN MILK (AVERAGE DATA)

	LCT Emulsion Soybean Oil Emulsion[1]	LCT Emulsion Soybean Oil–Safflower Oil Emulsion[2]	50% MCT/50% LCT Emulsion[3]	Olive Oil and Soybean Oil[4]	Human Milk[5]
TG (g/L)	200	200	100 + 100	200	40
Fatty acids (% of total)					
C_8	—	—	30	—	0.2
C_{10}	—	—	20	—	2
$C_{16:0}$	—	9	4.5	10.7	22
$C_{16:1}$	—	—	—	0.8	0.5
$C_{18:0}$	3	3	1.5	3	7
$C_{18:1}$	25	18	13	65	30
$C_{18:2}$	54	66	27	17	15
$C_{18:3}$	8	4	4	0.3	0.5
$C_{20:0}$	—	—	—	0.4	0.5
$C_{22:0}$	—	—	—	2	1
PL g/L	12	12	12	12	0.3
Glycerol g/L	22	25	25	22.5	—

[1]Intralipid 20% (Kabi-Vitrum, Guyancourt, Sweden).
[2]Liposyn II 20% (Abott Laboratories, Chicago, Illinois, USA).
[3]Medialipid 20% (B. Braun SA, Boulogne, France).
[4]ClinOleic 20% (Baxter SA, Maurepas, France).

The lipid emulsions are constituted mostly of triacylglycerols (as particles rich in tracyglycerol [PRTAG]) and of phospholipids (PL), which are used as emulsifiers. One part of the PL surrounds the lipid core of the PRTAG and the other part is organized into a particle rich in PL, which represents the PL excess.

The particles rich in triacylglycerol are cleared in the same way as the chylomicroms and are often called *artificial chylomicrons*. They undergo a hydrolysis of their triacylglycerols by lipoprotein lipases in the presence of apoprotein CII, with a release of free FA (FFA) and formation of remnants rapidly removed by the liver. Triglyceride clearance from the blood stream is the first step of lipid emulsion metabolic use and is dependent on lipoprotein lipase activity. The FFA can be captured immediately by the adjacent tissues or circulate bound to albumin, causing an increment in plasma FFA. FFA can be used as metabolic fuel in liver, heart, or skeletal muscles. They may also enter into adipose tissue where they can be re-esterified to triglycerides and stored. The rate of this hydrolysis varies according to the type of triglycerides (i.e., length of the FA, degree of saturation, position of the FA on the glycerol); for instance, MCT are more quickly hydrolyzed than TCL. The amount and type of PL may also interfere with the rate of hydrolysis and impede it.

The particles rich in PL have little energy, but they have potential deleterious effects when infused in excess. They inhibit lipolysis of PRTAG (artificial chylomicrons), stimulate tissue cholesterogenesis, and accumulate in the blood as lipoprotein, the metabolism of which ends up mainly in the reticuloendothelial system. It is apparent that providing these exogenous PL at a low rate decreases these potential deleterious effects.

Thus, when speaking of IV lipid emulsion metabolism and tolerance in the newborn infant the following points are important to consider: plasma triglyceride clearance and amount of PL infused, both being correlated with the infusion rate.

Plasma lipid clearance is less efficient in VLBW infants especially in small-for-gestational age[2, 27] than in older infants. It is also variable from one infant to another and, for the same dosage regimen, is improved when lipid emulsions are given as continuous infusion over 24 hours.[37] Clearance capacity is usually evaluated by evaluating the serum triglyceride concentration. The upper limit of serum triglyceride concentration that can be safely tolerated is not well known. In infants fed pooled human milk or formula, triglyceride concentrations of 100 to 200 mg dL are present.[17, 74] Because significant increases in plasma cholesterol, PL, and very low density lipoprotein (VLDL) have been described in infants on IV lipids when plasma triglyceride concentrations exceed 100 to 150 mg dL,[11, 20, 28] it seems reasonable to take these concentrations as an upper limit in the VLBW infant, especially in unstable clinical situations.

The lipid clearance capacity may also be modified with stress of any type (e.g., infection, inflammation, surgery) and in these circumstances use of IV lipids has to be more controlled, restricted, or even suppressed. Based on data in acutely ill patients[34] with potentially diminished bacterial defences,[19] and the immunoregulatory roles of lipids,[13] we commonly decrease IV lipid infusion any time there is an acute stress situation (e.g., acute sepsis, hemodynamic shock, and so forth). Indeed, hyperglycemia is often present in these circumstances. Agglutination of IV lipids, described in some sera of acutely ill patients, is not well understood but acute-phase proteins and calcium ions are said to be implicated.[34, 56]

Numerous studies have investigated the use of 10% versus 20% lipid emulsion.[12, 13, 24, 25, 30, 45] The difference between the two types of emulsion is that a 20% emulsion contains half the amount of PL emulsifier relative to the same amount of triglycerides. As seen previously, the higher amount of PL (i.e., particles rich in PL) perfused with a 10% lipid emulsion impedes the removal of triglycerides from plasma, leading to an increase in plasma triglyceride, cholesterol, and PL concentrations.[4, 30] When the clearance mechanism of the exogenous PLs is exceeded, there is formation of lipoprotein X.[4, 27] When a 10% lipid emulsion with reduced PL emulsifier content, which offers a PL triglyceride ratio similar to the ratio used for 20% lipid emulsion, is provided to VLBW infants, excessive increases in triglycerides or cholesterol concentration are not observed,[25] confirming the negative role of the infused PL. Similarly, it has been shown that a 30% lipid emulsion is preferable to 10% lipid emulsion in critically ill patients.[36] It is now clear that 20% lipid emulsions need to be infused instead of 10% lipid emulsions.

Understood to be important in older infants and adults, the infusion rate is certainly a crucial point in VLBW or ELBW infants because they have less mature metabolic pathways. It is well known and accepted that intravenous glucose or intravenous aminoacids have to be given at a constant infusion rate and at dosages that do not induce metabolic disturbances or exceed the metabolic capacities of these infants. The same rationale has to be applied when IV lipids are infused. Therefore, it is of importance not to consider the daily intake of IV lipids that may be given to an infant, but the infusion rate, that is the amount given by unit of time ($g \cdot kg^{-1}$ min^{-1} or h^{-1}), in order not to exceed the plasma clearance capacity. This point is very well illustrated in the study by Kao et al.[37] Instead of saying that 1 or 2 $g \cdot kg^{-1}d^{-1}$ of IV lipids may be given to one infant, it is more appropriate to say that a rate of 0.04 or 0.08 $g \cdot kg^{-1}h^{-1}$ can be infused and to remember that increasing this rate of infusion may be harmful as it is harmful to increase suddenly the glucose infusion rate.

Oxidation of infused lipid appears to depend on the total energy expenditure of the infant and on the concomittant amount of carbohydrate intake. Either

in the adult or the pediatric patient, it is generally understood that when the amount of energy given as carbohydrate exceeds the level of energy expenditure, the amount of lipid simultaneously perfused, which is oxidized, is diminished.[10, 18, 53, 59] Data show[10, 53] that above a glucose intake of 20 $g \cdot kg^{-1}d^{-1}$, most infused lipid may be stored and not oxidized. Thus, use (i.e., oxidation) of infused lipid emulsion as an energy source depends on the level of total energy intake, the total glucose intake (i.e., glucose to fat ratio), and on the level of energy expenditure.

Carnitine function mainly facilitates transport of long-chain FA through the mitochondrial membrane, allowing their oxidation for energy, particularly in heart and skeletal muscles, and ketogenesis in the liver. Recent data suggest that carnitine is also needed for medium-chain FA oxidation in skeletal and cardiac muscle.[7]

Studies have shown that plasma and tissue carnitine concentrations decrease in the neonate receiving carnitine-free TPN.[6, 32, 50, 61] In these circumstances, carnitine supplementation of the TPN with or without lipid at a dose of approximately 50 $\mu mol \cdot kg^{-1}d^{-1}$ restored plasma carnitine concentrations[6, 32, 44, 50] and biochemical data suggest an increased fat oxidation. Helms et al[32] reported a significantly higher concentration of plasma carnitine, higher ketone bodies (BOH butyrate and acetoacetate/FFA ratio) in neonates receiving carnitine during TPN with 1.8 $g \cdot kg^{-1}d^{-1}$ of IV lipid. Similarly, Bonner et al[6] studied VLBW infants (750 to 1500 g birth weight) on TPN with lipid, randomly assigned to control or carnitine-supplemented (50 $\mu mol \cdot kg^{-1}d^{-1}$) group. Neonates receiving carnitine had higher plasma total carnitine concentrations than the control group but erythrocyte carnitine concentration decreased in the control group and in the smallest infants receiving carnitine (i.e., in infants less than 1000 g) but not in the largest infants (i.e., infants 1001 to 1500 g). This suggested a higher requirement of carnitine in the smallest infants being evaluated. Levels of BOH butyrate decreased significantly in the control group but not in carnitine-supplemented groups.

Hypocarnitinemia or biochemical perturbations may be relatively easy to detect, but an abnormal clinical symptom correctable by carnitine administration, such as muscle, myocardial, or hepatic dysfonction, is not easy to detect in infants receiving carnitine-free TPN. Animal studies, however, suggest that carnitine supplementation may be important. In a piglet model, Penn et al[48] demonstrated that carnitine-deprived piglets on TPN were in negative carnitine balance and had lower blood, urine, and tissues (i.e., muscle, heart, liver) carnitine concentrations than carnitine-supplemented animals. It was also found that lipid deposition in liver was twofold higher in carnitine-deprived than in carnitine-supplemented animals and that in vitro hepatic FA oxidation, as studied by ^{14}C incorporation into acid-soluble products from ^{14}C U-palmitate, was lower in carnitine-deprived than in carnitine-supplemented animals.

When on enteral nutrition, neonates receive carnitine. The carnitine content of human milk varies from 9 to 10 $\mu mol/dL^{-1}$ during the first 2 weeks to 6 $\mu mol/dL^{-1}$ in mature milk and a similar amount is now provided by proprietary formulas.[49] The European Society of Paediatric Gastroenterology and Nutrition Committee recommended that infant formula contains at least 7.5 $\mu mol/100\ kcal^{-1}$.[16] Thus, an infant receiving 160 to 180 $mL \cdot kg^{-1}d^{-1}$ of milk gets around 10 $\mu mol \cdot kd^{-1}d^{-1}$ of carnitine. In contrast, none of the parenteral solutions contain carnitine. Furthermore, it has to be pointed out that most metabolically stressed neonates are receiving no exogenous carnitine.

If there is still discussion about adding carnitine supplementation to VLBW infants on TPN because there is no convincing evidence of a physiologic benefit,

it may be prudent to keep tissue carnitine stores or the plasma carnitine concentration at the levels observed in enterally human-milk–fed VLBW infants. The amount to be given is still debatable. In most of the studies a dosage of 50 $\mu mol \cdot kg^{-1}d^{-1}$ has been provided,[6, 32, 44, 61] but higher intake (100 $\mu mol \cdot kg^{-1}d^{-1}$ has been suggested[32] in the smallest infants. Because increased metabolic rate and decreased fat and protein deposition have been reported in preterm infants on TPN receiving around 300 $\mu mol \cdot kg^{-1}d^{-1}$.[68] It is not recommended that such a dose be administered even if an increase in fat oxidation is clearly demonstrated. Finally, an intake around 50 $\mu mol \cdot kg^{-1}d^{-1}$ is probably advisable.

IS EARLY INITIATION OF INTRAVENOUS LIPID EMULSION DANGEROUS TO THE VLBW INFANT?

Early initiation of IV lipid may be of interest because it provides essential FA, increases caloric intake in a small fluid volume with low osmolarity, and reduces carbon dioxide production. Because of concerns of impaired lipid tolerance, which might result in adverse effects, its early use is still controversal. We try to address the various problems raised by early initiation of IV lipid emulsion with a review of data from the literature.

General Mortality and Morbidity. A few studies have been specifically designed to evaluate if early initiation of lipid emulsion is appropriate in the VLBW or the ELBW infant.

In Sosenko's et al study,[65] the objective was to investigate whether IV lipid infusion within 12 hours of birth to ventilator-dependant premature infants decreases the incidence and the severity, or both, of chronic lung disease (CLD). One hundred thirty-three infants were randomly assigned to receive 20% Intralipid (IL) or not during the first week of age. The infants were separated in two weight groups: one group weighed from 600 to 800 g and 42 infants received IL versus 37 who did not. Another group weighed from 801 to 1000 g and 28 received IL versus 26 who did not. The IL groups were given lipids at less than 12 hours of age starting at 0.5 $g \cdot kg^{-1}d^{-1}$ and then increased to 1.5 $g \cdot kg^{-1}d^{-1}$ and were maintained through day 7. The lipids were being perfused over 24 hours. Control groups received no IV lipid before day 7. Both groups received the same amount of a multivitamin solution. In the total population, there were no significant differences in mortality rate (32.9% versus 25.4%, IL versus control) but the mortality was higher in the 600- to 800-g group in infants receiving IL (20 of 41 = 47.5%) versus the control (9 of 37 = 24.3%). In the weight group, 600 to 800 g, patient clinical data were similar between the IL group and control, but the number of infants whose mothers had received antenatal corticosteroids was significantly higher in the control (30%) than in the IL group (7%). This may have introduced a considerable bias if one considers the influence of antenatal corticosteroids administration on the survival rate of ELBW infants. It is also important to emphasize that in the 801- to 1000-g group, the opposite was observed (i.e., there were more than twice the number of deaths in the control [7 of 26 = 26.9%] than in the IL group [3 of 28 = 10.7%]). In that group maternal corticosteroid administration was 19% and 11% (control versus IL). In that study, no significant differences were observed relative to the incidence of CLD. There was a significant increase in pulmonary hemorrhage and a greater number of infants requiring supplemental oxygen at day 7 in the lipid groups. It was remarkable, however, that on day 28 the number of infants requiring supplemental oxygen was higher in the control groups for both weight groups and the number of infants requiring O_2 at 60 days was more than twice as high

in the control group the infant in the IL group. The author's conclusion was that IV lipids do not protect from CLD. Because of the higher mortality rate in the IL group, the study was terminated before completion of enrollment of the predetermined number of patients.

Hammerman and Aramburo's study[29] was undertaken to evaluate the hypothesis that dietary alteration can affect prostanoid synthesis with clinical and hemodynamic consequences. The investigators compared two groups of VLBW infants less than 1750 g at birth on TPN randomly assigned to receive TPN with or without 10% lipid emulsion for 5 days. Infants with severe hyperbilirubinemia or receiving indomethacin were not included. One group received a 10% lipid emulsion after the 3rd day and the other received the lipid emulsion only after the 8th day of life. Lipids were started at 0.5 $g \cdot kg^{-1}d^{-1}$ and progressively increased to 2.5 $g \cdot kg^{-1}d^{-1}$. All neonates received 1 mL/d^{-1} of a multivitamin preparation. CLD appeared to increase in duration and tended to be severer after lipid intake as the number of days of ventilation (37 ± 35 versus 21 ± 18 days) and of oxygen therapy (51 ± 39 versus 28 ± 23 days) was increased significantly in the lipid group. In that study the vasoconstrictor metabolite thromboxane B_2 was more elevated in the IL group in comparison with the group receiving no lipid.

The aim of Gilberston's[23] study was to determine whether ventilator-dependent VLBW infants tolerate IV lipid from the first day of life and its effect on glucose homoestasis. Twenty-nine VLBW infants less than 1500 g were studied. They received isocaloric, isonitrogenous parenteral feedings from day 1 with either a 20% IV lipid emulsion given at 1 $g \cdot kg^{-1}d^{-1}$ from day 1, to 3 $g \cdot kg^{-1}d^{-1}$ from day 4 (IL group, n = 16), or IV lipid given only after day 8 (control group, n = 13). Lipids were administered over 20 hours. Only infants with major congenital abnormalities and infants of diabetic mothers were excluded. They did not demonstrate any difference between the two groups for CLD, jaundice, septicemia, periventricular hemorrhage, necrotizing enterocolitis (NEC), patent ductus arteriosus (PDA), hypoglycemia or hyperglycemia, or any other selected parameter. The only statistical difference between the two groups was a higher peak inspiratory pressure in the control group (26.3 ± 2.3 versus 20.3 ± 1 cm H_2O; control versus IL group). They concluded that, when lipid infusion is given at a rate not exceeding 0.15 $g \cdot kg^{-1}h^{-1}$ (3 $g \cdot kg^{-1}d^{-1}$ over 24 hours), with stepwise dose increases from the first day of life, sick VLBW infants can tolerate it without higher incidence of adverse effects.

More recently, Fox et al[21] did a meta-analysis of six randomized clinical trials designed to assess the effect of early (day 1 to 5) versus late (day 5 to 14) introduction of IV lipid. They did not show any significant trend or effect on the incidence of death or CLD at 28 days or at 36 weeks.

Jaundice. The use of lipid emulsions has been discussed in jaundiced neonates because the FA released during hydrolysis can displace bilirubin from albumin-binding sites, producing unbound bilirubin and increasing the risk of kernicterus.

In vitro studies have shown that below a FFA–serum albumin (Alb) molar ratio of 4, no free bilirubin is released.[70] In vivo, no generation of unbound bilirubin is demonstrated if FFA:Alb is below 6.[2] There are even some data[69] showing that IL has a higher affinity for bilirubin than for cell membranes and may enhance the carrying capacity of serum for bilirubin, resulting in a protective effect on tissue.

In the study by Sosenko et al[65] where VLBW infants were given IV lipid in the first day of life, jaundice was not an exclusion criteria. In the study by Hammerman and Aramburo,[29] severe hyperbilirubinemia was an exclusion crite-

ria. In these patients, however, there was no detectable difference in bilirubin concentration between the lipid group and the control group either at day 1, day 3, or day 5 (day 3 :7.3 ± 3.9 versus 7.7 ± 2.8 mg·dL^{-1}, day 5 :5.6 ± 2.6 versus 6 ± 2.9 mg·dL^{-1}; IL group versus control). In Gilbertson's et al study,[23] where IV lipid was given at 1 g·kg^{-1}d^{-1} on day 1 and increased stepwise to 3 g·kg^{-1}d^{-1} on day 4, it was noted that the FFA:Alb remained below 3 in all cases. The incidence of significant jaundice, defined as serum bilirubin levels above 200 mmol·L^{-1} (11.7 mg·dL^{-1}) and of phototherapy requirements (2.5 ± 0.4 days versus 2.2 ± 0.5; IL group versus control) were similar in both groups.

Adamkin et al[1] studied specifically the effect of 10% lipid emulsion administration on triglycerides, FFA, Alb, and unconjugated bilirubin in 26 VLBW weighing less than or equal to 1500 g at birth. Six were < 750 g. Lipid emulsion was started at the 4th postnatal day at 0.5 g·kg^{-1}d^{-1}. For infants below 1200 g, lipid intake was advanced by 0.5 g·kg^{-1}d^{-1} beginning on postnatal day 7. For those above 1200 g, lipid intake was advanced to 1 g·kg^{-1}d^{-1} on postnatal day 5 and increased 0.5 g·kg^{-1}d^{-1} beginning on postnatal day 7. The maximum lipid intake of 3.5 g·kg^{-1}d^{-1} was achieved by postnatal day 10. The lipid infusion time was 18 h/day. Data were provided for 8 days of lipid-inclusive TPN. Five VLBW neonates experienced a single serum triglyceride value above 200 mg·dL^{-1}, defined as hypertriglyceridemia. All infants had FFA:Alb ratio below 3. Mean peak serum unconjugated bilirubin of 5.8 mg·dL^{-1} observed on postnatal day 3 was stable or fell during the next 10 days of lipid infusion. Unbound bilirubin was not measured in that study.

Brans et al[9] studied 38 neonates below 1500 g on TPN, divided into three groups: group 1 received fat emulsion at a constant rate over 24 hours, starting to 1 g·kg^{-1}d^{-1} increasing by 1 g·kg^{-1}d^{-1} to a maximum of 4 g·kg^{-1}; group 2 received the same intake of fat emulsion but over 16 hours; and group 3 received the fat emulsion over 24 hours but starting at a dosage of 4 g·kg^{-1}d^{-1}. The study was stopped if an infant was unable to tolerate fat emulsion (i.e., plasma frankly creamy). Blood samples were obtained every 24 hours (i.e., 8 hours after the end of fat infusion in group 2). One infant in group 2 and one in group 3 had severe hyperlipemia. In all groups FFA increased significantly. Serum total bilirubin concentration were not statistically different from preinfusion concentrations and similar between groups for a given day. Serum unbound bilirubin ranged from 1 to 45 mmol·L^{-1} and the investigators found no correlation with the FFA concentration. Similarly, Rubin et al[58] observed no correlation between FFA and free bilirubin in two groups of premature neonates receiving either an LCT emulsion or a mixture of LCT and MCT triglycerides. For these investigators, it was concluded that lipid infusion should not be withheld from the jaundiced infant on TPN.

In conclusion, these studies show that IV lipid emulsion can be given to jaundiced VLBW infants if the serum FFA concentration stayed within casual range. Once again, the infusion rate of the IL emulsion is the key issue.

Pulmonary Function and Pulmonary Vascular Resistance. Numerous studies have addressed the concern of a potentially deleterious effect of fat emulsion on pulmonary function in VLBW infants. This deleterious effect may be due to alteration of vascular tone leading to a state of pulmonary hypertension, or to infiltration of pulmonary tissue by lipids.

The study by Brans et al,[8] where VLBW infants less than 1500 g at birth were given IV lipid according to the protocol described previously,[9] showed that VLBW infants receiving 4 g·kg^{-1}d^{-1} of IL emulsion over 16 hours (i.e., an infusion rate equivalent to 6 g·kg^{-1}24h^{-1}) had an increased pulmonary alveolar-arteriolar gradient of oxygen when compared with infants receiving the same

amount over 24 hours. Their data confirm again than the infusion rate is much more important to control than the total daily amount infused.

Shulman et al[62] compared retrospectively the necropsy data of neonates, some of whom were not VLBW, who received lipid infusion or did not. Lipids were infused continuously over 24 hours and the rate of infusion was decreased when triglyceride concentrations were above 150 $mg \cdot dL^{-1}$. Fourteen of 26 infants in the lipid group and 2 of 13 in the non–lipid group were found to have pulmonary vascular lipid deposition. The fact that pulmonary vascular lipid deposits were present even in infants who had never received intravenous fat, which was reported also by Hertel et al,[33] indicates that it is dangerous to draw a definite relationship between intravenously given fat and lung lipid deposition. The investigators concluded, however, that their study suggested that vascular deposit was partly determined by the amount and duration of intravenous fat administration.

Prasertsom et al[52] studied 11 preterm infants with respiratory distress syndrome receiving a 20% lipid emulsion and used two-dimensional echocardiography to estimated pulmonary vascular resistance from right ventricular preejection period to ejection time ratio (RVPEP : ET). IV lipid was started on the second postnatal day at a dose of 0.0625 $g \cdot kg^{-1}h^{-1}$ (1.5 $g \cdot kg^{-1}24h^{-1}$) for 24 hours and increased to 0.125 $g \cdot kg^{-1}h^{-1}$ (3 $g \cdot kg^{-1}24h^{-1}$) on the third day. IV lipid was discontinued for 24 hours on the 4th day, and then restarted for 24 hours on the sixth day at 0.0625 $g \cdot kg^{-1}h^{-1}$. They observed an increase of 20% of the RVPEP:ET ratio after 24 hours of IV lipid at 1.5 $g \cdot kg^{-1}24h^{-1}$, and of 45% after 24 hours at 3 $g \cdot kg^{-1}24h^{-1}$. The RVPEP : ET ratio returned to baseline 24 hours after the IV lipid had been discontinued. The increases in RVPEP:ET were not observed immediately after starting or restarting IV lipid but after several hours of infusion and the investigators discussed the role of changes in eicosanoid metabolism, suggesting that the dose-dependant increase in pulmonary arterial pressure was thromboxane mediated. None of their infants were said to be hyperlipaemic, although serum triglyceride concentration were not measured. Similar data have been observed by Lloyd and Boucek,[42] in six premature infants (birth weight between 1500 and 2500 g) receiving 0.1 to 0.45 $g \cdot kg^{-1}h^{-1}$ (2.4 to 10.8 $g \cdot kg^{-1}d^{-1}$) over 2 hours, but in that study, the increase in RVPEP:ET was observed within 2 hours of infusion, this faster response being assumed to be due to the high fat infusion rate.

IL Emulsion and Peroxydation. As shown in Table 1, IL emulsions contain a large amount of polyunsaturated FA. Unsaturated FA are known to be highly susceptible to peroxydation, and the products (i.e., hydroperoxides) can interfere with arachidonic acid metabolism or react to form organic free radicals, which can initiate peroxidative injury in tissues. It may be also that stimulation of cyclooxygenases results in increased production of prostaglandine H_2, then to prostacyclin (PGI_2) and thromboxane A_2, which are important vasoactive products that have been incriminated as possible factors of increase in pulmonary arterial pressure.

Several studies have shown that lipid peroxydation occurs in IV lipid emulsion,[31, 51] and this may have a major clinical consequence in the preterm infant.[5, 26, 35, 43, 54, 60, 63] The concentration of lipid hydroperoxides is variable between bottles and is said to increase under light exposure, especially phototherapy light.[47, 51, 67] Protecting the emulsions from light with aluminum foil or by adding antioxidant products, such as ascorbic acid, directly to the bottles eliminates the phototherapy effect.[47] It has to be pointed out that exposure to phototherapy during enteral tube feeding increased similarly peroxidation in infant formula.[72] Other factors or nutrients, however, may contribute to in vitro genera-

tion of peroxydes. Lavoie and Chessex[40] showed that free-iron admixture to parenteral nutrition induces the formation of free radicals. Indeed, these investigators[39] demonstrate that multivitamin preparations added to parenteral nutrition were a major contributor to generation of peroxides, with a 10-fold increase in a fat-free TPN solution but only a fourfold increase in a lipid-containing TPN solution. They showed a dose-response relationship between the concentration of multivitamin preparation and peroxide concentrations, and the effect of light was the strongest in the presence of multivitamins. For these investigators, lipid emulsion had a significant but minor additive effect compared with the multivitamin preparation. According to these data, it may be desirable to protect IV emulsion from light, particularly from phototherapy light, until more data are available on the consequences of peroxide production in the TPN preparation.

REMARKS ON LIPID EMULSIONS COMPOSITION AND THEIR CONSEQUENCES

Composition of representative lipid emulsions is listed in Table 1. Only 20% lipid emulsion are listed because it is clear that only emulsions that contain less PL are those that should be used. LCT emulsion based on soybean oil or on a mixture of soybean and safflower oil are rich in polyunsaturated FA, mainly in linoleic acid (i.e., about 60% of the total FA), which may be proned to peroxydation. At the usual dosages given during TPN, this intake exceeds polyunsaturated FA requirements and even may impairs essential FA metabolism with a reduced derivatives long-chain polyunsaturated FA synthesis.

Fifty percent MCT–50% LCT emulsions contained less polyunsaturated FA than LCT emulsions and this may be an advantage. MCT are also known to be more rapidly cleared, hydrolyzed, and oxidized than LCT. Infusion at usual dosage of MCT-LCT emulsion induces smaller increase in serum FA concentration and lower cholesterol plasma concentration than an LCT emulsion.[41] It also has been shown that FA composition of fat emulsion affects plasma FA composition and the lower content in linoleic acid and the better adapted linoleic:alpha linolenic ratio of these emulsions may better promote formation of their important derivatives. Studies have also shown that MCT-LCT emulsions lead to fewer liver fat reaction,[57, 75] less negative effects on monocyte or neutrophil function,[22, 73] and less effects on pulmonary hemodynamics and gas exchanges.[55, 64] No definite advantages, however, have been clearly demonstrated from a nutritional point of view relative to the possible improved nitrogen balance.[71] MCT may increase energy expenditure when infused at a high rate, which should never be the case when infusing lipid emulsion.

The other LCT emulsion listed in Table 1 contains a mixture of olive oil and soybean oil. It offers the theoretic advantage of a lower amount of linoleic acid, most of it being replaced by oleic acid. In preliminary data, this emulsion has been shown to be less sensible to peroxydation,[3] which may also be due to its high content in vitamin E and to enhance significantly more linoleic acid derivative synthesis (i.e., $C_{18:3}$ and $C_{20:3}$) than a soybean emulsion.[3, 46] Similarly, in a group of 33 preterm infants receiving since birth parenteral nutrition with either olive oil emulsion or a standard soybean oil emulsion, Koletzko et al[38] found no difference in plasma PL acids for arachidonic acid and total n-6 and n-3 long-chain FA, but the linoleic acid metabolites $C_{18:3}$ n-6 and $C_{20:3}$ n-6 showed a significant increase with olive than with soybean oil emulsion. Further studies are needed to confirm these data that LCT lipid emulsion appears more balanced in its FA composition.

CONCLUSION

From this review of published data and from our experience we summarize our own utilization of IL emulsion in VLBW infants during the first days or weeks of life, when enteral feeding is poorly tolerated as following:

- Start IV lipid on the second or third day of life when the most acute phase of respiratory distress or other life-threatening event is controlled.
- Start with 0.5 $g \cdot kg^{-1}d^{-1}$ of a 20% IV lipid solution and increase stepwise up to 2 $g \cdot kg^{-1}d^{-1}$ (with an infusion rate of not more than 0.08 $g \cdot kg^{-1}h^{-1}$). Any further increase in the infusion rate, which is sometimes suppressed, has to be monitored in order to stay within triglycerides concentration observed during enteral nutrition (i.e., 100 to 150 $mg \cdot dL^{-1}$).
- Because a generally accepted concentration of nonprotein energy intake for VLBW infant on TPN is around 90 to 100 $kcal \cdot kg^{-1}d^{-1}$, a mixture of 18 to 20 $g \cdot kg^{-1}d^{-1}$ of glucose and 2 $g \cdot kg^{-1}d^{-1}$ of IV lipid should allow acceptable growth if there is adequate intake of others nutrients, micronutrients, and minerals. In circumstances of no increased need for calorie intake, increasing glucose intake above 20 $g \cdot kg^{-1}d^{-1}$ decreases fat use as a source of energy.
- If any stress happens, such as sepsis, either stop or decrease lipid infusion rate in order to avoid hyperlipemia or hyperglycemia because glucose intolerance may also be observed during stress.
- Because there are data of possible side effects or possible advantages we also recommend
  - carnitine use,
  - protection from light, especially if lipids are mixed with glucose, amino acids, and multivitamin preparations
- use of IV lipid emulsion with decreased concentration of polyunsaturated FA and better ratio of linoleic to alpha-linolenic acid

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