Tolerance of mixed lipid emulsion in neonates: effect of concentration

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Abstract

Aims—To compare the effect of concentration of a mixed lipid emulsion (50:50 medium chain triglyceride/long chain triglyceride) (MCT/LCT) on lipid tolerance in neonates.

Methods—A prospective randomised controlled trial of 75 neonates requiring prolonged parenteral nutrition was conducted in the neonatal intensive care units of the Royal Maternity Hospital, Belfast, and the Waveney Hospital, Ballymena. Thirty eight infants received 10% and 37 20% lipid emulsion. Infants were randomly assigned to groups at the start of parenteral nutrition and studied if they required seven or more days of this. Lipid tolerance was assessed by twice weekly measurements of plasma triglyceride and cholesterol concentrations and weekly measurement of non-esterified fatty acids and β hydroxy butyrate. Anthropometry was carried out weekly.

Results—The mean cholesterol in the 10% group was significantly higher within the first seven days of the study compared with the 20% group (3.5 vs 2.87 mmol/l), and continued to rise over the study period in contrast to the 20% group. A similar pattern was observed with the triglyceride concentrations. There was no significant difference in non-esterified fatty acids, β hydroxy butyrate, or growth between the two groups.

Conclusion—Sick neonates show better biochemical tolerance to 20% MCT/LCT emulsion than to 10% emulsion.

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The importance of providing adequate nutrition for sick preterm infants is now well recognised. In the short term undernutrition may predispose to infection,¹ impair respiratory muscle function,² and have a role in the aetiology of bronchopulmonary dysplasia,³ as well as limiting growth. Long term effects on brain development and function have been demonstrated in both animal and, more recently, human studies.^{4 5}

Premature infants are often slow to establish on enteral feeds and hence require parenteral nutrition. Energy intake is limited by inadequate tolerance of carbohydrate and protein. Lipid emulsions are a useful substrate as they are calorie dense, of low osmotic value

(enabling infusion through a peripheral vein), prevent essential fatty acid deficiency⁶ and permit the infusion of fat soluble vitamins. Unfortunately, premature infants have a limited, and often unpredictable, ability to utilise parenteral fat, due to low concentrations of lipoprotein lipase,⁷ required for the hydrolysis of triglycerides, and of carnitine,⁸ which is required for long chain fatty acids to enter the mitochondria where β oxidation occurs. This may lead to lipid accumulation with impairment of neutrophil function,⁹ interference with macrophage activity,¹⁰ displacement of bilirubin from albumin,¹¹ decreased oxygenation in infants with pre-existing lung disease,¹² and possibly predisposition to bronchopulmonary dysplasia (BPD).^{13 14} Medium chain triglycerides (MCT) may be more easily tolerated than long chain triglycerides (LCT) as they are metabolised independently of carnitine, have less affinity for albumin, and are more rapidly oxidised.¹⁵ In a randomised controlled trial Rubin *et al* demonstrated a significant lower fraction of unbound bilirubin in premature neonates given 50:50 MCT/LCT emulsion compared with those given 100% LCT emulsion.¹⁶ Lima *et al*, in another randomised controlled trial, reported lower plasma cholesterol concentrations in neonates given MCT/LCT compared with those receiving LCT.¹⁷

Concentration of pure LCT emulsion is important in lipid clearance, with 20% solution being better tolerated than 10%.¹⁸ The aim of this study was to compare the effect of concentration on an emulsion containing equal amounts of MCT and LCT.

Methods

This study was carried out in the regional neonatal unit at the Royal Maternity Hospital, Belfast and at the Waveney Hospital, Ballymena, over an 18 month period. Infants were randomly allocated to receive either 10% or 20% MCT/LCT emulsion at the beginning of parenteral nutrition. Randomisation was by computer generated numbers in sealed envelopes and was stratified for birthweight. Only those infants who required seven or more days of parenteral nutrition were studied.

Parenteral nutrition was started during the first 48 hours of life when possible and followed an established protocol.¹⁹ Both groups received an isovolumetric, isocaloric regimen, differing only in the concentration of lipid used.

Lipid infusion (Lipofundin MCT/LCT, B Braun Ltd, Melsungen, Germany) was started on the third day of life at 0.5 g/kg/day over a 20

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hour period. This was increased daily by 0.5 g/kg increments to a maximum of 3 g/kg/day. In the event of hyperlipidaemia (cholesterol > 4.9 mmol/l or triglyceride > 1.9 mmol/l), severe sepsis, or jaundice requiring phototherapy, the dose was decreased to 1 g/kg/day. Parenteral nutrition was infused through a silastic percutaneous central venous catheter where possible; lipids were infused simultaneously using the same line. As enteral feeds became established, the quantity of lipid infused was reduced proportionately.

Infants left the study when full enteral feeding was established.

Anthropometry was carried out weekly. Weight was measured on electronic scales accurate to 5 g; head circumference was measured with paper tape measure and length by neonatometer.

Blood was taken twice weekly at the end of a four hour lipid free period for cholesterol and triglyceride values. Non-esterified fatty acids and β hydroxy butyrate concentrations were measured weekly during lipid infusion.

Cholesterol and triglyceride concentrations were analysed enzymatically using Kodak Ektachem Clinical Chemistry Slides. Non-esterified fatty acids were estimated in serum by an enzymatic colorimetric method using a kit manufactured by Wako Chemicals GmbH, Neuss, Germany. β hydroxy butyrate was measured using a kinetic enzymatic method with a kit supplied by Randox Laboratories Ltd, Crumlin, Northern Ireland. Initial disease severity for each infant was calculated using the CRIB score.²⁰

Data were analysed using the Statistics for Social Sciences Package. Student's *t* test was used for comparison of means of continuous variables. The χ^2 test was used to compare categorical variables. A *P* value of less than 0.05 was regarded as significant.

Parental informed consent and approval from the Research Ethical Committee of the Queen's University of Belfast were obtained.

Results

One hundred and four infants were randomly allocated to the study but nine died (4 and 5, respectively, in the 10% and 20% groups) and 20 (10 in each group) attained full enteral feeds within seven days. Seventy five infants were therefore studied, of whom 38 were randomly allocated to 10% and 37 to 20% MCT/LCT emulsion. Two deaths occurred—one in each group. Both infants died on the 10th day of life, one of pulmonary haemorrhage and one of gastric perforation. There was no significant difference between the two groups in terms of birthweight, gestational age, or requirement for ventilation in the first 24 hours (table 1). The group allocated to 20% MCT/LCT, however, was significantly sicker, having higher CRIB scores: this reflects a higher mortality risk at 12 hours.

The mean (SD) duration of lipid infusion was 15.3 (9.4) days in the 10% group and 15.6 (9.8) days in the 20% group. Figure 1 represents median parenteral lipid intake over

the study period: there was no significant difference at any stage. There was no difference between the two groups in terms of daily protein, carbohydrate, or total energy intake.

The mean (SE) cholesterol concentration for the four seven day periods is shown in fig 2. The cholesterol concentration was significantly higher (*P* = 0.03) within the first seven days in the 10% group than in the 20% group. The mean difference increased over the study period as the mean cholesterol concentration in the 10% group rose, unlike the 20% group.

A similar pattern was seen for the triglyceride concentration (fig 3). Non-esterified fatty acid concentrations were not increased in either group and there was no significant difference between the groups (data not presented). The concentration of β hydroxy butyrate was always less than 0.35 mmol/l.

Median weight gains during the study were 4.7 g/kg/day and 5.3 g/kg/day (*P* = 0.93) in the 10% and 20% groups, respectively. There was also no difference in length or head circumference gain in the two groups.

The clinical outcome of the infants is shown in table 2. Retinopathy of prematurity (ROP) was significantly more common in the infants who had received 20% Lipofundin—three of these had grade 1, 13 grade 2, and 1 grade 3—compared with 0, 2, and 3 in the 10% group. There was no significant difference in other clinical outcomes.

Discussion

This study showed that premature infants have better biochemical tolerance of 20% MCT/L

Figure 1 Median parenteral lipid intake (g/kg/day)

Figure 2 Mean (SEM) cholesterol concentrations in both groups

Table 1 Patient characteristics (values are given as mean (SD))

	10% MCT/LCT (n=38)	20% MCT/LCT (n=37)	P value
Birthweight (g)	1221 (607)	1164 (606)	0.04
Gestational age (weeks)	28.9 (3.2)	28.2 (3.2)	0.87
Number (%) small for gestational age	16 (42)	9 (24)	0.10
Number (%) requiring intermittent positive pressure ventilation	24 (63)	26 (70)	0.10
CRIB score	4.4 (3.4)	6.8 (3.9)	0.01

Table 2 Clinical outcomes of both groups

	10% MCT/LCT (n=38)	20% MCT/LCT (n=37)	P value
Days of IPPV mean (SD)	10.3 (13.7)	14.8 (16.5)	0.20
Days of phototherapy mean (SD)	3.9 (4.4)	3.1 (2.8)	0.33
Number (%) developing BPD	7 (18)	10 (27)	0.37
Number (%) developing intraventricular haemorrhage	16 (42)	15 (40)	0.59
Number (%) developing ROP	5 (13)	17 (46)	0.001

LCT emulsion than 10% emulsion. The two emulsions differ only in the amount of phospholipid emulsifier infused per gram of triglycerides (the phospholipid:triglyceride weight ratio is 0.12 for 10% and 0.06 for 20% emulsion). This produces fat emulsion particles consisting of a triglyceride core surrounded by a phospholipid coat. Once in the bloodstream apolipoproteins of the A, C, and E classes migrate to join the particle coat. Binding to lipoprotein lipase at the capillary endothelium then takes place, with hydrolysis releasing free fatty acids into the circulation. The amount of phospholipid emulsifier present in fat emulsions is higher than that in naturally occurring chylomicrons. The excess has been shown to exist in phospholipid bilayers resembling liposomes.²¹ In 10% emulsions two thirds of the phospholipids are present as liposomes, compared with one third in the 20% emulsion. This means that 10% emulsions have four times the liposomal content of 20% emulsions. In LCT emulsions these liposomes, along with the redundant outer coat of the triglyceride rich particles after hydrolysis has taken place, accumulate large amounts of endogenous cholesterol. A low density lipoprotein complex known as lipoprotein X is then formed.²² Lipo-

protein X competes for lipoprotein lipase binding sites, thus increasing triglyceride concentrations.²³

The biochemical results from this study show a gradual rise in cholesterol and triglyceride in the group receiving 10% MCT/LCT emulsion. This suggests that lipoprotein X is being formed in MCT/LCT emulsion use in the same way as in pure LCT emulsion. Ketone body production rises during pure MCT infusion in animal studies.²⁴ β hydroxy butyrate concentrations remained low throughout the study period in both groups. The most likely explanation for this is the adequate glucose supply provided, but it is possible that increased production was matched by high utilisation by the developing brain. Non-esterified fatty acids (which have a half life of one to two minutes in the circulation) were not increased, showing that systemic oxidative removal mechanisms were not saturated at infusion rates of 3 g/kg/day. This is important as neurological toxicity has been shown to occur with an increase in plasma medium chain fatty acids.²⁵

The significantly higher rate of retinopathy of prematurity in the group receiving 20% emulsion was unexpected. This disorder is associated with the use of lipid emulsion. Hammerman and Aramburo¹⁴ showed that infants who received Intralipid were more likely to develop it than those having fat free parenteral nutrition. They suggested a role for either prostanoids or lipid peroxidation. But the two groups in our study received the same quantity of both medium and long chain triglycerides, differing only in the quantity of phospholipid infused. The explanation may be that the 20% group were sicker at the time of randomisation, as indicated by the difference in CRIB scores. The CRIB score gives only a mortality risk and therefore cannot be used statistically to correct the risk of retinopathy of prematurity.

In conclusion, this study shows that preterm infants have better biochemical tolerance to 20% MCT/LCT emulsion than 10%, as has been shown for pure LCT emulsion. A possible association between the use of intravenous lipids and retinopathy of prematurity requires further study.

Figure 3 Mean (SEM) triglyceride concentrations in both groups

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