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4. Lipids

METHODS

Literature Search

Timeframe: publications from 1992–2003, in addition relevant publications from 1971 and after 2003 were considered.

Type of publications: original paper, meta-analyses and overviews.

Language: English.

Key Words: parenteral nutrition, lipid/fat emulsions, paediatrics, lipoprotein lipase, free fatty acids.

LIPIDS

Background

Lipid emulsions are used in paediatric parenteral nutrition (PN) as a non-carbohydrate source of energy in a low volume and with low osmolarity. In addition they provide essential fatty acids. The use of lipid emulsions decreases CO_2 production compared with parenteral nutrition containing a high carbohydrate content (1–3). Net-nitrogen balance can be improved by the addition of lipid emulsions to PN solutions (1,4,5).

Recommendation

- Lipid emulsions are an integral part of paediatric parenteral nutrition providing high energy needs without carbohydrate overload and supplementing essential fatty acids. **GOR D**

Composition of Macronutrients

Fat oxidation depends on the total energy intake and expenditure, the total intake of carbohydrates and triglycerides and the carbohydrate/fat ratio administered ((1,2) (LOE 1)). As carbohydrate intake increases fat oxidation diminishes in favour of lipid storage. In infants net lipogenesis occurs at glucose intakes above 18 g/kg per day, whereas it occurs at lower glucose intakes in older children (1,6). Maximum fat oxidation occurs when intravenous lipid emulsions provide 40% of the non-protein PN calories in newborns (3) and 50% in infants (1). Generally a lipid intake of 25 to 40% of non-protein calories is recommended in fully parenterally fed patients.

Recommendations

- Lipid intake should usually provide 25–40% of non-protein calories in fully parenterally fed patients. **GOR D**
- Glucose intakes above 18 g/kg per day, which tend to induce net lipogenesis in infants, should usually be avoided in infants. **GOR B**

Fat Intake

Omission of lipid emulsions from total parenteral nutrition may lead to biochemical evidence of essential fatty acid deficiency within a few days in preterm infants (7–9).

In order to prevent biochemical evidence of EFA (essential fatty acids) deficiency, 0.25 g/kg per day linoleic acid should be given to preterm infants (7,9). In term infants and older children the supply of 0.1 g/kg per day linoleic acid may be sufficient to prevent EFA deficiency. When prescribing lipid emulsions the different LA content of the available lipid emulsions needs to taken into account (see annex).

Minimum requirements of plasma alpha-linolenic acid are difficult to define. Most of the data about alpha-linolenic acid deficiency is derived from animal studies (10). In children there is one case report of alpha-linolenic acid deficiency in a 6 years old girl (11). In Europe, all lipid emulsions used for children contain alpha-linolenic acid.

The upper limit of lipid administration is difficult to determine. In preterm infants a lipid supply of 3 g/kg per day as continuous infusion was tolerated well based on measurement of serum triglycerides, cholesterol and molar ratios of free fatty acids/albumin (12–14). However preterm infants weighing less than 1000 g deserve special attention because their tolerance to intravenous lipids may be limited (15) (LOE 2–3).

In term infants fat oxidation reaches a maximum at 4 g/kg per day, given that the maximum glucose intake does not exceed maximal oxidative glucose disposal of about 18 g/kg per day (1,2). However, especially in premature and VLBW infants, a lipid supply exceeding fat oxidation may be desirable to achieve fat deposition. The metabolic utilisation of intravenous lipids varies with gestational and postnatal age, severity of disease and other factors. Therefore, monitoring of indicators of

lipid utilisation such as plasma triglycerides (or ideally lipid oxidation) may help in defining adequate intakes (LOE 3–4).

Recommendations

- In order to prevent EFA deficiency a minimum linoleic acid intake of 0.25 g/kg per day should be given to preterm infants and 0.1 g/kg per day to term infants and older children. **GOR D**
- Parenteral lipid intake should usually be limited to a maximum of 3–4 g/kg per day (0.13–0.17 g/kg per hour) in infants (**GOR B**) and 2–3 g/kg per day (0.08–0.13 g/kg per hour) in older children. **GOR D**

Application

The triglyceride portion of lipid emulsion particles is hydrolyzed by endothelial lipoprotein lipase (LPL). The liver rapidly removes lipid emulsion particle-remnants. Free fatty acids (FFAs) and glycerol are metabolized in a similar way to enteral lipids (16–18). FFAs can be captured by the adjacent tissues or circulate bound to albumin, for use in other tissues or uptake by the liver. The rate of hydrolysis varies according to the type of the triglyceride substrate (i.e., length of the fatty acid, degree of saturation, position of the fatty acid on the glycerol) (19). The amount and type of phospholipid emulsifier may also interfere with the rate of hydrolysis of the lipid particles of intravenous emulsions.

If the lipid emulsion is infused at a rate that is equal to or less than the rate of hydrolysis, a marked change in plasma triglyceride concentration reflecting accumulation of the infused triglyceride emulsion is unlikely. However, if the rate of infusion exceeds the rate of hydrolysis, plasma triglyceride concentration will rise and may cause adverse effects. Furthermore, if the rate of hydrolysis exceeds the rate at which the released free fatty acids are taken up and oxidized, the plasma concentration of free fatty acids will also increase. There were case reports about a condition called ''fat overload syndrome'', which may appear with rapid infusion of high dosages of lipid emulsions and may present with coagulopathies, hepatomegaly, elevated liver enzymes, hyperbilirubinaemia, respiratory distress and thrombocytopenia (20,21).

In preterm infants tolerance of lipid emulsions is improved by continuous infusion over 24 hours versus an intermittent regimen with lipid-free intervals (12,14,22). Although there are no comparable studies in older children, continuous infusion of lipid emulsions is recommended whenever possible. However, under stable conditions, lipid emulsions may also be well tolerated when given intermittently as part of cyclic home PN (LOE 4). There is no evidence that gradual increments in the infusion rate of lipids improve fat tolerance (22). An incremental increase in lipid infusion of 0.5 to 1 g/kg per day may help to monitor for possible hypertriglyceridaemia.

Clearance of lipid emulsions from the blood depends on the activity of LPL. Post heparin lipoprotein lipase activity can be increased by relatively high doses of heparin (23,24). However, heparin does not improve utilization of intravenous lipids. The increase in LPL activity by heparin leads to an increase in FFAs, which may exceed the infants ability to clear the products of lipolysis and may weaken the binding of LPL to the endothelium (24–26).

Lipid metabolism results in lipid peroxidation and free radical formation (27–29). The enhancement of fat utilisation by reducing the carbohydrate-fat ratio, at stable lipid intakes, and thus reducing energy intake reduces lipid peroxidation and free radical production (30). Soybean oil based lipid emulsions contain only small amounts of alpha-tocopherol (biologically active form of vitamin E), unless they are supplemented (31), whereas olive oil based lipid emulsions are higher in alpha-tocopherol content (32). Patients on PN should be supplemented with a multi-vitamin preparation that includes vitamin E (alpha-tocopherol) which acts as a free radical scavenger and anti-oxidant (33–35).

Recommendations

- Dosage of lipid emulsions should not exceed the capacity for lipid clearance and should be adapted if marked hyperlipidaemia occurs. **GOR B**
- In infants, newborns and premature babies lipid emulsions should usually be administered continuously over about 24 hours. **GOR B**. If cyclic PN is used, for example in home PN, lipid emulsions should be given over the same duration as the other PN components. **GOR D**
- There is no evidence that gradual increments in the infusion rate of lipids improve fat tolerance. If lipid infusion is increased in increments of 0.5 to 1 g/kg per day, it may be possible to monitor for hypertriglyceridaemia. **GOR D**
- Heparin does not improve utilisation of intravenous lipids and should not be given with lipid infusion on a routine basis, unless indicated for other reasons. **GOR B**

Monitoring

Plasma clearance of infused triglycerides can be assessed by measurement of plasma triglyceride concentrations. However, it is unclear at what serum level of triglycerides adverse effects may occur (36). In infants fed human milk or formula, triglyceride concentrations

of 150 to 200 mg/dl are frequently encountered (14,37). However, it seems reasonable to accept slightly higher triglyceride levels of 250 mg/dl during lipid infusion as the upper limit in newborns, premature and term infants (LOE 4). For older children, serum levels of triglycerides of 300–400 mg/dl may be acceptable based on the fact that lipoprotein lipase is saturated at around 400 mg/dl (38) (LOE 4). Checking serum triglyceride levels should be considered with each increase of 1.0 g/kg per day of intravenous lipids and weekly after the maximum dose is achieved.

Recommendations

- Triglyceride levels in serum or plasma should be monitored in patients receiving lipid emulsions, particularly in cases with a marked risk for hyperlipidaemia (e.g. patients with high lipid dosage, sepsis, catabolism, extremely low birthweight infants). **GOR D**
- Reduction of the dosage of lipid emulsions should be considered if serum or plasma triglyceride concentrations during infusion exceed 250 mg/dl in infants or 400 mg/dl in older children. **GOR D**

Available Lipid Emulsions

The lipid emulsions currently used contain soybean oil with egg yolk phospholipid as the emulsifier and glycerol to make the emulsion isotonic (see annex). Recently, the use of a new olive oil/soybean oil based lipid emulsion was studied in children, infants and premature newborns with encouraging results (32,39). The suggested advantages include prevention of lipid peroxidation, supply of less PUFA (polyunsaturated fatty acids) and thus enhancement of linoleic acid conversion and provision of higher antioxidant intake which results in an improved vitamin E status which is important especially in premature infants. However, there is currently not enough data to justify a recommendation towards any specific product (40) (LOE 1–2).

Soybean and olive oil based lipid emulsions contain LCT (long-chain triglycerides). Fat emulsions containing equal proportions of LCT and MCT (medium-chain triglycerides) are available. They contain less PUFA (polyunsaturated fatty acids) and their MCT part is oxidized more rapidly (19). Another possible advantage is that the oxidation of MCT is much less dependent on carnitine than oxidation of LCT. Adult and paediatric studies suggested that MCT/LCT emulsions lead to higher net fat oxidation, reduced liver derangement, improved white blood cell function, and less effects on pulmonary haemodynamics and gas exchange than LCT emulsions (41–45), while there were no major differences for plasma lipids and fatty acids (41,46–48). There are conflicting data about the effect of mixed MCT/LCT emulsions on nitrogen retention with some studies finding an increase in nitrogen retention (49,50), while another study found less positive leucine balance when compared to LCT emulsions (51). The available data in children and neonates (41,47,52–54) does not justify the preferential use of MCT/LCT emulsions over LCT emulsions (40,48).

There is insufficient data on the use of fish oil or structured lipid containing intravenous fat emulsions in paediatric patients, and thus their routine use is not recommended until further evidence may become available.

Standard 20% emulsions contain a lower ratio of phospholipid emulsifier/triglycerides than standard 10% lipid emulsions (55) and should preferably be used for intravenous PN (56,57). Higher amounts of PL (i.e. particles rich in PL) impede the removal of triglycerides from plasma, leading to an increase in plasma triglyceride concentration and accumulation of cholesterol and phospholipids in low-density lipoproteins (57). When the clearance mechanism of the exogenous phospholipids is exceeded, formation of lipoprotein X occurs (58). A 10% lipid emulsion with the same phospholipid/triglyceride ratio as the standard 20% emulsion did not show increased triglyceride and cholesterol concentrations (59).

Statement and Recommendations

- The use of commercial lipid emulsions based on LCT (soybean oil or olive oil/soybean oil), or physical mixtures of MCT and LCT can be considered generally safe in infants and children. **LOE 1**
- There is currently no evidence (based on clinical outcome data) supporting the advantage of any of the lipid emulsions that are currently available. **GOR D**
- Lipid emulsions used should not contain a higher phospholipids/triglyceride ratio than standard 20% lipid solutions to decrease the risk of hyperlipidemia. **GOR B**

Lipid Emulsions in Special Disease Conditions

Critical Illness and Infection

There is very little data concerning the use of lipid emulsions in critically ill and septic children. To our knowledge there are no outcome studies investigating the effect of lipid emulsions in this group of patients. One study in critically ill children showed that

hypermetabolic patients mainly used fat for oxidation. In these patients fat oxidation was reduced by increasing carbohydrate intake (60). Similarly, an adult study suggested that the administration of fat may be beneficial in critically ill patients to decrease de novo lipogenesis from glucose and CO_2 production associated with a high carbohydrate intake (61).

There is conflicting data about lipid clearance during infection. Some studies state that lipid clearance is reduced (62–64) whilst another found no association between hypertriglyceridemia and infection (65). In septic premature infants triglyceride levels tended to be higher and fatty acid oxidation was lower than in non-septic patients (63,64). However, it is difficult to define an upper limit of lipid intake based on these data, since high doses of heparin were applied and 10% lipid emulsions were used, which lead to increased plasma triglyceride concentrations when compared to the standard 20% lipid emulsions.

In addition to alterations in the metabolism of lipid emulsions in critically ill and septic patients, hyperactivation of the reticuloendothelial system has been described in children on long-term PN at the time of septic episodes (66). However, the use of lipid emulsions may be important in such patients to avoid excessive carbohydrate intakes and to provide essential fatty acids. In critically ill and in septic patients, close monitoring of plasma triglycerides and adjustment of lipid infusion rate if necessary is recommended.

Recommendation

- In critically ill or infected patients receiving lipid emulsions, more frequent monitoring of plasma triglyceride concentration and dose adjustment in case of hyperlipidaemia are recommended. **GOR D**

Respiratory Failure

Concerns have been raised regarding the possible adverse effects of intravenous lipid emulsions on pulmonary function (67), especially in premature neonates and those with acute lung injury. Severe adverse oxygenation effects are considered as part of the ''fat overload syndrome'' (68). While it has been thought that impaired pulmonary function (e.g. decreased pulmonary diffusion capacity with increased alveolar-arterial oxygen gradient, reduced oxygenation) was attributable to hypertriglyceridaemia, it has recently been hypothesized that it is actually due to the conversion of polyunsaturated fatty acids in the emulsion to prostaglandins causing changes in vasomotor tone with resultant hypoxemia (36,67,69). The production of hydroperoxides in the lipid emulsion might also contribute to untoward effects by increasing prostaglandin levels (29,70,71).

Recent evidence from studies in adults with acute respiratory failure suggests that infusion of an MCT/LCT emulsion in very high dosage induces significant alterations in lung function and haemodynamics, with inflammatory changes, oedema and surfactant alterations (72), which may depend on the rate of infusion (73) and on the type of lipid emulsion used (44). Other studies suggested that a mixture of MCT/LCT has less adverse effects in patients with respiratory failure than LCT lipid emulsions (42,44). Although there are no studies in children with acute respiratory failure, it might be prudent to limit lipid intake during the acute phase of respiratory failure.

Recommendation

- Although there is no firm evidence of the effects of lipid emulsions in children with severe acute respiratory failure with or without pulmonary hypertension, it appears prudent to avoid the supply of lipid emulsions in high dosages. However, lipid supply should generally be continued at least in amounts supplying the minimal essential fatty acids requirements. **GOR D**

Premature and Newborn Infants

Administration of lipids is important in premature infants requiring PN to provide essential fatty acids and increase caloric intake with a low volume. Premature infants fed parenterally without lipids may develop biochemical evidence of essential fatty acid (EFA) deficiency within 2–3 days (7,8). Intravenous lipids may be well tolerated from the first day of life onwards (74).

However, early administration of lipid emulsions remains controversial because the possibility of adverse effects on subsequent CLD (chronic lung disease) and mortality was raised. A study performed by Sosenko et al. (75) suggested that early administration to premature infants weighing less than 800 g at the age of less than 12 hours increases mortality rate and the risk of pulmonary hemorrhage. However, the number of infants whose mothers had received antenatal corticosteroids was significantly higher in the control than in the Intralipid group, possibly introducing a bias. There was no significant difference between the two groups concerning the incidence of CLD.

A study investigating the effect of early administration of intravenous lipid emulsions found an increased risk of CLD (76), whereas other studies showed no increase in the risk of respiratory impairment (74) or development of CLD (77,78). A meta-analysis, published only in abstract

form, of six randomized clinical trials designed to assess the effect of early (day 1 to 5) versus late (day 5 to 14) introduction of intravenous lipids reported no effect on the incidence of death or CLD at 28 days or at 36 weeks post conception (79).

Although this issue has not been settled conclusively, it appears that the benefits of intravenous lipid administration in premature infants weighing more than 800 g outweigh this potential risk, especially if 20% lipid emulsions are infused slowly (over 24 hours) (22) and serum triglyceride levels are monitored to identify intolerance ((74) (LOE 1–2)).

FFA (free fatty acids) compete with free bilirubin for albumin binding sites (80). A high FFA/albumin ratio may be associated with an increased risk of hyperbilirubinemia. High levels of FFA released from triglycerides may thus increase the risk of bilirubin toxicity especially in very premature infants. However, there is evidence that intravenous lipid emulsions do not have a significant effect on indirect hyperbilirubinemia in populations of newborn infants (81,82). To limit the risk of increasing hyperbilirubinemia lipid emulsions should be administered as continuous infusion (81). Serum triglyceride and bilirubin levels should be monitored and lipid infusion rate be adjusted accordingly. The exposure of lipid solutions to phototherapy light may result in the formation of triglyceride hydroperoxides that may be harmful, especially to premature infants. Thus, lipid emulsions should always be protected from phototherapy light by special light-protected dark tubing (83) (LOE 2). In addition, some authors recommend light-protected tubing for ambient light as well (83,84). In vitro studies have suggested that administering multivitamins containing ascorbic acid with the lipid emulsions via dark delivery tubing provides the most effective way of preventing peroxidation of the lipid and also limiting vitamin loss (84).

Recommendations and Statement

- In newborn infants who cannot receive sufficient enteral feeding, intravenous lipid emulsions should be started no later than on the third day of life, but may be started on the first day of life. **GOR B**
- Early administration of intravenous lipids in the first days of life does not increase the incidence of chronic lung disease or death in premature infants when compared to late administration of intravenous lipids (LOE 1). However there are concerns about potential adverse effects of early administration of lipid emulsions in VLBW (very low birth-weight) infants weighing less than 800 g. **LOE 2**
- Lipid emulsions have not been demonstrated to have a significant effect on hyperbilirubinaemia in populations of premature infants (LOE 2). It is unclear which level of bilirubin can be considered as safe in premature infants. In parenterally fed infants at risk of hyperbilirubinaemia, serum triglyceride and bilirubin levels should be monitored and lipid infusion rate be adjusted if deemed necessary. **GOR D**
- Lipid emulsions should be protected by validated light-protected tubing during phototherapy to decrease the formation of hydroperoxides. **GOR B**

Thrombocytopenia

Intravenous lipid emulsions do not seem to affect platelet number or function (85–87). However, some concerns were raised regarding the effect of lipid emulsions on platelet aggregation (88). Long-term administration of PN with lipid emulsions induced hyperactivation of the monocyte-macrophage system with haematologic abnormalities, including recurrent thrombocytopenia due to reduced platelet lifespan and haemophagocytosis in bone marrow (66). Therefore, it seems advisable to monitor serum triglyceride levels (20), and consider decreasing parenteral lipid intake in conditions of severe thrombocytopenia or coagulopathy (e.g. sepsis, DIC). A supply of essential fatty acids meeting minimal requirements is necessary to maintain normal platelet function (89) (LOE 2–3).

Recommendations

- In patients with severe unexplained thrombocytopenia serum triglyceride concentrations should be monitored and a reduction of parenteral lipid dosage be considered. **GOR D**
- Lipids in amounts supplying at least the minimal essential fatty acids requirements should always be given to maintain normal platelet function. **GOR B**

Adverse Effects

Cholestasis

Concerns have been raised regarding possible adverse effects of intravenous lipid emulsions on liver function. Liver dysfunction was associated with lipid intolerance in newborns who received intravenous fat (65) (LOE 3). Among other factors, intravenous lipids are also

considered as one of the risk factors for PN-associated cholestasis (90) (LOE 3) (see also chapter on complications). Thus it is important to monitor liver function tests when lipid emulsions are given. If there is evidence of progressive hepatic dysfunction or cholestasis a decrease in lipid supply should be considered, especially if there are other concurrent morbidities (e.g. sepsis, thrombocytopenia).

Recommendation

- In patients with marked progressive cholestasis associated with PN, unrelated to acute infection, potential causes should be explored and a decrease or even a transient interruption in intravenous lipid supply should be considered. **GOR D**

Effects on Immune System

The effects of intravenous lipids on the immune system are controversial. Interpretation of available data is complicated by the use of inappropriately high lipid doses in some studies, the use mostly of only soybean emulsions, and of different in vitro models.

In vitro studies showed adverse effects of lipids on the survival of monocytes derived from children (91) and binding of IL-2 to its receptors (92). On the other hand, in vivo studies in paediatric patients did not reveal adverse effects of lipid emulsions on complement factors (93) or polymorphonuclear leukocyte function (94,95).

Whereas Dahlstrom et al. (62) did not find an impairment of monocyte activation and complement factors in children on long term PN, Okada et al. found decreased whole blood bactericidal activity in infants on long term PN (96). However, it was not possible to differentiate between the effect of lipid emulsions and other components of the PN solution.

There are concerns that the administration of lipid emulsions may increase the risk of coagulase-negative staphylococcal bacteraemia in premature infants (97,98), possibly by a contribution of lipid emulsions to survival and growth of coagulase-negative staphylococci on contaminated catheters (99). Although this issue has not been settled conclusively, it appears that the nutritional benefits of intravenous lipid administration outweigh the potential risks.

Statement

- The nutritional benefits of the use of lipid emulsions seem to outweigh the potential risks of adverse effects on the immune system. **LOE 4**

Carnitine

Carnitine facilitates the transport of long-chain fatty acids across the mitochondrial membrane, and thus makes them available for beta-oxidation (100). Carnitine is present in human milk and cows' milk formulae, but currently PN solutions do not contain carnitine. Carnitine is synthesized in the liver and kidney from lysine and methionine, both of which are essential amino acids (101). Controversy exists as to the need to provide a source of carnitine to infants receiving total PN. Tissue carnitine stores of newborn infants fewer than 24 hours of age show a positive correlation with gestational age (102). It has been calculated that the skeletal muscle carnitine pool in the adult is four times larger than that of a term infant, and 10 times larger than that of the very premature infant, on a per kilogram body weight basis (103,104). Both gestational age and exogenous carnitine supply affect tissue carnitine reserves, and infants receiving carnitine-free PN are not able to synthesize enough carnitine to maintain body stores (105,106). Studies evaluating carnitine supplementation in infants and children have yielded controversial results. Carnitine levels decrease during prolonged carnitine-free PN, especially in small preterm infants (103) (LOE 1). However, a Cochrane-based meta-analysis showed no benefit of parenteral carnitine supplementation on lipid tolerance, ketogenesis or weight gain in neonates requiring PN (53) (LOE 1). Carnitine supplementation should be considered on an individual basis in infants exclusively on PN for more than 4 weeks (107,108).

Statements and Recommendations

- Decreased levels of carnitine occur during prolonged PN without carnitine supplementation. **LOE 1**
- There is no documented benefit of parenteral carnitine supplementation on lipid tolerance, ketogenesis or weight gain of neonates requiring PN. **LOE 1**
- Carnitine supplementation should be considered on an individual basis in patients receiving PN for more than 4 weeks. **GOR D**

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