The use of alternative lipid emulsions in paediatric and neonatal parenteral nutrition

Saayman BD, BScDiet (Hons), RD (SA)
Department of Dietetics, Red Cross War Memorial Children's Hospital
Correspondence to: Bernadette Saayman, e-mail: bsaayman@pgwc.gov.za

S Afr J Clin Nutr 2011;24(3): S32-34

Introduction

Lipid emulsions are an important part of paediatric parenteral nutrition as they provide energy, fat soluble vitamins and are a source of essential fatty acids. Soya bean based oil emulsions have however been identified as one of the major causative factors in the development of PN related cholestasis. The newer lipid emulsion containing fish oil has been shown to reduce the risk of such complications. Nevertheless, some centers advise that parenteral lipid intake should be discontinued when parenteral nutrition associated cholestasis (PNAC) develops. This practice is, however, not recommended as it can be detrimental to infants who have limited fat stores. Such practices, could also potentially lead to growth failure and essential fatty acid deficiency. Increasing daily intravenous glucose intake as a compensatory measure for the omission of lipid emulsions is not recommended as it may induce insulin resistance and the risk of liver steatosis due to lipogenesis.[1,2]

Prolonged parenteral nutrition (PPN) is essential in those paediatric patients who are unable to meet their full dietary requirements via the enteral route. Many of these patients are dependant on parenteral nutrition (PN) for growth, development and survival. Lipid emulsions form an important part of parenteral nutrition as a non- carbohydrate source of energy and supplies both essential fatty acids and lipid-soluble vitamins.[3]

Long-term PN is related to various serious complications with PN associated liver disease having been identified as one of the most serious complications as it may progress to cirrhosis and liver failure.[4,5] The prevalence of parenteral nutrition associated cholestasis (PNAC) has been reported to be more frequent and severe in infants than in adults with a 30-70% prevalence of hepatic dysfunction seen in infants.[5,6] Children with PNAC also predominantly present with a cholestatic picture. Hepatic immaturity has been identified as a major predisposing factor with an increased prevalence seen in premature, very low birth weight and small for gestational age infants. Treatment options are limited and is associated with a relatively high mortality.[2]

The etiology of PNAC is multi-factorial and risk factors for its development include sepsis, e.g. catheter infections or necrotizing enterocolitis, bacterial overgrowth, impaired bile acid recirculation as seen in short bowel syndrome, multiple operative procedures, delayed enteral feeding, prolonged parenteral nutrition, overfeeding via parenteral nutrition and IV lipid emulsions.[2,5-7]

When a patient develops PNAC it is important that all possible contributing factors are identified and addressed. The early introduction of Enteral Nutrition (EN) may slow the progression of PNAC and cholestasis may be reversed once PN is discontinued. This may however prove challenging especially in the presence of poor EN tolerance due to intestinal dysfunction.[2] Other management strategies include preventing and/or treating bacterial overgrowth, pharmacotherapy, and considering modifications to the PN solution.[5]

The use of soya bean oil based lipid emulsions

Soya bean oil has been the standard lipid emulsion used in parenteral nutrition for many years due to the lack of alternative options. It is composed of long chain triglycerides and contains > 60% polyunsaturated fatty acids (PUFA). It also acts as a reliable source of essential fatty acids with an omega 6:omega 3 ratio of 5.5:1.[8] Soya bean oil has been implicated in PNAC with clinical observations showing a dose related relationship in the development of PNAC. The potential causative factors identified include enhanced oxidative stress, prolonged inflammation and the role of phytosterols.[7,8]

Oxidative stress

Lipid metabolism results in lipid peroxidation and free radical formation.[3] Reactive oxygen species cause functional damage to hepatocytes and lead to reduced bile production and cholestasis in animal models. Soya is a relatively poor source of alpha-tocopherol, which, if not supplemented, may lead to reduced levels in plasma lipoproteins and depletion of anti-oxidant defenses during long-term PN usage.[6] There appears to be an enhancement of lipid peroxidation when the supply of parenteral polyunsaturated fatty acids is increased in the presence of a low supply of alpha tocopherol.[1]

The increased risk of lipid peroxidation is of particular concern in premature infants who are known to be exposed to oxidative stress and are more vulnerable to its effects when compared to neonates.[9,10] This patient population is also prone to being dependant on PN while enteral intake is being established.

Prolonged inflammation

Prolonged inflammation is a component of PNAC that contributes to progressive liver damage, cholestasis and fibrosis. Soya bean emulsions provide large amounts of linoleic acid which can be converted to arachidonic acid (AA), a pre-cursor of potent pro-inflammatory mediators.[6]

Phytosterols

Recent studies suggest that phytosterols contribute to cholestasis due to their effect on biliary secretion.[2] Phytosterols are not metabolized efficiently by the liver.[5] Regular use of phytosterols in animal models have shown to lead to reduced bile flow and increased bile acid levels. Accumulation of phytosterols has also been seen in blood samples of children with PNAC.[6]

There have been reports of unfavorable changes in lipid profiles in patients on soya based PN. These include hypertriglyceridaemia, hypercholesterolaemia, decreased HDL and increased LDL concentrations.[4]

Fish oil based lipid emulsions

The use of fish oil has been proposed as a possible alternative option to soya bean as a lipid emulsion especially in treating and/or preventing PNAC. The addition of fish oil leads to the reduction in some of the adverse effects of soya and the provision of the beneficial effects of fish oil.

The addition of fish oil achieves a reduction in omega 6 fatty acids and a higher intake of omega 3 fatty acids. Long chain polyunsaturated fatty acids, especially omega 3 fatty acids from fish oil, possess the most potent immunomodulatory and anti-inflammatory properties.[3] Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from fish oil have anti-inflammatory properties and may be beneficial in hyper inflammatory settings. They are however susceptible to peroxidation especially during inadequate antioxidant availability.[6,11] Fish oil based emulsions also contain no phytosterols. This composition allows for the improvement of anti oxidant defenses and the suppression of the adverse effects of phytosterols.[8] Recent studies have suggested that fish oil based emulsions may lead to faster reversal of cholestasis when replacing standard soya bean oil. Gura et al have reported a median time of 9.4 weeks to reversal of cholestasis vs. 44.1 weeks when compared to a control group receiving soya bean oil. The authors also documented a 4.8 times faster reversal of cholestasis in the treatment group.[6]

A double blind randomized controlled trial assessed the effect of fish oil omega 3 fatty acids on oxidative stress in preterm infants. The authors found a decrease in oxidative stress and an increase in vitamin E levels when compared to a standard lipid emulsion.[9] Furthermore, Le et al observed an improvement in the lipid profiles of patients receiving a fish oil based emulsion. Positive changes seen included a decrease in LDL, VLDL, cholesterol and triglyceride concentrations and an upward trend in HDL levels.[4] These changes may be due to the ability of omega 3 fatty acids to reduce the hepatic triglycerides synthesis,[2,4] a reduction which could reduce inflammation in the liver.[4]

Mixed lipid emulsions

Long-term use of fish oil as the sole lipid source provides lesser amounts of essential fatty acids than those needed in infants and young children. Both omega 6 and omega 3 fatty acids have been shown to be essential for growth and development.[7] In this regard, available evidence indicates that the sole use of fish oil based emulsions is not essential and that the same beneficial effects on the liver may be derived by combining fish oil with other lipid emulsions with the addition of alpha tocopherol.[7]

SMOFlipid 20% (Fresenius Kabi) is a new lipid emulsion that contains a mixture of 30% soya bean oil, 30% medium chain triglycerides (MCT), 25% olive oil and 15% fish oil. It contains added alpha tocopherol (200 mg/liter) and provides an omega 6:omega 3 ratio of 2.5:1.This ratio is within the optimal range to provide an anti-inflammatory effect and correlates with the composition of breast milk.[8,10]

Medium chain triglycerides are sourced from coconut or palm kernel oil and acts as a rapidly available energy source. They are eliminated faster from the bloodstream than long chain triglycerides and do not depend on carnitine for mitochondrial transport. MCTs are less susceptible to lipid peroxidation and do not accumulate in the liver. MCTs are also widely used in infants and neonates and have been shown to be safe for long term administration.[6,10]

Olive oil is rich in monounsaturated fatty acids thereby reducing excessive polyunsaturated fatty acid use. Olive oil lipid emulsions have also been shown to be safe in the use of premature infants and older children. Olive oil emulsions though do not provide sufficient omega 3 fatty acids.[10] A study evaluating the effects of soybean oil vs. an olive oil and soybean oil emulsion on peroxidation and plasma phospholipids fatty acids in premature infants found a better vitamin E status and a fatty acid composition more similar to breastfed infants in the olive oil group.[1]

Evidence from controlled trials have shown that by even including part of the lipid emulsion as fish oil can provide similar beneficial effects. By increasing the ratio of omega 3: omega 6, the metabolism of AA is reduced, which is thought to be associated with a reduced production of the pro-inflammatory cytokines implicated in PNAC.[10] Soya bean oil was included in the lipid emulsion as it is a reliable source of essential fatty acids in the form of linoleic acid and alpha linoleic acid. This is particularly important since the risk of essential fatty acid deficiency is high in the infant population and clinical signs of deficiency have been reported in situations where fat free TPN has been used.[1]

A double blind randomized controlled trial conducted in 28 paediatric patients (ages five months-11 years) on home PN evaluated the safety, tolerability and efficacy of SMOF lipid over a 4 week period at a dose of 1g/kg IV lipid/day. The authors found a positive influence on serum alpha tocopherol levels and omega 3 fatty acid status without changing lipid peroxidation parameters. A significant decrease was also seen in bilirubin levels as well as an improvement in liver function tests. This lipid emulsion was well tolerated.[10] Similarly, such beneficial effects were also reported in 51 premature infants on PN who were randomized to receive either SMOF lipid PN or conventional soya based PN. The infants received an average lipid intake of 1.6 g/kg/day. The changes observed were an increase in alpha tocopherol, decrease in gamma-glutamyl transpeptidase (GGT) levels and an increase in the availability of omega 3 fatty acids. The increased availability of the omega 3 fatty acids is seen as beneficial for this patient population as DHA accumulation is most active in the last intrauterine trimester.[11]

The new lipid emulsions used in recent trials were well tolerated and the mean triglyceride levels were well below critical levels being 0.62 mmol/l at baseline for both groups and remaining at 0.87 mmol/l and 0.82 mmol/l at termination of the study. The monitoring of triglyceride levels is seen as the primary safety variable during the administration of PN. Premature neonates are at higher risk of hypertrygliceridaemia due to their limited muscle and fat mass and subsequent decreased hydrolytic capacity of lipoprotein lipase.[11] These positive effects may serve to protect premature infants from increased levels of oxidative stress and benefit their cognitive development and visual capacity.[11]

It is of utmost importance that treatment strategies for the prevention of PNAC is incorporated into the management plan of all patient who are receiving long term parenteral nutrition. The use of a multi-lipid emulsion is advised as one of the preventative and/or treatment strategies as it has been identified as a safe and well tolerated vehicle to combine the beneficial aspects of different lipid emulsions in both the prevention and treatment of parenteral nutrition associated liver disease.

References

1. Krohn K, Koletzko B. Parenteral lipid emulsions in paediatrics. Curr Opin Clin Nutr Metab Care 2006;9:319-323
2. Gura KM, Duggan CP, Collier SB, Jennings RW, Folkman J, Bistrian BR, Puder M. Reversal of parenteral nutrition associated liver disease in two infants with short bowel syndrome using parenteral fish oil: implications for future management. Pediatrics 2006;118:197-201
3. ESPGHAN Guidelines on parenteral nutrition-lipids. JPGN 2005,41(2)
4. Le HD, De Meijer VE, Robinson EM, Zurakowski D, Potemkin AK, Arsenault DA et al. Parenteral fish –oil based lipid emulsion improves fatty acid profiles in parenteral nutrition dependent children. Am J Clin Nutr July 2011:1-10
5. Kumpf VJ. Parenteral Nutrition associated liver disease in adult and pediatric patients. Nutrition in clinical practice 2006; 21: 279-290
6. Gura KM, Lee S, Valim C, Zhou J, Kim S, Modi BP et al. Safety and efficacy of a fish oil based fat emulsion in the treatment of parenteral nutrition associated liver disease. Pediatrics 2008; 121:e678-e686
7. Koletzko B, Goulet O. Fish oil containing intravenous lipid emulsions in parenteral nutrition associated cholestatic liver disease. Curr Opin Nutr Metab Care2010;13:321-326
8. Goulet O, Joly F, Corriol O, Colomb-Jung V. Some new insights in intestinal failure associated liver disease. Curr Opin Organ Transplant 2009; 14:256-261
9. Skouroliakou M, Konstantinou D, Koutri K, Kakavelaki C, Stathopoulou M, Antoniadi M et al. A double blind randomized clinical trial of the effect of omega 3 fatty acids on the oxidative stress of preterm neonates fed through parenteral nutrition. European Journal of Clinical Nutrition 2010; 1-8
10. Goulet O, Antebi H, Wolf C, Talbotec C, Alcindor L-A, Corriol O et al. A new Intravenous fat emulsion containing soybean oil, medium chain triglycerides, olive oil and fish oil: a single center double blind randomized study on efficacy and safety in pediatric patients receiving home parenteral nutrition. JPEN 2010; 34:485-495
11. Tomsits E, Pataki M, Tolgyesi A, Fekete G, Rischak K, Szollar. Safety and efficacy of a lipid emulsion containing a mixture of soybean oil, medium chain triglycerides, olive oil and fish oil: a randomized, double blind clinical trial in premature infants requiring parenteral nutrition. JPGN 2010;50:1-8