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Parenteral lipid emulsions and phagocytic systems

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Lipid emulsions (LE) for parenteral use are complex emulsions containing fatty acids, glycerol, phospholipids and tocopherol in variable amounts and concentrations. In clinical practice, LE have been employed for more than 30 years. Fatty acids may have different impacts on phagocytic cells according to their structure. Experimental and clinical studies have consistently shown that LE modify monocyte/macrophage and polymorphonuclear phagocytosis. The inhibitory effect of LE on the functional activity of the phagocytic system, although still clinically controversial, may have a harmful impact because total parenteral nutrition with lipids may be recommended in hypercatabolic conditions where inflammation and infection are present. LE based on triglycerides containing long chain fatty acids (termed long chain triglycerides or LCT) are the main parenteral fat source and are typically rich in *n*-6 polyunsaturated fatty acids. They may have adverse effects on the immune system, especially when given in high doses over a short period of time. However when administered properly they can be used safely. LE containing medium chain triglycerides (MCT) may have some advantages because of their positive effects on polymorphonuclear cells, macrophages, and cytokine production, particularly in critically ill or immunocompromized patients. New parenteral LE containing *n*-3 polyunsaturated fatty acids or monounsaturated olive oil are already available in Europe. Judicious use of these new LE is mandatory especially relating on their potential impact on the immune system. New experimental and clinical studies are required to further establish the role of LE in clinical nutrition.

Parenteral nutrition: Macrophage: Lipid: Neutrophil: Phagocytosis

General considerations

Indian scriptures dating back to 5000 BC have documented that nutritional status has been associated with health (Chandra, 1985). Nutritional depletion results in immunosuppression, and therefore host defense impairment, favoring increased infection and mortality rates (Mullen *et al.* 1980). Improvement of nutritional state with nutritional interventions may re-establish immune competence and decrease the frequency and severity of infectious complications in hospitalized patients (Dudrick *et al.* 1969). Total parenteral nutrition (TPN) is one well-established nutritional therapy, which allows intravenous feeding of patients without an available enteral route (Koss *et al.* 1979). TPN is widely applied in hospital settings and consists of a solution containing amino acids, glucose, electrolytes and vitamins as well as lipid emulsions (LE). In TPN regimens, LE function as calorie dense nutrients and a source of essential fatty acids.

Fatty acids (FA) are the main component of cell membranes. They are responsible for membrane structural integrity and the production of eicosanoids. Lipids are also major metabolic regulators and can modulate the immune response (Meade & Mertin, 1978; DeWille *et al.* 1979; Kinsella, 1990).

Research on the effects of fatty acids on the immune response date back for over 30 years (Piette & Saugier, 1970; Mertin & Meade, 1977). The impact of intravenously infused isolated fatty acids on the immune system has been studied since 1972 (Di Luzio, 1972). It is well known that changes in the quality and amount of dietary fat (Hwang, 1989), as well as abnormalities in lipid metabolism (Koss *et al.* 1979; Beisel, 1981) can alter the immune response. There is much evidence that LE also have an impact on

Abbreviations: LE, lipid emulsions; TPN, total parenteral nutrition; LCT, long chain triglycerides; MCT, medium chain triglycerides; FA, fatty acids.

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mononuclear phagocytic function, particulary phagocytosis (Strunk *et al.* 1979; Wiernik *et al.* 1983; Cleary & Pickering, 1983; Waitzberg *et al.* 1996). The purpose of this review is to examine the effects of different LE on the phagocytic process of macrophages and polymorphonuclear cells.

Lipid emulsions

LE are the parenteral source of essential fatty acids. They can be infused alone or together with glucose and amino acids, in malnourished or hypercatabolic patients. LE are triglyceride droplets enveloped with a stabilizing superficial layer of phospholipids (Shils *et al.* 1998) and their formulation includes substances other than triglycerides, such as lecithin, glycerol and alpha-tocopherol in variable amounts. The triglycerides may be presented structurally as long chain triglycerides (LCT) or medium chain triglycerides (MCT). LCT LE have been used in clinical practice for over 30 years. LCT contain fatty acid chains with 14, 16, 18, 20 and 22 carbon atoms and sometimes with double bonds. The number of double bonds present defines the fatty acids in LCT as saturated, mono or polyunsaturated. The double bonds can be found in different places in the carbon chain, their position follows rules governed by the specificity of the enzymes responsible for inserting them. If the first double bond is on carbon number 3, 6 or 9 from the methyl end of the carbon chain then the fatty acid is *n*-3, *n*-6 or *n*-9, respectively. LE which are commercially available for parenteral use are based on LCT containing a high proportion of *n*-6 polyunsaturated fatty acids usually derived from soybean or safflower oil, although LCT containing *n*-3 polyunsaturated fatty acids, derived from fish oil, and *n*-9 monounsaturated fatty acids from olive oil are also available. Saturated fatty acids with chains containing 6, 8, 10 or 12-carbon atoms form the MCT emulsions. MCT are found in high amounts in coconut oil. For clinical purposes MCT is used as a 50 % physical or structured mixture with LCT. Thus MCT/LCT LE have a lower proportion of LCT volume/volume than LCT LE.

Recently in Europe LE containing LCT or LCT/MCT enriched with fish oil (FO) became available for research. FO includes long chain triglycerides with twenty or more carbon atoms where the first double bond is located between the third and the fourth carbons from the methyl terminal of the fatty acids chain (omega-3 or *n*-3).

The incorporation of *n*-3 fatty acids into macrophage membranes occurs in 3–6 hours *in vitro* and in 3 days *in vivo*. The incorporation of different fatty acids may change membrane fluidity, alter phosphatidylinositol production and dienoic eicosanoid secretion and modulate the generation of interleukins and tumour necrosis factor (TNF) in response to lipopolysaccharide (LPS) stimulation. These effects are related to the membrane *n*-6:*n*-3 fatty acid ratio and to the total amount of *n*-3 and *n*-6 FA infused.

The physicochemical nature of the infused triacylglycerol (i.e. carbon chain length, saturation degree, size of the particle and nature of fatty acid) may determine structural changes and alterations in the phagocytic cell activity.

Effects of lipid emulsions on monocyte-macrophages

Monocyte-macrophages are immune cells involved in phagocytosis, antigen presentation and cytokine production. A number of experimental and clinical studies investigating the effects of currently used LE on monocyte-macrophage functions are summarized in Table 1.

Experimental studies

Experimental studies regarding the effects of LE on phagocytosis by monocyte-macrophages are controversial. Several trials have used rats, guinea pigs, and mice infused with different LE alone or as a component of TPN and studied the effects on circulating and resident macrophages.

Experimental lipid-TPN infusion for a week has been associated with decreased phagocytosis and increased superoxide production by peritoneal macrophages, splenic macrophage proliferation and bacterial translocation (Shou *et al.* 1994). Intravenous infusion of LCT LE and MCT/LCT LE into rats infected by *Escherichia coli (E. coli)* was followed by hyperplasia of Kupffer cells and splenic histiocytes (Waitzberg *et al.* 1992). The infusion of TPN with LCT LE into guinea pigs reduced phagocytosis of *E. coli* by Kupffer cells and splenic macrophages (Hamawy *et al.* 1985).

TPN with LCT LE was associated with inhibition of pulmonary bacterial phagocytosis but this was not observed with TPN with MCT/LCT (Sobrado *et al.* 1985). These changes were not verified in a similar experimental model in septic rats infused with TPN containing 50 % non-protein calories in the form of LCT LE (Vallgren *et al.* 1986).

Despite reports indicating inhibitory effects of LCT LE, including anatomical-pathological alterations of monocytes and macrophages (Strunk *et al.* 1979; Nugent, 1984), other evaluations of the effect of LCT and MCT/LCT LE infusions in animals showed no alterations of phagocytosis and other monocyte/macrophage functions at different doses and periods and rates of infusion (Nishiwaki *et al.* 1986; Allen & Murray, 1986; Waitzberg *et al.* 1996). Moreover it seems that there are distinct macrophage responses to intravenous infusion of LE according to the anatomical origin of macrophages. The total number of liver and spleen macrophages were reduced but pulmonary phagocytosis was increased when TPN enriched with LCT LE was compared to an oral diet (Cukier *et al.* 1999). These differences between studies may be attributed to differences in the experimental models used, and the amount of lipids administered (Table 1).

The addition of a fish oil LE to LCT and MCT/LCT LE increased total liver and lung macrophage number and phagocytosis in rats after 96 h of intravenous infusion (Cukier *et al.* 1999).

Human studies

Not many human clinical studies have investigated the effects of LE on monocyte function. Wiernik *et al.* (1983) infused 20 % soybean oil emulsion intravenously for 2 h into healthy volunteers. During the infusion a significant increase in nitroblue tetrazolium-reduction by blood

Table 1. Studies of lipid emulsions on monocyte/macrophage function

Reference	Study in	Type of LE	Via	Dose	Time (h)	Function	Findings
Waitzberg *et al.* 1997	Gastric cancer patients (10) (+TPN)	LCT 10 %	i.v.	10 kcal/kg per day (0·08 g/kg per h)	48	Chemotaxis	No alteration
		MCT/LCT 10 %				Bacterial killing	No alteration
						Phagocytosis	No alteration
Wiernik *et al.* 1983	Healthy volunteers (18)	LCT 20 %	i.v.	20–100 mg/ml	0·5	NBT reduction	↑
Strunk *et al.* 1979	Guinea pigs	LCT 10 %	i.v.	93–375 mg/l	48	Ability of peritoneal Mϕ to spread	↓
						Number of membrane ruffles	↓
						Complexity of membrane ruffles	↓
						Phagocytosis	↓
Nugent, 1984	Mice	LCT	i.v.	40 % vol	18	Appearance of peritoneal Mϕ	Rounded and more dense
						Phagocytosis	↓
						Pinocytosis	↓
Allen & Murray, 1986	Mice	LCT	i.v.	2 g/kg per d	240	PHI	No alteration
						Liver and spleen size	No alteration
Nishiwaki *et al.* 1986	Septic rats	LCT	i.v.	25 % of NPC	72	Phagocytosis	No alteration
Waitzberg *et al.* 1992	Rats with *E. coli* peritonitis	LCT 10 %	i.v.	5 ml/kg per h	44	Chemotaxis	No alteration
		MCT/LCT 10 %				Phagocytosis	No alteration
		MCT 10 %				Bacterial killing	No alteration
Cukier *et al.* 1999	Rats	LCT 10 %	i.v.	2 ml/kg per h (31 % of NPC)	96	PHI of liver Mϕ	↑
		LCT + FO (9:1 vol/vol)				PHI of liver and lung Mϕ	↑
		LCT + FO (1:1 vol/vol)				PHI of liver and lung Mϕ	↑
		MCT/LCT + FO (9:1 vol/vol)				PHI of liver and lung Mϕ	↑
						PHI of liver and lungMϕ	↑

Abbreviations used: FO, fish oil; i.v., intravenous; LCT, long chain triglyceride; Mϕ, macrophages; MCT, medium chain triglyceride; NBT, nitroblue tetrazolium; NPC = non protein calories; PHI = phagocytic index; TPN, total parenteral nutrition.

Table 2. Studies of lipid emulsions on PMN function

Reference	Study in	Type of LE	Via	Dose	Time (h)	Function	Findings
Waitzberg *et al.* 1992	Rats with *E. coli* Periotonitis	LCT 10 % MCT/LCT 10 % MCT 10 %	i.v.	0·5 ml/kg per h	44	Chemotaxis Phagocytosis Bacterial killing	No alteration No alteration No alteration
Waitzberg *et al.* 1996	Rats	LCT 10 % MCT/LCT 10 %	i.v.	1 ml/h 1 or 1·5 ml/h	30 44	Phagocytosis Chemotaxis	No alteration No alteration
	Rats	LCT 10 % MCT 10 % MCT/LCT 10 %	i.v.	20 mg/ml	0·5	Phagocytosis Bacterial killing Chemotaxis	↓ (LCT & MCT/LCT) ↓ (MCT) ↓ (MCT)
Jarstrand *et al.* 1978	Healthy volunteers	LCT 20 %	i.v.	20–100 mg/ml	0,5	NBT reduction Bacterial killing	↓ ↓
	Patients (8)	LCT 20 %	i.v.	100 ml/h	1	NBT reduction	↓
	Patients (6)	LCT 20 %	i.v.	100 ml/h	1	Bacterial killing	↓
Nordenstrom *et al.* 1979	Healthy volunteers (12)	LCT 20 %	i.v.	50–200 ml/h	2	Chemotaxis	↓ (dose dependent)
Fischer *et al.* 1980	Healthy volunteers	LCT	i.v.	12·5–100 mg/ml	0·5	Chemotaxis	↓
English *et al.* 1981	Healthy volunteers	LCT 10 %	i.v.	80 mg/ml	0·5	Chemotaxis Superoxide production Chemiluminescence	↓ if LCT not dialysed ↓ if LCT not dialysed ↓ if LCT not dialysed No alteration if LCT dialysed against saline
Palmblad *et al.* 1982	Crohn's Disease (4)	LCT 20 %	i.v.	21 ml/h	10	Bacterial killing	No alteration
	Healthy volunteers (10)	LCT 20 %	i.v.	85 ml/h	6	Chemiluminescence Chemotaxis	No alteration ↑
Wiernik *et al.* 1983	Healthy volunteers (18)	LCT 20 %	i.v.	20–100 mg/ml	0·5	NBT reduction Chemotaxis	↓ ↓
Cleary *et al.* 1983	Healthy volunteers	LCT10 %	i.v.	15–100 mg/ml	0·5	NBT reduction O_2 consumption Bacterial killing Phagocytosis	↑ (dose dependent) ↑ (dose dependent) ↑ (dose dependent) ↑ (dose dependent) But ↓ of all functions with high dose
Ota *et al.* 1985	Cancer patients (40)	LCT 20 % (+TPN)	i.v.	500 ml/day	240	Phagocytosis Chemotaxis Bacterial killing	No alteration No alteration No alteration
Escudier *et al.* 1986	Surgical cancer patients (9)	LCT 20 % (+TPN)	i.v.	83 ml/h	6	Chemotaxis	No alteration
Rasmussen *et al.* 1988	Minor surgical patients (24)	LCT 20 %	i.v.	100 ml/h	4	Opsonization time O_2 consumption Superoxide production Phagocytosis *Candida albicans* killing Chemotaxis	No alteration No alteration No alteration No alteration No alteration No alteration
Monico *et al.* 1988	Healthy volunteers (40)	MCT/LCT 10 %	i.v.	120 ml/h	5–7	Chemotaxis Adherence to nylon fibers Phagocytosis	No alteration No alteration No alteration
Robin *et al.* 1989	Patients (25)	LCT10 %	i.v.	100 ml/h	4–6	Chemiluminescence	↓
	Healthy volunteers (10)	LCT 10 %	i.v.	400 mg/l	0·75	Chemiluminescence	No alteration
Herson *et al.* 1989	Ill neonates (10)	LCT	i.v.	1 g/kg	16	Chemotaxis	No alteration

Table 2. *Continued*

Reference	Study in	Type of LE	Via	Dose	Time (h)	Function	Findings
			i.v.	100 mg/ml	0·5	Chemotaxis	No alteration
Bellinatti-Pires *et al.* 1992	Healthy volunteers	LCT 10 %	i.v.	20 mg/ml	0·5	Chemotaxis	↓ (dose dependent) in MCT groups
		MCT 10 %					
		MCT/LCT 10 %					
Bellinatti-Pires *et al.* 1993	Healthy volunteers (20)	LCT 10 %	i.v.	20 mg/ml	0·5	NBT reduction	↓ in MCT groups
		MCT 10 %				Phagocytosis	↓ in MCT groups
		MCT/LCT 10 %				H_2O_2 production	↓ in MCT groups
						Bacterial killing	↓ in MCT groups
Waitzberg *et al.* 1997	Gastric cancer patients (10)	LCT 10 %	i.v.	10 kcal/d (0·08 g/kg per h)	48	Chemotaxis	No alteration
		MCT/LCT 10 % (+TPN)				NBT reduction	No alteration
						Bacterial killing	↓
Heine *et al.* 1999	Healthy volunteers (10)	LCT	i.v.	60–600 mg/ml	<0·5	Respiratory burst	↓
		MCT/LCT					↑
		LCT with FO					↓
Kruimel *et al.* 2000	Healthy volunteers	LCT	i.v.	1–100 mmol/l	0·5	Chemiluminescence	↑ with MCT/LCT
		MCT/LCT				ROS production	↑ rate and amount with MCT/ILCT
		MCT/LCT structured					

Abbreviations used: FO, fish oil; i.v., intravenous; LCT, long chain triglyceride; MCT, medium chain triglyceride; NBT, nitroblue tetrazolium; TPN, total parenteral nutrition.

monocytes was noted. Preincubation of monocytes *in vitro* with LCT LE (20–100 mg/ml) for 30 min was found to increase the ability of the cells to migrate chemotactically and to phagocytose yeast particles.

In a prospective, randomized, cross-over clinical trial malnourished gastric cancer patients received a 48 h TPN (40 kcal/kg) with 25 % of energy provided as LCT or MCT/LCT LE (infused at the rate of 0·08 g/kg per h). No alteration in monocyte-macrophage function and phagocytosis was found with either LE compared to the appropriate controls (Waitzberg *et al.* 1997).

Effects of lipid emulsions on neutrophils

Neutrophils are cells related to natural immunity. They represent the first cellular defense against microorganisms. Their initial functions are to phagocytose and inactivate invasive agents. Despite numerous reports about interactions between lipids and the phagocytic system, the effects of LE on the metabolic and microbial killing activities of neutrophils are still controversial (Table 2).

Experimental studies

Experimental data indicate an inhibitory effect of LCT and MCT/LCT LE on rat neutrophil phagocytosis *in vitro* (Waitzberg *et al.* 1996), but no differences in *ex vivo* phagocytosis, chemotaxis and bacterial killing were observed in healthy and septic rats when LCT LE, MCT/LCT LE or saline were intravenously administrated (Waitzberg *et al.* 1992, 1996).

From the *in vitro* studies performed using human polymorphonuclear cells a dose dependent response to LE is apparent. For instance, soybean oil emulsions showed an inhibitory effect on neutrophils when used at concentrations ranging from 15 mg/ml to 100 mg/ml but when concentrations higher than 100 mg/ml were used, no alterations in neutrophil functions were found (Jarstrand *et al.* 1978; Wiernik *et al.* 1983; English *et al.* 1981; Bellinati-Pires *et al.* 1992). Moreover, with MCT/LCT LE a stimulatory effect was documented (Robin *et al.* 1989; Bellinati-Pires *et al.* 1992; Bellinati-Pires *et al.* 1993; Heine *et al.* 1999), when low doses were used.

In clinical studies, the capacity of neutrophils to phagocytose was not altered with LCT LE (Ota *et al.* 1985; Rasmussen *et al.* 1988), or MCT/LCT (Monico *et al.* 1988; Dominioni & Dionigi, 1987). Chemotaxis was also unchanged in five studies with LCT-LE (Ota *et al.* 1985; Rasmussen *et al.* 1988; Escudier *et al.* 1986; Herson *et al.* 1989; Waitzberg *et al.* 1997). However, a dose-dependent inhibitory effect was detected in a single study (Nordenstrom *et al.* 1979) and also the opposite, a stimulatory effect, has been demonstrated. (Palmblad *et al.* 1982). Bacterial killing by polymorphonuclear neutrophils (PMN) is controversial: three studies did not find any alteration (Ota *et al.* 1985; Palmblad *et al.* 1982; Rasmussen *et al.* 1988) and two studies showed an inhibition with LCT LE (Jarstrand *et al.* 1978; Waitzberg *et al.* 1997). In a clinical trial with gastric cancer patients receiving TPN with LCT or MCT/LCT LE, bacterial killing by neutrophils was the only function reduced after LCT LE, although this function remained within the normal range values in 80 % of the patients. In conclusion, LCT LE moderately decreases neutrophil bacterial killing.

There is little literature involving nitroblue-tetrazolium (NBT) reduction and superoxide anion production.Two studies showed no change (Rasmussen *et al.* 1988; Waitzberg *et al.* 1997) and one study an inhibitory effect (Jarstrand *et al.* 1978).

There are no data available regarding the effect of *n*-3 fatty acid-containing LE or olive oil emulsion on neutrophil function.

Potential immunomodulatory mechanisms of lipid emulsions

In the last years, several mechanisms have been proposed to explain the different effects of LE on the immune system. They are associated mainly with fatty acid incorporation and modification of cell membrane composition (Palombo *et al.* 1997).

The effects of fatty acids on phagocytic activity *in vivo* and *in vitro* are controversial. The presence of dietary polyunsaturated fatty acids may inhibit microbicidal activity. However, polyunsaturated fatty acids may stimulate this activity when directly added to cell culture. One possible explanation for the controversial results is provided by Mahoney *et al.* (1977, 1980). These authors calculated that, in normal conditions, the phagocytosis of an erythrocyte results in approximately 7 % internalization of the macrophage surface area.

Membrane fatty acid composition influences membrane fluidity, cell permeability, eicosanoid production, as well as membrane receptors, enzymes and second messenger signaling processes. Although *n*-6 and *n*-3 polyunsaturated fatty acids are incorporated into cell membranes, it remains to be proved if medium chain triglycerides or saturated fatty acids are also incorporated into cell membranes when present in doses higher than in a normal diet. Fatty acids may interfere with other immune modulating mechanisms such as modulation of adhesion molecules, regulation of nitric oxide (NO) production, modulation of signal transduction pathways and direct modulation of gene expression (Yaqoob, 1998).

Enzymes such as lipoxygenases and cyclooxygenases produce proinflammatory lipid mediators such as leukotriene (LT) B_4 and prostaglandin (PG) E_2 from arachidonic acid. Several eicosanoids such as LTB_4 and thromboxane B_2 (TXB_2) have chemotactic effects. When exposed to higher concentrations of *n*-3 polyunsaturated fatty acids, lipoxygenases and cyclooxygenases produce less biologically active mediators as LTB_5 and PGE_3 (Magrum & Johnston, 1983). An *n*-3 fatty acid rich diet lowers PGE_2, 6-keto-PGF_1-alpha, LTB_4 and TXB_2 production when compared to an *n*-6 fatty acid rich diet. *n*-6 Fatty acids augment PGE_2, LTB_4, LTC_4, LTD_4, 6-keto-PGF_1-alpha and TXB_2, probably via arachidonic acid, the eicosanoid precursor.

Membrane phospholipids can be transformed by phospholipases to yield second messengers (such as phosphatidylinositol-4,5-bisphosphate generating diacylglycerol and inositol-1,4,5-trisphosphate) and can be involved in activating or stabilizing enzymes in signaling pathways

(such as phophatidylserine that is required for the activation of protein kinase C). All phospholipids and some of the second messengers that they generate contain fatty acyl chains, and it is possible that changes in membrane fatty acid composition may alter properties of these compounds. (Serhan *et al.* 1996; Ballou *et al.* 1996; Yaqoob, 1998).

Recent evidence shows that lipids are direct modulators of gene expression. Therefore, changes in cellular fatty acid profiles or in fatty acid metabolites could affect the activity of specific transcription factors, which alter gene transcription (indirect modulation of gene expression). The peroxisome proliferator-activated receptor family (PPAR – a group of key nuclear receptors involved in the regulation of lipid homeostasis) regulate the expression of target genes by binding to DNA sequence elements. It has been shown that several unsaturated fatty acids bind directly to PPAR-alpha (Yaqoob, 1998). Through these actions fatty acids could regulate expression of adhesion proteins, such as integrins and selectins, thus altering cell adhesion.

NADPH oxidase is an enzyme present in neutrophils which produces free radicals and may be stimulated by arachidonic acid. Diets enriched with *n*-6 or saturated fatty acids are associated with decreased peroxide and free radical production by activated neutrophils and to down regulation of glucose-6-phosphate-dehydrogenase. The latter is one of the most powerful inducers of NADPH synthesis, and an essential substrate for free radical production by NADPH oxidase. NO production is catalysed in phagocytic cells by NO synthetase induction. Transcription of NO synthetase and NO production may be inhibited by polyunsaturated fatty acids.

Despite the different immunomodulating properties of fatty acids it should be kept in mind that LE for parenteral use are complex nutrient sources composed not only of fatty acids but also including phosphatidylcholine, glycerol, and α-tocopherol. Besides that, LE contain various types of triglycerides in a physical or structured mixture. The interaction of these distinct substances may alter the effects observed with isolated fatty acids (Kruimel *et al.* 2000; De la Fuente, 2000).

Clinical impact and conclusions

In clinical practice, LE for parenteral use have been employed for more than 30 years. The inhibitory effect of LE on the functional activity of the phagocytic system, although still controversial, may be an important harmful impact because TPN with lipids may be recommended in hypercatabolic conditions where inflammation and infection are present.

LCT LE are still the main parenteral fat source and are rich in *n*-6 fatty acids. The concerns about the association of LE with infectious morbidity were raised after a report of an increased risk of bacteriemia related to the use of LE in neonates (Freeman *et al.* 1990). However in an extensive clinical trial in patients undergoing bone marrow transplantation while receiving TPN there was no evidence that moderate doses of a LCT LE were associated with the incidence of bacterial or fungal infections (Lenssen *et al.* 1998).

LCT LE may have adverse effects on the immune system, especially when they are given in high doses over a short period of time. However, when administered properly they can be used safely for clinical purposes (Klein & Miles, 1994).

MCT containing LE, in a physical or structured way, may bring some advantages because of their positive effects on polymorphonuclear cells, macrophages, and cytokine production, particularly in critically ill or immunocompromized patients. This is one of the reasons to consider substitution of LCT LE with MCT/LCT LE. Accordingly, there is a tendency to prefer MCT/LCT emulsions in critically ill patients before and after surgery and in sepsis. LCT LE should be limited in specific clinical conditions like burns, cancer, hepatic dysfunction, immunocompromized status and metabolic stress.

On the other hand, fish oil containing LE, may have some advantages in patients with autoimmune diseases such as rheumatoid arthritis and intestinal inflammatory diseases or in special clinical situations where an anti-inflammatory activity is desirable (Calder, 1998).

In spite of the optimistic preliminary results concerning the parenteral use of olive oil, its effects need to be confirmed by more prospective, randomized clinical trials. Variables like amount, and type of fatty acids, infusion rates and TPN duration should also be considered.

New parenteral lipid emulsions containing *n*-3 polyunsaturated fatty acids and monounsaturated olive oil are already available in Europe. Judicious use of these new LE is mandatory especially relating to the impact on the immune system. New experimental and clinical studies are required to further establish the role of LE in clinical nutrition.

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