Lipids in parenteral nutrition: biological aspects

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Abstract

Lipid emulsions are an integral part of parenteral nutrition, and traditionally have been regarded as an energy-dense source of calories and essential fatty acids. For many years, lipids used in parenteral nutrition have been based on vegetable oils (e.g. soybean oil emulsions). However, soybean oil emulsion may not have an optimal fatty-acid composition under some circumstances when used as the only lipid source, as soybean oil is particularly abundant in one omega-6 polyunsaturated fatty acid (PUFA), linoleic acid. Hence, a progressive series of more complex lipid emulsions have been introduced, typically combining soybean oil with one or more alternative oils such as medium-chain triglycerides (MCT), and/or olive oil, and/or fish oil. The wide range of lipid emulsions now available for parenteral nutrition offers opportunities to alter the supply of different fatty acids, which potentially modifies functional properties, with effects on inflammatory processes, immune response, and hepatic metabolism. Fish oil has become an important component of modern, composite lipid emulsions, in part owing to a growing evidence base concerning its biological effects in a variety of pre-clinical models. These biological activities of fish oil are mainly attributed to its omega-3 PUFA content, particularly docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). DHA and EPA have known mechanisms of action, anti-inflammatory, immunomodulatory, and anti-oxidative properties. Specialized pro-resolving mediators such as resolvins, protectins, and maresins are synthesised directly from DHA and EPA, are key for the resolution of inflammation, and improve outcomes in many cell- and animal-based models, and recently in some clinical settings.

Introduction

This manuscript is based upon presentations given at the international summit 'Lipids in Parenteral Nutrition' on November 2–4, 2018 (Miami, FL, USA). Statements from the consensus document by Martindale et al.[1] that are most relevant to this article are shown in Table 1. The full consensus document is also available as part of this supplement.[1] These consensus statements provide practical advice regarding the use of lipid emulsions in

parenteral nutrition, and as such complement formal nutrition society guidelines on this subject.

Lipid emulsions are an integral component of parenteral nutrition, providing a major source of non-protein calories, and lowering the amount of carbohydrate that needs to be provided as part of nutritional support.[2,3] Lipids provide the building blocks for cell membranes, and supply essential fatty acids, thus preventing essential fatty-acid deficiency (EFAD).[4,5] Moreover, they allow the delivery of fat-soluble vitamins.[4] In humans, the omega-6 polyunsaturated fatty acid (PUFA) linoleic acid and the omega-3 PUFA α-linolenic acid are termed essential fatty acids as their *de novo* synthesis is not possible, and so they must be supplied exogenously.[6] These fatty acids are synthesized in plants, and so many plant ('vegetable') oils (e.g. soybean oil) are rich sources of essential fatty acids.[5] The types of lipids used in parenteral nutritional are primarily triglycerides with either medium-chain fatty acids (caprylic, capric, lauric, and myristic acids), long-chain fatty acids (palmitic, oleic, linoleic, and α-linolenic acids) or very long-chain fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) as their major components.[4] Fatty acids differ by chain length, and the presence, number and position of double bonds. These factors can affect fatty-acid properties, influencing processes such as metabolism, inflammation, immune response, oxidative stress, blood coagulation, organ function and wound healing.[4,7] Importantly, the different fatty-acid composition of lipid emulsions can result in a range of biologic effects, which may translate into changes in clinical outcomes.[4,8]

The blend of lipids used in clinical nutrition therapy has evolved over time. A pure soybean oil-based lipid emulsion has been used worldwide since its introduction in 1962, but one potential disadvantage of using only soybean oil emulsions is their relatively high omega-6 PUFA content: over 50% of the fatty acid content consisting of linoleic acid.[3,4] Following concerns that an excessive supply of omega-6 PUFA might be pro-inflammatory and immunosuppressive, more complex blends of lipid emulsions were developed using a

mixture of different oil sources.[9] A wide variety of commercially available lipid emulsions is now available for use in parenteral nutrition (Table 2).[4] Differences in fatty-acid supply can influence functional properties (biological activity) including regulation of membrane structure and function; regulation of intracellular signaling pathways, transcription factor activity and gene expression; and regulation of the production of bioactive lipid mediators.[7] Modulating the supply of fatty acids can influence health, well-being, and risk of disease states.[7] Other lipid emulsion components include phytosterols (cholesterol-like structures present in plant oils, known to inhibit bile flow); α-tocopherol (vitamin E) that acts as an antioxidant to prevent oxidative lipid damage; and phospholipids, usually phosphatidylcholine (sometimes called lecithin) used as an emulsifier.[2,4,6]

Soybean oil, omega-6 PUFA, and inflammation

Soybean oil has traditionally been used as the lipid emulsion of choice for parenteral nutrition.[2] Whilst soybean oil consists of about 53% linoleic acid it also contains omega-3 fatty acids (approximately 8% α-linolenic acid), and so it's omega 6:omega-3 fatty-acid ratio is about 7:1. However, it is important to differentiate between the plant-derived omega-3 fatty acid, α-linolenic acid, and the omega-3 fatty acids DHA and EPA, usually derived from marine (i.e. fish) sources. The main metabolic role of α-linolenic acid is to be converted into DHA and EPA, but as conversion to DHA is poor, α-linolenic acid cannot act as a substitute for DHA.[7] In the body, the omega-6 fatty acid linoleic acid is converted by the action of elongase and desaturase enzymes to form arachidonic acid. Arachidonic acid is the key omega-6 substrate for the eicosanoid pathway involved in inflammation, immunosuppression, and thrombosis.[6] Arachidonic acid is converted into eicosanoids such as 2-series prostaglandins (PGs) and thromboxanes (TXs), 5-hydroxy-eicosatetraenoic acid (HETE), and 4-series leukotrienes (LTs), thus participating in inflammatory processes and potentially suppressing cell-mediated immunity.[3] The omega-3 and omega-6 fatty acids share the same biosynthetic pathways involving the same desaturases and elongases

(Figure 1).[6,10] Thus, conversion of α-linolenic acid to EPA (and onwards to DHA) competes with the conversion of linoleic acid to arachidonic acid, because the same enzymes are used, excess linolenic acid can inhibit DHA and EPA biosynthesis.[10] Overall, a high exogenous supply of omega-6 fatty acids may create a less optimal inflammatory, immunosuppressive and coagulatory environment, and can lead to poor outcomes.[11] A preponderance of omega-6 fatty acids may worsen the biphasic immuno-inflammatory response to a traumatic insult (Figure 2), characterised by increased generation of inflammatory mediators, and then a shift towards a hyper-inflammatory yet immunosuppressed state. Thus, there is growing consensus that lipid emulsions based entirely on soybean oil should be avoided in favor of parenteral lipid emulsions in which the linoleic acid and α-linolenic acid content may be partially replaced by medium-chain triglycerides (MCTs), olive oil providing monounsaturated fatty acids (MUFA), and/or fish oil providing EPA and DHA.[8,12] Using such alternative lipid emulsions may be particularly valid for critically ill hypermetabolic patients in highly inflammatory states, such as following major surgery, trauma, burns, and those with sepsis.[8,12]

Alternatives to pure soybean oil emulsions

A range of lipid emulsions other than those containing pure soybean oil are available in many countries, and all of these reduce the proportion of fatty acids supplied as omega-6 PUFAs (Table 2).[4] These alternatives contain different proportions of fatty acids such as MCTs (caprylic, capric, lauric and myristic acids), oleic acid, DHA and EPA, and thus have at least the potential to deliver different bioactivities. For example, MCTs, derived from purified coconut oil or palm kernel oil, are a readily available energy source that is ketogenic, protein sparing, and relatively resistant to peroxidation, whilst not affecting blood triglyceride levels.[4,8] MCTs are absorbed and metabolised rapidly with little tendency to deposit as body fat.[13] Furthermore, MCTs are generally regarded as relatively ‘immune neutral’ in comparison with pure soybean oil lipid emulsions.[8]

Oleic acid, an omega-9 MUFA, is the main fatty acid supplied by olive oil, and considered to have less potential impact on immune function, inflammation and blood coagulation than lipid emulsions with a higher omega-6 PUFA content.[4,14] Lipid peroxidation may be a potential problem for PUFAs as they contain multiple carbon double bonds (which are peroxidation targets), whereas MUFAs such as oleic acid only have one such bond.[8] Thus, because of its high MUFA content, olive oil is thought to be more resistant to peroxidation and oxidative stress than soybean oil.[8] Lipid emulsions rich in olive oil may have a less potential effect on host immune response than pure soybean or MCT/soybean oil lipid emulsions, with little effect on lymphocytes, natural killer cells and neutrophils.[8,15] However, *ex vivo* experimental model studies for ulcers and necrosis colitis have shown that olive oil/soybean oil lipid emulsions may cause more unfavourable effects than soybean oil or soybean oil/MCT.[16] The effects of parenteral nutrition incorporating fish oil, in particular DHA and EPA, are covered in the following section.

Focus on lipid emulsions containing fish oil

There is growing evidence that standard lipid emulsions based solely on soybean oil should be avoided in some clinical situations in favor of lipid emulsions containing alternatives such as fish oil, which is rich in the very long-chain fatty acids, DHA and EPA.[12] In general, omega-3 fatty acids work by opposing and so modulating the actions of omega-6 fatty acids (Figure 2), with DHA and EPA exerting beneficial effects on blood lipids, blood coagulation, inflammation, hepatic metabolism, endothelial function and cardiovascular disease.[3,4] Not only does the inclusion of fish oil decrease the provision of potentially oxidative, inflammatory/immunosuppressive, and prothrombotic omega-6 fatty acids, but DHA and EPA have biologic effects including anti-inflammatory, immunomodulatory, and anti-oxidative properties, and seem likely to reduce the risk of infections and length of hospital or ICU stay.[4,12,17,18] These potential clinical benefits may occur by a range of mechanisms with DHA and EPA acting via changes in the composition of cell membranes (Figure 3).[19]

Just as enzymatic conversion of the omega-6 PUFA arachidonic acid gives rise to bioactive eicoisanoids (see earlier), EPA is converted to 3-series PGs and TXs, and 5-series LTs using the same pathways. The EPA-derived mediators are typically less potent than the mediators derived from arachidonic acid.[3] Moreover, the discovery of potent specialized pro-resolving mediators (SPMs) has provided an additional molecular basis for the many of the health benefits attributed to the omega-3 fatty acids.[20,21] EPA and DHA give rise to SPMs such as resolvins (both EPA and DHA), protectins and maresins (DHA only), which play a key role in resolution of inflammation, reduction of tissue injury and promotion of wound healing.[4,22] SPMs can control the extent and duration of inflammation and speed the return to homeostasis.[22,23] A summary of the anti-inflammatory actions attributed to omega-3 PUFAs and the likely mechanisms involved are shown in Table 3.[24]

The paradigm for an acute inflammatory response can now be viewed as consisting of two stages: initiation (productive and transition phases) and resolution.[25] Traditionally, there has been a view that excess inflammatory mediator production underlies chronic inflammation, but increasingly evidence shows that disruptions in production of endogenous SPMs may be at least as equally important, as they not only actively terminate the production of inflammatory mediators but also directly stimulate macrophage phagocytosis of both apoptotic cells and bacteria, promote egress of phagocytes from sites of inflammation, regulate polymorphonuclear neutrophil (PMN) apoptosis, promote chemokine scavenging, and stimulate tissue repair and regeneration.[26] Thus, SPMs have been shown to improve outcomes in many cell- and animal-based models, limiting neutrophilic infiltration and enhancing macrophage resolution responses, and thus may have an important role in conditions characterized by excessive uncontrolled inflammation.[3] It is also important to note that some chronic inflammatory diseases are associated with defects in production of SPMs.[26] Furthermore, administration of DHA or EPA increases resolvin production in animal models of inflammation, and human studies have shown that omega-3 PUFA intake increases the concentration of resolvins and their biosynthetic pathway markers in plasma or

serum.[26,27] EPA and DHA may also exert anti-inflammatory effects by acting via other pathways, including suppression of nuclear factor κB signaling and activation of peroxisome proliferator activated receptor gamma, thus inhibiting production of inflammatory cytokines, adhesion molecules, cyclooxygenase-2, inducible nitric oxide synthase and matrix metalloproteinases.[4]

In summary, EPA and DHA are direct precursors of potent SPMs (resolvins, protectins, maresins), have desirable bioactivities with known mechanisms of action, and are likely to exert any clinical benefits via anti-inflammatory and pro-resolution pathways. Thus, there appears to be a firm biologic basis for fish oil in particular alongside other alternative lipid emulsions to partially replace soybean oil as a component of parenteral nutrition.

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Figure legends

Figure 1. Metabolic processing of omega-3 (n-3), omega-6 (n-6), and omega-9 (n-9) polyunsaturated fatty acids (PUFAs) by shared elongases and desaturases. Fatty acids in bold are key intermediates: arachidonic acid, eicosapentaenoic acid (EPA) and docosahexaenic acid (DHA).

Figure 2. The biphasic immuno-inflammatory response to a traumatic insult, characterised by increased generation of inflammatory mediators and then a shift towards an anti-inflammatory immunosuppressed state, may be further worsened by a preponderance of omega-6 fatty acids but improved by the presence of omega-3 fatty acids DHA and EPA. DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HLA, human leukocyte antigen; NFκB, nuclear factor kappa B.

Figure 3. Mechanisms by which docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) act via changes in the composition of cell membranes (area shaded gray), potentially leading to beneficial clinical outcomes. Figure reproduced with permission from Calder PC. Intravenous lipid emulsions to deliver bioactive omega-3 fatty acids for improved patient outcomes. *Mar Drugs.* 2019;17(5):274.[19]

Table 1. Consensus statements from the lipids in parenteral nutrition – international summit (November 2–4, 2018, Miami, FL, USA) relevant to this article.[1]

Statement number	Consensus statement	Expert voting results
1	We recognize that lipid emulsions are an integral part of PN. Originally, lipid emulsions were an energy-dense source of calories and provided essential FAs.	100% agreement (16 agree, 0 do not agree, 0 do not wish to answer).
2	Subsequent generations of lipid emulsions include combinations of various lipid components, predominantly with the aim of improving the safety profile of ILEs. Each lipid has its own FA composition and biological effects, which may be more or less beneficial on, for example, pro- or anti-inflammatory, immune-stimulating or modulating properties.	100% agreement (17 agree, 0 do not agree, 0 do not wish to answer).
3	An important component of modern, composite lipid emulsions is fish oil. The group recognizes that the biological effects of fish oil are increasingly characterized in preclinical studies (different models). The biological effects of fish oil can mainly be attributed to omega-3 polyunsaturated FAs, especially EPA and DHA, and include anti-inflammatory and immunomodulatory and anti-oxidative properties.	94% agreement (16 agree, 1 does not agree, 0 do not wish to answer).
4	In the view of the group, the latest findings regarding the role of specialized pro-resolution mediators (SPMs) in immune modulation adds considerably to our understanding of the biological characteristics of fish oil. SPMs are a new class of mediators, which are produced directly from EPA and DHA, and are increasingly recognized as key mediators in the resolution of inflammation.	94% agreement (16 agree, 0 do not agree, 1 does not wish to answer).

DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FA, fatty acid; ILE, intravenous lipid emulsion; PN, parenteral nutrition; SPM, specialized pro-resolution mediator.

Table 2. Typical fatty acid compositions (% of total) of commercially available lipid emulsions for use in parenteral nutrition. Reproduced from Calder et al., 2018. Lipids in the intensive care unit: Recommendations from the ESPEN Expert Group. *Clin Nutr*. 2018;37(1):1–18.[4] Note: need to seek permission

	Pure soybean oil[a]	**Soybean Oil/MCT oil blend[b]**	**Restructured soybean oil/MCT oil blend[c]**	**Pure fish oil[d]**	**Olive oil/soybean oil blend[e]**	**Fish oil blend 1[f]**	**Fish oil blend 2[g]**
Lipid source	100% SO	50% SO, 50% MCT	64% SO, 36% MCT	100% FO	20% SO, 80% OO	40% SO, 50% MCT, 10% FO[j]	30% SO, 30% MCT, 25% OO, 15% FO[c]
SFA	15	58	46	21	14	49	37
MUFA[h]	24	11	14	23	64	14	33
PUFA	61	31	40	56	22	37	30
n-3 PUFA:	8	4	5	48	3	10	7
ALA	8	4	5	1	3	4	2
EPA	–	–	–	20	–	3.5	3
DHA	–	–	–	19	–	2.5	2
n-6 PUFA[i]	53	27	35	5	19	27	23

ALA, α-linolenic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FO, fish oil; LCT, long-chain triglycerides; PUFA, polyunsaturated fatty acid; MCT, medium-chain trigylcerides; MUFA, monounsaturated fatty acid; OO, olive oil; SFA, saturated fatty acid; SO, soybean oil.

[a]Intralipid®; [b]Lipofundin® MCT/LCT; [c]Structolipid®; [d]Omegaven®; [e]ClinOleic®; [f]Lipoplus®/Lipidem®; [g]SMOFlipid®; [h]mainly oleic acid; [i]mainly linoleic acid; [j]the fatty acid composition of fish oil is more variable than that of vegetable oils so that the precise contribution of different fatty acids may differ in different batches. Note that the fish oil used in Lipolus® is more concentrated in EPA and DHA than that used in SMOFlipid® so that 10% fish oil in Lipoplus® provides more EPA and DHA than 15% fish oil in SMOFlipid®.

Table 3. Summary of the anti-inflammatory actions attributed to marine omega-3 polyunsaturated fatty acids and the likely mechanisms involved. Reproduced from Calder PC. Omega-3 polyunsaturated fatty acids and inflammatory processes: nutrition or pharmacology? *Br J Clin Pharmacol*. 2013;75(3):645–662.[24] Note: need to seek permission

Anti-inflammatory effect	**Likely mechanism involved**
Reduced leukocyte chemotaxis	Decreased production of some chemo-attractants (e.g. LTB4); down-regulated expression of receptors for chemo-attractants
Reduced adhesion molecule expression and decreased leucocyte–endothelium interaction	Down-regulated expression of adhesion molecule genes (via NF**κ**B, NR1C3 (i.e. PPAR-**γ**) etc.)
Decreased production of eicosanoids from arachidonic acid	Lowered membrane content of arachidonic acid; inhibition of arachidonic acid metabolism
Decreased production of arachidonic-acid-containing endocannabinoids	Lowered membrane content of arachidonic acid
Increased production of 'weak' eicosanoids from EPA	Increased membrane content of EPA
Increased production of anti-inflammatory EPA- and DHA-containing endocannabinoids	Increased membrane content of EPA and DHA
Increased production of pro-resolution resolvins and protectins	Increased membrane content of EPA and DHA; presence of aspirin
Decreased production of inflammatory cytokines	Down-regulated expression of inflammatory cytokine genes (via NF**κ**B, NR1C3 (i.e. PPAR-**γ**) etc.)
Decreased T cell reactivity	Disruption of membrane rafts (via increased content of EPA and DHA in specific membrane regions)