

## Novel lipid sources in parenteral and enteral nutrition

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Lipids are an important energy source in the parenteral and enteral nutrition of critically-ill patients because of their high energy density (37.6 kJ/g) and low osmolarity, although in conventional parenteral nutrition only the recently available 300 g lipid/l emulsions (12.5 MJ/l) are more energy dense than 700 g dextrose/l (9.6 MJ/l) as starting components in total parenteral admixtures, e.g. 200 g lipid/l at 8.3 MJ/l and 100 g lipid/l at 4.2 MJ/l. Lipids also serve as a source of two fatty acids,  $\alpha$ -linolenic and linoleic, that are essential in human nutrition at less than 0.5% and about 1.0% total energy respectively; however, up to 4% of energy as linoleic acid will further improve N utilization. Fat-soluble vitamins (A, D, E, K) and other important nutrients which have not been established as being essential (i.e. carotene, lycopene, flavonoids) have improved absorption in the presence of fats. Man is unable to desaturate long-chain fatty acids at either C-3 ( $\alpha$ -linolenic) or C-6 (linoleic) from the methyl end ( $\omega$ -C) but can at C-9, a situation that results in three common families of fatty acids in human metabolism  $n$ -3,  $n$ -6, and  $n$ -9.  $\alpha$ -Linolenic acid (18:3 $n$ -3) thus serves as the precursor for eicosapentaenoic acid (20:4 $n$ -3; EPA) and docosahexaenoic acid (22:6 $n$ -3; DHA) and linoleic (18:2 $n$ -6) for dihomo- $\gamma$ -linolenic acid (20:3 $n$ -6; DHLA) and arachidonic acid (20:4 $n$ -6; AA) after elongation of the C chains and further desaturation but preservation of their  $n$ -3 or  $n$ -6 identity. These latter compounds have unique importance in that they serve as precursors for the eicosanoids (EPA, DHLA, AA) which are ubiquitous second messengers or have unique effects (DHA in vision and brain function, AA as a second messenger) in addition to their properties as polyunsaturated fatty acids. These three families of fatty acids have numerous interrelationships which have considerable clinical impact. For example,  $\alpha$ -linolenic acid can be converted in man to EPA or DHA but with limited efficiency (Meydani *et al.* 1993) which makes this a less-rapid and effective means of increasing the EPA content of membranes. Although  $\alpha$ -linolenic acid inhibits the elongation and desaturation of linoleic acid to DHLA and AA, EPA has a much larger impact on AA concentration in tissue membrane phospholipids (Wu *et al.* 1996).

### LIPIDS IN CLINICAL NUTRITION

Fat is a preferred fuel in stressed individuals (Macfie *et al.* 1981) with maximal benefit at approximately 10–15% of total energy (Mochizuki *et al.* 1984; Trocki *et al.* 1987; Gollaher *et al.* 1993; Selleck *et al.* 1994; Garrel *et al.* 1995). Long-chain triacylglycerols improve N balance as well as reducing triacylglycerol accumulation in critically-ill animals and human subjects (Macfie *et al.* 1981; Pomposelli *et al.* 1986). Excess parenteral administration of parenteral long-chain-triacylglycerol emulsions can impair reticulo-endothelial system function in man (Seidner *et al.* 1989; Jensen *et al.* 1990) which may have been a factor in the increased morbidity due to infection in patients receiving pre-operative total parenteral nutrition containing fat compared with glucose and amino acids alone as the energy source (Muller *et al.* 1982). It has been stated that the adverse effects of parenteral long-chain-triacylglycerol administration have only been seen when lipid is

infused at rates greater than total energy expenditure (0.11 g/kg per h; Klein & Miles, 1994).

#### ADVERSE EFFECTS OF LIPIDS

A second proposed mechanism for adverse consequences due to lipid administration has been the dietary  $n-3:n-6$  value. Over the tens of thousands of years of an agriculture-based existence, the dietary  $n-3:n-6$  remained stable at about 1; however, in the past 100 years or so revolutionary changes in the food supply and dietary habits have caused this ratio to fall dramatically, to less than 0.1 (Simopoulos, 1991). There is now considerable evidence that this has provided a more pro-inflammatory condition related to changes in membrane fluidity, to types and amount of eicosanoid production as second messengers in cellular signalling, and to arachidonic acid availability as a second messenger in its own right. AA and EPA are prominent components of the lipid membranes of essentially all cells, and it is when these fatty acids are in the 2-position of membrane phospholipids that their release is provided by the action of phospholipase A<sub>2</sub> (EC 3.1.1.4) particularly after cytokine or endotoxin stimulation. The third major family of unsaturated fatty acids is the  $n-9$  fatty acids. Oleic acid (18:2 $n-9$ ) is the counterpart of  $\alpha$ -linolenic and linoleic acid which can be elongated and desaturated by the same enzymes to produce eicosatrienoic acid (20:3 $n-9$ ). This compound, also called the Mead acid, is not a precursor for eicosanoids, but does indicate essential fatty acid deficiency when present, because it is only formed when there is insufficient  $\alpha$ -linolenic or linoleic acid for elongation or desaturation. Although in animal studies essential fatty acid deficiency improves the outcome from endotoxin shock by limiting eicosanoid production, particularly thromboxane A<sub>2</sub> (Cook *et al.* 1980), this has limited clinical application, since essential fatty acid deficiency produces severe immunodeficiency. In fact, several of the infants in whom essential fatty acid deficiency in human subjects was first identified, died of infection, as a consequence of consuming a linoleic acid-deficient formula (Hansen *et al.* 1963).

#### MARINE OILS

The reported benefits of marine-oil feeding have been principally attributed to changes in receptor function and signalling efficiency related to membrane fluidity, with greater fluidity with increased polyunsaturation and decreased cholesterol incorporation, and to changes in the type and amount of eicosanoids produced (Kinsella *et al.* 1990). Fish-oil supplementation has been shown to reduce the production of interleukin-1 and tumour necrosis factor by peripheral blood mononuclear cells in response to endotoxin or plant lectins (Endres *et al.* 1989), presumably through signal modulation. Eicosanoids arising from AA are prostaglandins (PG), prostacyclins, and thromboxanes of the 2-series and leukotrienes of the 4-series, whereas EPA yields 3-series prostanoids and 5-series leukotrienes. PGE<sub>2</sub> is a potent immunodepressant and vasodilator, thromboxane A<sub>2</sub> a vasoconstrictor and platelet aggregator, and leukotriene B<sub>4</sub> a leuko-adherent and permeability-increasing factor; their counterparts arising from EPA are considerably less potent (Hwang, 1989; Kinsella *et al.* 1990). The reported effects of  $n-3$  polyunsaturated fatty acids on immune function have been contradictory (Payan *et al.* 1986; Meydani *et al.* 1991; Berger *et al.* 1993; Wu *et al.* 1996). These differences have been attributed to varied experimental conditions, including age, species, diet, feeding period etc., but the most prominent factor appears to be tocopherol content (Wu *et al.* 1996). Although it is widely accepted that higher polyunsaturated fatty acid intake increases the need for tocopherol,

this has been largely ignored. In this study in primates (Wu *et al.* 1996) fish oil with adequate tocopherol supplementation improved T cell-mediated mitogenic response and interleukin 2 production, but this effect was not seen with  $\alpha$ -linolenic acid, although both fatty acids reduced PGE<sub>2</sub> production in T cells. Similar effects of tocopherol supplementation of fish oil to improve immune function were proposed in human subjects after clinical study (Meydani *et al.* 1993). In the former study (Wu *et al.* 1996), the finding that  $\alpha$ -linolenic acid has less effect than EPA on EPA and AA levels in cellular membranes, PGE<sub>2</sub> production, and vitamin E content as well as immune function support the contention that EPA supplementation appears to be a more potent dietary manipulation.

#### CLINICAL STUDIES OF MARINE OILS

Human studies of fish-oil supplementation in enteral and parenteral nutrition are more consistently positive. In burn patients consuming one of three diets differing primarily in fat content, with equal and limited amounts of fish oil and safflower oil (approximately 15 % each of total energy) in one diet, moderate (approximately 12 % of total energy) amounts of maize oil in the second diet and large (approximately 28 % of total energy) amounts of soyabean oil in the third diet, serious nosocomial infections and death were significantly more common in the high-vegetable-oil diet (Gottschlich *et al.* 1990). Two studies by Daly *et al.* (1993, 1995) compared a fish-oil-containing diet, which also contained other putative immunostimulatory nutrients (arginine and nucleotides), to two different vegetable-oil diets following major abdominal surgery for cancer of the gastrointestinal tract. Nosocomial infection rates and length of stay were reduced by the experimental diet. A much larger study of the same fish-oil-containing diet in critically-ill patients in intensive care units demonstrated important trends for shortening of hospital stay (Bower *et al.* 1995). A recent trial in burned patients comparing a moderate (35 % of total energy) fat intake with two low-fat (15 % of total energy) diets with or without fish oil demonstrated lower infectious morbidity and shortened length of stay with both low-fat diets (Garrel *et al.* 1995), suggesting that level of fat intake may be particularly important. In preliminary form, a recent study in trauma patients who received either glucose and amino acids alone or with the addition of parenteral soyabean-oil emulsion at approximately 40 % of energy content demonstrated substantial prolongation of stay in the intensive care unit, ventilator dependence, and infectious morbidity along with laboratory evidence of cellular immunosuppression in the parenteral fat group (Battistella *et al.* 1995).

#### NOVEL LIPIDS

Most dietary lipids are triacylglycerol compounds which are esters of glycerol and C<sub>12</sub>–C<sub>18</sub> fatty acids and are designated long-chain triacylglycerols. By convention, C<sub>2</sub>–C<sub>4</sub> fatty acids are considered short-chain fatty acids and C<sub>6</sub>–C<sub>12</sub> fatty acids, medium-chain fatty acids. Short-chain and medium-chain fatty acids are found in combination with long-chain fatty acids in quantitatively significant amounts to form a mixed triacylglycerol in only a few naturally-occurring fats. These include about 5 g butyrate (4:0) and 10 g medium-chain fatty acids (6:0, 8:0, 10:0 and 12:0 in approximately equal amounts)/100 g total fatty acids in butter and 50 g medium-chain fatty acids (mostly 12:0)/100 g total fatty acids in a number of tropical oils (i.e. coconut, babassu, palm kernel). The majority of edible fats contain long-chain fatty acids only. Medium-chain triacylglycerols (MCT) are derived by physical separation of tropical oils which removes lauric acid (12:0) and other long-chain

fatty acids to leave chiefly caprylic (8:0) and capric acid (10:0) in a 2:1 ratio. There are a number of unique aspects of MCT metabolism, including no requirement for micelle formation before absorption, rapid absorption without the need for lipase (*EC* 3.1.1.3) action, absorption as medium-chain fatty acids bound to albumin in the portal vein, preferential oxidation, and limited capacity for storage (Bach & Babayan, 1982). MCT are widely employed in enteral products as diets for special medical purposes and are available as parenteral emulsions in Europe. Physical mixtures of MCT and long-chain triacylglycerols (LCT) have been shown to have a thermogenic effect in animals (Mok *et al.* 1984) and human subjects (Mascioli *et al.* 1991), and also to be N sparing (Mascioli *et al.* 1991). There is much better clearance by the reticulo-endothelial system without evidence of interference under conditions in which LCT emulsions demonstrate impairment (Seidner *et al.* 1989).

In clinical study of patients undergoing hepatic resection, peri-operative feeding with total parenteral nutrition including a MCT-LCT emulsion showed reduced infectious morbidity and improved hepatic function supporting their exceptional tolerance in the setting of impaired hepatic function (Fan *et al.* 1994). However, the thermogenic capacity of MCT, their lack of essential fatty acids, and limited parenteral and enteral tolerance have made them less than ideal substrates under certain circumstances unless combined with long-chain triacylglycerols (Sandstrom *et al.* 1995).

#### STRUCTURED LIPIDS

Structured lipids composed of various chemical combinations of long-, medium-, and/or short-chain fatty acids have unique properties not found in simple physical mixtures that reflect their unique parentage. They are produced by interesterification of mixtures of various triacylglycerols, particularly a long-chain triacylglycerol such as vegetable oil or fish oil, with an MCT. The commercial process of interesterification leads to randomization so that all possible structures are found including LML, LMM, LLM, MLM, MMM and LLL (where L and M represent long- and medium-chain fatty acids respectively at positions 1, 2 and 3 respectively of triacylglycerols; Klemann *et al.* 1994). The structured lipid MLM is more rapidly and efficiently absorbed than a long-chain triacylglycerol (Jandacek *et al.* 1987). A long-chain fatty acid in position 2, such as linoleic acid or EPA, is preferentially absorbed and preferentially retained to be stored in membrane phospholipids rather than to be oxidized (Jensen *et al.* 1994; Christensen *et al.* 1995). Thus, improved fat, as well as linoleic acid, absorption could be anticipated from these two species in malabsorptive states. Compounds in the form of LML and LMM would lead to absorption of the two monoacylglycerols of the medium-chain fatty acid, re-esterification in the intestinal cell as LML, with subsequent lymphatic absorption and appearance in the systemic circulation as a structured lipid. Such compounds have been convincingly demonstrated to improve protein metabolism in a variety of catabolic states in animals (DeMichele *et al.* 1988; Teo *et al.* 1989). Parenteral structured lipids have been shown in human subjects to be well tolerated and to have improved oxidation compared with conventional long-chain triacylglycerols.

A recent clinical study of the physiological and clinical consequences of a structured lipid made from a fish oil (400 g/kg) and medium-chain triacylglycerol (600 g/kg) has been conducted using jejunal feeding in patients after major surgery for upper gastrointestinal cancer (Kenler *et al.* 1996). Significant improvement in gastrointestinal tolerance to the experimental formula compared with a formula employing a physical mixture of vegetable oil and MCT was found. Furthermore, there was significant improvement in renal, hepatic,

and immune function also, presumably related to alteration in eicosanoid balance. As has been shown in animals being continuously fed with fats that have a composition that is considerably different from the normal diet composition (Palombo *et al.* 1996), rapid incorporation of EPA and reduction of AA within several days is characteristic of this mode of feeding, making this a relevant therapeutic option in the critically ill.

#### CONCLUSION

In summary, lipids have become an area of intense interest and investigation for use in parenteral and enteral nutrition, given their essentiality in nutrition and protein- and carbohydrate-sparing ability on the one hand, and their prominent potential impact for benefit or harm on the inflammatory response related to their total contribution to energy and their *n*-6:*n*-3 value on the other. The available evidence is quite strong that the next major advance in clinical nutrition in the critically ill, perhaps equivalent in importance to the dramatic reduction in energy intake now recommended, will be the determination of the optimal lipid type and amount when formulating a complete nutrient admixture.

B. R. B. is a consultant to Stepan Inc. which manufactures structured lipids and receives royalty payments from Sandoz Nutrition related to fish oil.

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