

N-3 lipids in sepsis

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Immunological modulation using lipids

Recent concepts in nutrition attempt to combine caloric support and modulation of the immune response (“immunonutrition”). Dietary n-3 lipids have long been recognized for their potential to change leukocyte activity, lipid mediator generation, and cytokine release. In an ICU setting often there is a need for parenteral nutrition in patients with acute inflammatory diseases such as sepsis and the adult respiratory distress syndrome (ARDS). The underlying mechanism of these diseases is a hyper-inflammatory response with exaggerated leukocyte activity, consecutive microcirculatory disorders, and secondary organ damage. The therapy of these patients is hampered by the fact that hyper-inflammatory and hypo-inflammatory phases alternate requiring an adapted therapy.

Lipid emulsions based on soy bean oil which are rich in n-6 long-chain triglycerides (LCT) have been the standard for lipid-based parenteral nutrition for a long time. In spite of this, experimental and clinical investigations have reported unfavourable results when these emulsions were employed. However, fish oil-based lipid emulsions, which are rich in n-3 lipids, are now available for parenteral nutrition, and thus offer an even better possibility to combine nutrition and pharmacological effects.

Biochemical basis of immunologic modulation - arachidonic acid- and eicosapentaenoic acid-based lipid mediators

Lipid mediators are synthesized via cyclooxygenase, lipoxygenase, and cytochrome P-450 pathways typically using arachidonic acid as substrate. These mediators include prostaglandins, thromboxanes, leukotrienes (LT) (all summed as eicosanoids), and platelet-activating factor (PAF), which affect the secretion of immune-regulatory cytokines, and the release of secondary mediators like reactive oxygen species or proteases. Eicosanoids control both pro-inflammatory and anti-inflammatory processes that are particularly relevant to sepsis. Furthermore, prostaglandins and thromboxanes influence vasomotor tone and regulate blood flow in various vessel beds. Modulation of inflammatory response by n-3 fatty acids is effected by the same enzymatic conversions but using eicosapentaenoic acid instead of arachidonic acid. Man is thought to have evolved in an environment where n-3 fatty acids were more abundant in nutrition than in our

western diet. Therefore a “regular” immune response may have involved lipid mediators based on both arachidonic acid and eicosapentaenoic acid. Leukotrienes, thromboxanes, and prostaglandins formed from eicosapentaenoic acid are generally considered to have less pro-inflammatory impact on immune response.

Polyunsaturated n-6 and n-3 fatty acids may furthermore alter protein-lipid-interactions and lipid-based signal transduction pathways. Dietary intake of n-3 fatty acids for several weeks resulted in a suppressed release of tumor-necrosis factor (TNF)- α and interleukin (IL)-1 from mononuclear cells. Receptor-operated signalling is based on cell membrane and second-messenger pathways within the cell. Many of these pathways are lipid-based or are sensitive to modulation by n-3 or n-6 lipids.

Difference of parenteral versus enteral administration of lipids

Although most epidemiological and therapeutic experiences with n-3 fatty acids are based on dietary application, oral therapy has some drawbacks. The therapeutic effect has a slow onset and it is therefore not feasible for acute diseases as sepsis. Using fish oil capsules, fatty acids that enter the circulation after crossing the intestinal border are packed as triglycerides in vesicles and the availability of *free* n-3 fatty acids is limited. In contrast, infusion of lipid emulsions bypasses these lipid remodeling pathways; synthetic lipid aggregates activate endothelial lipoprotein lipases and induce a translocation of the enzyme from the cellular binding site into the vascular compartment. The resultant acute increase in plasma free fatty acids is in excess of the local cellular uptake, and rapidly increases the concentration of free fatty acids. Infusion of lipid emulsions based on n-3 fatty acids generates increases in plasma free fatty acid concentrations that are an order of magnitude greater than that observed with oral administration.

Feeding a septic patient using lipid emulsions

Sepsis is the leading cause of death in non-coronary intensive care units. More than 750,000 cases of sepsis are diagnosed per year, with mortality rates ranging between 30 to 60 % accounting for about 200,000 deaths per year in U.S.A. alone. The number of patients with sepsis will increase by up to 1.5 % annually, faster than the anticipated growth of the population. The term systemic inflammatory response syndrome (SIRS) reflects the fact that such systemic inflammatory reaction is not only triggered by microbial invasion, but also encountered in response to severe tissue injury. Severe metabolic changes occurring during sepsis include a shift in substrates used for energy supply. With increasing severity of the disease, oxidation of glucose declines, whereas oxidation of lipids is intensified. Although physiological nutrition is based on enteral feeding, in an intensive care setting septic patients may require additional intravenous nutrition whenever the status of the

patient prevents enteral feeding. Patients with severe sepsis, septic shock, or adult respiratory distress syndrome (ARDS) may even need total parenteral nutrition.

Sepsis as a disease with changing immunological performance

In septic shock a massive hyper-inflammatory reaction is created by the host in the initial phase of the disease. In parallel, an anti-inflammatory reaction is also initiated, that has been termed "compensatory anti-inflammatory response syndrome" (CARS). It consists in a combination of an increase in anti-inflammatory cytokines, impaired neutrophil function, and inert monocytes which together lead to a weakened host defence and increased susceptibility to secondary infections. Until now, no fast and accurate method for the determination of the immune status of a septic patient is generally available. Based on this data, one therefore has to balance the advantages and disadvantages of any immune-modulating drug. The optimal use, timing, and dose of immune-modulating drugs in septic patients are an ongoing matter of debate.

Impact of a parenteral lipid emulsions based on pure fish oil in septic patients

The initial reaction in severe sepsis and septic shock consists of a hyper-inflammatory response, and thus may be a good target for anti-inflammatory drugs. This situation was judged as a good possibility for the use of a n-3 lipid-based emulsion not as a supplement to n-6 based lipid emulsion but as sole source of intravenous lipids.

Using a n-3 lipid-based emulsion in patients with severe sepsis, a complete shift in the patient's lipid profile was achieved. The fish oil-based preparation shifted the n-3/n-6 ratio of plasma free fatty acids from a n-6 to a n-3 predominance, and reduced the endotoxin-elicited monocyte pro-inflammatory cytokine generation. In contrast, endotoxin-induced monocyte cytokine generation was markedly amplified by an n-6 lipid infusion increasing the inflammatory response in this disease.

In a second study in septic shock patients requiring parenteral nutrition, a fish oil-based emulsion for intravenous administration was tested in comparison to a conventional lipid emulsion. Again, the plasma free fatty acid composition was shifted towards predominance of n-3 over n-6 fatty acids. This was accompanied by the appearance of n-3 derived prostanoids and leukotrienes. Neutrophil function, found to be consistently depressed in the septic shock patients, was partially restored in response to the n-3, but not in response to the n-6 lipid emulsion. Despite these promising results from pilot studies, a general recommendation for parenteral nutrition solely using fish oil-based lipids cannot be made, and should be restricted to studies or selected patients. However, the conventional lipid emulsions generally used in septic patients may have dramatic or even undesired effects on leukocyte function in these patients.

Going for a balanced n-6 / n-3 ratio

Different ratios of n-6/n-3 lipids used for parenteral nutrition may have differential effects on immune-function. An n-6/n-3-ratio of 370:1 or 1:7.6 exhibited the highest immuno-suppressive activity in a rat heart transplantation model using intravenous lipid emulsions. However, a ratio of 2.1:1 did not modulate the transplant rejection. This ratio is close to the “lipid environment” man developed in, and today a n-6 / n-3 ratio of about 2:1 to 3:1 are thought to have only minor if any impact on immune function. This ratio can be achieved by supplementation of conventional lipid emulsions with fish oil-based lipid emulsions, or with the use of commercially available latest generation lipid emulsions which offer a n-6/n-3 ratio of approximately 2.5 : 1. The idea of fish oil supplementation to conventional lipids to achieve a similar ratio was explored in a study in septic patients available in abstract form only. Conventional parenteral nutrition based on soy bean oil was compared to soy bean oil supplemented with fish oil. Patients receiving the supplemented nutrition exhibited less re-operations, a faster drop in C-reactive protein levels, and a shorter stay in the intensive care unit and in hospital. Using an intravenous lipid emulsion with a balanced n-6 / n-3 ratio in contrast to the action of conventional lipids, leukocyte function in septic patients are thought to be preserved, thereby preventing excessive hyper-inflammation and counter-regulatory immune-suppression.

Conclusion

Lipids used for intravenous nutrition have immune-modulating properties in addition to caloric support. They influence biochemical pathways and intra-cellular and inter-cellular signal transduction. The n-3 fatty acids present the possibility to counterbalance the negative effects of n-6 fatty acids on immune system function and the regulation of vascular tone. Employed as a supplement to achieve a balanced n-6 / n-3 ratio, fish oil-derived lipid emulsions might evolve as a new option to adapt nutrition to the metabolism of a septic patient and to prevent hyper-inflammation or immune-suppression generated by conventional lipid emulsions.