Introduction

The role of parenteral lipid emulsions in acute respiratory diseases still remains controversial amongst intensivists. This nutritional component, which has been considered so far as toxic in ARDS, would on the contrary probably have beneficial effects, able to reduce the inflammatory aspect of some pulmonary diseases. These emulsions would not only be nutrients, but real treatments of some pulmonary diseases. This article studied both the toxic and the beneficial aspects of these lipid emulsions in pulmonary diseases.

Lung toxicity of lipid emulsions

Long-chains triglycerides emulsions

A short time after the first soybean oil-based emulsions have first been used, relations between lipid emulsions and pulmonary function were noticed. Several studies showed that a 500 ml Intralipid® infusion in 4 hours in a healthy person induced an alteration of CO₂ diffusion, while PaO₂ was not significantly changed. The alterations in CO₂ diffusion were quickly reversible with the normalization of hypertriglyceridemia. On the whole, Intralipid®-induced hypertriglyceridemia did not seem to have any particular clinical consequence in adults with a normal pulmonary function [1,2]. Thus, studying burnt patients, Wilmore et al. did not find any alteration of the pulmonary function, after an infusion of 500 ml Intralipid® 10% in 4 hours. Their conclusion was that lipid emulsions were innocuous in stressed patients [3]. Later, several clinical studies showed it was not the same in patients with respiratory diseases. In stressed patients with acute respiratory failure, Venus B. et al. [4] noticed that a 10-hour infusion of 500 ml Intralipide® 20% induced a rise of the intrapulmonary shunt (13.7 ± 3.6% before infusion; 18.0 ± 6.5% after). This difference did normalize after the hypertriglyceridemia was corrected. The change in the intrapulmonary shunt occurred at the same time as a rise in pulmonary blood pressure and in pulmonary vascular resistances. The authors thought these abnormalities were due to hypertriglyceridemia, which induced lipid deposits in pulmonary capillaries, as well as platelet aggregation. They also made the hypothesis that high pulmonary blood pressure seen during lipid infusion could be the result of blood flow redistribution towards poorly ventilated pulmo-

Benefits of Parenteral Lipid Emulsions in Acute Respiratory Failure

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Abstract

Lipid emulsions in parenteral nutrition can interfere with pulmonary functions in patients displaying anomalies of the ventilation-perfusion ratio. The underlying mechanisms are unknown, but involve modifications of the production of vasoconstrictor and vasodilator eicosanoids as an effect of lipid infusion. Preferential synthesis of one or other of the eicosanoid types depends on the rate of administration of the lipids. Slow flow, corresponding to the administration of 100 g of triglycerides in 10-12 hours, leads to no change in the ventilation/perfusion ratio, and has no effect on gas exchange. TCM-based emulsions, which have little interference with eicosanoids, can be administered during ARDS. However, they have few benefits over a soy emulsion administered slowly. A new finding concerning lipid emulsions is the capacity of emulsions rich in long-chain polyunsaturated fatty acids of the n-3 series (DHA and EPA), derived from fish oil and of borage oil rich in gamma-linoleic acid, to affect pulmonary inflammation and bronchial reactivity. These factors open up new and promising perspectives in the prevention and treatment of ARDS.

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nary territories. After this, several authors showed that the effects of lipid emulsions on the pulmonary function depended on the underlying disease. In patients with COPD or infectious lung disease, lipid infusion only induced a small rise in the intrapulmonary shunt, and a small alteration of the PaO2/FiO2 ratio. On the other hand, in ARDS patients with artificial ventilation, an 8-hour infusion of a ternary parenteral nutrition induced a significant reduction of the PaO2/FiO2 ratio, a rise of intrapulmonary shunt, average pulmonary arterial pressure (mPAP), and pulmonary vascular resistance [5]. It did seem that a slow infusion of lipid emulsion preferentially induced a production of vasodilating eicosanoids, while a quick infusion rather induced a production of vasoconstricting eicosanoids [6]. In infected multi-injured patients with ARDS, Mathru et al. studied the effects of a 500 ml Intralipid® 20% infusion, in 5 hours for the «fast group» and 10 hours for the «slow group» [7]. Results in the slow group, showed a 50 % rise in the intrapulmonary shunt by the middle of the infusion, with normalization by the end of it. Slow infusion induced a significant reduction of PGF1α and of thromboxane A2. During fast infusion, mPAP increased significantly, without any change in the intrapulmonary shunt, in the PaO2/FiO2 ratio or in the PGF1α. These elements were in favor of an imbalance in production of vasodilating and vasoconstricting eicosanoids, induced by soybean oil, which is very rich in linoleic acid, a precursor of some of these substances. A slow infusion induced more vasodilating eicosanoids and increased the right-to-left shunt (Qs/Qt). These alterations also depend on the underlying respiratory condition and on the level of pre-existing imbalance in the ventilation/perfusion ratio. Patients with hypoxic vasoconstriction or chronic lung failure do not seem to be sensitive to a long-chain triglycerides infusion. In ARDS with gas exchange disorders and abnormalities in the ventilation/perfusion ratio, long-chain triglycerides can have a deleterious effect on gas exchange which can be avoided with a moderate quantity of lipid emulsion and a 8 to 10 hour-infusion.

**Medium-chain triglycerides emulsion**

As MCT/LCT emulsions only interfere a little with eicosanoids metabolism, it has been suggested to use them preferentially in ARDS. Radermacher P. et al. showed that in septic patients, MCT/LCT emulsion did not change urinary excretion of prostaglandin’s metabolites and did not have any effect on gas exchange [8]. In a study carried out in patients with hemodynamically stable ARDS, under artificial ventilation, Planas et al. compared the respective effects of LCT and MCT/LCT on gas exchange. Patients were divided into two groups, one getting a 20% LCT emulsion (Intralipid®), the other one a 20% MCT/LCT emulsion (Lipofondine®). In both groups, infusion lasted 12 hours, with a 2 mg/kg/min output. Results showed that lipid infusion did not change the LTB4 level, whereas thromboxane-B2 rather decreased under the action of lipids. The only relevant difference between the two groups was a significant decrease in 6-ketoPGF-α in the pulmonary artery in the LCT group [9].

The following year, Smyrniotis et al. compared the respiratory effects of LCT and MCT/LCT in septic patients with ARDS [10] and in patients with acute pancreatitis [11]. Their conclusion was that LCT emulsions induced a rise in the mPAP and in Qs/Qt and changed the PaO2/FiO2 ratio, whereas MCT emulsion increased oxygen use and cardiac index. In a prior study, Chassard et al. had already showed similar results, but with a greater lipid input [12].

On the whole, these studies carried out in ARDS, do not show a significant difference between LCT and MCT/LCT in terms of eicosanoids production and of hematosis perturbation, with doses of about 100g LCT given in 12 hours. These results can be explained by the fact that the eicosanoids synthesis depends on several factors, not only the amount of linoleic acid but also the availability of arachidonic acid, the activity of phospholipase A2 and variations in activity of cyclooxygenase and lipoxygenase induced by different drugs.

**Potentially beneficial effects of lipid emulsions on the pulmonary function**

Contrary to what has just been described, it is possible that some parenteral lipid emulsions rich in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have beneficial effects on some components of pulmonary diseases. The low rate of chronic pulmonary diseases in Eskimos could result from the high concentration of polyunsaturated fatty acids (PUFA) of the omega-3 series in this population’s usual food...
The potentially protecting effects on pulmonary function of fish oils are surely different in chronic conditions such as asthma, COPD or cystic fibrosis, as opposed to acute pneumopathy and ARDS. Fish oils can act on bronchial reactivity, but they have mostly been studied as modulators of inflammatory and anti-inflammatory reactions. It is probably in this way that they have a use in acute pneumopathy, cystic fibrosis and ARDS.

The immune response modulating the action of the long-chain PUFA of the omega-3 series acts at three different levels. The first one is the eicosanoid synthesis, powerful inflammation and immune reaction mediators. Under the effect of lipoxygenase and cyclooxygenase, the arachidonic acid (C20 : 4n-6) derived from linoleic acid, produces leucotrienes B4 (LTB4) and prostaglandins E2 (PGE2), pro-inflammatory and immunosuppressant substances. Docosahexaenoic acid (DHA ; C22 : 6n-3) and eicosapentaenoic acid (EPA ; C20 : 5n-3) lead, through the same enzymatic pathways, to leucotrienes B5 (LTB5) and to prostaglandins E3 (PGE3) which show weaker inflammatory and immunosuppressant actions. As the enzymatic pathways leading from PUFAs to eicosanoids are the same for all the fatty acids series, there is a competition between series 3 and 6. Hence, depending on the omega-3/omega-6 ratio, the inflammatory and immunosuppressant actions of the eicosanoids will change. When this ratio increases, the inflammatory reaction is minimized, for example with fish oils, naturally rich in EPA and DHA.

Fish oils also interfere with the immune system and inflammation by altering cytokines synthesis. They reduce the production of IL-6, TNF-α, IL-2 (by activated macrophages) and IL-2 receptors, and decrease the fixation of leukocytes on endothelial cells. This action, due to DHA and EPA, is partly transcriptional and exerts on nuclear receptors : PPAR-alpha, -beta and – gamma (Peroxisome Proliferator-Activated Receptor), NF-kappa B, HNF-4-alpha (Hepatic Nuclear Factor 4), and the family of SREBP (Sterol Regulatory Element Binding Protein) [14].

**Experimental data**

Considerable fundamental and experimental data lead us to believe that a nutritional manipulation could be an interesting therapeutic axis in ARDS. In this disease, the oxygen’s free radicals increase lipid peroxidation, and decrease the part of omega-3 and omega-6 series fatty acids in blood phospholipids [15]. Studying a model of endotoxin acute lung injury in rats, Mancuso et al. tested the effects of an enteral nutrition rich in EPA and in gamma-linolenic acid (GLA), a polyunsaturated fatty acid of the n-6 series (C18 : 3n-6) on the pulmonary capillary permeability, the composition of membranous phospholipids in alveolar macrophages and their ability to synthesize prostaglandins and leucotrienes [16]. Rats were fed for 21 days with hyperlipid diets. In the first group, they were given corn oil, rich in linoleic acid, and in the second group, a combination of fish oil and borage oil, bringing DHA, EPA and GLA. On the 22nd day, rats got an injection of Salmonella enteridi toxin. Results showed that in the second group, the part of arachidonic acid within the membrane’s phospholipids decreased. The pulmonary capillary permeability was increased with the corn oil diet and decreased with the fish and borage oils. With this second diet, there was a minimization of the hypotension induced by the endotoxin injection, and in the production of LTB4, LTB2 and PGE2 by the activated alveolar macrophages. This study showed that by pre-treating the rats with fish oil and borage oil, it was possible to minimize the intensity of the general and respiratory manifestations caused by the endotoxin injection.

Recently, the speed of action of a change in the lipid composition of a diet has been studied on the rat. Animals with a gastric catheter were fed for 4 days with a diet rich in lipids. The reference group got linoleic acid; the other groups were treated with a supplement of EPA for the first one and with EPA and GLA for the second one. The effects of these nutritional modifications were analyzed by studying alveolar macrophages and their ability to excrete eicosanoids when stimulated by an endotoxin. Results showed that the different PUFAs were quickly included within the cell membrane. Diets with less arachidonic acid induced a synthesis of less inflammatory and immunodepressant eicosanoids. For both diets with DHA, the LTB4/LTB5 ratio and the LTB2/LTB3 ratio decreased, without alteration in the macrophages’ bactericidal action [17]. Hence, a variation in the lipid part of a diet is able to quickly modify the production of eicosanoids, producing less inflammatory components, without changing the tensioactive characteristics of the lung surfactant, as shown by Murray et al. in a study on endotoxin shock in pigs [18].
Clinical data

In humans, therapeutic use of EPA and GLA has been tested in a controlled multicentric randomized study, carried out on 146 patients with infectious, post-traumatic or post-bronchial inhalation ARDS [19]. Enteral feeding was given to patients for 4 days with an energetic input of 1.3 times the basal energy expenditure. They were divided into two groups: one getting a standard nutrition, the other an isonitrogenic nutrition rich in EPA and GLA. In patients with EPA + GLA, the different bronchoalveolar lavage (BAL) showed an important decrease in the global cell count and in the percentage of polynuclear cells, an amelioration of the PaO₂/FiO₂ ratio, a reduction of ventilation needs, a decrease in the duration of artificial ventilation and of the length of stay in intensive care. In the treated group, 8% of the patients had an intercurrent complication during the study, as opposed to 28% in the control group. From this first study, the same authors showed that giving EPA and GLA reduced the quantity of IL-8, LTB4 and neutrophil polynuclear cells in BAL [20]. They also showed that giving EPA and GLA did not change the level of oxidative stress in the patients with ARDS, but restored the levels of some of the anti-oxidant systems components, especially beta-carotene and alpha-tocopherol [21].

Conclusion

Lung toxicity of lipid emulsions, which has raised a great many questions has finally turned out to be low and to have few clinical consequences. These emulsions can be used for intensive care patients with ARDS, but as with any active substance, administration methods have to be respected strictly. As a rule, the amount of lipid given to stressed patients must remain moderate and must not exceed 35% of non-protein energy. Emulsions must be given slowly, over a 10 to 12-hour period. A new and promising aspect of these lipid emulsions rich in long-chain PUFAs, especially of the omega-3 series, is their ability to modify pulmonary inflammation, and this could lead us to use them in patients at risk of or with ARDS.

References


