

## New developments in fat emulsions

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In Western countries, the transport of triacylglycerols by plasma triacylglycerol-rich lipoproteins (chylomicra and very-low-density lipoproteins (VLDL)) accounts for approximately 100 g lipids/d and represents a major pathway in the delivery of energy to tissues. Fat emulsions have been developed to resemble endogenous chylomicra (Wretling, 1981). However, if the particle size of emulsion droplets is within the range of chylomicra, significant differences in composition can be found between both types of particles; indeed, no cholesteryl ester is dissolved in the triacylglycerol core of artificial particles and no apoprotein is present on their surface; their phospholipid content is higher than that of chylomicra, this difference being particularly marked in 10% emulsions. In fact, it is possible by ultracentrifugation in saline (9 g sodium chloride/l) for 30 min to demonstrate that fat emulsions are made up of not one but two different particle populations: one consisting of triacylglycerol-rich particles and the other of phospholipids. These phospholipid-rich particles, which resemble liposomes, are present in a much greater proportion in 10% than in 20% emulsions. They have a number of important metabolic features which have been recently reviewed (Carpentier, 1989). Their elimination from the plasma is much slower than that of infused triacylglycerols. High concentrations of liposomal particles substantially delay the clearance of triacylglycerols (Carpentier *et al.* 1987) and form phospholipid-free cholesterol complexes which accumulate in the low-density-lipoprotein (LDL) density range (Griffin *et al.* 1979; Unrucht, 1982). Preterm neonates appear to be particularly sensitive to the presence of a high liposomal content in the emulsions. When infused at a dose of 2 g triacylglycerols/kg per d in the parenteral regimen of low-birth-weight infants, 10% emulsion induces high plasma levels of phospholipids, free cholesterol and triacylglycerols (Haumont *et al.* 1989a). These effects can be substantially reduced by the use of 20% emulsions which even allow increases of parenteral lipid intake (Haumont *et al.* 1989b).

The triacylglycerol fatty acid pattern of lipid emulsions also markedly differs from that of endogenous lipoproteins. For many years, soya-bean oil and to a lesser extent safflower oil have been used as sources of triacylglycerols. They contain exclusively long-chain triacylglycerols (LCT) and a majority of polyunsaturated fatty acids. More recently, a new emulsion has been developed, which provides an equal ponderal proportion of medium (mainly octanoate)- and long-chain fatty acids, both being present in the triacylglycerol core.

In vitro studies have demonstrated medium-chain triacylglycerol (MCT) emulsions to be a better substrate than LCT emulsions for hydrolysis by lipoprotein lipase and hepatic lipase. This is, at least partly, due to the much greater solubility of MCT *v.* LCT into phospholipid bilayers, which makes them more available for the endothelial bound

enzymes (Deckelbaum *et al.* 1990). This can also contribute to the fact that, during *in vitro* incubations, MCT particles can transfer more triacylglycerols to LDL and high-density lipoproteins (HDL) than LCT particles, but accept less cholesteryl esters (Richelle *et al.* 1986).

In the present review, we wish to summarize recent *in vivo* studies comparing the properties of a mixed MCT-LCT emulsion to a conventional soya-bean-based LCT emulsion, both manufactured by the same company (B. Braun, Melsungen, FRG) with the same egg-derived phospholipid emulsifier.

#### IN VIVO INFUSIONS IN NORMAL SUBJECTS

Short-term infusions in normal volunteers are used as a tool to detect differences in the intravascular metabolism of MCT-LCT compared with LCT emulsions. For this purpose, 10% emulsions, which are eliminated from the plasma more slowly than the corresponding 20% emulsions, are administered at a rate which largely exceeds that currently used in our clinical practice.

In an initial study, both 10% LCT and MCT-LCT emulsions have been infused for 6 h in six male volunteers at a rate providing 0.2 g triacylglycerols/kg body-weight. Infusion of MCT-LCT resulted in a significantly lower rise in plasma triacylglycerols than LCT infusion, demonstrating a faster plasma elimination of the mixed emulsion (Richelle *et al.* 1988). At the same time, an increase in plasma non-esterified fatty acid (NEFA) concentration was observed, which was twofold higher during MCT-LCT *v.* LCT infusion. Analysis of fatty acid pattern in plasma triacylglycerol and NEFA pools revealed that medium-chain fatty acids (and especially octanoate) were leaving emulsion particles faster than long-chain fatty acids, and contributed much more to the rise in plasma NEFA (Dahlan, 1989). Still, differences were observed between individual fatty acids in both the medium- and long-chain groups. As recently reported, this increase in plasma NEFA occurring during intravenous lipid infusion is associated with a rise in the measurable activity of lipoprotein lipase in the plasma (Carpentier *et al.* 1988); the current hypothesis is that during triacylglycerol hydrolysis at the endothelial site, a high local production of fatty acids does to some degree inhibit lipoprotein lipase activity but also disrupts the attachment of the enzyme to the endothelial wall and releases it into the circulation (Peterson *et al.* 1990).

Other studies were performed in normal subjects in order to compare the oxidative metabolism of MCT-LCT *v.* LCT emulsions. In these studies, glucose (0.16 g/kg per h) and amino acids (0.05 g/kg per h) were infused for 3 h before lipid infusion (0.1 g triacylglycerols/kg per h) was superimposed. Such combined infusion offers the advantages of reproducing the regimen administered to patients receiving parenteral nutrition and of stabilizing at low levels endogenous fat mobilization and oxidation. In this experimental model, infusions of MCT-LCT increased plasma NEFA much more than LCT. In addition, if LCT infusion induced an increase in  $\beta$ -hydroxybutyrate ( $\beta$ OHB) concentration slightly above the values observed after an overnight fast,  $\beta$ OHB concentrations were two- to threefold higher during MCT-LCT infusion (Richelle *et al.* 1987). By contrast, no differences in the values of respiratory quotient were observed between the infusion of MCT-LCT or LCT emulsions. These findings indicate that, in normal subjects, hepatic oxidation of lipids is increased to a higher level during

MCT-LCT *v.* LCT infusion; however, total body fat oxidation is not strikingly different between both types of infusion. Another interesting observation was that carnitine metabolism appears to be affected by infusion of the MCT-containing emulsion (Rössle *et al.* 1990). Indeed, a very marked increase in the plasma level of short-chain carnitine esters (which closely paralleled the rise in  $\beta$ OHB) was observed during infusion of MCT-LCT, indicating a substantial redistribution between free carnitine and short-chain acylcarnitine and probably a role for carnitine at some steps of the oxidative metabolism of medium-chain fatty acids.

The exchange of neutral lipids (triacylglycerol and cholesteryl esters) between triacylglycerol-rich and cholesterol-rich (LDL and HDL) lipoproteins was also studied during *in vivo* infusions of 10% MCT-LCT and LCT emulsions at a rate of 0.2 g triacylglycerols/kg per h (Richelle *et al.* 1988). As a confirmation of *in vitro* incubations, MCT-LCT appeared to transfer more triacylglycerol molecules to LDL and HDL, but to accept less cholesteryl esters from cholesterol-rich lipoproteins than LCT emulsion. Since triacylglycerols acquired by LDL and HDL are efficiently hydrolysed by lipoprotein lipase, the net result is that MCT-LCT induces less modifications in endogenous lipoproteins than LCT.

#### IN VIVO STUDIES IN TOTAL PARENTERAL NUTRITION (TPN) PATIENTS

In comparison with LCT, MCT-LCT infusions in normal subjects induce a higher rise in plasma NEFA and  $\beta$ OHB concentrations and less alterations in lipoprotein composition. Hence, it seemed important to investigate the comparative effect of MCT-LCT and LCT in patients receiving long-term parenteral nutrition, with a special interest in liver function tests, essential fatty acid pattern and lipoprotein composition. For this purpose, eight patients with inflammatory bowel disease (IBD) were randomly assigned to receive TPN with either 20% LCT or 20% MCT-LCT emulsions for a period of 3 months. TPN was adjusted to provide an energy intake corresponding to 125% of each patient's resting energy expenditure and an amino acid intake corresponding to 1 g nitrogen/630 kJ (150 kcal). Glucose and lipids provided an equal proportion of energy supply. Each emulsion was infused for a period of 3 months followed by the other, the order of administration being determined by randomization.

*Liver function tests.* None of these IBD patients showed abnormal liver function tests during the 3-month period of TPN with MCT-LCT. However, three of the eight patients developed abnormal tests after a variable period of TPN with LCT. In these three patients, LCT emulsion was replaced by the mixed emulsion after two consecutive observations of altered tests performed at a 1 week interval; after this change, liver enzymes and bilirubin progressively decreased to reach the normal range within 7–9 weeks of MCT-LCT administration (Carpentier *et al.* 1989).

During the period of this cross-over trial, five patients with short bowel syndrome (SBS) were prospectively followed while receiving our standard TPN regimen, but with the MCT-LCT emulsion exclusively, for a period of 2–11 months. None of these five patients developed any abnormal liver test during that period.

After these trials, all our home TPN patients were admitted in a prospective longitudinal study where MCT-LCT was used as the lipid source. Twenty-one patients have been included so far in the trial for a minimal period of 3 months, four of them having at present a 2-year follow-up. The results confirm the previous observation, *i.e.*

no deterioration in liver function tests, but on the contrary a progressive improvement in those who were started with abnormal levels (Carpentier *et al.* 1989).

Since long-term TPN in SBS and IBD patients is currently considered as bearing an incidence of abnormal liver tests ranging between 20 and 35%, our results appear unusually good. No direct explanation but only speculations can be offered concerning the protective effect of MCT-LCT on liver function. The difference between MCT-LCT and LCT emulsions could be due to the fact that:

(a) medium-chain fatty acids released in high amounts during MCT-LCT infusion are a better substrate for hepatocytes than long-chain fatty acids; medium-chain fatty acids are oxidized in greater proportion than long-chain fatty acids and induce less fat deposition; (b) ketone bodies, produced in higher amounts during MCT-LCT *v.* LCT infusion, are known to be a good substrate for the intestinal mucosa; hence, TPN with MCT-LCT could better protect the integrity of the gut barrier, which would result in less periportal inflammation by reducing the egress of toxins and bacteria from the intestine.

(c) MCT-LCT emulsions have a lower ability to acquire and transport cholesteryl esters and could induce fewer alterations in bile composition.

*Lipid pattern of endogenous lipoproteins.* The lipid pattern of endogenous lipoproteins (namely LDL and HDL) was regularly followed throughout the course of the study in those IBD patients who received TPN with both emulsions, each regimen being administered over a 3-month period (Richelle *et al.* 1989). For this purpose, blood samples were drawn 6–8 h after lipid infusion had been stopped.

No change in plasma lipids was observed with either emulsion over the study period. In addition, phospholipid and free cholesterol content of endogenous lipoproteins remained unchanged. This confirms the absence of phospholipid accumulation in adult patients when using 20% emulsions, even over a prolonged period of time. However, 3-month infusion of TPN with LCT resulted in a redistribution of cholesteryl esters between HDL and LDL, leading to a significant increase in the LDL:HDL-cholesteryl ester ratio. By contrast, no modification in cholesteryl ester distribution was observed during the period of MCT-LCT administration.

These findings are in agreement with previous *in vitro* and short-term *in vivo* investigations, showing a lesser ability for MCT-LCT emulsion to interfere with the plasma transport of cholesteryl esters and to modify the core composition of endogenous LDL.

*Essential fatty acid pattern.* Soya-bean-based emulsions provide large amounts of essential fatty acids both from the *n*-6 (as linoleate) and from the *n*-3 (as  $\alpha$ -linolenate) families. Since the supply of essential fatty acids provided by the MCT-LCT emulsion is only half (in weight) of that provided by the LCT emulsion, it was important to follow the fatty acid pattern of erythrocyte (RBC) membranes in patients receiving TPN with both emulsions, each for a period of 3 months in a randomized cross-over fashion (Dahlan *et al.* 1989).

After 3 months of TPN with LCT, an imbalance in the fatty acid pattern of RBC phospholipids was observed. This was characterized by an enrichment in linoleate (18: 2*n*-6 C) and a relative depletion in arachidonate (20: 4*n*-6), as well as a relative depletion in docosahexanoate (22: 6*n*-3 C). Both the arachidonate:linoleate and the *n*-3 fatty acids:*n*-6 fatty acids ratios were decreased below control values. In contrast, TPN with MCT-LCT, administered over the 3-month period, did not induce any imbalance in the fatty acid pattern of RBC phospholipids and even led to a correction of the altered

pattern in those patients who had received the LCT regimen during the first period. These findings suggest that LCT emulsion, when provided at a dose of approximately 1.5 g triacylglycerols/kg per d, supplies an excessive amount of linoleate. This can be avoided by the use of mixed emulsion.

#### CONCLUSIONS

Infusions of lipid emulsions induce an increase in the plasma concentration not only of triacylglycerols but also of phospholipids, free cholesterol and NEFA. These effects are particularly pronounced when phospholipid-rich emulsions are administered at a high rate. In clinical practice, we recommend 20% emulsions to be infused at a slow rate (<0.15 g triacylglycerols/kg per h).

MCT-containing emulsions are hydrolysed faster than the corresponding LCT emulsions; their infusion induces a lower rise in plasma triacylglycerols, but a higher increase in plasma NEFA, with a high proportion of medium-chain fatty acids. In addition, MCT-LCT emulsions induce less alterations in the lipid composition of endogenous lipoproteins.

In patients requiring long-term TPN, the administration of a 20% MCT-LCT emulsion is associated with a reduced incidence of metabolic complications such as: alteration of liver function tests, redistribution of cholesteryl esters between HDL and LDL and abnormal fatty acid pattern in RBC phospholipids.

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