Medium Chain Triglycerides and Structured Lipids as Unique Nonglucose Energy Sources in Hyperalimentation

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This brief review will discuss recent work concerning new intravenous lipid emulsions for future use in clinical patients. Intravenous lipid emulsions currently available in the United States are derived from soybean or safflower oils and serve as sources of nonglucose, nitrogen-sparing calories and the essential fatty acid linoleic acid. Because of concerns that much of the infused long chain triglyceride is not oxidized readily and that there may be some immune system impairment, newer emulsions utilizing medium chain triglycerides have been developed.
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Long chain triglycerides. Intravenous feeding of hospitalized patients has evolved rapidly. Before the availability of lipid emulsions suitable for intravenous use, glucose was the only nonprotein source of calories. Meeting the full caloric needs of the patient with glucose often led to hepatic lipogenesis and increased respiratory work to expire the excessive carbon dioxide produced during lipogenesis (1). Because intravenous fat emulsions made from soy or safflower oils contain linoleic acid, an essential fatty acid, their use was implemented. These long chain triglycerides (LCT) serve as a nonglucose fuel that provides energy so that the body can use amino acids as protein and not as a caloric source (2). Since fat burns at a lower respiratory quotient than glucose—that is, it produces less carbon dioxide for the same amount of oxygen uptake—this is a benefit for patients with pulmonary compromise having problems expiring all the CO_2 they are producing. In addition, long chain fatty acids will inhibit lipogenesis from carbohydrate, thereby decreasing fatty livers. In the diabetic patient, lipid calories decrease insulin requirements if substituted for glucose calories.

Essential fatty acids. The requirement for linoleic acid is met by supplying 4% of calories as the essential fatty acid. Since soybean oil is slightly more than one-half linoleic acid, supplying 10% of total calories as a soybean oil lipid emulsion easily meets essential fatty acid requirements. The issue of α-linolenic acid being essential has recently been raised by anecdotal reports as well as work by Neuringer et al. (3). Based on this work, it seems that long chain ω3 fatty acids, found in high concentrations in the brain and retina, are essential fatty acids. The primate work emphasizes their essentiality for infants but not necessarily for adults. Unlike safflower oil, soybean oil contains 7 or 8% α-linolenic acid, and since the current commercial lipid emulsions are derived from soybean oil in whole or in part, supplying these emulsions would probably meet requirements for both linoleic and α-linolenic fatty acids.

Immune system effects. Fischer et al. gave mice intraperitoneal Intralipid® and then followed that with the administration of intraperitoneal Streptococcus (4). In the lipid-treated group, there were significantly increased mortality and bacteremia and decreased neutrophil chemotaxis. Shaw and Wolfe were developing an *Escherichia coli* sepsis dog model and reported 100% mortality in the animals when 10% lipid was infused for 1 or 2 hr prior to intravenous injection of bacteria (5). The dose in these studies was ca. 115 mg per kg body weight per hr, a clinically relevant dose. Fraser and colleagues showed decreased chemotaxis of monocytes in patients as well as in normal subjects after the intravenous administration of 100 g of fat over 8 hr (6). The reticuloendothelial system (RES) is that collection of cells in the body concerned with phagocytosis of particulate matter in the bloodstream. It consists primarily of macrophages in the liver, spleen and bone marrow. A fourth study highlighting the clinical significance of a well-functioning RES was done by Rimola et al. (7). They studied 41 cirrhotic patients with routine clinical and laboratory parameters as well as liver-spleen scans and technetium-99 sulfur colloid clearance from the blood. They found that the only parameters that predicted mortality or the development of bacteremia were the tests of RES function such as the liver-spleen scans and technetium-99 sulfur colloid clearance rates. All other clinical and laboratory parameters were insufficiently sensitive to detect clinically vital outcomes such as the incidences of bacteremia and mortality.

A problem with LCT emulsions is slow clearance of the infused triglyceride from the bloodstream. Also, clearance is not synonymous with oxidation of the fatty acids, a primary purpose for using the emulsion. For these reasons, as well as the fact that medium chain fatty acids are rapidly cleared from the blood and are rapidly oxidized independent of carnitine transport and poorly stored in adipose tissue, medium chain triglyceride (MCT) emulsions were looked to for clinical intravenous use (8-10).

Medium chain fatty acid preparations. MCT oil consists essentially of octanoic and decanoic acids (8 and 10 carbons long, respectively), whereas soybean and safflower oil consist almost exclusively of fatty acids of 16 and 18 carbon chain length (Table 1). The fatty acids exist as triglycerides. In soybean and safflower oils, the fatty acids on the triglyceride are long chain; in MCT, they are

TABLE 1

Fatty Acid Composition of Selected Oils (As Percent of Total Fatty Acids)

Fatty acid	Soybean	Safflower	MCT
6:0			<2
8:0			70
10:0			30
12:0			<2
14:0	0.1	0.1	
16:0	10.5	6.7	
18:0	3.2	2.7	
18:1ω9	22.3	12.9	
18:2ω6	54.5	77.5	
18:3ω3	8.5		

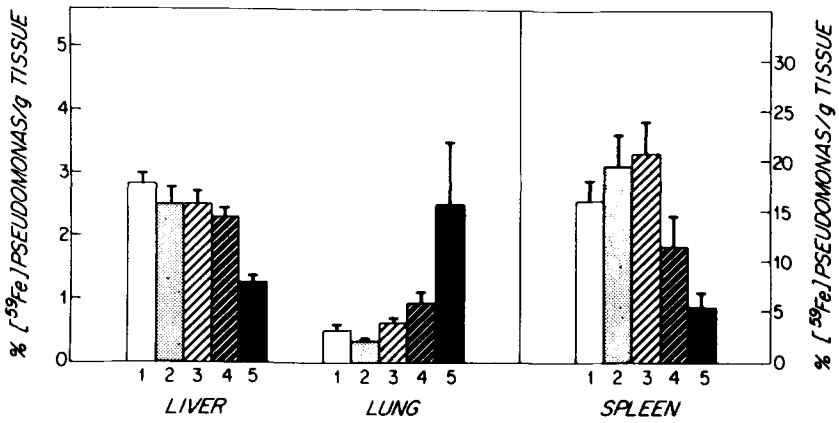

FIG. 1. Organ uptake of radiolabeled Pseudomonas following long chain triglyceride (LCT). Group 1, 100% glucose; group 2, 25% LCT/75% glucose; group 3, 50% LCT/50% glucose; group 4, 75% lipid/25% glucose; group 5, 100% LCT (ref. 11).

medium chain. A third group of triglycerides that has been investigated is that of structured lipids. These lipid molecules are triglycerides but are made from reesterified mixtures of MCT and LCT. The mixtures are hydrolyzed and allowed to reesterify randomly, thereby forming a triglyceride molecule of both medium and long chain fatty acids. As such, they are chemically distinct from physical mixtures of MCT and LCT.

Animal experiments. Our laboratory has recently published three experiments done on laboratory animals where these lipid emulsions were investigated. In the first experiment, rats were fed a total parenteral nutrition (TPN) regimen for three days (11). The rats had been given a 30% scald burn while anesthesized. At the end of three days, the animals were given a radiolabeled intravenous bacteremia; the clearance of this bacteremia into organs was measured. Rats were divided into groups that differed by the amount of fat (as LCT only) and glucose calories they received. It was shown that as the proportion of carbohydrate calories fell and that of lipid calories increased (the groups were equicaloric) there was a shift in the organ uptake of bacteria. Liver uptake decreased slowly with increasing lipid doses, whereas lung uptake of the radiolabeled bacteria increased markedly (Fig. 1). Next, different types of triglycerides at the same caloric proportions were given. The three lipids that were contrasted were LCT, MCT and structured lipid. LCT emulsions gave statistically increased lung uptake of the radiolabeled bacteria over that of the MCT and structured lipid groups (Fig. 2). Total caloric intake and proportion from fat calories were similar for these groups. This study emphasizes the fact that LCT blocks RES function whereas medium chain fatty acid-based lipid emulsions do not.

A second study was done by Hamawy et al. (12). Here, rats were given bilateral septic femoral fractures with the implantation of gauze containing *E. coli.* The animals were placed on TPN for four days and then studied. At the end of four days of TPN with septic fractures, blood was withdrawn and cultured to assess any bacteremia from the fractures. The group that received amino acids and dextrose but no lipid showed 10^3 bacteria/ml, as did

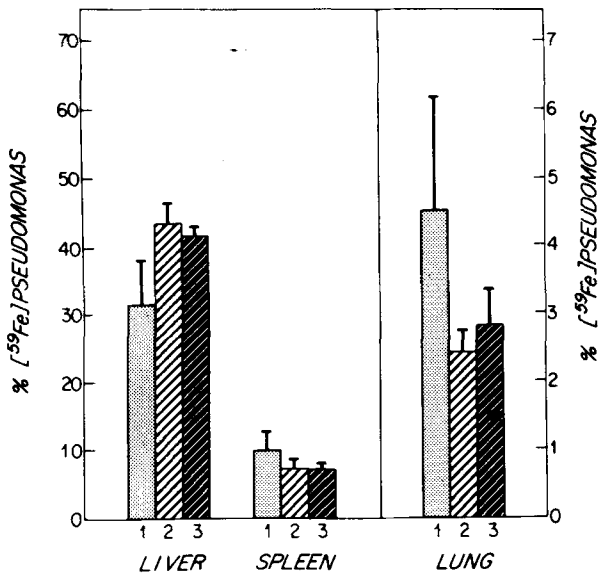

FIG. 2. Organ uptake of radiolabeled Pseudomonas following long chain (LCT), or medium chain triglyceride (MCT) or structured lipid. Group 1, LCT; group 2, MCT; group 3, structured triglyceride (ref. 11).

the group receiving one-third of its calories as LCT. The third group received a physical mixture of 75% MCT and 25% LCT as one-third of calories and showed no bacteremia (Fig. 3). Second, like in the experiment by Sobrado et al. described above, radiolabeled *E. coli* were injected into the blood. A statistically significant decrease in liver uptake of the *E. coli* bacteremia was seen in the LCT group compared with the 75% MCT and 25% LCT physical mixture group (Fig. 4). Inversely, in the lung, the MCT/LCT physical mixture group had a statistically significant lower uptake of bacteria compared with either the long chain or amino acid/dextrose TPN groups (Fig. 5). This study again highlights the significant difference in RES interference from intravenous lipid emulsions, with beneficial effects seen in the MCT/LCT physical mixture group.

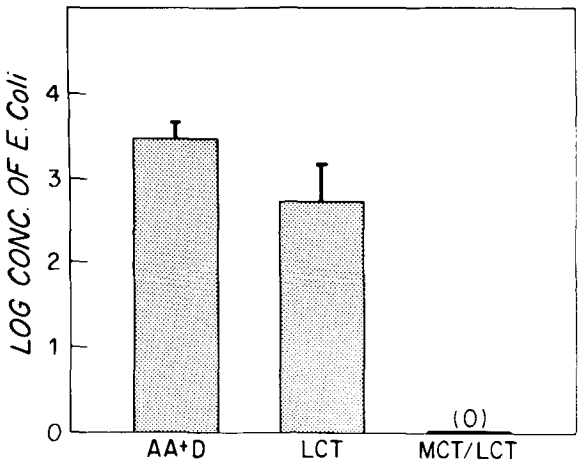

FIG. 3. Baseline bacteremia following septic fracture. AA + D, amino acids and dextrose; LCT, long chain triglyceride; MCT, medium chain triglyceride (ref. 12).

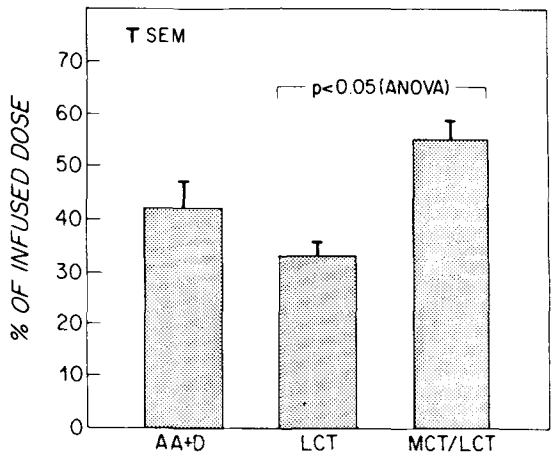

FIG. 4. Uptake of radiolabeled *E. coli* by the liver. AA + D, amino acids and dextrose; LCT, long chain triglyceride; MCT, medium chain triglyceride (ref. 12).

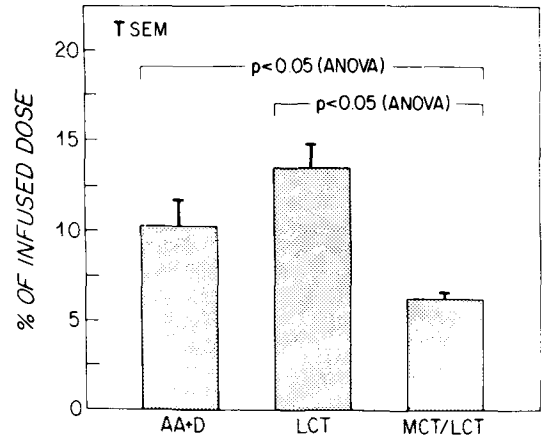

FIG. 5. Uptake of radiolabeled *E. coli* by the lung. AA + D, amino acids and dextrose; LCT, long chain triglyceride; MCT, medium chain triglyceride (ref. 12).

In the third study, by Mok et al. (13), rats also were given three days of TPN following a 25% scald burn done under anesthesia. The animals were divided into five groups according to TPN regimen. Group 1 was fed 200 calories per kg body weight per day as amino acids and dextrose and no lipid. Group 2 was fed ca. 300 calories/day, again consisting solely of amino acids and dextrose. Groups 3, 4 and 5 were fed ca. 300 calories/day with one-third of nonprotein calories as either LCT, MCT or structured lipid, respectively. The hypocaloric 200-kcal group and the MCT group lost weight during the experiment, whereas the other groups gained weight. This highlights the somewhat increased thermogenesis of MCT compared to other lipid fuels. Nitrogen balance did not differ significantly among the groups, but tended to show a higher balance in the structured lipid group. Albumin levels were measured and shown to be remarkably higher in the structured lipid group. This experiment shows the potential nitrogen-sparing benefits of structured lipid emulsions compared to other types of intravenous lipid.

Clinical data. We have begun to investigate intravenous MCT as a 75% MCT/25% LCT physical mixture in hospitalized patients. Preliminary analysis of the data shows that the fuels are safe and, as measured by serum triglyceride and free fatty acid analysis, are hydrolyzed and cleared rapidly. In addition, thermogenesis is noted in patients, but this was not accompanied by increased body temperature (14,15). European studies have shown similar results; they have had a 50/50 physical mixture of MCT and LCT available commercially for two years (16).

Studies to date support the notion that supplying all lipid calories in a TPN regimen as LCT is not the best nutritional care for patients. Giving a large proportion of these lipid calories as medium chain fatty acids, either as physical mixtures of MCT or as structured lipids, provides more readily oxidizable fuels with less interference of the reticuloendothelial component of the immune system.

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