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Metabolic Studies of a Lipid Emulsion Containing Medium-Chain Triglyceride in Perioperative and Total Parenteral Nutrition Infusions

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The effects of infusion of a 10% lipid emulsion containing equal proportions of long-chain and medium-chain triglyceride were studied in elective surgical patients and others receiving total parenteral nutrition (TPN). Nitrogen balance was better when the TPN patients received lipid containing medium-chain triglyceride than during a similar period when long-chain triglyceride alone was given. Only in the malnourished patients did the medium-chain triglyceride lipid emulsion produce a significant ketonemia. This emulsion was administered without side effects.

Intravenous lipid emulsions have been successfully used as an effective form of nutritional support for several decades [1–3]. Many studies have examined the effects of emulsions containing long-chain triglycerides (LCT), but there have been fewer studies with medium-chain triglycerides (MCT). Short-chain triglycerides (SCT) are toxic in animals [4]. However, if the fatty acid chain length is ≥ 8, they may be safely infused in humans [5–8]. There are theoretical reasons to suppose that MCT may be a superior lipid compared to LCT. MCT is rapidly cleared from plasma [9, 10] and does not contribute to adipose tissue stores [11]. MCT can be more ketogenic than LCT [5, 12, 13] and in these circumstances might be a better energy source [14, 15]. Medium-chain fatty acids (MCFA) are more rapidly translocated into the mitochondria for beta-oxidation; unlike long-chain fatty acids (LCFA) they are not dependent on carnitine acyl transferase [16, 17].

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The nitrogen-sparing effects of lipid emulsions containing LCT are well documented [18–20], but the effects of MCT on protein metabolism in humans have not been investigated in detail. Animal work using rats has shown that MCT-containing lipid emulsions have nitrogen-sparing qualities greater than LCT lipid emulsion [21] and may even be infused safely into animals with hepatic damage [22]. More recent work suggests that the magnitude of the nitrogen-sparing effects depends on the degree of ketonemia produced by the metabolism of MCFA; this contrast was seen in starved and then repleted animals compared with burn injured rats [23, 24].

We undertook 2 separate human studies comparing an LCT emulsion with an MCT-containing lipid, which was 10% weight/volume lipid comprising equal proportions of LCT and MCT. (B. Braun Melsungen, West Germany).

In Study 1 the metabolic effects of infusing either MCT/LCT, LCT alone, or 5% glucose in healthy surgical patients before, during, and after their operation were compared. Each infusion started 12 hours prior to operation and continued for 3 days.

In Study 2 the metabolic consequences of substituting conventional LCT with the new MCT/LCT lipid were compared in ill patients who received lipid, amino acid, and 50% glucose infusions as part of a total parenteral nutrition regimen.

Study 1

The purpose of the study was to examine the effects of an MCT-containing emulsion on postoperative metabolism in patients undergoing elective surgery. Similar groups of patients received single infusions

of 5% dextrose or 10% weight/volume LCT. High doses of lipid were infused (approximately 30 kcal/kg per day) to provide enough calories to meet anticipated energy requirements [25] and to provoke any side effects—not only of the lipid infusion alone, but also from theoretical interaction between the lipid and anesthetic agents, given to the patients while the lipid infusion was in progress.

Subjects and Methods

Twenty-four patients having elective abdominal surgery of moderate severity were studied. All were free of any serious cardiac, renal, hepatic, or metabolic disease (9 had cholecystectomy, 5 had hemicolectomy, 2 had sigmoid colon resection, 3 gastrectomy, 2 highly selective vagotomy, 2 abdominoperineal excision of rectum, and 1 colostomy closure).

Each patient was allocated to 1 of the 3 infusion groups, receiving either the MCT-containing lipid at 1.9 mg/kg per min, or isocaloric LCT (Lipofundin S®, B. Braun Melsungen, West Germany), or 5% glucose infusion at 1 mg/kg per min. All infusions were started at 1900 hr on the day prior to surgery, were continued perioperatively and postoperatively for a further 48 hours.

While it was possible to inject both the 5% glucose and LCT infusion into a peripheral vein, the MCT lipid was given by a "long line" to prevent thrombophlebitis of peripheral veins, which occurred with the first few infusions.

Patients were starved from 1900 hr in the evening prior to surgery. Operations commenced between 0900 hr and 1130 hr the following day. Only sips of water were allowed orally during the study period. In addition to the substrate infusions, 0.9% saline was given intravenously to maintain fluid and sodium balance.

Sampling

Continuous 24-hour urine collections were made daily; an indwelling urinary catheter was used when clinically indicated. Venous blood samples (10 ml each) were taken at the start of the infusion, during the operation, and at 1000 hr on postoperative days 1 and 2. Blood for ketone body assay was collected into chilled perchloric acid. Plasma was harvested from the remaining blood and stored for later assay of metabolites and insulin.

Analytical Methods

Urinary urea and creatinine were determined by a Technicon SMA 1260 autoanalyzer. Plasma glucose

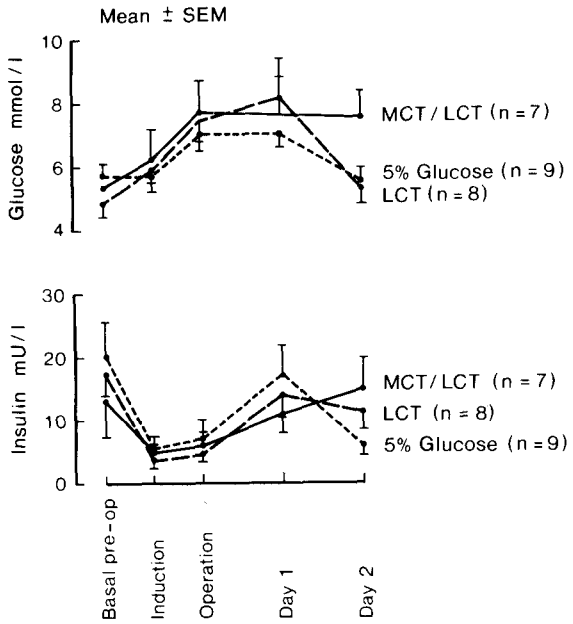


Fig. 1. Plasma glucose and insulin concentrations ($p < 0.05$, 5% glucose versus medium-chain triglyceride/long-chain triglyceride [MCT/LCT] infusions on day two).

was measured on a Beckman glucose analyzer. A radioimmunoassay was used to determine insulin concentrations, using a human insulin standard (Novo) [26]. Acetoacetate and beta-hydroxybutyrate were determined by a standard enzymatic method [27]. Plasma triglyceride (TG) was assayed by Sigma Chemicals kit no. 335; plasma nonesterified fatty acids (NEFA) were assayed by the method of Shimizu [28]. All data are expressed as the Mean ± S.E.M., and statistical analysis was by the Mann-Whitney *U*-test.

Results

The mean urinary urea losses on the first postoperative day were for 5% glucose, LCT, and MCT, respectively 3.75 ± 0.4, 2.3 ± 0.5, and 2.55 ± 0.2 m mol/kg, and for the 3 postoperative days 3.5 ± 0.3, 2.5 ± 0.2, and 2.6 ± 0.2 m mol/kg per day. The reduction in urinary urea excretion when either lipid was infused compared to (hypocaloric) glucose was significant ($p < 0.05$) for both the first 24 postoperative hours and the mean of 3 days.

Pre-infusion blood concentrations of all the parameters measured did not differ significantly between infusion groups.

Plasma glucose concentrations rose in all groups from basal levels during surgery (Fig. 1). By day 2 glucose concentrations had returned to pre-infusion levels except in the MCT group, in which they remained elevated.

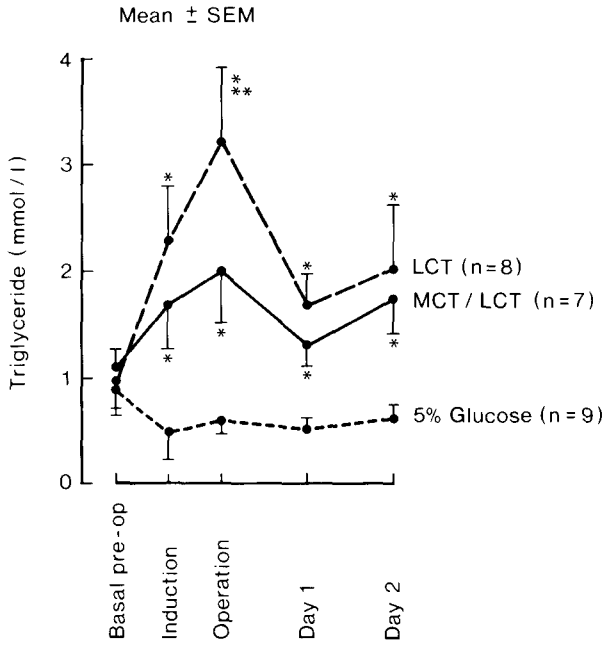


Fig. 2. Plasma triglyceride concentrations during infusions (* $p < 0.05$ either lipid versus 5% glucose, ** $p < 0.05$ medium-chain triglyceride/long-chain triglyceride [MCT/LCT] versus LCT).

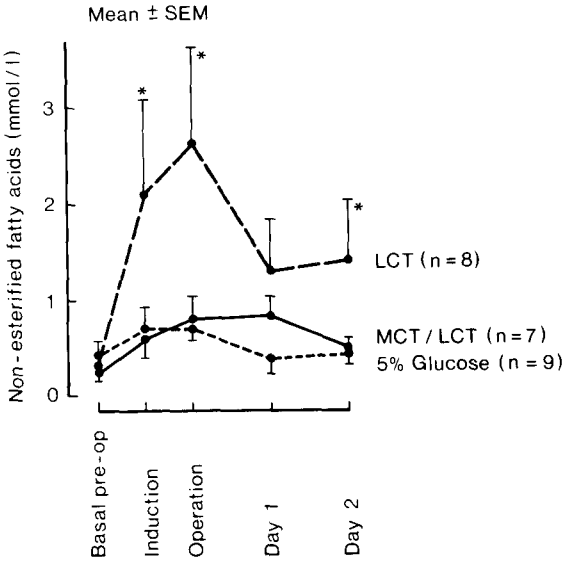


Fig. 3. Plasma nonesterified fatty acid concentrations during infusions (* $p < 0.05$ LCT versus MCT/LCT; LCT = long-chain triglyceride; MCT = medium-chain triglyceride).

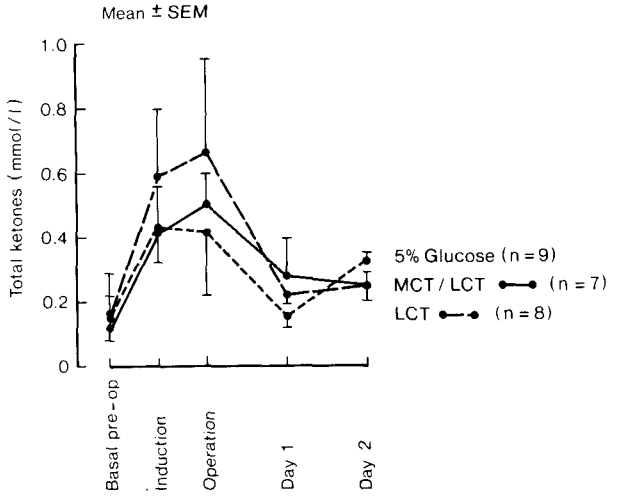


Fig. 4. Total blood ketone body concentrations during infusions (MCT = medium-chain triglyceride; LCT = long-chain triglyceride).

Plasma insulin concentrations were lowest during anesthesia and surgery, before returning to pre-infusion levels on day 1. By day 2 there was some divergence of concentrations (Fig. 1).

Plasma TG concentrations rose during both lipid infusions and were significantly different compared to glucose infusions (Fig. 2). During the operation, the triglyceride concentrations of the LCT group were significantly greater than those of the MCT infusion group, indicating a more rapid plasma clearance of MCT. Plasma NEFA concentrations were also elevated during LCT infusion compared to both MCT and 5% glucose infusions (Fig. 3).

Plasma total ketone body (KB) concentrations (acetoacetate and beta-hydroxybutyrate) showed a similar pattern for all 3 different infusions, without significant differences between the plasma concentrations at any point (Fig. 4).

No side effects, e.g., alterations in pulse, blood pressure, or respiration, were noted in the patients given either lipid infusion despite the relatively high doses given.

Discussion of Study 1

This study was undertaken to investigate the effects of an emulsion containing MCT in healthy patients experiencing moderate surgical stress. Short-duration infusion studies of MCT/LCT emulsions in humans in both starved volunteers and intensive care patients have demonstrated that such an emulsion is rapidly cleared from the plasma and metabolized to ketone bodies [5, 6, 7, 10]. Previous studies using LCT emulsions have shown the nitrogen-sparing effects in injured animals [29] and humans [30]. Studies in animals, using a lipid emulsion with a greater proportion of MCT to LCT (60:40), have shown that in the cases of injury and hepatic insufficiency, these emulsions have a superior nitrogen-sparing property over LCT [21, 22, 31]. Although urea excretion was similar in both lipid groups in this study, the results confirm a protein-sparing property of MCT in humans. Urea excretion was similar to the effects seen when isocaloric

50% glucose was infused in similar circumstances [25].

The mechanism of nitrogen sparing by lipid is not clear. It has been suggested that the glycerol content of the lipid emulsion may be responsible, by providing nonprotein gluconogenic substrate, for decreasing urinary nitrogen losses [32]. Thus, glycerol could diminish the amino acid requirement for gluconogenesis or keto-oxidation. However, glycerol could account for only a part of the nitrogen-sparing effect of lipid infusions since the quantity of glucose that could be synthesized from the available glycerol was less than that delivered in the 5% glucose infusion group in our study.

These data suggest that at least part of the fatty acid content of the lipid emulsions was oxidized to provide energy and decrease protein degradation, which would otherwise generate amino acids for gluconogenesis. This interpretation was supported by the observation that fat is preferentially oxidized in traumatized patients [33].

Carbohydrate metabolism was not directly influenced by either of the lipid infusions since both glucose and insulin concentrations were similar when 5% glucose was infused. Low insulin concentrations have been reported during operation [34], and the similar changes seen in our patients were unlikely to have been due to the infusions. Short-term infusion of MCT with LCT in healthy volunteers and TPN patients [5, 35] do not appear to affect plasma glucose or insulin concentrations; yet, in normal individuals, a lipid infusion may decrease glucose oxidation and storage [36].

Previous studies [5, 7] with MCT infusions, similar to this study, have also shown lower plasma TG and NEFA concentrations compared to LCT infusion. Eckart and Adolph [10] have demonstrated rapid clearance of triglyceride from serum lipoproteins within 60 minutes of intravenous infusion of an MCT-containing lipid, and also rapid clearance of MCFA from serum. The site of clearance and oxidation of parenterally administered MCT is not clear; but when enterally administered, MCT is rapidly oxidized in hepatic and nonhepatic tissues [37].

It was interesting to note the similar blood KB concentrations achieved during the 3 different infusions. Lipids are generally ketogenic [13, 38], and MCT infusion is usually associated with a greater ketonemia than is LCT infusion [13, 14]. Compared with a starvation model, trauma is generally associated with lower KB concentrations [33, 39], probably owing to increased consumption of ketones; this may explain the relatively low ketone concentrations seen in the postoperative period.

In conclusion a lipid emulsion containing 50% MCT and 50% LCT may be given in high doses for 3 days to general surgical patients without toxic effects, and the metabolic consequences are comparable to isocaloric amounts of LCT given alone. There is evidence that the MCT-containing emulsion was metabolized faster.

Study 2

The purpose of this study was to compare the MCT-containing lipid with the LCT lipid in a different study population, i.e., malnourished patients, and to investigate whether substrate interaction between lipids, amino acids, and glucose affected the metabolism of the 2 lipid emulsions differently.

Subjects and Methods

This study was a randomized prospective crossover trial to compare the clinical and metabolic effects of 2 different lipid emulsions, given in conjunction with glucose and amino acid solutions as part of a TPN regimen. The lipids compared were the same as in the previous study. The patients were entered into the study if it was considered that they required TPN for at least 10 days. The exclusion criteria were the same as study 1.

Fifteen patients, mean age 49 years (26–77 years), were entered. The majority were suffering from inflammatory bowel disease, and 5 had undergone surgery, e.g., gastrectomy.

The TPN feeding regimen consisted of: (a) amino acids (Synthamin 14®, Travenol) providing the equivalent of 14 g nitrogen/day; (b) lipid, either 1,000 ml 10% LCT (Lipofundin S®, B. Braun Melsungen, West Germany) or 1,000 ml Lipofundin MCT/LCT® (B. Braun Melsungen, West Germany), containing 5% MCT and 5% LCT; and (c) 50% glucose adjusted to provide 1,300 kcal/m^2 per day. Trace elements and vitamins were provided on a daily basis [40].

Both amino acid and glucose were infused continuously over 24 hours. The lipid was given over 8 hours commencing at 1400 hr daily.

The trial period was 10 days for each patient, the starting lipid was randomly allocated, and crossover occurred to the alternate lipid on day 6. Patients were observed for any adverse effects with regular monitoring of temperature, pulse rate, blood pressure, urine volume, and urine analysis.

Sampling and Analytical Methods

Venous blood samples were taken each morning at 0800 hr for routine biochemical and hematological

monitoring. Prothrombin times were measured twice weekly. Daily 24-hour urine samples were collected, and the urinary nitrogen content calculated from the urea concentrations. Nonurinary nitrogen losses were estimated from losses via fistulas, etc., by an independent observer.

In addition to routine blood sampling, sufficient for prealbumin assay, complement components C3 and C4, NEFA, TG, and KB were also collected. For TG, NEFA, KB, and complement components, blood for assay was also taken at 2 points (5 and 7 hr) after the start of each lipid infusion.

Urine analysis, TG, KB, and NEFA were assayed as for study 1. Albumin and prealbumin were assayed by laser nephelometry.

Results

There were no significant changes in concentrations of albumin or prealbumin over the whole study period of 10 days, nor during each 5-day period (Fig. 5).

Complement levels showed no significant changes over the 10 days, on 0800 hr samples; but during lipid infusion, complement concentrations were higher when MCT was being infused (Fig. 6).

Morning blood concentrations of TG, NEFA, and ketone bodies were similar irrespective of the day of trial. There were no significant differences in routine hematological parameters.

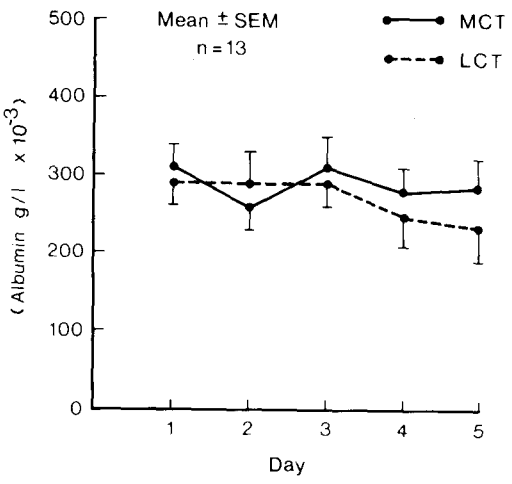
During lipid infusions the profiles of NEFA and TG diverged depending on the type of lipid infused. During MCT infusions there was a greater ketonemia and reduced concentration of TG at 5 and 7 hr of infusion compared to those during LCT infusions (Figs. 7 and 8).

Cumulative 5-day nitrogen balances calculated from urinary losses alone showed no difference. However, when nonurinary nitrogen losses were included, the nitrogen balance of the MCT-infused group was better (+4.7 ± 0.8 g MCT versus +1.2 ± 0.6 g LCT [Mean ± S.E.M.]).

Plasma bilirubin concentrations were significantly lower during MCT infusion periods compared with LCT infusion periods (19.9 ± 1.3μ mol/l versus 35.1 ± 2.4μ mol/l; $p<0.01$, $n = 15$). However, there were no differences in prothrombin times or liver enzymes in plasma, e.g., alkaline phosphatase or amino aspartate transaminase, between the different lipid infusion periods.

Discussion of Study 2

Chronic illness and malnutrition are associated with low carnitine concentrations, owing to a combination of decreased hepatic synthesis and dietary



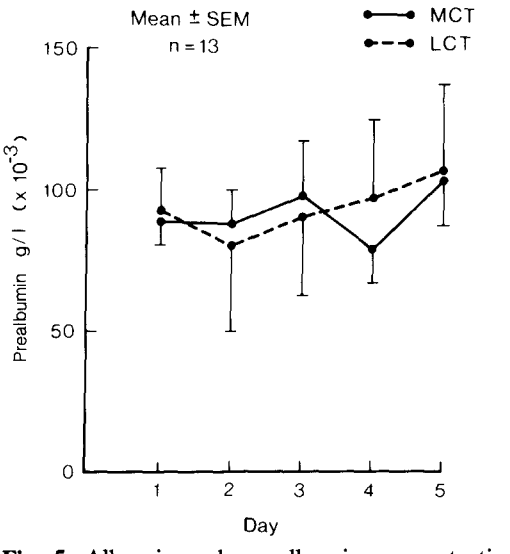


Fig. 5. Albumin and pre-albumin concentrations in patients receiving total parenteral nutrition for each 5-day period (MCT = medium-chain triglyceride; LCT = long-chain triglyceride).

intake [16, 17]. For lipid metabolism this may have important consequences since carnitine acyl transferase facilitates the transport of LCFA's into the mitrochondria, where they are oxidized. A lack of carnitine may limit the rate of the translocation of LCFA's into mitochondria and hence the production of acetyl CoA. This may account for the rapid clearance of MCT and increased rate of ketogenesis observed when MCT is infused.

In the present study plasma ketone concentrations in patients receiving lipid emulsions had returned to similar concentrations by 0800 hr each day. This indicates increased utilization in those patients receiving MCT. Many tissues are able to utilize ketones during starvation instead of glucose,

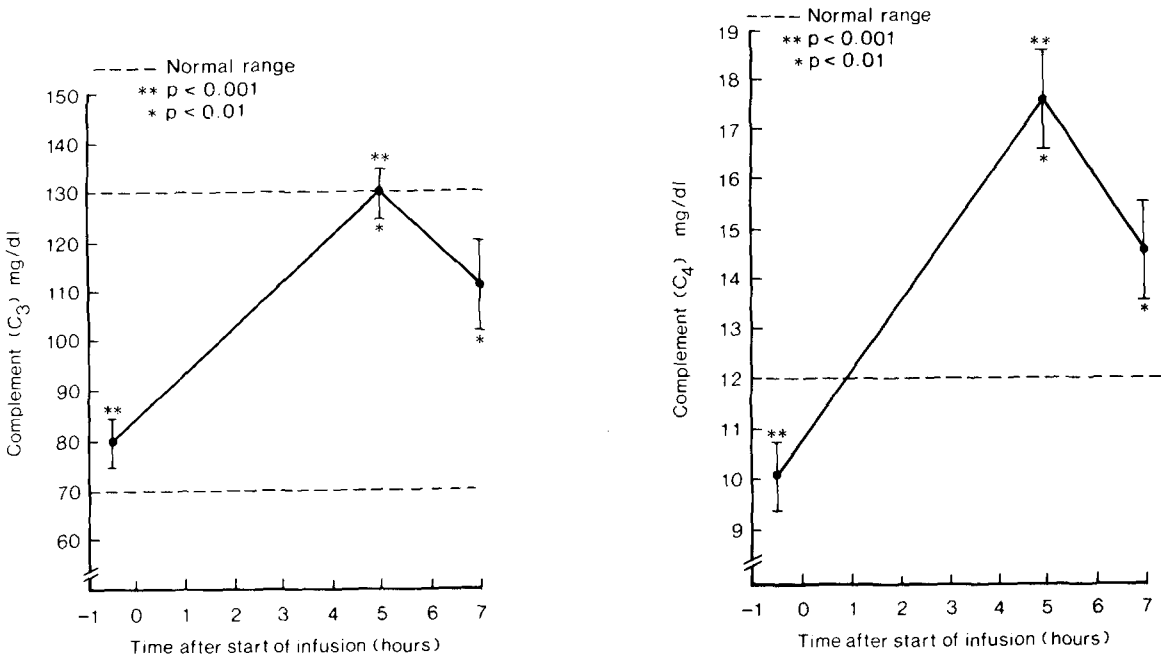


Fig. 6. Complement levels C_3 (*left*) and C_4 (*right*) during lipid infusions in patients receiving total parenteral nutrition. Mean ± S.E.M. n = 15.

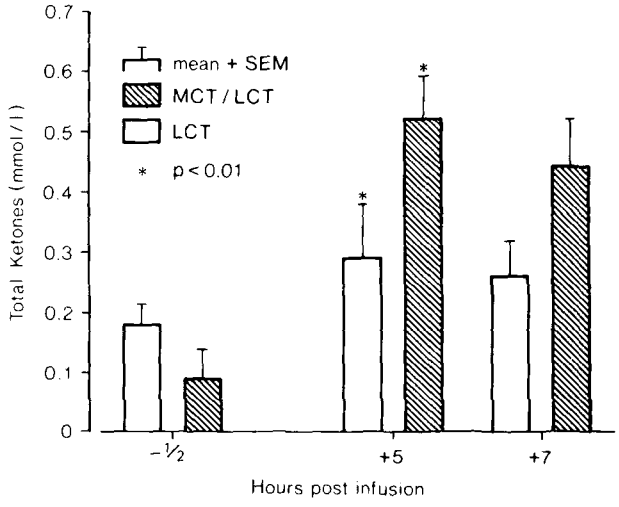


Fig. 7. Levels of ketone bodies related to lipid infusions in patients receiving total parenteral nutrition (MCT = medium-chain triglyceride; LCT = long-chain triglyceride).

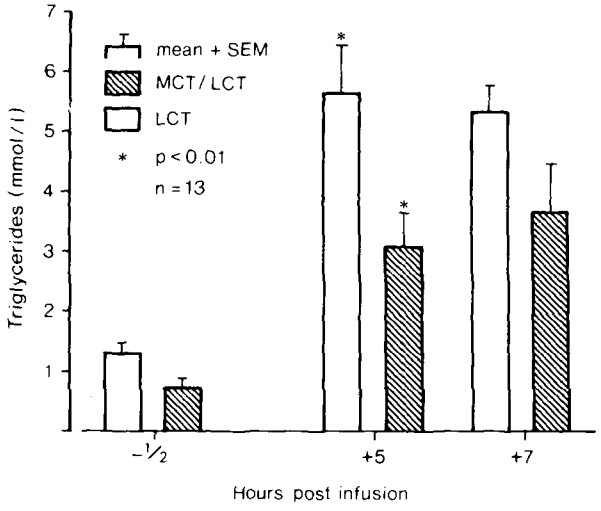


Fig. 8. Triglyceride levels related to lipid infusion in patients receiving total parenteral nutrition (MCT = medium-chain triglyceride; LCT = long-chain triglyceride).

which is therefore "spared" as the need for gluconogenesis is reduced. Such a hypothesis may explain the superior nitrogen balance observed during the MCT infusion period. An alternative hypothesis might have been that MCT is less toxic to the liver than LCT and allows increased protein synthesis. Possible evidence for this was the lower plasma bilirubin concentrations in the patients receiving MCT. No other parameter of liver function, however, showed any significant differences. In an attempt to assess hepatic protein synthesis albumin, prealbumin (half-life 2 days), and complement components C3, C4 were assayed. The plasma concentrations were, however, similar throughout all periods of the study.

The complement (C3 and C4) data show that neither lipid activated the complement systems in our TPN patients—further evidence of lack of toxicity for MCT and conventional LCT, and perhaps evidence of improved synthesis in patients receiving MCT infusions.

The results of this study indicate that MCT-containing lipid is at least as good as LCT lipid as a noncarbohydrate energy source and may possibly have nitrogen-sparing advantages. The MCT emulsion was not associated with any adverse clinical, hematological, or biochemical effects.

Final Discussion

Both studies demonstrate that a lipid emulsion that contains 50% MCT can be safely infused both perioperatively and as part of a TPN regimen. The higher plasma fatty acid concentrations obtained during the LCT infusions indicate that MCT is more rapidly metabolized than is LCT. Hyperketonemia with MCT occurred only in study 2. The latter patients were malnourished and likely to have higher initial plasma ketone concentrations [41] and reduced carnitine stores. Similarly, the better nitrogen conserving properties demonstrated with MCT in study 2 may reflect the associated hyperketonemia. Reduced nitrogen excretion and hyperketonemia have been reported in both trauma [42] and malnourished patients [43].

MCT was developed in the hope that it would bridge the gap between conventional lipid (LCT) and carbohydrate (i.e., glucose) fuels [44]. Structurally MCT is lipid, with the same calorific value, yet is cleared rapidly, like glucose, from plasma and is rapidly metabolized.

One of the difficulties encountered with infusing glucose is the high concentration required to limit the volumes needed to give sufficient calories. Fifty percent glucose must be given via a central line, and insulin may be needed to overcome intolerance. There is a limit to the total amount of glucose that can be handled per day by the liver—in the region of 1,800–2,000 kcal—before hepatic toxicity, e.g., fatty liver, may develop. Moreover, there is continuing obligatory fatty acid oxidation in both injured patients and those with sepsis despite the infusion of adequate amounts of carbohydrate calories [45, 46]. This requirement has been quantitatively related to the severity of sepsis, insulin resistance, and plasma cortisol concentration [47].

Excess LCT infusion may be implicated in causing fatty infiltration in the liver [48], and significant proportion of the LCFA derived from infused LCT may be utilized to support endogenous adipose stores rather than be available for immediate beta-oxidation. MCT appears to have none of these problems.

An MCT infusion, however, cannot be the sole lipid source in a feeding regimen, since LCT is required to provide essential fatty acids. The role of MCT is to substitute partially for both glucose and conventional lipid, reducing the complications associated with giving large quantities of the latter.

The disadvantages of MCT infusion are few. Systemic toxicity has not been seen even at the high rates of infusion of the first study. Severe hyperglycemia in a few patients in intensive care has been reported [6], and the infusion (of a MCT/LCT mixture) was curtailed. We noted thrombophlebitis of peripheral veins in the first few patients in study 1, but no other adverse reaction was seen. We did not encounter any problems of tolerance, gross metabolic disturbances, or interaction with anesthesic agents in study 1. In ill patients with critical respiratory exchange, MCT infusion may be theoretically dangerous; the report [24] of increased oxygen consumption by 39% in resting animals and 22% in norepinephrine-stimulated rats cannot be directly extrapolated to human physiology but do indicate the need for extra caution in patients with compromised lung function.

There have been no previous human studies of nitrogen sparing in patients receiving MCT, as part of a TPN regimen. Animal studies [23, 24, 49] performed suggest that simple physical mixtures of MCT/LCT may improve nitrogen balance only in injured animals. More recent work with structured lipid [24] has indicated that this formulation of MCFA, LCFA, and glycerol has better nitrogen-sparing characteristics in animals.

Conclusion

Medium-chain triglycerides are a new calorie source that can be safely infused in patients. The evidence to date is that it is rapidly cleared from the plasma of both fit and chronically ill patients without gross metabolic disturbances and can be usefully employed as part of a TPN regimen. Further studies are indicated to determine which formulation and in which patients MCT infusion will provide optimum benefit.

Résumé

Les effets produits par une perfusion d'une émulsion lipidique à 10% contenant des proportions égales de triglycérides à longue chaîne et de triglycérides à chaîne moyenne ont été étudiés chez des opérés soumis à une chirurgie élective et chez d'autres placés sous alimentation parentérale exclusive. L'équilibre azoté fut meilleur quand ces derniers reçurent des triglycérides à chaîne moyenne plutôt que des triglycérides à longue chaîne. C'est seulement chez les sujets dénutris que l'émulsion lipidique contenant des triglycérides à chaîne moyenne produisit une cétonémie significative. Elle ne provoqua pas d'effets secondaires.

Resumen

Los efectos de ahorro proteico de las emulsiones de lípidos que contienen triglicéridos de cadena larga (TCL) han sido bien documentados, pero los efectos de los triglicéridos de cadena media (TCM) sobre el metabolismo proteico en el hombre no han sido investigados en detalle. Realizamos dos estudios separados en humanos para comparar una emulsión de TCL con un lípido que contiene TCM, una solución al 10% que está constituída por iguales proporciones de TCL y TCM. Los efectos de la emulsión de lípido al 10% con iguales proporciones de TCL y TCM fueron estudiados en pacientes sometidos a cirugía electiva y en pacientes malnutridos en regímenes de nutrición parenteral total (NPT). El balance de nitrógeno fue mejor cuando el regimen de NPT administrado contenía lípidos con TCM, al compararlo con regímenes que sólo contenían lípidos con TCL. Unicamente en los pacientes malnutridos se observó cetonemia de significación producida por la emulsión lípida de TCM. Las emulsiones lípidas con TCM fueron administradas sin que se presentaran reacciones colaterales adversas.

Acknowledgments

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