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Parenteral Infusion of Long- and Medium-Chain Triglycerides and Reticuloendothelial System Function in Man*

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ABSTRACT. Previous study demonstrated that patients who received total parenteral nutrition (TPN) with standard intermittent infusion of long chain triglyceride (LCT) at 0.13 g $kg^{-1}hr^{-1}$ over 10 hr for each of three days showed a significant decline in ^{99}Tc-sulfur colloid (TSC) clearance rate by the reticuloendothelial system (RES). The present studies evaluated eight patients who received the same total lipid dose of LCT infused continuously as in a three-in-one admixture, and another nine patients receiving the same amount of fat as a medium chain triglyceride (MCT)/LCT (75%/25%) emulsion intermittently over 10 hr at 0.13 g $kg^{-1}hr^{-1}$ for three consecutive days. Patients were given continuous total parenteral nutrition (TPN) comprised of protein, 1.5 g $kg^{-1}day^{-1}$, and dextrose, 4.5 g $kg^{-1}day^{-1}$. RES function was examined by measuring the clearance rates of intravenously injected TSC while receiving TPN containing only protein and dextrose, and again after three days of fat infusion. Mean (±SEM) clearance rate constants before and after continuous LCT infusion were 0.38 ± 0.09 and 0.41 ± 0.08 min^{-1}, respectively, while those before and after intermittent MCT/LCT infusion were 0.50 ± 0.18 and 0.73 ± 0.24 min^{-1}, respectively. In contrast to intermittent LCT infusion, the administration of continuous LCT or an intermittent MCT/LCT mixture does not impair TSC clearance by the RES. These findings suggest that condensing the daily period of LCT infusion at standard dosage may exceed the rate of metabolic utilization, resulting in increased fat removal and diminished TSC uptake by the RES. The provision of fat principally as MCT or by a continuous mode of administration may enable adequate metabolism of lipid emulsion without RES dysfunction, and so may be of particular benefit in critically ill or septic patients. (*Journal of Parenteral and Enteral Nutrition* **14**:467–471, 1990)

Mixed fuel systems that incorporate intravenous lipid emulsion are increasingly utilized in total parenteral nutrition (TPN). Lipid is supplied as an isotonic emulsion containing polyunsaturated long chain triglyceride (LCT) from soybean or safflower oils. Mixed formulations offer reduced metabolic complications and comparable lean tissue repletion in comparison to glucose-based formulae.[1,2] Unfortunately, there are concerns regarding reticuloendothelial system (RES) impairment, slow clearance from the bloodstream, and visceral fat deposition when fat is administered in substantial amounts.[3]

The RES functions in the phagocytosis of microorganisms and foreign material as well as in the secretion of chemical mediators of the inflammatory response. It has also been implicated in the clearance of lipid particles associated with infusion of lipid emulsion.[4,5] Animal studies suggest that the intravenous administration of LCT emulsion may impair RES function and clearance of bacteremia.[6,7] Higher mortality has been reported in patients who received preoperative TPN with half of the nonprotein calories as lipid emulsion.[8] ^{99}Tc-sulfur colloid (TSC) is cleared from the circulation by the RES, and decreased TSC clearance is associated with increased infection and mortality in patients with cirrhosis.[9]

Recent work in our laboratory demonstrated that standard intermittent infusion of LCT emulsion at 43% of nonprotein calories over 10 hr for each of three days was sufficient to significantly depress TSC clearance by the RES.[20] Since the dose of LCT administered and the rate of infusion are potential factors in RES impairment, we evaluated TSC clearance in patients who received the same total lipid dose infused continuously as a three-in-one admixture (study 1).

The potential detrimental effects of LCT infusion have prompted a search for alternative lipid sources. Medium chain triglycerides (MCT) are derived from palm kernel or coconut oils and contain saturated fatty acids of chain length 6 to 12 carbons.[10,11] They offer potential advantages that include: rapid clearance from the bloodstream, rapid utilization with mitochondrial uptake and metabolism independent of the carnitine shuttle, and a thermogenic effect that results in a reduction in net lipid storage in comparison to an equivalent amount of LCT.[10-13] They are as nitrogen sparing as LCT and are well tolerated by enteral or parenteral routes. Animal studies suggest that MCT does not depress RES function,[6,7] and in the present paper (study 2) we evaluated TSC clearance in p[illegible]ceived intermittent infusions of an MC[illegible] (75%/25%) emulsion in

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amounts previously shown to impair TSC clearance when given as 100% LCT.

MATERIALS AND METHODS

Patients

This was a prospective study of patients at New England Deaconess Hospital who required at least five days of parenteral nutrition support and had oral/enteral intakes of less than 500 kcal daily. Other exclusion criteria included age less than 18 years, insulin-dependent diabetes mellitus, hyperlipidemia or pancreatitis with triglyceride greater than 400 mg/dl, inability to tolerate large intravenous volumes, severe liver disease with history of encephalopathy, or renal failure requiring dialysis. This study was approved by the Institutional Review Board, and written informed consent was obtained.

Eight and nine patients were enrolled in studies 1 and 2, respectively. Diagnoses are summarized in Tables I and II. Albumin less than 3.5 g/dl was evident in most patients, and nearly half had suffered moderate to severe weight loss in the preceding 6 months at greater than 10% of usual body weight (Tables III and IV). Some patients exhibited moderate renal or hepatic dysfunction at the time of study (Tables V and VI).

Total Parenteral Nutrition

Multilumen central venous catheters were placed for TPN infusion and sampling. Patients were given continuous TPN-containing amino acids at 1.5 g kg^{-1} day^{-1} and dextrose at 4.5 g kg^{-1} day^{-1} throughout the studies and for at least 24 hr before baseline TSC clearance measurement. In study 1, soybean emulsion (Travamulsion 20%; Clintec, Deerfield, IL) was infused as a continuous three-in-one admixture[14] with fat at 1.3 g kg^{-1} day^{-1} over 24 hr for each of the three days following baseline TSC clearance determination. In study 2, MCT/LCT (75%/25%) emulsion (Clintec, Deerfield, IL) was infused over 10 hr at 0.13 g kg^{-1} hr^{-1} for each of the three days

TABLE I
Patient characteristics: study 1

Patient No.	Age (years)	Sex	Diagnosis
1	59	M	Studied 2 weeks after pancreaticoduodenectomy for chronic pancreatitis/peptic ulcer.
2	70	M	Studied 3 days after exploratory laparotomy for bowel obstruction, revealed metastatic gastric carcinoma. Lysis of adhesions, jejunal resection, tube ileostomy, and jejunocoloenterostomy were performed.
3	35	F	Studied 2 weeks after partial small bowel resection for gunshot wound.
4	49	M	Crohn's disease with multiple previous surgeries and short bowel. Studied after venous access disc replacement for infection.
5	38	F	Hepatocellular carcinoma, status post extended left hepatic resection. Studied 3 days postoperatively.
6	62	M	Studied 4 weeks after pancreaticoduodenectomy for common bile duct obstruction.
7	60	M	Studied 2.5 weeks after resection of pelvic tumor.
8	87	M	Studied 1.5 weeks after fascial repair for hematoma complicating hip fracture.

TABLE II
Patient characteristics: study 2

Patient No.	Age (years)	Sex	Diagnosis
9	60	M	Studied 1 week after esophagogastrectomy for esophageal carcinoma.
10	71	M	Obstructing esophageal carcinoma. Studied after gastrostomy placement.
11	61	F	Studied 1 week after partial small bowel resection for recurrent colon carcinoma.
12	79	M	Studied during hospitalization for intramural esophageal dissection.
13	70	M	Studied 1 week after partial small bowel resection for recurrent colon carcinoma.
14	35	M	Ulcerative colitis. Studied during exacerbation.
15	62	F	Studied during hospitalization for sigmoid obstruction secondary to recurrent colon carcinoma.
16	76	F	Studied 1 week after end sigmoid colostomy for diarrhea management in patient with functional short bowel, status post resection of endometrial carcinoma and radiation therapy.
17	77	M	Studied during TPN for duodenalcutaneous fistula complicating left colon resection for carcinoma.

TABLE III
Nutritional parameters: study 1

Patient No.	Height/ weight (cm/kg)	% Ideal body weight	% Usual body weight	Albumin (g/dl)	Total lymphocyte count/mm^3
1	170/72.0	108	−10	2.3	1064
2	170/61.3	92	−12	1.8	780
3	160/46.0	79	−8	3.4	1936
4	175/65.2	94	0	3.8	702
5	157/110.0	178	0	3.5	1728
6	180/80.0	111	−5	2.2	1218
7	165/66.8	105	0	2.9	511
8	178/63.1	89	−20	2.4	158

TABLE IV
Nutritional parameters: study 2

Patient No.	Height/ weight (cm/kg)	% Ideal body weight	% Usual body weight	Albumin (g/dl)	Total lymphocyte count/mm^3
9	178/73.5	104	−8	2.1	774
10	168/67.5	104	−8	3.0	660
11	155/65.0	117	0	2.7	144
12	173/50.9	75	−18	2.9	552
13	171/77.0	115	−4	2.8	1044
14	173/59.0	87	−13	2.8	465
15	168/55.8	89	−20	2.7	*
16	163/43.5	72	−23	2.1	186
17	182/89.7	123	−17	2.4	*

* No data.

TABLE V
Patient physical and laboratory data: study 1

Patient No.	Temperature (°C)*	Hgb/WBC (g/dl)/(mm³)	BUN/Cr (mg/dl)	Bili/AST (mg/dl)/(mU/ml)	Nitrogen balance (g/day)
1	AF	11.4/15.2	25/0.8	0.3/23	−1.9
2	AF	8.2/6.5	11/0.7	0.8/21	−0.3
3	AF	12.1/8.8	13/0.7	0.7/23	−0.9
4	AF	16.5/7.8	13/0.9	0.5/57	+0.2
5	AF	10.0/14.4	15/0.5	1.6/71	+5.3
6	38	9.3/17.4	53/1.7	1.8/274	−2.2
7	AF	10.4/7.3	19/1.3	2.9/229	+1.7
8	AF	12.9/7.9	21/0.8	1.1/114	−0.5

AF, afebrile, temperature <38°C.

TABLE VI
Patient physical and laboratory data: study 2

Patient No.	Temperature (°C)*	Hgb/WBC (g/dl)/(mm³)	BUN/Cr (mg/dl)	Bili/AST (mg/dl)/(mU/ml)	Nitrogen balance (g/day)
9	39	10.5/8.6	21/0.4	0.4/29	−3.5
10	AF	13.1/13.2	22/1.1	1.4/33	+1.3
11	AF	9.9/7.2	41/1.8	1.1/20	+6.3
12	AF	12.1/27.6	29/1.0	0.7/19	−1.4
13	AF	10.7/11.6	28/0.3	0.6/62	−2.4
14	AF	8.6/9.3	10/0.6	0.1/28	−3.3
15	AF	10.2/9.3	29/0.9	0.6/36	−1.0
16	AF	10.3/9.3	20/0.6	**/23	**
17	AF	9.6/7.6	23/1.0	0.4/23	**

* AF, afebrile.
** No data.

following baseline TSC clearance determination. Both TPN systems provided approximately 33 kcal kg^{-1} day^{-1}, with 43% of the nonprotein calories as lipid.

TSC Clearance

RES function was evaluated by measurement of TSC clearance as described in detail previously.[20] In brief, TSC clearance measurements were undertaken on baseline TPN containing only protein and dextrose, and again after three days of intermittent lipid infusion. For each clearance determination, a baseline sample of blood was obtained and then TSC (0.3–0.5 mCi) was injected as a bolus through the distal central venous access port. Serial blood samples were then drawn into heparinized tubes from a more proximal central venous access port over a 60-min period. Plasma samples were submitted for gamma counting on a Beckman 4000 Gamma Counter (Irvine, CA).

Counts were corrected for decay and plotted as a function of time. These TSC counts were best described by two exponential terms representing a two-compartment model with a reversible rate constant (K12) probably reflecting binding of TSC to tissue proteins and an irreversible rate constant (K10) reflecting elimination of TSC by the RES. The differential equations describing TSC contents in compartments 1 and 2 are $dC_1/dt = C_2K21 - C_1K12 - C_1K10$ and $dC_2/dt = C_1K12 - C_2K21$, with C_1 and C_2 representing the TSC contents of the two compartments, respectively. The irreversible rate constant from plasma was estimated by nonlinear least squares analysis. The clearance rate constants have proven highly reproducible within a given patient with a mean coefficient of variation of 15.3%.

Statistics

The paired *t*-test was done on the TSC clearance rate constants, with each patient serving as their own control.

RESULTS

All patients completed the studies without complications. Isolated fevers were noted in two patients and several patients exhibited relative leukocytosis, but none had documented septicemia (Tables V and VI). Liver function tests were not adversely affected. Serum triglycerides remained in the 62–374 mg/dl range for both studies.

The mean TSC clearance rate constants for study 1 before and after three days of continuous LCT infusion were 0.38 ± 0.09 (±SEM) and 0.41 ± 0.08 min^{-1}, respectively. The individual TSC clearance rate constants are depicted in Figure 1.

The mean TSC clearance rate constants for study 2 before and after three days of intermittent MCT/LCT infusion were 0.50 ± 0.18 (±SEM) and 0.73 ± 0.24 min^{-1}, respectively. Figure 2 shows the TSC clearance rate constants for individual patients.

There was no significant impairment of TSC clearance with either continuous LCT administration or intermittent MCT/LCT infusion.

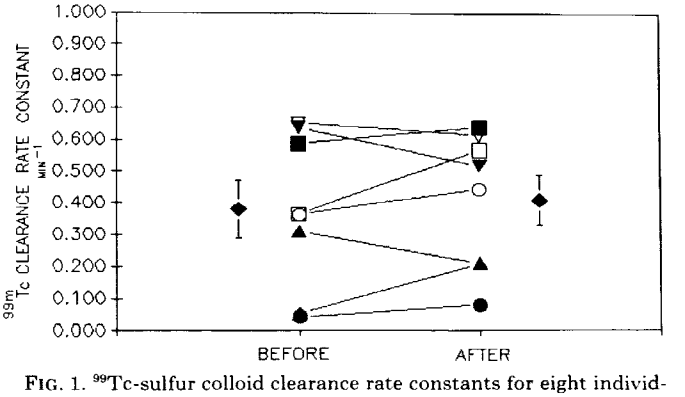

FIG. 1. ^{99m}Tc-sulfur colloid clearance rate constants for eight individual patients before and after 3 days of continuous LCT infusion. The rate constants reflect K_{10} data as described in the text. Means ± SEM are depicted to either side.

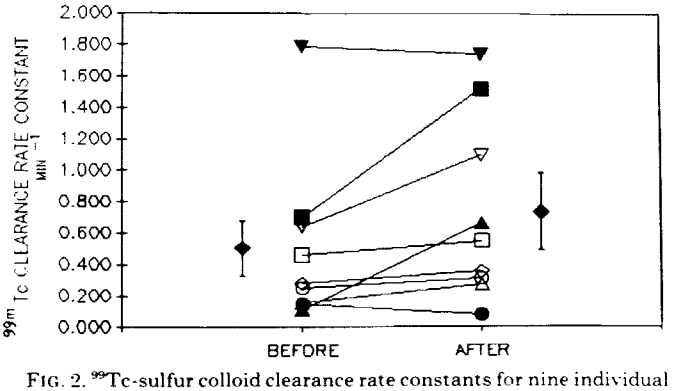

FIG. 2. ^{99m}Tc-sulfur colloid clearance rate constants for nine individual patients before and after 3 days of intermittent MCT/LCT (75%/25%) infusion. The rate constants reflect K_{10} data as described in the text. Means ± SEM are depicted to either side.

DISCUSSION

We previously found that patients given standard intermittent infusion of LCT emulsion (approximately 60–100 g of fat) over 10 hr for each of three days showed a significant decline in the TSC clearance.[20] The present results (study 1) differed only in that the same total lipid dose was infused continuously over 24 hr as a three-in-one admixture, and no significant impairment of TSC clearance was detected. The provision of 43% of the nonprotein calories as LCT is well within the 20 to 80% range of typical TPN formulae, and comparable to the daily administration of 500 ml of 20% lipid emulsion. These findings suggest that condensing the daily period of lipid infusion exceeds the rate of metabolic utilization, resulting in increased fat removal and decreased TSC uptake by the RES. Administration of continuous LCT may enable adequate metabolism without impairment of TSC clearance by the RES.

In the present paper (study 2), infused intermittent doses of MCT/LCT (75%25%) were given with a dosing regimen identical to that which produced a significant decline in TSC clearance using 100% LCT. The provision of fat principally as MCT may allow for rapid metabolic utilization without RES dysfunction, because no significant impairment of TSC clearance was detected.

The RES dysfunction associated with LCT infusion may be of particular consequence in critically ill patients. When rats were given bilateral septic femur fractures and then three days of TPN, those given dextrose or LCT as nonprotein calories became bacteremic, while those given MCT did not exhibit bacteremia.[6] Impaired macrophage function[15,16] and increased postoperative infections and mortality[8] have been described in humans given LCT emulsion at conventional rates, although in the latter study the potential adverse impact of parenteral fat was not part of the original study hypothesis. TSC is specifically extracted from the sinusoidal microcirculation and cleared by the liver's RES macrophages, the Kupffer cells. While TSC clearance may not specifically measure RES phagocytic function,[17] it does correlate with infection and mortality in patients with cirrhosis.[9]

The safety and utility of mixed fuel TPN systems that include fat are well established, with decreased metabolic complications and comparable lean tissue repletion to glucose-based formulations.[1,2] Essential fatty acids are provided. Hepatic *de novo* lipogenesis is decreased. There is a reduction in carbon dioxide production and respiratory quotient that may be of particular benefit in patients with respiratory compromise and difficult weaning from mechanical ventilators.

Thus, while it is common practice to give intermittent infusions of LCT emulsion to obtain the benefits of a mixed fuel system, it may be preferable to utilize a continuous mode of administration to avoid the potential risk of excessive infusion rates. In addition to fat administration at a rate and dose that allows adequate metabolic utilization without RES impairment, benefits of the three-in-one admixture include decreased administration costs and less need for nursing supervision.[14] Furthermore, there is probably no greater risk of bacterial contamination of a three-in-one formulation.[18] A cautious approach may be prudent in critically ill or septic patients, and in this setting we recommend that LCT be infused continuously as 25 to 35% of nonprotein calories, generally corresponding to 30 to 60 g daily.

MCT is a promising fat substrate for use in critically ill or septic patients. It is used enterally for a variety of malabsorption syndromes, but is approved for parenteral use only in Europe. An MCT/LCT mixture supplies both rapid and slowly metabolized fuels as well as essential fatty acids. Further refinement of this approach has culminated in the development of structured triglycerides, a chemical mixture of long and medium chain fatty acids incorporated on the same glycerol backbone by hydrolysis, and random re-esterification of a physical mixture of LCT and MCT.[19] Such a compound may have additional benefits, particularly an improved protein-sparing effect when compared to LCT. Preliminary animal studies suggest that structured triglycerides may be more protein-sparing than MCT with an equivalent sparing of the RES system, while MCT has a unique thermogenic effect, and appears to maintain serum albumin levels in injury models.[7,13] The ideal lipid substrate for parenteral nutrition will likely incorporate desirable qualities of a variety of fat sources. Thus, the ultimate role for MCT and other specialty lipids awaits further investigation.

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