Correction of the malabsorption of the preterm infant with a medium-chain triglyceride formula

After receiving a milk-based formula for one week, 16 preterm infants, weighing 1,300 to 1,800 gm, were fed two isocaloric formulas containing either medium-chain or long-chain triglycerides for 15 days; the alternate formula was given for a second period of identical duration. While receiving MCT, the infants had greater (P < 0.01) percent fat absorption (83.4--97.1%) and weight gain (7.5--11.5 gm/kg/100 calories). Because metabolic acidosis occurred with the LCT formula, the chloride content was adjusted to that of the MCT diet for the second part of the study involving nine infants. The beneficial effects of MCT were confirmed and, in addition, there was a higher (P < 0.01) percent retention of nitrogen (67.3--82.1).

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THE LOW CONCENTRATIONS of duodenal bile acid and lipase found in both full-term and premature infants are currently thought to explain the well-known fat malabsorption observed in the neonatal period.

Medium-chain triglycerides are well absorbed even when there is impairment of lipolysis and of micellar solubilization. Experimentally, they are thought to enhance monosaccharide and amino acid absorption. Their role in promoting absorption of bile acids has been suggested and subsequently reported albeit without any comment.

The purpose of the present study was to document the extent of fat malabsorption in preterm infants fed long-chain triglyceride diets and to demonstrate if a MCT formula would alleviate the steatorrhea and the resultant caloric deficiency.

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Abbreviations used
MCT: medium-chain triglycerides
LCT: long-chain triglycerides

MATERIAL AND METHODS
A total of 25 neonates was studied. The birth weights varied from 1,300 to 1,800 gm and were appropriate for gestational age. These preterm neonates did not have major congenital anomalies, hemolytic disease, or hyaline membrane disease requiring treatment.

During the first week of life, the infants received the routine premature nursery care and SMA* formula. Baseline studies included concentrations of blood glucose, serum electrolytes, and base excess values. On the seventh day of life, the preterm infants received either the MCT diet or one of two LCT formulas (Table I). An initial 15-day feeding period was followed by a second period of identical duration during which each infant was given the alternate formula. In the first part of the study, 16 infants were fed MCT and the LCT formula (LCTH) with a chloride content of 33 mEq/l. In the second part of the study, nine subjects were given MCT and the LCT formula (LCTBH) in which the

*Wyeth Canada Ltd.
chloride concentration was that of the MCT diet (21 mEq/l). The formulas were administered at a recommended dilution of 20 calories/ounce. The new formula was gradually introduced over a 3-day period. During the first week of life, SMA formula was fed to most infants by gavage. With the beginning of the study, total daily intake was regulated by the infants, since they were bottle fed ad libitum. The amount of formula ingested, the number and character of the stools, as well as the clinical condition of the infants were carefully monitored. Weights of the infants were recorded daily. Blood glucose concentrations, pH, total CO₂, bicarbonate, and base excess were measured on arterialized capillary samples every third day. Serum electrolyte concentrations were determined at least once before starting the study and twice during each of the two 15-day feeding periods.

During the last 3 days of each test feeding period, a timed stool collection was carried out by administering two carmine red markers 72 hours apart at a dose of 10 ml of a 3% solution. Diapers were lined with plastic film during collection periods. Stools were immediately placed in a Dry Ice box kept at the bedside. In addition, 3-day nitrogen balance studies were performed on the nine neonates admitted to the second part of the study. For this purpose, they were placed on metabolic beds and fitted with urine collecting bags.

Carbohydrate, fat, electrolyte, calcium, and phosphorus contents were determined by the manufacturer on the specific lots of formulas prepared for the present study. Nitrogen was measured in aliquots of formulas, urine, and stools by the micro Kjeldahl method. Stool fat was determined by a technique which quantitatively extracts medium- as well as long-chain fatty acids. The assay of bile acids in feces was performed by a modification of the enzymatic method. Serum base excess, pH, and total CO₂ were measured with the Astrup microapparatus, serum sodium and potassium with a flame photometer, and chloride by a colorimetric method. Unless otherwise specified, results were expressed as mean ± SEM and differences were evaluated using student’s t test.

RESULTS

Gastrointestinal tolerance for the MCT as well as for the two LCT formulas was good. When MCT was fed to the infants, the water content of stools increased in relation to the amount of solid fecal material and mild to moderate abdominal distention was noted. Transit time, calculated as the interval separating the administration of the carmine red marker from its appearance in the stools and expressed as the mean ± SD of two values obtained during each test feeding period, did not change. The transit time (hours) of infants receiving the MCT preparation was 10.7 ± 7.2 compared to 11.2 ± 5.2 when LCTH was fed and 15.3 ± 2.6 while receiving LCTBH. Fewer stools (P < 0.05) were noted with MCT (2.4 ± 0.8) and LCTBH (2.6 ± 0.3) than with LCTH (3.5 ± 0.5) feedings.

MCT vs LCTH. Calories ingested by the 16 infants during each of the two test-feeding periods with MCT and LCTH formulas did not differ. The better weight gain with MCT feedings became more evident when the two periods were pooled and the values were expressed as gm/kg/100 calories (Table II). Data presented in Fig. 1 indicate that percent fat absorption associated with MCT (97.1 ± 0.4) was greater (P < 0.01) than with LCTH (83.4 ± 2.5). There was no difference in the percent nitrogen absorption. Fecal losses of bile acids (mg/kg/24hr) were lower (P < 0.01) when MCT was fed (3.0 ± 0.6) than with the LCTH preparation (7.8 ± 1.2).

During MCT feeding, only one infant had mean base excess (B.E.) values below −5. In contrast, 10 of 16 de-

<table>
<thead>
<tr>
<th>Period</th>
<th>Diet</th>
<th>No.</th>
<th>Calories (kg/day)</th>
<th>Weight gain* (gm/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seventh to</td>
<td>MCT</td>
<td>9</td>
<td>117.3 ± 5.4</td>
<td>139 ± 1.2</td>
</tr>
<tr>
<td>twenty-first day</td>
<td>LCTH</td>
<td>7</td>
<td>119.5 ± 6.6</td>
<td>99 ± 1.7</td>
</tr>
<tr>
<td>Twenty-second to</td>
<td>MCT</td>
<td>7</td>
<td>144.5 ± 5.2</td>
<td>160 ± 1.8</td>
</tr>
<tr>
<td>thirty-sixth day</td>
<td>LCTH</td>
<td>9</td>
<td>164.8 ± 8.0</td>
<td>115 ± 1.9</td>
</tr>
</tbody>
</table>

*When expressed as g/Kg/100 calories, weight gain during MCT feeding was 115 ± 0.7 and 75 ± 0.7 with LCTH (P < 0.01).

Table I. Composition of the formulas at a dilution of 20 calories/30 ml

<table>
<thead>
<tr>
<th></th>
<th>MCT</th>
<th>LCTH</th>
<th>LCTBH</th>
</tr>
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<tr>
<td>Protein</td>
<td>2.2%</td>
<td>2.2%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>8.8%</td>
<td>8.5%</td>
<td>8.6%</td>
</tr>
<tr>
<td>Lipid</td>
<td>0.56%</td>
<td>2.6%</td>
<td>2.6%</td>
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<tr>
<td>Major mineral components</td>
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</tr>
<tr>
<td>Sodium (mEq/l)</td>
<td>16.4</td>
<td>13.6</td>
<td>13.0</td>
</tr>
<tr>
<td>Potassium (mEq/l)</td>
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<td>25.3</td>
<td>25.6</td>
</tr>
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<td>Chloride (mEq/l)</td>
<td>21.0</td>
<td>33.0</td>
<td>21.0</td>
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<tr>
<td>Calcium (mg/l)</td>
<td>997.0</td>
<td>960.0</td>
<td>900.0</td>
</tr>
<tr>
<td>Phosphorus (mg/l)</td>
<td>104.0</td>
<td>61.0</td>
<td>75.0</td>
</tr>
<tr>
<td>Osmolality (mOsm/kg)</td>
<td>544</td>
<td>568</td>
<td>572</td>
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</tbody>
</table>

Table II. Caloric intake and weight gain of 16 infants fed MCT and LCTH
developed a significant degree of metabolic acidosis with LCT_H feeding. The acidosis (B.E.: -8.8 ± 0.7) was hyperchloremic in type (Cl⁻: 113.1 ± 0.8). Despite its severity, the acidosis was well tolerated. Except for mild hyperpnea, it seldom became manifest clinically. However, anorexia and vomiting developed in one baby and forced discontinuation of the study. In 10 subjects who, during the 15-day period of LCT_H feedings, were noted to have a base excess of -8 or below, sodium bicarbonate was added to feedings at a dosage of 3 mEq/kg/day.

**MCT vs LCT_BH.** Because the lower percent fat absorption and weight gain associated with LCT_H feeding in the first part of the study could have been secondary to the hyperchloremic acidosis, the chloride content of the LCT diet (33 mEq/l) was reduced by the manufacturer to that of the MCT formula (21 mEq/l) by replacing some of the chloride with citrate. The modified diet (LCT_BH) was fed either before or after MCT to each of nine preterm newborn infants in successive 15-day intervals. The acid-base problems noted previously did not occur.

Caloric intake during the early and the late test-feeding periods were identical. The mean weight gain was greater when MCT was fed but the difference was not significant during the early period. However, when the data from both feeding periods were pooled and expressed as gm/kg/100 calories there was a greater gain with MCT than with LCT_BH (Table III). As seen in Fig. 2, the percent fat absorption was significantly higher (P<0.01) with MCT (94.9 ± 0.8) than with LCT_BH (77.9 ± 2.1). The percent nitrogen absorption was also greater (P<0.05). Fecal fat excretion (gm/24 hr) with MCT feeding was 0.6 ± 0.2 and 2.7 ± 0.2 with LCT_BH; corresponding bile acid sequestration (mg/kg/24 hr) was 4.6 ± 0.9 and 7.9 ± 1.0 (P<0.05).

Results of the nitrogen balance study performed on each of the nine infants during the final 3 days of the two test-feeding periods are presented in Fig. 3. Medium-chain triglyceride feedings led to a lower percent fecal and urinary nitrogen excretion as well as to a greater percent nitrogen retention (82.1 ± 2.7) than when LCT_BH was given (67.3 ± 2.2) at daily nitrogen intakes which were comparable.

**DISCUSSION**

This study confirms the presence of fat malabsorption in premature infants. The average percent fat absorption of 83.4 and 77.9 with the two corn oil diets (LCT_H and LCT_BH) was notably higher than the 45-60 reported with butter fat formulas^6,14-16 and was within the range of values published for breast-fed premature infants.^4,15 Fat malabsorption varies little during the first month of life in full-term^17 as well as in premature infants. The present data indicate that the percent fat absorption remained essentially the same during both the early and the late feeding periods.

The intraluminal phase of lipid absorption is defective in the newborn infant. Low concentrations of

<table>
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<tr>
<th>% ABSORPTION</th>
<th>FAT</th>
<th>NITROGEN</th>
<th>FAT</th>
<th>NITROGEN</th>
</tr>
</thead>
<tbody>
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<td>MCT</td>
<td><img src="image" alt="MCT" /></td>
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<td><img src="image" alt="MCT" /></td>
<td><img src="image" alt="MCT" /></td>
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<tr>
<td>LCT(H)</td>
<td><img src="image" alt="LCT(H)" /></td>
<td><img src="image" alt="LCT(H)" /></td>
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</table>

**Fig. 1.** Percentage absorption of fat and of nitrogen from the MCT and the LCT_H diets. Horizontal lines represent the mean of each group. Nitrogen determinations were carried out on 11 of the 16 babies.

<table>
<thead>
<tr>
<th>% ABSORPTION</th>
<th>FAT</th>
<th>NITROGEN</th>
<th>FAT</th>
<th>NITROGEN</th>
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</thead>
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<td><img src="image" alt="MCT" /></td>
<td><img src="image" alt="MCT" /></td>
</tr>
<tr>
<td>LCT(BH)</td>
<td><img src="image" alt="LCT(BH)" /></td>
<td><img src="image" alt="LCT(BH)" /></td>
<td><img src="image" alt="LCT(BH)" /></td>
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</tr>
</tbody>
</table>

**Fig. 2.** Percentage absorption of fat and nitrogen from the MCT and the LCT_BH diets. Horizontal lines represent the mean of each group.
duodenal lipase have been reported following a test meal in a certain proportion of full-term infants.\textsuperscript{2} Following pancreozymin, average values were much lower in both full-term and premature than in older infants.\textsuperscript{4} Further evidence of impaired lipolysis relates to the presence of unhydrolyzed glycerides in the feces of newborn infants.\textsuperscript{18} Impaired micellar solubilization of lipolytic products is perhaps more important in the pathogenesis of the fat malabsorption of the premature infant. Supportive data include values of duodenal bile acids below the critical micellar concentration of 3 mM/\textsuperscript{1} and a contracted bile acid pool.\textsuperscript{19}

Within the past 5 years, two studies have documented improvement of fat absorption and weight gain in premature infants fed formulas containing MCT.\textsuperscript{20, 21} In recent years a number of reports indicate that they are of value in malabsorption syndromes which arise either from a deficiency of pancreatic lipase,\textsuperscript{22} bile acids,\textsuperscript{23} or intestinal absorptive area.\textsuperscript{24} In the present study preterm infants fed a formula in which 80% of its lipid content was derived from MCT had a 4-fold decrease in stool fat and normalization of the percent fat absorption (≈95%). The decrease in fecal excretion of bile acids observed when the infants were fed the MCT formula confirms similar reports in adults.\textsuperscript{8, 9} The reduced loss of bile acid could be secondary to an increased intestinal reabsorption of bile acid or to a contraction of the bile acid pool as recently reported in Rhesus monkeys fed MCT.\textsuperscript{25} Despite the large osmolar load and high carbohydrate content of the MCT formula as well as the ketogenic properties of MCT, gastrointestinal tolerance was good, and blood glucose, serum acid-base, and electrolyte concentrations remained within normal limits.

The relationship between diet and metabolic acidosis has been well studied,\textsuperscript{27-30} it often leads to a poor weight gain.\textsuperscript{30} This was confirmed since the 16 infants who received the LCT formula (LCT\textsubscript{BH}) with high chloride content gained less weight than the nine infants who were fed a similar formula with respect to nutritional content but without acidogenic properties (LCT\textsubscript{BH}). The poor weight gain with the high-chloride diet was not secondary to a change in caloric intake or wastage since calories ingested and percent fat absorption with the two LCT formulas did not differ significantly.

Eleven of the 25 infants lost more than 2 gm fat/kg/day while being fed LCT formulas. This corresponds to a caloric wastage of 18 calories/kg/day and to an average 15% loss of total caloric intake. The vigorous full-term infant can readily compensate for such a loss by increasing his intake. Small premature infants may well be unable to do so and have reduced rates of growth.\textsuperscript{17} The premature infants admitted to this study were healthy; yet, their average caloric (108 calories/kg/day) and protein intake (2.4 gm/kg/day) during the seventh to twenty-first day feeding period was below the minimum daily recommended levels of 120 calories/kg and 3 gm protein/kg.\textsuperscript{31} It is likely that the degree of undernutrition would have been greater had smaller and sick neonates been studied.

The present study suggests that MCT have a place in the nutritional management of preterm infants. Further studies are necessary to see if the beneficial effects of MCT feeding in terms of weight gain, lipid absorption, and nitrogen retention also apply to newborn infants who are small for gestational age. Because of the possible relationship between high osmolarity formulas and necrotizing enterocolitis,\textsuperscript{32} the gastrointestinal tolerance

Table III. Caloric intake and weight gain of nine infants fed MCT and LCT\textsubscript{BH}

<table>
<thead>
<tr>
<th>Period</th>
<th>Diet</th>
<th>No.</th>
<th>Calories (cal/kg/day)</th>
<th>Weight gain* (gm/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seventh to</td>
<td>MCT</td>
<td>5</td>
<td>101.9 ± 9.9</td>
<td>13.9 ± 2.5</td>
</tr>
<tr>
<td>twenty-first day</td>
<td>LCT\textsubscript{BH}</td>
<td>4</td>
<td>100.4 ± 9.9</td>
<td>10.6 ± 2.2</td>
</tr>
<tr>
<td>Twenty-second to</td>
<td>MCT</td>
<td>4</td>
<td>132.3 ± 13.6</td>
<td>17.3 ± 1.9</td>
</tr>
<tr>
<td>thirty-sixth day</td>
<td>LCT\textsubscript{BH}</td>
<td>5</td>
<td>133.3 ± 32.4</td>
<td>11.8 ± 0.9</td>
</tr>
</tbody>
</table>

*When expressed as gm/kg/100 calories, weight gain during MCT feeding was 13.1 ± 0.5 and 9.6 ± 0.9 with LCT\textsubscript{BH} (P < 0.01)
of the small-for-date newborn infant for the MCT formula requires close observation. Even though extensive studies have been carried out in animals after prolonged administration of MCT, the effects of long-term MCT feeding on developmental patterns as well as on carbohydrate and lipid metabolism still need to be investigated in low-birth-weight infants.

The authors acknowledge the invaluable assistance of the attending, resident and nursing staffs of the Premature Nursery. Particular thanks go to D. Théberge, R.N., and T. Frigon, R.N., without whose dedication and interest, this study could not have been done.

REFERENCES


