Some aspects of the use of fats in enteral and parenteral nutrition in infancy

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Introduction

In infant nutrition, fat acts as an immediate source of energy, as a combustible reserve in the form of fat deposits, and in the case of some fats as a structural component of tissues. At the same time they serve to prevent deficiencies of certain essential fatty acids. A number of factors to do with human physiological growth to maturity may limit the normal functioning of fat absorption and metabolism, and these physiological mechanisms may also be upset by various pathological states.

If the gastrointestinal tract can be used, the nutritional requirements both of intake and of storage can be met by the enteral method. The method used depends on the degree of intraluminal digestion preserved, the preservation of a sufficient area of the absorptive surface, the degree of retention of the food absorbed, the age of the child and the type of disorder. If the gastrointestinal tract cannot be used, it is then bypassed, and recourse must be had to parenteral nutrition with various formulae according to the case.

Aspects of the metabolism of fats administered either enterally or parenterally

Some of these depend on the stage of maturity reached by the patient. The premature infant, apart from having a very limited reserve of lipids, presents a series of limiting factors, amongst which are the degree of activity of the lipase enzyme [1], reduced storage of bile salts [2], decrease in the concentration of bile salts in the intestine which does not reach the critical micellar concentration of 4 mmol [3], the actual structure of the triglycerides administered [4] and, in pathological cases, the various degrees to which the intraluminal phase of digestion and processes to do with the function of the intestine are affected, whether by lesions of the mucosa itself or by selective effect on the digestive enzymes or transport proteins.

These circumstances may give rise to abnormal pancreatic secretion, disturbance of the activity of the bile salts, lymphatic effects at the level of the gastrointestinal tract, or malfunction of the enterocytes.

In the enteral method, the compounds used to increase the energy intake must have a good coefficient of absorption as well as good clinical tolerance. For this reason, we use fatty acids with a chain of 8 and 10 carbon atoms medium-chain triglyceride (MCT), which are carried through the intestinal mucosa and pass directly into the portal circulation, since they are not dependent on pancreatic lipase nor on previous solubilization by bile acids for their absorption. The MCT are hydrolyzed in the enterocytes by an intestinal lipase [5]; about 90% [6] are absorbed, arriving at the liver through the portal vein and passing quickly through the mitochondrial membrane without needing carnitine, and being quickly oxidized. The ketogenic effect is higher than that of long-chain fatty acids [7].
The long-chain fatty acid content of the triglycerides in the various preparations may vary according to the circumstances of their use, but it is important that they should be compounded with polyunsaturated fatty acids, which can prevent deficits and meet the needs for storage, as well as the developing infant organism’s requirements of structural fats. Their composition will vary according to the source of the fat, whether it be mother’s milk, cow’s milk or vegetable fats such as corn, soya, sunflower, palm, coconut, etc.

**Fats in the enteral nutrition of infants**

When there are serious disorders which affect digestion and intestinal absorption, and which may or may not be accompanied by changes in electrolytes, administration of individual nutrients or mixtures gastrointestinaly, intermittently or continuously, offers a simple, economical and easily tolerated method and should be considered first.

In enteral feeding, the following principles should be observed: the nutrients themselves have a direct trophic effect on the gastrointestinal tract [8] and help to maintain the tissue structure.

<table>
<thead>
<tr>
<th>common name</th>
<th>synonym</th>
<th>abbreviation</th>
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<tbody>
<tr>
<td>caprylic</td>
<td>octanoic</td>
<td>C 8:0</td>
</tr>
<tr>
<td>capric</td>
<td>decanoic</td>
<td>C10:0</td>
</tr>
<tr>
<td>lauric</td>
<td>dodecanoic</td>
<td>C12:0</td>
</tr>
<tr>
<td>myristic</td>
<td>tetradecanoic</td>
<td>C14:0</td>
</tr>
<tr>
<td>palmitic</td>
<td>hexadecanoic</td>
<td>C16:0</td>
</tr>
<tr>
<td>palmitoleic</td>
<td>7-hexadecenoic</td>
<td>C16:1, n-7</td>
</tr>
<tr>
<td>stearic</td>
<td>octadecanoic</td>
<td>C18:0</td>
</tr>
<tr>
<td>oleic</td>
<td>9-octadecenoic</td>
<td>C18:1, n-9</td>
</tr>
<tr>
<td>linoleic</td>
<td>9,12-octadecadienoic</td>
<td>C18:2, n-6</td>
</tr>
<tr>
<td>α-linolenic</td>
<td>9,12,15-octadecatrienoic</td>
<td>C18:3, n-3</td>
</tr>
<tr>
<td>arachidonic</td>
<td>5,8,11,14-eicosatetraenoic</td>
<td>C20:4, n-6</td>
</tr>
<tr>
<td>timnodonic</td>
<td>5,8,11,14,17-eicosapentaenoic</td>
<td>C20:5, n-3</td>
</tr>
<tr>
<td>clupanodonic</td>
<td>4,7,10,13,16,19-docosahexaenoic</td>
<td>C22:6, n-3</td>
</tr>
</tbody>
</table>

* Double bonds numbered from the carboxyl end.
** Fatty acid formulae have been abbreviated in the form x, y, m where x = number of carbon atoms in the molecule, y = number of double bonds, and m = position of the 1st double bond numbered from the methyl end. Thus, palmitic acid is (16:0) and linoleic acid (18:2, n-6).

From: FAO/WHO. Dietary fats and oils in human nutrition.

The maintenance of the tissue reserves of gas- trin depends partly on the existence of food in the gastrointestinal tract [9]. During enteral alimentation there is greater disaccharidase activity, and the activity of pancreatic trypsin reaches significantly higher levels than during parenteral alimentation [10]; and at the same time there is a better secretion of enzymes from the brush-border of the intestinal mucous membrane. Intermittent enteral nutrition is more physiological than continuous nutrition, but it must be given slowly and in small doses since there is a greater risk of aspiration and abdominal distention.

During continuous administration, small volumes should be used initially, increasing progressively as tolerance increases. Continuous feeding may produce constantly high levels of insulin which cause a decrease in the mobilization of glycogen and fat. The administration of different formulae should begin in diluted form, and then increase to concentrations of 67 kcal/100 ml. In cases where there is intolerance, the rate of infusion should be reduced, but not so as to produce a deficit. If necessary, fluid intake should be complemented by peripheral intraveneous means.

**Mixtures of nutrients to be used**

Various preparations are available: elementary and semi-elementary diets, and diets with complex and modular diets.

Elementary diets use free or hydrolyzed amino acids as the source of protein, together with mono- or oligosaccharides as the source of carbohydrate, and they contain little or no fat. This type of diet is usually hyperosmolar. The dipeptides and tripeptides which they contain are absorbed better than the amino acids [11]. The presence of oligopeptides helps to reduce the hypertonicity of this diet, which is also poor in residue; the carbohydrate requires little amylase activity and, if the diet contains a little fat, it helps the intake of polyunsaturated fatty acids, which prevents a deficiency of essential fatty acids, although it should be borne in mind that in a case of malabsorption, or of a reduction in the ab-
sorptive surface and reduction of bile salts in the duodenum, long-chain triglycerides may be difficult to tolerate, aggravating the malabsorption and accelerating peristalsis.

In complex nutritional solutions, the carbohydrates have a high molecular weight. These formulae contain fat which helps the calorie intake and they are generally iso-osmolar. Pancreatic secretion is less in a continuous administration of an elementary diet than in that of a complex diet [12]. Hyperosmolar solutions of more than 320 mosmol/l may produce osmotic diarrhoea, with a risk of dehydration and hypoglycaemia. In addition, the osmolarity of the formula is a critical factor for gastric emptying and intestinal transit velocity [13]. Modular diets consist of special solutions in which the combination of single nutrients (modified proteins, fats, carbohydrates) allows special combinations to be prepared for the treatment of specific disorders. They are more individualized, allowing changes in the content of particular nutrients. Sometimes a complex formula can be used as a base to which other nutrients can be progressively added. Semi-elementary diets can be made up by adding mixtures of amino acids and oligopeptides derived from the hydrolysis of casein or lactalbumin, so that the antigenic proteins of cow’s milk and soya proteins are excluded, and carbohydrates with or without small quantities of starch and/or glucose, giving a formula with low osmolarity and exclusion of lactose. Fat intake takes the form of MCT which need neither pancreatic lipase nor bile salts for their digestion; and the intake of variable quantities of triglycerides derived from cow’s milk fat, corn oil or sunflower oil, which help to meet the requirements for essential fatty acids and part of the energy requirements. At the same time, it must contain the electrolytes, oligo-elements and vitamins necessary for maintenance.

Initially, the semi-elementary diet ought to facilitate intestinal regeneration and prevent the onset of malnutrition. In some serious cases, this semi-elementary diet can only be started after a period of peripheral, intravenous parenteral administration of fluids and electrolytes, occasionally with the addition of amino acids and glucose.

If there are serious disorders of intraluminal digestion and intestinal absorption, then the administration of fibre, lactose, gluten, soya and whole proteins, as well as long-chain triglycerides, should be avoided; that is to say, the choice of one product or another will depend on the digestive capacity, the degree of intestinal absorption and the nutritional state of the patient. During this enteral feeding, it is useful to make a frequent examination of the faeces, observing their volume and appearance, and also to detect fat by direct microscopic examination, and the excretion of sugars. The total energy intake should be regulated according to the pathological situation and age of the child, and varies from 80 to 130 kcal/kg/day. The water intake may vary from 120 to 260 ml/kg/day during periods of exclusive enteral feeding, or split into smaller volumes administered enterally and by intravenous drip; but in every case the iso-osmolar situation of the formula administered by the enteral method must be maintained. Care should be taken to ensure aseptic conditions during the preparation of the formulae, and to make frequent bacteriological checks to avoid bacterial contamination. They must be kept refrigerated at 4°C and must be well homogenized to keep the solutes well dispersed.

**Indications**

The results obtained from the exclusive use of enteral feeding will depend on intestinal tolerance of the volume and of the osmotic load administered, as well as on absorptive capacity in relation to the area and intensity of the lesions in the mucosa and the existing absorptive surface. The accompanying degree of possible malnutrition should also be taken into account. Indications may be numerous, and include severe enteropathies which have caused partial or total atrophy of the intestinal villi and a resulting malabsorption syndrome, sometimes in the form of untreatable diarrhoea; the short intestine syndrome, either primary or secondarily to intestinal resections, in which case the
Some aspects of the use of fats in enteral and parenteral nutrition in infancy

absorptive capacity will depend on the length of the remaining intestine and the loss or not of Bauhin's valve; intestinal enterocutaneous fistulae following surgery; inflammatory diseases of the intestine such as Crohn's disease; disorders of intestinal transport, and various afflictions of the oesophagus, stomach or pancreas.

Continuous enteral feeding may help to maintain the nutritional state in malignant tumours where there may be gastrointestinal disorders related to abdominal irradiation and/or chemotherapy. We also use it in patients with immune deficiency problems, and other conditions which have been treated with bone marrow transplants, presenting with syndromes of diarrhoea and difficulties of oral ingestion. It has also been used on children with various renal conditions [14]. In many of these situations, a semi-elementary diet needs to be supplemented with a peripheral intravenous feed or with continuous enteral feeding, started after a few days of exclusive total parenteral feeding. In some patients with congenital cardiopaties who show associated malnutrition related to a previous poor energy intake, with corresponding loss of intestinal absorptive surface area, a period of continuous parenteral feeding may be useful, though it should be remembered that tolerance of volume of fluids in this type of child may be limited. In all cases it should be borne in mind that tolerance of long-chain triglycerides may be very limited, and that in situations where there is cholestasis and pancreatic insufficiency, the absorption of long-chain lipids may be poor.

Whatever the indication for continuous enteral feeding, the contra-indications which may arise must be borne in mind, both from the catheter, in the form of intestinal occlusion, perforation or haemorrhage, and from the ingredients of the diet given. These may produce increased malabsorption by the use of long-chain triglycerides in excessive quantities, by high osmolarity in the mixture or by its lactose content. They may also produce gastrointestinal reactions to the mixture in the form of vomiting and diarrhoea and abdominal pain, which may sometimes be overcome by decreasing the dosage and rate of infusion. Possible blockage of the opening of the catheter and aspiration of the gastric contents must also be taken into account.

Continuous enteral feeding of the premature infant

In theory, the best diet for the very low-birthweight infant would be one that gave a rate of growth similar to that during the last trimester of gestation, and a tissue composition similar to that of the fetus. In practice, the rate of growth can be roughly simulated, but the accretion of fat is different. The absence of oral feeding has an adverse effect on the maturation of the digestive functions [15], and in gravely underweight children it is important to maintain the water and calorie balance from the outset. Enteral feeding by the naso-duodenal route in the first days of life, using only human milk complemented by the administration of amino acids, glucose and electrolytes gives good results [16]. Formula using enriched human milk have also been recommended [17-19]. In premature with very low-birthweight (less than 1200 g) and in newborns of any weight and gestational age with particular pathological problems, it is necessary to avoid aspirations and abdominal distention, but at the same time to administer energy. For this reason we recommend during the first 3 days of life only the use of an exclusive parenteral mixture. We begin by supplying 35 kcal/kg/day, rising to 50 kcal on the 3rd day of life. This calorie intake is composed of intravenous glucose the 1st day, together with 1.5 g of amino acids/kg/day. From the 2nd day, we add to this mixture 1 g of lipids/kg/day (10% emulsion) and, from the 4th day of life, we add to this parenteral feed a semi-elementary diet administered by the nasogastric route, with a calorie intake of 13, 20 and then 27 kcal/kg/day, which increases on the following days, and eventually results in the termination of parenteral feeding between the 10th and 12th day of life, reaching a calorie intake of 120 kcal/kg/day by the continuous enteral method with a liquid intake of only 175 ml/kg/day on the 13th day. In premature infants of very low weight (below 1200 g), we have used 2 kinds of diet of
which the composition is given in Table II. Both diets contain in addition the corresponding electrolytes, oligo-elements and vitamins.

Table II: Composition of the semi-elemental diets A and B (100 g of powder)

<table>
<thead>
<tr>
<th></th>
<th>diet A</th>
<th>diet B</th>
</tr>
</thead>
<tbody>
<tr>
<td>carbohydrate</td>
<td>52.7</td>
<td>51.7</td>
</tr>
<tr>
<td>polysaccharides</td>
<td>96.3</td>
<td>—</td>
</tr>
<tr>
<td>dextrin-maltose</td>
<td>—</td>
<td>86.9</td>
</tr>
<tr>
<td>maltose</td>
<td>2.5</td>
<td>—</td>
</tr>
<tr>
<td>glucose</td>
<td>1.2</td>
<td>—</td>
</tr>
<tr>
<td>starch</td>
<td>—</td>
<td>11.6</td>
</tr>
<tr>
<td>lactose</td>
<td>—</td>
<td>1.5</td>
</tr>
<tr>
<td>hydrolyzed proteins</td>
<td>14.0</td>
<td>18.2</td>
</tr>
<tr>
<td>oligopeptides</td>
<td>70.0</td>
<td>80.0</td>
</tr>
<tr>
<td>amino acids</td>
<td>30.0</td>
<td>20.0</td>
</tr>
<tr>
<td>lipids</td>
<td>29.8</td>
<td>24.0</td>
</tr>
<tr>
<td>C 8:0</td>
<td>26.67</td>
<td>24.85</td>
</tr>
<tr>
<td>C10:0</td>
<td>27.74</td>
<td>19.70</td>
</tr>
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<td>C12:0</td>
<td>1.65</td>
<td>2.31</td>
</tr>
<tr>
<td>C14:0</td>
<td>0.43</td>
<td>4.32</td>
</tr>
<tr>
<td>C16:0</td>
<td>4.15</td>
<td>14.10</td>
</tr>
<tr>
<td>C16:1, n-7</td>
<td>0.10</td>
<td>0.66</td>
</tr>
<tr>
<td>C18:0</td>
<td>2.33</td>
<td>3.89</td>
</tr>
<tr>
<td>C18:1, n-9</td>
<td>11.52</td>
<td>14.53</td>
</tr>
<tr>
<td>C18:2, n-6</td>
<td>25.03</td>
<td>14.95</td>
</tr>
<tr>
<td>C18:3, n-3</td>
<td>0.38</td>
<td>0.69</td>
</tr>
<tr>
<td>vitamins and mineral salts</td>
<td>2.1</td>
<td>3.1</td>
</tr>
</tbody>
</table>

In premature infants, with no associated pathological problems and weighing over 1200 g, we administer intermittent feeding, or in rare cases continuous feeding by nasogastric tube, with an appropriate formula.

We also use formulae A and B in the diet of newborn infants who have been operated on for gastrointestinal conditions such as atresia of the oesophagus, intestinal resection, meconial peritonitis, malformations, omphalocele, etc. The use of dextrinomaltose in semi-elementary diets seems adequate given that between 26 and 34 weeks maltase already has 70% of the activity of the newborn at term [20]. It is important that the formulae have an osmolarity no higher than 300 mosmol. Frequent checks for glycosuria and glycaemia are fundamental. With high-osmolarity formulae necrotizing enterocolitis occurs more frequently, reaching as much as 27% in infants weighing less than 1200 g [21]. It helps if small volumes can be given in low doses, since large volumes can contribute to persistent ductus arteriosus [22]. The osmolarity of the formula mixture is slowly increased. Some authors stop the intravenous supplement when the intravenous volume of glucose and amino acids administered by the enteral method reaches 100 ml/kg/day [23]. The use of the nasojejunal route can sometimes produce malabsorption and diarrhoea [24] and an abnormal proliferation of bacteria in the digestive tract [25].

With the use of MCT in these semi-elementary diets and in the formulae, one obtains a significant increase in the percentage absorption of fats from the formula, but there are no differences in the percentage retention and absorption of calcium and phosphorus [26]. Nor are there any advantages in using formulae with high proportions of up to 80% of the fat in the diet in the form of MCT, as against others with a proportion of 40% [6]. ESPGAN [27] has recommended a maximum limit for MCT of 40% of the fat. Diets with higher proportions allow no better rate of energy loss, nor any increase in energy reserves [28] and high concentrations may cause flatulence, vomiting and diarrhoea [29]. It has been observed that low-birthweight premature infants who receive MCT show signs of organic aciduria with the excretion of dicarboxylic acids and ω-1 hydroxyfatty acids [30], though there is no evidence to show that the elimination of these products of oxidization of MCT has any adverse effects. Besides, MCT should always be administered as part of a complete formula, and never on their own as a supplement. The aspiration of MCT in the form of undiluted oil can produce serious lung complications [31].

The important problem of fat intake in premature infants lies not only in giving enough energy to meet the needs of growth, but also in administering the essential fatty acids. These act in 3 important ways: a) as components of the phospholipids of the cellular membranes; b) in the transport and oxidi-
zation of cholesterol; c) as precursors of the prostanoids [32]. Linoleic acid is considered as the prototype of essential fatty acid. Arachidonic acid cannot any longer be considered strictly essential after the demonstration that it can be synthesized in vivo from linoleic acid [33]. Linoleic acid cannot be synthesized in vivo, but its complete role in metabolism is not yet fully understood, though it is known that it plays an important part in the composition and function of some specialized tissues [34]. A shortage of essential fatty acids may even begin in the lst week of life [35] in cases where enteral or parenteral feeding is given free of fat, and is relative to the low level of essential fatty acid stores and its gestational age. From the biochemical point of view, this shortage is marked by a lessening in the amounts of linoleic and arachidonic acid in the plasma phospholipids and an increase in palmitic, oleic and 5,8,11-eicosatrienoic acid, as well as an increase of more than 0.4 in the proportion of trienoic/tetraenoic fatty acids. It is also accompanied by a fall in the synthesis of prostaglandins, and it has been observed [36] that there is a drop in the urinary excretion of the principal metabolite of the prostaglandins PGE₁ and PGE₂, 7α-hydroxy-5,11-diketotetranorprostane-1,16-diononic acid, which corrects itself after the administration of essential fatty acids. The same changes in the pattern of fatty acids may be found in the lipid strata of the red cells as are found in the plasma when there is a deficit in PUFA [37]. One of the primary roles of the essential fatty acids in the premature infant is to act as structural fats for the development of the brain. During the last 3 months of gestation and in the immediate postnatal period, there are a number of changes in the pattern of the essential fatty acids in brain structure related to maturation, with an increase in the content of fatty acids of the n-3 family in the phospholipids of the brain, leading to an increase in the n-3/n-6 index, chiefly at the expense of C22:6,n-3 [38]. There seem to be signs of competitive inhibition produced by the n-3 family of fatty acids on the metabolism of n-6 family and vice versa, perhaps because both families are sometimes substrates of the same enzymes. The question of determining what is the ideal proportion of linoleate to linolenate in semi-elementary formulae and diets is difficult to determine. It seems logical to maintain the same proportion as that of human milk. Human milk, in which linolenic acid represents 1.5% of the energy content as opposed to 5% of linoleic acid, may be taken as a model until more is known about this subject. The metabolites of linolenic acid are found as structural components of the phospholipids of the brain and retina, and C22:6,n-3 must have a specific function in the photoreceptors of the retina [39]. It would be desirable to include an intake of products of the elongation and desaturation of C18:2, n-6 and C18:3, n-3, that is to say C20:4, n-6, C20:5, n-3 and C22:6, n-3, in the diet of the premature infant fed by the enteral method, but the quantities are still uncertain since these will depend on the capacity of their precursors, linoleic for arachidonic and linolenic acid for the rest, in relation to the activity of the desaturases. Research undertaken on the formulae for semi-elemental diets reveals that they contain the correct quantities of linoleic and linolenic and no arachidonic, C20:5, n-3 or C22:6, n-3. We have added small supplements of cod-liver oil, whose make-up of fatty acids was shown in our laboratory to be C14:0 = 7.0%, C16:0 = 20.9%, C16:1, n-7 = 10.6%, C18:0 = 4.3%, C18:1, n-9 = 19.4%, C18:2, n-6 = 32.0%, C18:3, n-6 = 0.2%, C18:3, n-3 = 11.7%, C20:4, n-6 = 0.6%, C22:6, n-3 = 9.7%, administering with this supplements of elongations of linolenic acid. It should also be remembered that excessive quantities of linolenic acid administered over a period of time may cause problems.

**Fats in parenteral feeding**

The availability for many years now of emulsions of fat for intravenous use provides an effective means of supplying energy and essential fatty acid requirements; at the same time, by permitting total parenteral feeding, it circumvents many problems such as those which come from fat-free mixtures of glucose and amino acids, especially in relation to high osmolarity, hyperglycaemia due to large car-
bohydrate intake, difficulties in large energy intake, and shortage of essential fatty acids.

With fat-free parenteral feeding, after a week of intravenous administration the amount of C18:2, n-6, C20:4, n-6 and C22:6, n-3 in the plasma fall significantly [40]. The ability of suckling infants to use lipids administered intravenously as a source of energy depends on the degree of efficiency of the hydrolysis of the triglycerides by the lipoprotein lipase, and appropriate enzyme activity in the liver and adipose cells which metabolize the resulting free fatty acids.

Premature infants of less than 33 weeks of gestation hydrolyze triglycerides more slowly than infants older than 33 weeks. Those of low weight for gestational age show higher levels of triglycerides and free fatty acids during the infusion, and the clearing of lipids from the plasma is slower [41], as a result of a deficiency in the activity of the lipoprotein lipase. Furthermore, in these children, and in those suffering from malnutrition, the number and size of the adipose cells is smaller, resulting in less uptake, together with difficulties in the transport mechanisms across mitochondrial membranes for free fatty acids [42, 43] due to a reduction in the level of activity of acylcarnitine transferase, and it appears that ketogenesis is slowed down. This ketogenesis is a reflection of the degree of oxidation of free fatty acids in the liver cell. Nevertheless, even when lipolytic activity is reduced, the released fatty acids may oxidized, as is proved by the increase of 3-hydroxybutyrate concentration in the plasma 4 h after the perfusion of fat. It has been suggested that there is an increase in the oxidation of endogenous fat between days 1 and 2 of life [44]. It is calculated that the maximum capacity for clearing plasma of injected triglycerides must be in the order of 0.3 g triglycerides/kg/h [45]. After the 1st week of life, tolerance to intravenous fat is increased, which may be related to an increase in the activity of lipoprotein lipase [46]. Quantities of more than 150 mg/100 ml of triglycerides in the plasma lead to a saturation of the enzyme system and reduce the clearing of the injected emulsion [47]. On the other hand, persistently high levels of free fatty acids in plasma after perfusion may depend, in the case of premature infants, on low levels of plasma albumin and a consequently low binding-power [48].

The smaller the child, the less the lipid tolerance. In the end, it depends on the activity of the lipoprotein lipase, the scarcity of adipose tissue reserves, the degree of immaturity of the liver and the possible presence of hypoalbuminaemia. The premature and underweight infant therefore runs greater risks of hyperlipaemia.

The effect of lipid perfusion in prematures on the regulation of glucose is revealed in a temporary increase in insulin levels and a sustained increase in glycaemia. This hyperglycaemia is the result of an increase in the oxidation of free fatty acids because of their greater availability, but it may also be due to a low tissue response to insulin and even to the conversion of glycerol into glucose [49].

Carnitine

Carnitine facilitates the transport of fatty acids across the mitochondrial membranes and plays an important part in their oxidation and in ketogenesis. The initial levels of free carnitine concentration in the newborn child depends on the level in the mother [50]. The amounts of muscle carnitine in immature infants are low, and are related to gestational age [51]. The newborn infant has little capacity for endogenous synthesis of carnitine and for maintaining blood levels [52]. Since its tissue reserves are limited, from birth, the amounts depend on the exogenous intake [53]. Carnitine accumulates in the muscle and adipose tissue amongst others, and contributes to the increase of lipolysis by the adipose cells [54]. In parenteral feeding without carnitine the concentration of muscle carnitine is low. A supplement of carnitine of the order of 10 mg/kg/day in children receiving parenteral feeding [55] yields higher levels in plasma than in those without the supplement. Premature infants of less than 34 weeks gestational age, who have been fed parenterally with lipids, develop a carnitine deficiency which alters the oxidation of fatty acids and ketogenesis. The FFA/β-
Some aspects of the use of fats in enteral and parenteral nutrition in infancy

hydroxybutyrate index is higher, and that is an expression of unpaired ketogenesis [55]. Similarly, in parenteral feeding without carnitine the concentration of muscle carnitine is low; after 15 days of unsupplemented parenteral feeding low levels of carnitine are found in liver and heart [56]. After an infusion of lipids, newborns who have received carnitine supplements show higher levels of β-hydroxybutyrate and acetoacetate [57]. In our formula A, the carnitine supplement is 20 mg/kg/day and, in the special formulae with cow's milk for feeding premature infants, the level of carnitine is equal to that of human milk, whereas there is no carnitine in soya-milk foods [58]. It is therefore clear that it is necessary to supplement parenteral feeding of premature infants or prolonged parenteral feeding at any age with extra carnitine.

Types of fat emulsions

Essentially, we use 10% soya oil emulsions stabilized with lecithin, with a particle size of less than 1 μm. The emulsion is rendered isotonic by adding 2.5% glycerol.

Another preparation which we have used is made from safflower triglycerides. The essential fatty acid content of each of the two emulsions is different. In the soya-based preparation the linoleic acid content is 54% and the linolenic acid 9%, while in the safflower-based one they are 77% and 0.1% respectively. We have also used a mixture of both, 50% soya and 50% safflower. The plasma levels of linolenic acid rise when the two are mixed and fall when only safflower is used. By administering 2 different concentrations of safflower to newborn infants with total parenteral nutrition, with about 0.1% and 3% of linolenic acid, after 2 weeks the C22:6, n-3 fell in both groups and there was also a significant drop in C20:4, n-6 [59]. A decrease of C20:4, n-6 in the plasma phospholipids and cholesterol esters has been observed as well as in the adipose tissue of children who have been given a soya emulsion, probably because of the high concentration of C18:2, n-6 in the emulsion itself [60]. It may be said that there is some competi-

tion between the n-6 and n-3 families of fatty acids for the reserves in the tissues. The affinity of delta-6 desaturase is higher in vitro for linolenic than for linoleic acid, and the triene is desaturated preferentially to equal concentrations of the 2 substrates [61]. In our opinion, the ideal ratio of linoleic to linolenic acid is not yet clearly established.

The higher triglyceridaemia observed when safflower is used may reflect a disparity in the size of the particles in emulsions made from different substrates [62].

Indications and dosage

The basic indication for lipid emulsions is the incorporation of fat into parenteral feeding with amino acids and glucose when the enteral method cannot be used. In some cases, this method is used for short periods and exclusively enteral feeding is then resumed, and in others, such as very low-birthweight premature infants, continuous enteral feeding can be combined with part of the daily diet being administered by peripheral intravenous perfusion. Sometimes, a regular administration of small quantities of fat emulsion may be indicated to meet the requirements for essential fatty acids when there is severe malabsorption, as in cystic fibrosis of the pancreas.

As for dose, 2 to 4 g/kg/day of lipids have been recommended [63]. In infancy, doses of 3 g/kg/day are generally maintained [64]; with newborn infants requiring parenteral feeding we start with 1 g/kg/day rising to 2.5 g/kg/day. It is always difficult to predict the dose of lipids that can be administered safely, so it should not be thought that any specific dose can be tolerated by all children [65], and it seems prudent to start parenteral feeding with small doses which are subsequently increased. A simple method used for monitoring the dose is to measure plasma turbidity, but this method gives quite uncertain predictions. The evaluation of turbidity by the light scattering index method [66] with a micropelheterometer has the advantage of requiring only a capillary sample. If
the lipid emulsion plasma level exceeds 100 to 150 mg/dl, the rate of perfusion of lipids must be decreased. Another method which has been recommended is fluorometry, which correlates well with the results of micronephelometry [67]. At any event, it is most advisable to make periodic checks of the triglycerides in the blood and of the free fatty acids. When lipids are given by infusion, there may be hypertriglyceridaemia, even with low doses in the region of 0.3 g to 0.6 g/kg/day, which may also depend on the rate of infusion, especially in the premature infants; hence the necessity for recommending frequent measurement of triglycerides. On the other hand, it is preferable that emulsions of lipids be administered slowly and continuously over 24 hours, and not as a bolus. When plasma levels of lipid emulsion exceed 100 mg, there may be hyperbetalipoproteinæmia, and increases in triglycerides, cholesterol and phospholipids [68]. However, some children are particularly resistant to hyperlipidaemia. The dose to be given will also depend on the clinical state of the patient, as for instance the degree to which respiration is affected, or jaundice. During the 1st week of life, it has been seen [69] that small premature infants who receive 1 g/kg of fat are more susceptible to hyperlipidaemia and hypoxaemia, though there are no changes in pulmonary function. Tolerance also depends on the state of bilirubinæmia, given that the increased free fatty acids may displace the bilirubin from its bond with albumin, producing free bilirubin. It has been suggested that the molar index of free fatty acids: albumin in plasma should be monitored in any child undergoing lipid infusion, and that this index should be kept below 6 [70].

Side effects

Until 1984 there were 36 known cases of fat deposits in the pulmonary vessels, from case studies at 9 different centres [71]. Deposits have also been found in children who have never received fat intravenously [72], but their incidence is greater amongst those who have received a fat emulsion, and it has been suggested that pulmonary-vascular lipid deposits are partly connected with the duration and quantity of the administration of fat, and that such deposits cannot be predicted in relation to the levels of triglycerides in the plasma. In a series of 23 autopsies on newborns and infants who had received parenteral feeding with fats for varying periods, and studied in our hospital, 39.3% showed fat deposits in the pulmonary capillaries. In the early stages, the small branches of the pulmonary arteries had characteristic sub-endothelial accretions of fat with massive penetration of the intima, sometimes penetrating the wall of the vessel towards its outer border, partly mediated by lipophages, causing secondary narrowing of the lumen of the vessel. In more advanced stages, there were residual lesions resulting from thickening and fibrosis of the intima. These lesions had a segmented appearance; in more advanced stages, it was also possible to observe focal desquamative lipidic alveolitis, which may have been the expression of the removal of lipid through the lung. We believe the previous existence of vascular lesions in the wall of the vessel helps the circulating lipids to penetrate the wall. These pre-existent lesions may be caused by anoxia and acidosis in newborn infants in distress [73].

Deposits of pigment may be found in the reticulo-endothelial system which persist for many years, although without any apparent risk [74]. A significant decrease in PO₂ levels has been noted in newborn infants in the 1st week of life during fat infusion [69]. This disorder of oxygenation may be the result of a disorder in the diffusion of oxygen due to the effect of the lipids enveloping the erythrocytes [75], to alterations in the microcirculation of the lung [76], or to the effect of the fat deposits in the vascular walls we have commented on above. There are also descriptions of hepatobiliary complications related to the total parenteral nutrition, especially in the period immediately after birth. Although calcium bilirubinate may be responsible for retention and stones, there is no valid explanation for the presence of large quantities of indirect-reacting bilirubin in the gallbladder and in the biliary tracts in children on total paren-
Some aspects of the use of fats in enteral and parenteral nutrition in infancy

Nor can we rule out the possibility of toxicity in the amino acids administered [78]. The appearance of cholelithiasis has been observed using ultrasound in 9 children out of a series of 21 who received long-term total parenteral nutrition [79]. Cholestasis, particularly in premature, in the absence of obstruction of the biliary tract, or hepatitis, has also been described during total parenteral nutrition [80, 81]. Most of the cases began 2 to 10 weeks after the start of parenteral feeding and at 13 weeks up to 90% of the cases develop cholestasis. Any increase in conjugated bilirubin ought to put us on our guard against this complication. The existence of a thick bile syndrome has also been reported [82].

The fat overload syndrome is characterized at the outset by jaundice, fever, spontaneous haemorrhages, irritability, hepato-splenomegaly and hyperlipaemia [83]. In these cases the administration of fat should be suspended.

Amongst the side-effects of intravenous fat administration we also know of a decrease in phagocyte activity [84, 85], but a study on newborn infants [86] shows that an infusion of fat emulsion of 1 g/kg/day produced no changes in the chemoluminescence of neutrophils, nor any alterations in their oxidative functions as opposed to what has been observed in adults.

Changes in tissue composition after the administration of fats

Some years ago we described changes in the profile of fatty acids which may occur in the subcutaneous tissue, liver, brain [87] and red cells [37]. Recently we have published the changes observed in the composition of fatty acids of the phosphoglycerides of ethanolamine and choline in the liver and brain of newborn infants, with gestational ages of from 20 to 44 weeks, who had received total parenteral nutrition. They were compared with controls consisting of dead infants of the same gestational ages who had not received intravenous lipid emulsions. We observed that in the liver there was an increase of C18:2,n-6 and a decrease in the elongation/desaturation of linoleate towards members of the series with longer chains, as well as a decrease of C22:6,n-3. In the brain we have only seen an increase of C18:2,n-6 in choline phosphoglycerides, and we called attention to the possible adverse effects on the tissues of high doses of C18:2,n-6 [88]. Alterations of lipids in the brain after total parenteral nutrition have also been observed by other authors [89, 90]. Another unknown potential factor is the presence of small quantities of phytosterols in the fat emulsion, and the possible role in substitution with cholesterol which these sterols might have on the nervous system of the developing child. Although MCT have been used intravenously in the total parenteral nutrition of adults [91], it does not seem advisable in infancy because of the ketone bodies which it may produce.

Risk of peroxidation of the fatty acids

Formation of peroxides and production of free radicals in the organism may occur when polyunsaturated fatty acids are administered in large quantities if there is a deficiency of vitamin E, and it should be borne in mind that these peroxidated fatty acids are toxic. Nutritional deprivation accelerates the peroxidation of lipids in newborn rats [92], and the peroxidation of lipids in the newborn infant is greater than in adults and may be increased by the parenteral administration of lipids. Increase in essential fatty acid intake in conjunction with decreased anti-oxidant activity may lead to increased peroxidation of the lipids and respiratory elimination of volatile hydrocarbons [93]. This peroxidation is lessened by vitamin E [94] which protects the PUFA of the membrane phospholipids. In premature infants the problem is more complex, since there may be a greater availability of essential fatty acids from the substrate by virtue of total parenteral feeding, together with a reduced quantity of adipose tissue, which limits the total reserve of vitamin E in the organism; and to the existence in the premature infant of a possibly reduced activity of glutathione peroxidase, catalase and superoxide glutathione dismutase, which

103
can act as anti-oxidative agents [95]. Likewise, newborn infants are deficient in ceruloplasmin, which is another anti-oxidant. The Committee of nutrition of the American Academy of Pediatrics recommends that children to 1 year receive from 3 to 4 mg of α-tocopherol, and from 5 to 8 mg from 1 to 11 years [96], and it should also be borne in mind that there are considerable losses of the dose administered [97].

References

Some aspects of the use of fats in enteral and parenteral nutrition in infancy


