Dicarboxylic aciduria and medium chain triglyceride supplemented milk

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SUMMARY Pronounced dicarboxylic aciduria was observed in preterm infants fed a medium chain triglyceride supplemented milk formula. As many special formulas contain a medium chain triglyceride oil attention needs to be drawn to its metabolic effects, regarding the diagnosis of inborn errors of metabolism and that dicarboxylic acids might be harmful.

One of the more common abnormalities detected during analysis of urine for organic acids is a raised excretion of the dicarboxylic acids; suberic, sebacic, and adipic. These metabolites are excreted in excess as the result of a variety of metabolic disturbances,[1] including several inborn errors of metabolism.

The medium chain length dicarboxylic acids sebacic, suberic, and adipic are produced in the cytoplasm by ω oxidation of medium chain fatty acids. Sebacic acid can be β oxidised to suberic and adipic acid, but adipic acid cannot be further metabolised.[1] This is normally a minor metabolic pathway, and only small amounts of dicarboxylic acid are excreted in the urine.[2] Fasting and ketosis may provoke a moderate increase in the excretion of adipic acid. Large amounts of dicarboxylic acids are excreted by children with inherited defects of fatty acid oxidation or carnitine metabolism.[1] Dicarboxylic aciduria is known to be provoked by treatment with sodium valproate[1] and has also been reported to be associated with medium chain triglyceride feeding.[3 4]

Subjects, materials, and methods

Urine samples were collected from 18 preterm infants (mean gestational age 29 weeks). Dicarboxylic acids were analysed as the trimethyl silyl derivatives, using capillary gas chromatography (Chrompack sil 5CB column and a Perkin Elmer gas chromatograph). Creatinine concentration was measured on a Beckman Astra clinical chemistry analyser.

The infants in the study were initially maintained on intravenous nutrition, consisting of dextrose, Vamin, and Intralipid, with additives. They were subsequently weaned on to oral feeds of either Nenatal, SMA Goldcap, or breast milk. Urinary dicarboxylic acid excretion was studied in infants on each of these feeding regimens and in several cases was measured serially as babies moved from one feeding regimen to another.

The content of medium chain triglyceride in the feeds used in the study are as follows: Nenatal (Cow and Gate) 1·8 g/100 ml; SMA Goldcap (Wyeth) 0·44 g/100 ml; Intralipid (Kabi Vitrum) contains none; breast milk varies in content of medium chain triglyceride but it is in the region of 0·15 g/100 ml.

Results

The Table shows the mean urine concentration and range for each dicarboxylic acid in each feeding group. Infants fed Nenatal were of similar gestational and postnatal age to those fed expressed breast milk or SMA Goldcap. Only in infants receiving Nenatal were significant amounts of dicarboxylic acids found. Nenatal contains no detectable amounts of adipic, suberic, or sebacic acids, which therefore presumably derive from metabolism of the medium chain triglyceride with which it is supplemented.

Table *Urinary dicarboxylic acid excretion (μmol/mmol creatinine) in infants on different feeding regimens. Values are mean (range)*

Feed	*No of patients*	*Type of dicarboxylic acid*		
		Adipic	*Suberic*	*Sebacic*
Intravenous dextrose	8	9 (0–36)	2 (0–12)	2 (0–13)
Total parenteral nutrition with Intralipid	12	8 (0–51)	0 —	2 (0–15)
SMA Goldcap or expressed breast milk (150–200 ml/kg)	10	23 (0–61)	10 (0–25)	4 (0–21)
Nenatal (170 ml/kg)	7	287 (221–444)	159 (92–248)	351 (154–618)

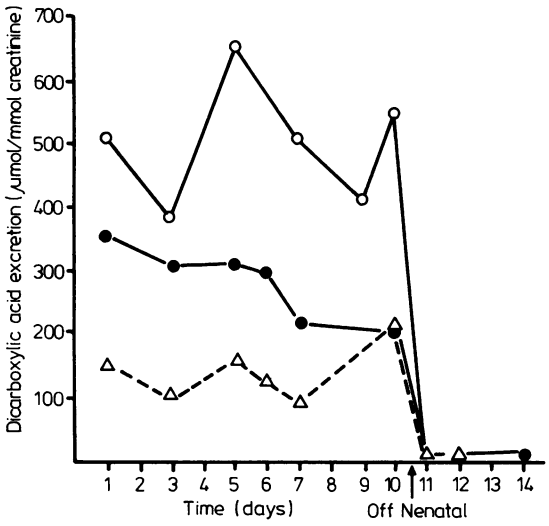

Figure *Daily urinary dicarboxylic acid concentrations (●——●=adipic acid, ○——○=sebacic acid, △- - -△=suberic acid) in an infant fed Neonatal until day 10 when he was changed to breast milk.*

The Figure shows serial measurements of urinary dicarboxylic acid concentration in a single infant.

Discussion

It has been reported previously, in adults[3] and in infants of 2–9 months,[4] that oral medium chain triglyceride feeding can provoke dicarboxylic aciduria. In reporting our findings in preterm neonates fed a medium chain triglyceride supplemented milk we would like to extend this observation and to point out that it may not be obvious that an infant is receiving these supplements. It was only when the manufacturer's stated composition of the milk was examined that the presence of medium chain triglyceride was discovered. Many specially formulated milks for low birthweight babies, and indeed other special milks, are supplemented with medium chain triglyceride oil, and it is important for clinicians and scientists involved in the investigation of inborn errors of metabolism to be aware of this. It may also be of interest in this respect to note that infants given Intralipid were not found to have an increased excretion of dicarboxylic acids.

It is generally assumed that the production of increased amounts of dicarboxylic acids is not directly harmful. It has been observed, however, that children with congenital β oxidation defects may deteriorate clinically on medium chain triglyceride challenge before becoming hypoglycaemic (Lenard J. Personal communication, 1985), thus raising the possibility that some of the clinical symptoms are the result of a toxic effect of the dicarboxylic acid. Also there is the recent demonstration of an antimitochondrial effect of dicarboxylic acids, which, in a topical cream, have been used effectively for the treatment of melanocytic skin tumours.[5] The possibility that dicarboxylic acids may be toxic warrants further study.

References

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