Weight loss at 1 week of age, expressed as a percentage of birthweight was less in the orotic acid treated group (mean 5.3%, range 0-11%) than in those receiving aspartic acid (mean 7.2%, range +1.6-15%) or glucose (mean 7.9%, range 1-16%). Maximum serum bilirubin levels were not related to weight loss at 1 week whether expressed in this fashion or in absolute amounts, nor were they closely related to the initial weight of the infant.

The infants were closely observed in an intensive care unit throughout the study but showed no adverse effects from these products. Of the 34 infants, 27 (80%) have now been examined at the age of 9 months. All are developing normally.

Discussion

These observations do not support the findings of Matsuda and Shirahata (1966) who in 60 term infants in Japan recorded that both aspartic acid and orotic acid significantly lowered serum bilirubin levels. In their report these authors do not indicate whether the infants studied were male or female, though, as found in this study, it has been reported that in males serum bilirubin levels are higher than in females (Trolle, 1965). A dosage schedule similar to ours was used in their study but they make no comment on dietary intake. The dose of aspartic acid used in this trial is equal to the anticipated daily intake of an infant fed on cow's milk, but the dose of orotic acid is 10 times that derived daily from milk. In spite of this no adverse effects were noted though this agent may cause adverse effects in rats but not necessarily in other species (Valli, Sarma, and Sarma, 1968).

This study does not refute the possibility that the administration of uridine precursors may enhance uridine formation in man, as they have been shown to do in experimental animals (Bresnick, Mayfield, and Mossé, 1968). Certainly they had no effect on serum bilirubin concentrations, but these are governed by many other factors. On the basis of evidence presented, neither aspartic acid nor orotic acid is a useful therapeutic agent in the management of neonatal hyperbilirubinaemia.

Summary

In a double-blind trial, administration of uridine precursors (aspartic acid, orotic acid) did not affect the serum bilirubin levels in healthy preterm newborn infants.

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False Negative Screening Tests in Phenylketonuria

The routine screening of babies for phenylketonuria is now widely practised, using either a blood sample (Guthrie test) or a urine sample (paper chromatography or ferric chloride methods). The validity of the test depends on an adequate dietary protein intake, and a false negative may result if the
infant is tested too early in life, if the infant is feeding poorly, or if the infant is vomiting. Two infants are reported in whom the diagnosis was not made at the initial testing because of the inappropriate timing of the sampling.

Case Reports

Case 1. Delivered instrumentally at term with a birthweight 2650 g. She was vigorous at birth and sucked well; however after 3 to 4 minutes at each breast she seemed hungry and a complement of a cow's milk formula was offered on the third day. From the fourth day of life she started to vomit, and over the next 3 days she vomited most of her feedings. No cause for this vomiting was found and she subsequently settled. A Guthrie test was performed on day 6 and was negative. By 4 weeks she was completely bottle-fed and only having occasional small vomits, she caused no concern otherwise. A routine filter paper urine sample was collected at 10 weeks and found to contain an excess of phenylalanine.

The baby was seen at 12 weeks and the diagnosis of classical phenylketonuria confirmed by a fasting serum phenylalanine level 47.6 mg/100 ml, a poor tyrosine response to phenylalanine loading, and o-hydroxyphenylacetic acid in the urine.

Her subsequent developmental progress and dietary control has been excellent.

Case 2. Delivered at term with a birthweight 4200 g. He was bottle-fed and was well till 7 days when he started to vomit. The vomiting became projectile and he was admitted to hospital at 15 days. He was minimally dehydrated and no tumour was palpated. Serum Na 132 mEq/l., K 3.9 mEq/l, Cl 73 mEq/l, total protein 6.7 g/100 ml, capillary pH 7.38, Pco2 51 mmHg, standard bicarbonate 26.5 mEq/100 ml. A barium meal suggested hypertrophic pyloric stenosis, which was confirmed at laparotomy. For the 4 days before the operation in the ward his urinary 'Phenistix' was negative and remained negative after he had resumed normal milk feedings for 5 days.

A filter paper urine was examined in the screening survey at 12 weeks and found to contain excess phenylalanine.

Classical phenylketonuria was confirmed by a fasting serum phenylalanine 46 mg/100 ml, a poor tyrosine response to phenylalanine loading, and phenylpyruvic acid in the urine.

His progress on a low phenylalanine diet has been very good.

Discussion

These cases illustrate the unfounded security which routine screening may produce. The error of sampling too early in life has already been stressed (Hsia and Dobson, 1970) while our 2 infants show the potential error of sampling when infants are not feeding well or are vomiting. Sampling for routine screening tests should not be performed unless there has been an adequate protein intake for a minimum of 4 days.

Vomiting is a particular problem, as infants with phenylketonuria tend to vomit more frequently than normal infants. Partington (1961) reported that 3 of his 36 infants had projectile vomiting severe enough to merit laparotomy and pyloromyotomy. In our group of 48 children with classical phenylketonuria, pyloromyotomy was performed in 2, while in 3 others hypertrophic pyloric stenosis was seriously considered.

In Case 2 who had several ferric chloride tests performed on his urine at 2 to 4 weeks, it seems likely that had a serum phenylalanine level been estimated, it would have been raised to a level which would have merited further investigation. Current detecting methods using urine chromatography, bacterial inhibition assay, and chemical analysis make the unreliable ferric chloride test an outmoded screening procedure.

The possibility of missing infants with atypical phenylketonuria with its lower serum phenylalanine levels is even greater. While there is no agreement as to whether children should be treated with this type of phenylalanine abnormality (Yu, Stuckey, and O'Halloran, 1970), there is agreement that the ascertainment of all such cases is necessary for the understanding of the genetics of the disease.

When a neonate is vomiting excessively, tests designed to detect phenylketonuria should be evaluated cautiously. The test should be repeated several weeks later. In children with neurological or developmental problems, no reliance should be placed on the fact that a screening test has been performed or on its presumed normality.

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