12 weeks. We should like to reassure him that the megaloblastic changes were unequivocal. The figure (Case 2) shows an undoubted megaloblast which was fully haemoglobinised. This was one of 82 such cells found in a buffy-coat smear made from approximately 50 μl blood. The time-scale at which a poor folate intake produces megaloblastosis is very different when a healthy adult physician¹ is compared with rapidly growing tiny babies whose folate requirements may be relatively much greater.² The megaloblastic preterm infants described by Gray and Butler² were even younger (3 to 6 weeks) and other affected babies have been under 12 weeks.⁴⁻⁵

We found, as have others,⁶ that a mild reticuloctysis was common in preterm infants in the first 3 months and was unrelated to megaloblastosis. Even so, the mean value (2.6%) in our groups of both normoblastic and megaloblastic infants was below that reported by Oski and Barness,⁷ and Ritchie et al.,⁸ in infants with haemolytic anaemia due to vitamin E deficiency, namely 8.2 and 6.1% respectively.

The rate at which Hb rose after treatment with folic acid would be modified by physiological factors in infancy, such as growth and concomitant expansion of plasma volume, and should not be compared with that expected in an adult. Nevertheless, the falling Hb in each affected infant was invariably reversed after folic acid, even though in some the dose was probably suboptimal.

We are aware that lack of vitamin E has been suggested as a cause of megaloblastic anaemia in malnourished infants but even in these cases described by Majaj et al.,⁹ folate deficiency was not completely excluded. Perhaps lack of vitamin E may affect the uptake of folate through cell membranes although in the vitamin E-deficient infants described by Oski and Barness,⁷ and Ritchie et al.,⁸ the bone marrows examined were normoblastic.

In our infants treatment with folic acid but no other addition to diet was followed within a few days by complete normoblastic change associated with a reticulocyte response. As our facts do not fit with Professor Ozsoyul’s theories, we suggest the theories be changed to fit the facts.

References


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Sodium nitroprusside and RDS—
primum non nocere

Sir,

There have been two reports on the use of sodium nitroprusside (NaNP) to reduce pulmonary vascular resistance in severe respiratory distress syndrome (RDS).¹⁻² This new indication for an old drug represents an innovative pharmacological approach to the treatment of pulmonary hypertension in the newborn. However, several aspects of this drug must be evaluated before the apparent success reported leads to widespread use in nurseries. As most neonatal therapeutic tragedies have occurred due to altered drug metabolism and disposition in the newborn infant, this aspect needs to be investigated urgently.
The metabolism of the drug has been studied in animals and adults. It is a salt of ferric cyanide with nitric acid, containing five cyanide (CN) molecules which are released nonenzymatically when the drug reacts with haemoglobin and blood, and tissue sulphhydril groups. One free CN reacts with methemoglobin forming cyano-methemoglobin and the remaining four free CN are metabolised through other pathways. Most of the free CN is converted to thiocyanate, in the presence of thiophosphate, via the hepatic and renal rhodanase systems. Thiocyanate is then excreted unchanged by the kidney, with a half-life of about one week in man. The free CN not rapidly converted to thiocyanate or carried in blood by erythrocytes binds to tissue cytochrome oxidases producing cytotoxic hypoxia resulting in cellular anaerobic metabolism. This is manifested by severe lactic acidosis, base deficits, increasing mixed venous oxygen, and subsequent death. As free CN binds rapidly to tissues and as erythrocyte CN has no toxic importance, measurement of blood CN concentration will not accurately reflect the degree of toxicity. Thiocyanate is also potentially toxic and fatalities are reported at significant plasma concentrations (20 mg/100 ml). Since detoxification of CN to thiocyanate is slow, significant concentrations of this metabolite will only appear after chronic administration of the drug.

Even though early detection of toxicity of this potent drug is necessary, serial measurements of CN and thiocyanate may not be helpful. Several investigators have recommended monitoring of metabolic changes (lactic acidosis, base deficits, and increased mixed venous oxygen) caused by anaerobic metabolism as the most sensitive and accurate indicators of early toxicity. However, this may be particularly difficult to assess in a neonate who is already hypoxic and acidic from ongoing RDS.

No data have been published about rhodanese activity and endogenous thiosulphate availability in the premature newborn. Moreover, since good nutritional status is required for endogenous thiosulphate availability, the poor nutritional status of these infants will further compromise the detoxification process. Other compounds—such as nitrate, thiocyanate, and hydroxocobalamin—have been reported to be protective against CN toxicity by supplying alternate metabolic pathways for CN. It is possible that pretreatment with these compounds exerts similar protection against CN toxicity in the neonate. Further investigation is needed, particularly on an evaluation of the pharmacology of these agents in the neonate.

Even though NaNP is a potent hypotensive drug, there are no specific dose recommendations based on dose-response or kinetic data. In children, it has been used with a broad range (0.5–12.0 µg/kg per min), the objective being to reduce the existing blood pressure to the desired level or to provide a ‘dry field’ for surgery. Toxicity also depends both on the rate of infusion and on the total amount of infused drug. In the newborn, Beverley et al. used 120 µg/kg per hour rate or 2.88 mg/kg per day which equals the LD95 in rabbits and is close to an approximate LD50 in humans (3–6–12 mg/kg). With so many uncertainties, the use of this drug in an attempt to reduce pulmonary vascular resistance in the newborn is not yet warranted. It is a toxic drug that has not been adequately studied in the newborn. Further studies to define metabolism, disposition, and toxicity in the newborn animal are needed before investigative studies on human neonates are performed. Later, prospective controlled studies on efficacy, pharmacodynamics, kinetics, and toxicity are necessary before this drug is used routinely in the human neonate. If a critically ill neonate treated for several days with NaNP for RDS were to succumb, the role of CN poisoning as a contributing factor to mortality might be a possibility.

More knowledge about this drug in the neonate must be obtained before it is used in infants with RDS. The rational and safe use of a drug such as NaNP can only be derived from adequate pharmacological studies in adult and newborn animals and human subjects.

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