Short reports

Controlled trial of antenatal barbiturates in rhesus haemolytic disease

The enhancing effect of barbiturates on bilirubin conjugation has been recognized for over a decade (Catz and Yaffe, 1962). Attempts have been made to utilize this effect to prevent or diminish neonatal jaundice (Trolle, 1968; Ramboer, *et al.*, 1969). McMullin *et al.*, (1970) showed that phenobarbitone given postnatally could significantly reduce the number of exchange transfusions required in rhesus haemolytic disease. We now describe a small controlled trial to test the value of sodium amytal given antenatally to infants affected by rhesus haemolytic disease.

Patients and methods

All mothers attending the West Cheshire Maternity Wing who were thought to be carrying a child at risk from rhesus haemolytic disease were admitted to the trial. Mothers were allotted to a treatment or a control group randomly by the hospital pharmacy, except that a mother who was known to have already had barbiturates during the current pregnancy was allotted to the treatment group. In fact, only one mother, known to have had amytal earlier in the current pregnancy, was so allocated. For the rest treatment or placebo was prescribed as 'Satrial tabs. 1 nocte' for 7 days before induction. The treated group received sodium amytal 100 mg in tablets; the control group received placebo tablets of identical colour, shape, and size. The nature and aim of the trial was explained to the mothers when given the prescription. The timing and mode of delivery was determined from the clinical findings and the amniocentesis results when available. The infants were managed along standard lines, but no phototherapy was used and no barbiturates were given postnatally.

The criteria for exchange transfusion were as follows: cord blood haemoglobin <13 g/dl; cord blood serum bilirubin >87 $\mu\text{mol/l}$ (5 mg/100 ml); subsequent serum indirect bilirubin >350 $\mu\text{mol/l}$ (20 mg/100 ml). Serum bilirubin was estimated by the method of White *et al.* (1958). Vitamin K₁ 1 mg was given intramuscularly to all infants at birth.

Thirty mothers of 30 infants were admitted to the trial (17 controls and 13 treated). Comparison of the two groups of mothers for age, parity, and number of previously affected infants showed no significant differences between the two groups in respect of these factors as judged by Student's 't' test. The mean birthweights, gestational ages, and cord blood haemoglobin levels of the two groups of infants are compared in Table 1. No significant differences are shown.

Table 1 Mean ($\pm$ SEM) birthweights, gestational ages, and cord blood haemoglobin levels of infants in treatment (Tr) and control groups

Birthweights (g)		Gestational age (weeks)		Cord blood Hb (g/dl)	
Tr	Control	Tr	Control	Tr	Control
3110 ± 43	3180 ± 45	38 ± 2	37.7 ± 2	14.0 ± 1.3	13.6 ± 1.3

Results

Table 2 shows the comparative levels of cord blood bilirubin in the two groups together with the numbers of early exchange transfusions (that is, those done on the basis of the cord blood bilirubin and/or haemoglobin levels), late transfusions (those performed because of subsequent bilirubin levels), and all exchange transfusions.

Table 2 Comparison of cord blood serum bilirubin levels and exchange transfusion rates in treated and control infants

	Treated	Controls
No. of infants	13	17
Mean cord blood serum bilirubin ($\mu\text{mol/l}$)	61	75
Range	35-116	47-235
Exchange transfusions	14	23
Exchange transfusions per infant	1.1	1.36
Early exchange transfusions	7	8
Early exchange transfusions per infant	0.55	0.41
Late exchange transfusions	7	15
Late exchange transfusions per infant	0.55	0.95

The differences between the two groups in all respects are insignificant. The differences between the two groups in respect of numbers of exchange transfusions per infant were analysed by means of the Wilcoxon rank-sum test. There was a difference of 24% in favour of the treated group in respect of the number of late exchange transfusions per infant, but this gives a χ^2 value of 1.95 ($P > 0.01$) by this test.

One very severely affected infant in the control group (cord blood Hb 7.5 g/dl, serum bilirubin 88 $\mu\text{mol/l}$ (5.5 mg/100 ml)) died during exchange transfusion. Hydrops fetalis was found at necropsy.

Discussion

The dose of sodium amytal given in this trial was small, equivalent to about 1.5 mg/kg body weight per day. Ramboer *et al.* (1969) gave phenobarbitone 60 mg/day from the 31st to 33rd week of pregnancy. Trolle (1968) gave phenobarbitone 50–200 mg/day for at least 8 days before delivery. There are, however, theoretical grounds for questioning the safety of larger doses of antenatal barbiturates (Wilson, 1969). We chose the smallest dose we thought likely to be effective. Possibly in a larger series the difference between the two groups in respect of late exchange transfusions might have reached statistical significance. But we ended the trial when Moller and Ebbesen (1975) reported a controlled trial of phototherapy in rhesus-haemolytic disease, since withholding phototherapy no longer seemed ethically justified. It remains probable, on the basis of the work of Trolle (1968) and of Ramboer *et al.* (1969), that larger doses of barbiturates given antenatally for longer periods would reduce the need for exchange transfusions in rhesus haemolytic disease.

Summary

In a double-blind controlled trial sodium amytal 100 mg was given antenatally to infants with rhesus incompatibility. The drug was given nightly for 7 days before delivery to mothers in a treated group. Placebo tablets were given to mothers in a control group. There was no significant difference between the two groups in their cord blood bilirubin levels or the number of exchange transfusions required by defined criteria. We conclude that antenatal sodium amytal, as used in this trial, is of no value in the management of rhesus haemolytic disease of the newborn.

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The stomach in malnutrition

Protein-energy malnutrition is one of the major health problems facing mankind. Recent reports from Central America (Mata *et al.*, 1972), Australia (Gracey and Stone, 1972), South-East Asia (Gracey *et al.*, 1973), and Africa (Heyworth and Brown, 1975) indicate that the contents of the upper small intestine of malnourished infants and children are contaminated with bacteria. This may contribute to the production of diarrhoea and malnutrition in these children and thus worsen their state (Gracey *et al.*, 1975). Bacterial proliferation in the upper intestine in malnutrition may result from repeated contamination from polluted living conditions, impaired immune defence mechanisms, and a breakdown in normal intrinsic defence mechanisms in the gastrointestinal tract. Gastric acid secretion is one of these normal defences and is important in controlling the intestinal microflora (Drasar *et al.*, 1969), but there are no reports of the adequacy of this function in malnourished infants and children. This was investigated in a group of patients in Jakarta, Indonesia.