

factor and mast cell degranulation, suggesting hypersensitivity to this drug.

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Phenobarbitone prophylaxis of intraventricular haemorrhage

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SUMMARY Thirty preterm infants (birthweight under 1500 g) were treated with phenobarbitone to examine its effectiveness in reducing the incidence of intraventricular haemorrhage (IVH), the control group comprising 28 infants. The treated group had 57% incidence of IVH and mortality of 13% compared with 68% and 14%, respectively, in controls.

Since barbiturates have been shown to have neuroprotective effects several reports have examined the effectiveness of phenobarbitone in the prevention of intraventricular haemorrhage (IVH) in preterm infants. The conflicting results obtained in these trials led us to re-evaluate this issue using the protocol of Donn *et al*, who showed that phenobarbitone reduced the incidence of IVH.¹

Subjects and methods

We studied 58 preterm infants (birthweight less than 1500 g) who had no congenital malformations and whose mothers had not received phenobarbitone before their delivery. We randomly allocated these infants into control and treatment groups. The two groups were comparable with respect to birthweight, gestational age, race, sex, mode of delivery, and Apgar score. The control group (n=28, birthweight 1120 (SD 218) g) received supportive care only. The treatment group (n=30, birthweight 1119 (SD 264) g) received phenobarbitone for the first

week of life, starting at less than 6 hours of age. We administered phenobarbitone in a loading dose of 20 mg/kg divided into two equal doses administered intravenously 12 hours apart and a maintenance dose of 2.5 mg/kg every 12 hours. We obtained blood concentrations of phenobarbitone before the first maintenance dose and then at 3-5 days of age and adjusted the dose to achieve phenobarbitone trough blood concentrations of 20-30 µg/ml.

We obtained ultrasound brain scans on days 1, 3, and 7 of life and subsequently at weekly intervals in infants with IVH. Haemorrhages were graded as follows: grade 1, germinal matrix haemorrhage; grade 2, intraventricular haemorrhage with normal ventricle size; grade 3, intraventricular haemorrhage with ventricular dilatation; grade 4, intraparenchymal haemorrhage. The data were analysed by Student's *t* test to compare the means and χ^2 test to compare the proportions in the two groups. Differences were considered significant if the value of *p* was 0.05 or less.

Results

The number of infants in the two groups who required assisted ventilation, treatment with bicarbonate, volume expansion, and indomethacin for patent ductus arteriosus was comparable. In addition, the number of infants who developed hypoxia (arterial oxygen tension <40 mm Hg), hypercarbia (arterial carbon dioxide tension >60 mm Hg), or pneumothorax was also similar. Blood concentrations of phenobarbitone (mean (SD)) before the

Table Effectiveness of treatment with phenobarbitone in 30 infants compared with 28 control infants in reducing intraventricular haemorrhage (IVH). Values are number (%) of infants

	No IVH	Degree of haemorrhage				Total IVH	Deaths
		Grade 1	Grade 2	Grade 3	Grade 4		
Treated infants (n=30)	13 (43)	1 (3)	2 (7)	9 (30)	5 (17)	17 (57)	4 (13)
Control infants (n=28)	9 (32)	3 (11)	6 (21)	8 (29)	2 (7)	19 (68)	4 (14)

Degree of haemorrhage: grade 1, germinal matrix haemorrhage; grade 2, intraventricular haemorrhage with normal ventricular size; grade 3, intraventricular haemorrhage with ventricular dilatation; grade 4, intraparenchymal haemorrhage.

first maintenance dose was 25 (9) $\mu\text{g/ml}$ and after 3–5 days of treatment was 34 (19) $\mu\text{g/ml}$. No complications related to administration of phenobarbitone were noted except for apnoea in one infant who had a blood concentration of phenobarbitone of 65 $\mu\text{g/ml}$.

The Table shows the outcome of our study. Post-haemorrhagic hydrocephalus developed in four (14%) of the control group and in five (17%) of the group given phenobarbitone. There was no significant difference in the two groups with regard to the incidence and severity of IVH or mortality.

Discussion

Our results indicate that phenobarbitone administered in anticonvulsant doses to very low birth-weight infants in the first week of life is ineffective in reducing the incidence or severity of IVH. These results are in contrast to those of Donn *et al*, who have shown a significant decrease in the incidence of IVH from 47% in control infants to 13% in treated infants. We achieved similar blood concentrations of phenobarbitone, which were maintained over the first week of life. We have also been unable to confirm the results of Bedard *et al* who have shown decreased severity of IVH in treated infants.² Our results are, however, in agreement with those of

Morgan *et al* and Whitelaw *et al*, who were unable to show any benefit from treatment with phenobarbitone.^{3,4}

In conclusion, despite achieving blood concentrations of phenobarbitone in our treated infants that seemed to be effective in one trial,¹ we were unable to show a decrease in either the incidence or severity of IVH in very low birthweight infants treated with phenobarbitone.

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