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Prophylactic ethamsylate for periventricular haemorrhage

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SUMMARY Drug prophylaxis with ethamsylate for periventricular haemorrhage in very low birthweight infants significantly reduced the incidence of periventricular haemorrhage in survivors. A reduction in abnormalities at follow up and in insertion of ventriculoperitoneal shunts was also noted.

Although there has been a rapid increase in survival of very low birthweight infants requiring intensive care, neurodevelopmental sequelae remain a problem in some. Improvements in non-invasive techniques for imaging the neonatal brain have made it possible to diagnose periventricular haemorrhage (PVH) and some ischaemic lesions in vivo.[1] The association of PVH with neurodevelopmental sequelae at follow up is well documented.[2] Drug prophylaxis of PVH with phenobarbitone or ethamsylate has been claimed to reduce the incidence of PVH on ultrasound examination, but no information on outcome is available.[3 4] We report follow up data in a group of ventilated infants of very low birthweight treated prophylactically with ethamsylate during a 2 year period and compare these infants with a similar group of untreated infants admitted during the same period.

Patients and methods

A double blind, randomised, placebo controlled trial of ethamsylate prophylaxis of PVH was carried out at this hospital in 1980–1, and the results were published elsewhere.[4] For the following 6 months no effective prophylaxis was given, and at a later date open use of ethamsylate began (in all ventilated infants <1500 g). To have enough infants to form a follow up study, all very low birthweight infants admitted to the unit over a two year period were considered, whether they were included in the original trial or not. Only infants born in this hospital and weighing 501–1500 g at birth; who were free from PVH on initial ultrasound examination; ventilated for at least 6 hours; free from lethal congenital malformations, meningitis, or Down's syndrome; and who survived to be followed up for at least one year were included. Forty three such infants had been treated with ethamsylate 12·5 mg/kg 6 hourly for 16 doses beginning within two hours of birth. Forty eight had not been treated with ethamsylate and formed the control group. Table 1 gives clinical data for the group receiving treatment and for the controls.

Follow up examinations were performed at this unit at regular intervals, except in a few cases where for social or economic reasons follow up examination had to be performed at the referring district hospital. All infants were followed for between one and three years and were assessed, as appropriate, by neurological examination, Denver Developmental Screening test, and Stycar tests of hearing and vision. Infants identified as having abnormalities were referred for specialist developmental, ophthal-

Table 1 *Clinical data for infants receiving treatment and for controls*

	Infants receiving ethamsylate (n=43)	*Controls (n=48)*	*P*
Mean birthweight (g)	1082	1125	ns
Mean gestation (weeks)	29·1	28·8	ns
Apgar score <3	5	10	ns
Arterial carbon dioxide pressure >8kPa*	10	11	ns
pH <7·15*	12	9	ns
Pneumothorax†	6	9	ns
PVH	10	28	<0.01

* during first 48 hours
† during first 72 hours

Table 2 *Abnormalities found at follow up in treated and control infants*

Case no	*Abnormalities*
Control group (n=48)	
1	Spastic quadraplegia, VPS, severe developmental delay
2	Spastic diplegia, developmental delay
3	Moderate developmental delay
4	Hemiplegia, developmental delay
5	VPS, mild developmental delay
6	VPS, severe developmental delay
7	Moderate developmental delay
8	Mild spastic diplegia
9	VPS, severe developmental delay
10	VPS, moderate developmental delay
Group receiving ethamsylate (n=43)	
11	Spastic diplegia, developmental delay
12	VPS, moderate developmental delay
13	Hypotonic cerebral palsy, developmental delay
14	VPS

mic, or audiometric assessment when required. The assessment of neurodevelopmental disability in this study is a combination of all assessments made. Table 2 shows abnormal findings.

Results

No significant difference in clinical data was seen between the group receiving ethamsylate and the controls except in the incidence of PVH ($P < 0.01$) (Table 1). At follow up there were four abnormal infants out of the 43 in the group receiving ethamsylate and 10 out of 48 in the control group. Two abnormal infants in the group receiving ethamsylate and five in the control group had progressive hydrocephalus requiring ventriculoperitoneal shunting (VPS). One infant in the group receiving ethamsylate and two in the control group were without PVH but had neurodevelopmental problems at follow up (Table 3).

Table 3 *Cases of abnormality and grades of haemorrhage at follow up in the two groups*

	Infants receiving ethamsylate		*Controls*	
	No	*Abnormal at follow up*	*No*	*Abnormal at follow up*
No PVH	33	1	20	2
Subependymal haemorrhage	5	0	15	1
Intraventricular haemorrhage	4	2	4	0
Parenchymal haemorrhage	1	1	9	7

Discussion

Ethamsylate (diethylammonium 2,5-dihydroxybenzenesulphonate) seems to reduce the incidence of PVH in infants of very low birthweight when given prophylactically. The drug reduces capillary bleeding time,[5] and, as an abnormally prolonged bleeding time usually precedes PVH,[6] this may be its mode of action. Because PVH may coexist with other brain lesions in the newborn, such as those following ischaemia,[7] its presence may only act as a marker rather than the cause of subsequent neurodevelopmental abnormality. Preventing the marker of PVH alone would then not improve the eventual outcome of infants treated prophylactically. If this were the case, an excess of abnormal infants who did not suffer PVH would be seen in the group treated with the drug. This was not so, however; of those who did not have PVH, only one infant receiving ethamsylate and two controls were abnormal at follow up.

Although the small numbers included in this study prevent conclusions being drawn about the size of reduction of later disability that might be expected with drug prophylaxis, it is interesting to note that the significant reduction in PVH observed is accompanied by a proportionate reduction in abnormal follow up examinations and VPS placements. The reduction of disability in babies of very low birthweight who have received intensive care requires the improvement of management of ventilated infants in whom PVH is so common. Drug prophylaxis may play a subsidiary yet helpful role in achieving this aim.

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