

ETAMSYLATE = Ethamsylate (former BAN)

[ARCHIVED MONOGRAPH]

**Use**

Prophylactic treatment with etamsylate reduces the incidence of intraventricular bleeding in babies of less than 32 weeks gestation, but it does not seem to reduce the number who die or survive disabled.

**Pharmacology**

Etamsylate (diethyl ammonium 2,5-dihydroxybenzene sulphonate) is a water-soluble non-steroidal drug which has been used for several decades to reduce capillary bleeding in adults during surgery. It is thought to work principally by maintaining capillary integrity, probably by promoting polymerisation of mucopolysaccharide in vessel walls. It may also inhibit the action of prostacyclin in adrenaline-induced platelet aggregation. Following systemic administration the mean bleeding time is significantly reduced without any effect on cell counts, fibrinolysis, prothrombin time or clotting time. The drug is excreted unchanged, mainly in the urine. It is known to cross the placenta and some also appears in breast milk but there is no evidence that such exposure constitutes any risk to the baby. Adults sometimes experience nausea; transient headaches and skin rashes have also been reported on occasion.

A double-blind, placebo controlled, multicentre trial of early prophylactic treatment in babies of <1.5 kg in the UK in 1986 was initially interpreted as showing that etamsylate can reduce the incidence of ultrasound-diagnosed intraventricular haemorrhage (IVH) by a third. However, such a clear cut benefit could only be identified by excluding from analysis those children who died and those children who had evidence of haemorrhage when first examined shortly after birth. A more recent European trial, completed in 1994, found no such benefit, but a recent overview of all available trial data does suggest that the total incidence of intraventricular bleeding is reduced. Unfortunately the long term follow up of the children from these two trials shows that this does not translate into any reduction in the number who fail to survive or only survive with significant disability. Recent work suggests that etamsylate modifies prostaglandin biosynthesis, and this may help to explain the apparent reduction in symptomatic patent ductus in etamsylate treated babies in the UK trial.

**Strategies for preventing IVH**

Other strategies that have been tried include giving phenobarbital or vitamin K before birth or fresh frozen plasma, ibuprofen, indometacin, phenobarbital, or vitamin E (q.v.) after birth. Even prophylactic ibuprofen and indometacin, the most successful strategies studied to date, have not been shown to improve long term outcome convincingly as yet, even though they do reduce the number of babies developing ultrasound evidence of serious periventricular bleeding. Many of the early trials were launched before it became clear that long-term disability is seldom seen in survivors unless there has been parenchymal haemorrhage (haemorrhage into the brain substance) or posthaemorrhagic hydrocephalus as well as intraventricular or subependymal bleeding. More recently it has become clear that ischaemia, rather than bleeding, causes much of the perinatal brain damage seen in babies of less than 32 weeks gestation. Whether measures of total cerebral perfusion (as documented by measuring superior vena caval blood flow) are a useful marker of this remains unclear. Blood flow, rather than blood pressure, would seem to be what counts, but flow (unfortunately) can not be measured as easily as pressure. Changes in vascular tone may, in addition, influence local tissue perfusion even when total cardiac output and gross regional perfusion seems to be more than adequate (and hypocapnia and hyperoxia can both have a major influence on cerebral vascular tone).

**Prophylaxis**

A small number of units in the UK still offer 'at risk' babies prophylactic etamsylate. The regimen used is 12.5 mg/kg IV or IM within one hour of birth, and further IV doses every 6 hours for the first four days of life (i.e. a total of 200 mg/kg over 4 days).

**Supply**

2 ml ampoules containing 250 mg of etamsylate could be ordered by the pharmacy on special request. They cost 82p per ampoule. This gives a preparation containing 12.5 mg in 0.1 ml.

**References**

See also the relevant Cochrane reviews ©

Benson JWT, Drayton MR, Hayward C, *et al.* Multicentre trial of ethamsylate for prevention of periventricular haemorrhage in very low birthweight infants. *Lancet* 1986;ii:1297–300. (see also *Lancet* 1987;i:623–4). [RCT]

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Sanghvi KP, Merchant RH, Karnik A, *et al.* Role of ethamsylate in preventing periventricular-intraventricular hemorrhage in premature infants below 34 weeks of gestation. *Indian Pediatr* 1999;36:653–8. [RCT]

Elbourne E, Ayers S, Dellagrammaticas H, *et al.* Randomised controlled trial of prophylactic etamsylate: follow up at 2 years of age. *Arch Dis Child* 2001;84:F183–7. [RCT]

Schulte J, Osborne J, Benson JWT, *et al.* Developmental outcome of the use of etamsylate for prevention of periventricular haemorrhage in a randomised controlled trial. *Arch Dis Child* 2005;90:F31–5. [RCT] (See also F3–5.)