Effect of prenatal phenytoin treatment on postnatal development

M.M. ATA & F.M. SULLIVAN

Department of Pharmacology, Guy's Hospital Medical School

Adult pregnant Wistar rats were treated with phenytoin (100 mg/kg) orally from day 7–19 of pregnancy, and a control group was pair-fed during the whole treatment period. Within 24 h after parturition, the offspring were culled to eight per litter and reared by fostering or cross-fostering. The physical and behavioural development of the offspring was observed up to 90 days of age.

Prenatal phenytoin treatment reduced the fertility and litter size of the rats. There was also a reduced survival of the offspring and a reduction in body weight which persisted to the end of the experiment, though both of these effects could be reduced by cross-fostering. There was a wide variation in time of ear opening, eye opening and tooth eruption in the treated compared with the control groups. Chromodacryorrhea was present in the treated animals and remained up to age 90 days.

Certain neurological deficits were also seen in the prenatal phenytoin group. For example, there was a delay of up to 15 days in the development of the dynamic righting reflex, a decrease in ability of offspring to stay on a rotating rod, and a decrease in ability to walk along a narrow elevated path. There seemed also to be some loss of visual depth perception. However, there was no change in the development of crawling and walking activities at 9–21 days of age, and no changes were observed in a head dipping test or in a conditioned avoidance test at 26–34 days.

There was a significant decrease in the brain weight of the treated group at age 3 days which remained significantly lower than the controls even at 90 days, but no change in the brain weight/body weight ratio. There was no difference in the cerebellar DNA content.

Prenatal phenytoin treatment caused a significant decrease in the R.B.C. ghost cholinesterase activity at age 30 and 70 days, an increase in the brain and cerebellar cholinesterase at age 90 days but no significant change in plasma cholinesterase activity at 30 days of age. There was a marked increase in the serum and brain tryptophan, and brain 5 H.T. and 5 H.I.A.A. levels at 3 days of age but not at 90 days. This seemed to be related to early feeding problems.

Comparative teratogenicity of six antiepileptic drugs in the mouse

PATRICIA R. McELHATTON & F.M. SULLIVAN

Department of Pharmacology, Guy's Hospital Medical School

Evidence has accumulated associating the birth of congenitally malformed children to epileptic women with anticonvulsant medication (Speidel & Meadow, 1972). As most epileptic patients are on multiple drug therapy it is difficult to assess which drug or combination of drugs, if any, is responsible for the defects observed.

Animal studies to date have been mainly concerned with testing phenytoin and phenobarbitone. Therefore, in the present study six commonly used antiepileptic drugs were tested in pregnant CD1 mice ($n = 16$) to see if they were teratogenic, and if so, whether they could be placed in some order of teratogenicity.

The drugs used were all given at 3, 9 and 18 times the therapeutic dose and were carbamazepine (40, 120 and 240 mg/kg), clonazepam (0.3, 0.9 and 1.8 mg/kg), ethosuximide (60, 180 and 360 mg/kg), phenobarbitone (10, 30 and 60 mg/kg), phenytoin (15, 45 and 90 mg/kg), and primidone (30, 90 and 180 mg/kg) together with carboxymethylcellulose (CMC) and absolute control groups. All drugs were suspended in 1% CMC and given by gavage on days 6–16 of pregnancy which covers the period of embryogenesis.

The main defects observed in the treated groups were cleft palate (with the exception of clonazepam) and enlarged cerebral ventricles. Other major defects such as exencephaly, exomphalos, phocomelia, open eyes, and undescended testes were seen less frequently. If the results obtained for each drug are pooled on either a per foetus or a per litter basis, the drugs can be divided into three main categories of teratogenicity.

On a per foetus basis, phenytoin is in a category of its own in that it produced the highest incidence of foetal defects (20.9%). Primidone, carbamazepine and phenobarbitone fall into the next category, the