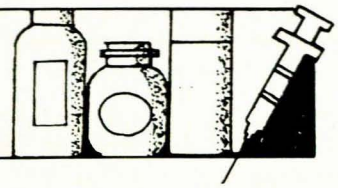
Drugs in Practice/Medisyne in die Praktyk



Teratogenic potential of valproate

Valproic acid, or dipropylacetic acid, and its salt, sodium valproate, are used to treat a wide variety of seizure disorders. Until recently there was no convincing evidence demonstrating a teratogenic effect in humans. However, the association between other anticonvulsant drugs and congenital malformations has been recognized for more than a decade,[1,2] and this, together with the lack of convincing data for valproate, may have favoured the use of valproate during pregnancy.

Valproate is known to be teratogenic in rabbits, rats and mice.[3–5] In the mouse, abnormalities include neural tube defects, craniofacial deformities[6] and dose-dependent growth retardation and embryo lethality.[5] We have confirmed a dose-dependent increase in mouse embryo mortality both in the pre- and post-implantation embryo, growth retardation and a substantial incidence of exencephaly. We have also found decreased esterase enzyme activity in pre-implantation embryos and a decrease in brain acetylcholinesterase levels of treated 18-day mouse fetuses (unpublished data).

Valproate is known to cross the human placenta.[7] Numerous case reports associating a variety of birth defects with the drug have been published;[8–14] these include craniofacial abnormalities, thoracic cage abnormalities, spina bifida, hydrocephalus, diastasis recti abdominis, hernias, genito-urinary tract abnormalities and low birth weight. Recent reports suggest a substantial association between maternal valproate therapy and neural tube defects,[15,16] which must be taken seriously. In the Rhône-Alpes region of France 72 cases of spina bifida were notified between 1979 and 1982. Ten of the mothers were epileptic, and 9 of them were receiving valproate (alone in 5, combined in 4). Further data from this region supporting the notion that valproate can cause spina bifida have been presented.[17,18] In the Netherlands 10 cases of spina bifida with prenatal exposure to valproate have been found.[19] The higher than expected number of spina bifida cases, the high rate of valproate exposure among these cases, and the high proportion of cases exposed to valproate only (6 out of 10) support an association between valproate and spina bifida.

More recently a distinct fetal valproate syndrome has been described.[20] Seven children who had been exposed to valproate *in utero* had a consistent facial phenotype consisting of epicanthic folds, flat nasal bridge, small upturned nose, long upper lip with a relatively shallow philtrum, a thin upper vermilion border, and downturned angles of the mouth. Other birth defects noted in 4 of the children were hypospadias, strabismus, psychomotor delay and low birth weight. Several previous reports have also suggested that an abnormal facial appearance might result from valproate.[8,9,11,21,22] The descriptions of the faces in these cases are suggestive of the findings in the above group of 7 children.

The data that valproate is potentially teratogenic are impressive and this should be borne in mind when prescribing the drug in women of childbearing age. However, the relative teratogenic risk is not accurately known, although it has been reported that spina bifida occurs in about 1% of births after first-trimester valproate exposure.[15] Good control of seizures in pregnancy is desirable and decisions on therapy must rest on clinical judgement, balancing the benefits against the possible hazards. If women are exposed to valproate during the first trimester they should be informed of the risk and offered counselling and amniocentesis.

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I. Kola

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Albendazole in hydatid disease

Until recently the only effective treatment for hydatid disease caused by *Echinococcus granulosus* has been surgical removal of cysts, but there have been obvious disadvantages to this. Mebendazole has been shown to have a beneficial effect but prolonged courses of treatment for many months have failed to improve the condition in some patients. Another benzimidazole