

UPDATE ON TERATOGENICITY OF ANTIEPILEPTIC DRUGS

E. Beghi

Laboratory of Neurological Disorders, Istituto Mario Negri, Milano, Italy

The teratogenicity of antiepileptic drugs is a well-defined issue. The risk of major malformations in the offspring of mothers with epilepsy treated with antiepileptic drugs (AEDs) is about 6-8% and exceeds that in untreated women with epilepsy (2-5%) and in the general population (2-4%) (Beghi & Annegers, 2001; Battino & Tomson, 2007; Holmes et al, 2001). The risk is higher with polytherapy (6-9%) compared to monotherapy (4-6%). Occasionally, a clear relationship between daily dose and risk of malformations has been documented (Morrow et al, 2006). Selected drugs are thought to be associated with specific malformations. Higher malformation rates have been reported with exposure to valproate compared to other AEDs. The teratogenic effects of valproate appear to be dose dependent, with higher risks at dosage levels higher than 1000 mg/day (Battino & Tomson, 2007). Congenital heart defects and, to a lesser extent, cleft palate have been observed in patients treated with phenobarbital, phenytoin and primidone (Lindhout & Omtzigt, 1992), neural tube defects and hypospadias have been mostly associated with valproate (Lindhout & Omtzigt, 1992; Alsdorf & Wyszynski, 2005), and facial cleft with lamotrigine (Holmes et al, 2008). Neurodevelopmental delay, behavioral disorders, or learning disabilities as an outcome of in utero exposure to AEDs and especially valproate, have been also observed (Nicolai et al, 2008).

Although some of these findings are unquestionable, several unsolved questions still remain. First of all, the comparative role of each drug is ill-defined and data from patients exposed to second-generation AEDs are scanty and incomplete for the small number of exposed individuals. Second, the teratogenicity of monotherapy and low daily doses is as yet unsettled. Third, as opposed to major malformations, the incidence of minor malformations is ill-defined because of differing definitions and interpretations. Fourth, the (adverse) effects of AEDs on the long-term psychomotor development of the offspring are poorly defined. Fifth, it is still unknown to what extent malformations can be attributed to the drug treatment, the underlying disease, the family history of malformations, and seizures occurring during pregnancy. In fact, tonic-clonic seizures and status epilepticus have been associated with fetal asphyxia and death (Teramo et al, 1982; Yerby, 1987). Fetal exposure to AEDs may be also influenced by drug transporting proteins in the placenta, including P-glycoprotein, multidrug resistance protein 1, and breast cancer resistance protein (Atkinson et al, 2007). Genetic variations in the expression and activity of these transport proteins may influence fetal exposure to AEDs and thus the risk of teratogenicity.

The characteristics of the target populations, the small sample size, and the differing study designs are limiting factors in the interpretation of the published observations. For these reasons, pregnancy registries have been activated in several countries by drug companies and independent investigators (Beghi & Annegers, 2001). The principal aim of these registries is to enroll large numbers of exposed women to be subjected to prospective monitoring and standardized recording of AED treatments and the occurrence of major and minor malformations.

References

- Alsdorf R, Wyszynski DF. Teratogenicity of sodium valproate. *Expert Opin Drug Saf* 2005; 4: 345-353.
- Atkinson DE, Brice-Bennett S, D'Souza SW. Antiepileptic medication during pregnancy: does fetal genotype affect outcome? *Pediatr Res* 2007; 62: 120-127.
- Battino D, Tomson T. Management of epilepsy during pregnancy. *Drugs* 2007; 67: 2727-2746.
- Beghi E and Annegers JF for the Collaborative Group for the Pregnancy Registries in Epilepsy. Pregnancy registries in epilepsy. *Epilepsia* 2001; 42:1422-1425.
- Holmes LB, Harvey EA, Coull BA, et al. The teratogenicity of anticonvulsant drugs. *N Engl J Med* 2001; 344:1132.
- Holmes LB, Baldwin EJ, Smith CR, et al. Increased frequency of isolated cleft palate in infants exposed to lamotrigine during pregnancy. *Neurology* 2008; 70: 2152-2158.
- Lindhout D, Omtzigt JG. Pregnancy and the risk of teratogenicity. *Epilepsia* 1992; 33 (suppl 4): S41-S48.
- Morrow JI et al. Malformation risks of anti-epileptic drugs in pregnancy: A prospective study from the UK Epilepsy and Pregnancy Register. *J Neurol Neurosurg Psychiatry* 2006;77:193-198.
- Nicolai J, Vles JS, Aldenkamp AP. Neurodevelopmental delay in children exposed to antiepileptic drugs in utero: a critical review directed at structural study bias. *J Neurol Sci* 2008; 271:1-14.
- Teramo K, Hiilesmaa VK. Pregnancy and fetal complications in epilepsy pregnancies. In: Janz D, Dam M, Richens A, et al (eds), *Epilepsy, Pregnancy and the Child*, New York, Raven Press, 1982:53-59.
- Yerby MS. Problems and management of the pregnant woman with epilepsy. *Epilepsia* 1987; 28:29-36.