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Review

Valproic acid in pregnancy: How much are we endangering the embryo and fetus?

Asher Ornoy

Laboratory of Teratology, Hebrew University Hadassah Medical School and Israeli Ministry of Health, Jerusalem, Israel

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ABSTRACT

Valproic acid (VPA) is a known human teratogen. Exposure in pregnancy is associated with approximately three-fold increase in the rate of major anomalies, mainly spina bifida and only rarely anencephaly (NTD), cardiac, craniofacial, skeletal and limb defects and a possible set of dysmorphic features, the "valproate syndrome" with decreased intrauterine growth. This was demonstrated by prospective and retrospective studies. There is also, mainly in the children with the "valproate syndrome", a significant increase in the rate of developmental problems, manifested by decreased verbal intelligence often with communication problems of the autistic spectrum disorder (ASD). VPA is teratogenic in most animal species tested, but the human embryo seems to be the most susceptible. A daily dose of 1000 mg or more and/or polytherapy are associated with a higher teratogenic risk. It seems that several other AEDs potentiate the teratogenic effects of VPA. Thus, when valproate cannot be avoided in pregnancy, the lowest possible effective dose should be prescribed in 2–3 divided doses, preferably as monotherapy. Women exposed to valproate in pregnancy should be given periconceptional folic acid and followed up in a high risk pregnancy clinic. Appropriate ultrasonographic and other examinations, focusing on the possible different anomalies described with this agent, should be carried out. The specific inhibition by VPA of histone deacetylase and changes in gene expression may explain the teratogenicity of this drug. Other possible explanations are: increased fetal oxidative stress induced by VPA, with the brain being more susceptible to oxidative tress in comparison to other fetal organs, or the folic acid inhibitory action of this drug.

Contents

E-mail address: ornoy@cc.huji.ac.il.

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1. Introduction—basic principles in teratology

The human conceptus undergoes 3 major developmental periods: The pre-organogenetic period during the first 2.5 weeks after fertilization, active organogenesis from weeks 3 to 8 post fertilization and afterwards the fetal period. It is commonly accepted that in the first period the developing embryo is generally not susceptible to teratogens. If the damage caused by a teratogen is very severe, the pregnancy may end in a spontaneous abortion or fetal death. Although the most sensitive period to teratogens is during active organogenesis, there are some organs (i.e. teeth, external genitalia, brain) that continue to be very active developmentally beyond that period and may therefore still be affected by teratogens. Hence, teratogens that affect the brain, especially antiepileptic and psychotropic drugs, may cause damage even if the fetus is exposed beyond the first trimester of pregnancy [1–4]. Even in organs that continue their development throughout pregnancy, the earlier during embryonic and fetal development the exposure, the larger may be the damage. Thus, exposure to a teratogen throughout pregnancy (i.e. antiepileptic drugs) is usually more dangerous than exposure during a limited time period. In most cases the damage is dose dependent and interacts with the embryonic and fetal genetic background [1–5].

2. Teratogenic effects of antiepileptic drugs—general comments

Antiepileptic drugs (AEDs) are used to control various types of convulsive disorders or as mood stabilizers. However, many of these drugs are teratogenic as their use by the pregnant mother has been associated with an increased risk of major congenital abnormalities in the embryo and fetus [3,5–10]. These anomalies are anatomical and/or functional and may also have neurological, behavioral and cognitive effects. Yet, in the majority of epileptic women planning a pregnancy, antiepileptic drugs cannot be discontinued because of the risk of seizures during pregnancy, which can be harmful to both mother and child [4]. However, there is a variation in the rate and degree of teratogenic potential of the different antiepileptic drugs. There seems to be sufficient data to imply that valproic acid (VPA) is a highly tratogenic drug [6–10].

Although there is some debate as to the extent of involvement of epilepsy in the increased rate of anomalies in AEDs treated pregnant women [11–13], more recent studies on larger numbers [14,15] do not seem to support a defined role of epilepsy in the increased rate of anomalies following AEDs exposure. Hence, it is reasonable to assume that the teratogenic effects of the AEDs result from the direct effects of the drugs on the developing embryo and fetus.

Generally, embryonic and fetal damage caused by AEDs may be manifested in 3 major areas:

(1) An increase in major congenital anomalies (MCA), mainly congenital heart defects, cleft lip and cleft palate, anomalies of the urinary tract, of the limbs and of the brain, especially neural tube defects (NTD).
(2) A specific syndrome, mainly affecting the cranio-facial complex causing facial dysmorphism, but often also affecting other organs such as external genitalia (i.e. phenytoin syndrome) and neural tube (valproate syndrome, carbamazepine syndrome).
(3) Developmental disorders, mainly affecting cognitive function and behavior. These changes may affect language development, learning abilities and even cause "Autism".

It is generally recommended to continue treatment with antiepileptic drugs, if administered for seizure controls, as long as there is a possibility of seizures. Many of these drugs (VPA included) may also cause withdrawal symptoms in the newborn infants

The more tratogenic drugs seem to be valproate, phenytoin, phenobarbitone and carbamazepine. Trimethadione and paramethadione seem also to be highly teratogenic, but they are replaced by newer, more effective drugs.

For some of the antiepileptic drugs, there is very little information as to their potential hazardous effects on the developing embryo and fetus. However, for many, especially the more "classic" AEDs that are widely used, there is sufficient human data. Although the main discussion is related to VPA, there will also be some reference to the other "classic" AEDs—carbamazepine, phenytoin, phenobarbital and to lamotrigine, but only in relation to co therapy with VPA, a fact that may significantly elevate their overall teratogenic potential.

We searched in Medline prospective and retrospective studies on the effects of valproic acid in pregnancy. This is not a complete evaluation of the literature because we discuss only the studies relevant to the different issues raised in this review. For the evaluation of the rate of major anomalies or of developmental problems we used both retrospective and prospective studies, but only if they describe, among the antiepileptic drugs, also results of valproic acid exposure in pregnancy. Generally we did not evaluate reviews unless they reported cases not published in other studies or they relate to the mechanisms of action of VPA or to the effects of epilepsy on the offspring. The data in the tables had sometimes to be calculated from the figures and tables of the relevant studies.

3. Effects of valproic acid (VPA) in pregnancy—neural tube defects (NTD) and major congenital anomalies (MCA)

VPA is on the market as an anticonvulsant since 1974, and is used in many countries because of its efficiency against several types of epilepsy and as a mood stabilizer. One of its main actions is the increase in the level of gamma amino butyric acid (GABA) in the brain. GABA is an important inhibitor of seizures, and reduction of GABA levels may potentiate seizures. For seizure control, the daily doses range between 300 mg to 2 g, aiming to achieve therapeutic plasma levels of 50–100 μg/mL. Lower doses are usually administered in the treatment of bipolar disorder—for manic patients, and against migraine.

The use of VPA during pregnancy is associated with a 1–2% incidence of NTD. Although this term refers to all types of neural tube defects, including anencephaly/exencephaly, VPA is associated mainly with lumbosacral meningomyelocele (spina bifida aperta), the latter being 10–20 times the rate in the general population [15–22]. In addition, abnormalities of many different organs as well as developmental delay and autism and a specific "fetal valproate syndrome" has also been suggested in various reports [23–56]. This is based on prospective and retrospective studies of about 3000 children born to VPA treated mothers.

The first reports suggesting teratogenicity of valproic acid in humans, increasing the rate of lumbosacral spina bifida with meningomyelocele or meningocele in children whose mothers took valproic acid in the first trimester of pregnancy were published in the early 1980s [16–20]. A French case–control study found an unusually high proportion of infants with spina bifida whose mothers used valproic acid in the first trimester of pregnancy. Their calculated odds ratio for the association of spina bifida after exposure to valproate was 20.6 [19,20]. The findings were confirmed by the International Clearinghouse for Birth Defects Monitoring Systems [20]. In an evaluation of the spectrum of 34 infants with NTD following in utero exposure to AEDs, mainly VPA, Lindhout et al. found [21] that most infants had open defects of the spinal cord and in some there was involvement of the brain, in addition to a high rate of other midline defects. In a prospective cohort study