EXPERT OPINION

Foetal safety of old and new antiepileptic drugs

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Introduction: Drugs teratogenicity has been studied for many years, especially teratogenic effects of antiepileptic drugs, because of the important impact that epilepsy has always had for young women, but data from literature are often conflicting.

Areas covered: We have carried out a critical review of all human studies about the antiepileptic drugs teratogenicity. A systematic search was performed in Medline and PubMed up to May 1, 2015. The use of older antiepileptic drugs in pregnancy is associated with an increased risk of fetus malformations; in particular, Valproate can determine neural-tube-like defects; in Phenytoin and Phenobarbital-exposed pregnancies, orofacial clefts, cardiac and genitourinary malformations are the major anomalies described. Spina bifida is the only specific major congenital malformation significantly associated with exposure to Carbamazepine monotherapy Despite the small number of studies on the teratogenic effects of new antiepileptic drugs, the analysis of the literature shows that exposure of the fetus to the new antiepileptic drugs is associated with a lower risk of major congenital malformations compared to the use of older drugs.

Expert opinion: Where possible, Valproate should be avoided in women of childbearing potential. Results about the safety of newer antiepileptic drugs require validation and further investigation.

Keywords: antiepileptic drugs, foetal malformations, neurodevelopmental disorders, teratogenicity

Expert Opin. Drug Saf. [Early Online]

1. Introduction

The purpose of antiepileptic therapy in pregnancy is to balance potential foetal adverse effects against the risks of uncontrolled maternal disease [1].

The first report that antiepileptic drugs (AEDs) may have teratogenic effects dates back over 40 years. Since that time, evidence has been accumulated demonstrating that AEDs are associated with an increased risk of congenital malformations and may have long-term effects on intellectual development during childhood [2].

It is estimated that 0.3 – 0.5% of all children are born to a mother with epilepsy. With the increased use of AEDs for other indications, such as psychiatric disorders, migraine and pain, the number of women using AEDs during pregnancy is considerably higher [3,4].

Over 90% of women with epilepsy have a normal pregnancy [5]. This point should be emphasized to the patient who is likely to have many fears and anxieties regarding the risks. The rates of malformation in the general population are 2 – 4%, 4 – 6% in women with epilepsy taking older AEDs. Moreover, women who have had one child with a congenital malformation are at an increased risk of having other children with malformations [5]. Nonetheless, there are a number of foetal and obstetrical complications associated with women with epilepsy. It is important

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Article highlights.

- Epilepsy is an important health problem for young women, in particular during pregnancy.
- Physicians should know the teratogenic potential of antiepileptic drugs (AEDs).
- Older AEDs (in particular Valproate) have an increased risk of teratogenicity than newer ones.
- Prenatal exposure to antiepileptic therapy may also be to determine effects on neurological and cognitive development.
- Where possible, Valproate should be avoided in women of childbearing potential and newer AEDs should be used.

This box summarises key points contained in the article.

for physicians and women with epilepsy to be aware of these as careful planning and management of pregnancy can increase the odds of a favourable outcome [6].

During the last 20 years, studies have been directed towards the valuation of the problems with the use of first-generation AEDs in women: in particular, Valproate (VPA) has demonstrated the highest teratogenic potential among the first-generation AEDs [7]. Therefore, the recent trend is to prefer the use of second-generation AEDs in fertile women, a trend confirmed by a recent analysis of AEDs prescription patterns in a nation-wide population: Lamotrigine (LTG), Gabapentin (GBP) and Topiramate (TPM) were more frequently used in female, whereas Carbamazepine (CBZ), VPA, Phenytoin (PHT) and Oxcarbazepine (OXC) were used to a larger extent in male rather than in female epileptic patients [8].

We have carried out a critical review of all human studies about AEDs teratogenicity. A systematic search was performed in Medline and PubMed up to May 1, 2015. The studies were identified searching Medline (PubMed), the keywords used were AEDs, teratogenicity, foetal malformations, randomised, review, human, and neurodevelopmental disorders. The list of references of all the relevant articles was also studied to include all reports and reviews related to the subject.

The research included the works and data available in English. For each clinical study, the number of patients assessed, the type of study and comparisons made, the products and the dosages used, their efficacy and their safety were identified.

We have also analyzed evidences of a neurodevelopmental delay in children exposed to AEDs which will be shortly reported for each drug, as since the eighties, some case reports have documented learning disabilities, low IQ and educational difficulties in children exposed to AEDs while *in utero* [9-13].

In more recent years, several experimental and clinical studies have been done to investigate whether cognitive difficulties were associated with the maternal use of AEDs during pregnancy [14-17].

The purpose of this article is to provide a review of the safety and risk associated with prenatal exposure to antiepileptic therapy, to describe the main malformation patterns associated with the various AEDs and to discuss the possible detrimental effect of AEDs on neurological and cognitive development.

2. Old antiepileptic drugs

2.1 Carbamazepine

Among the various studies about major congenital malformations (MCMs), one of the most important is the study performed by Holmes LB *et al.*, who found microcephaly and growth retardation in the 58 infants exposed to CBZ monotherapy among the 386 women who had taken one or more anticonvulsant drugs during pregnancy [18].

The literature review yielded an overall prevalence for a MCM of 3.3% after exposure to CBZ monotherapy in the first trimester of pregnancy; this result is obtained from data collected until 2010 [19]. Spina bifida is the only specific MCM significantly associated with exposure to CBZ monotherapy (0.9% of foetus exposed *in utero* to CBZ vs 0.18% of general population), but the risk was smaller for CBZ than for VPA (odds ratio 0.2, 0.6) [19,20]. There was no evidence for an association with total anomalous pulmonary venous return (no cases with CBZ exposure), cleft lip (with or without palate), diaphragmatic hernia, or hypospadias compared with no exposure to AEDs [19-22]. In agreement with these results, in the United Kingdom Epilepsy and Pregnancy Registry, compared with other AEDs, CBZ was associated with the lowest rate of MCMs: 2.2% [23]. Similarly, in the North American AED pregnancy and in the EURO-CAT Antiepileptic Study Database, the risk of foetal malformations associated with CBZ monotherapy was 2.9% and 3.3%, respectively [24-26]. The data from EURAP registry show that the risk of MCMs was 3.4% (for dosage lower than 400 mg per day) [7].

Some contrasting data show that, in early ages, children exposed to CBZ exhibit poorer performance than children from women without epilepsy [14,27]. A controlled cohort study of these data found significantly worse global intelligence measures in CBZ-exposed children, although, when the level of heterogeneity of the population explored was considered, the estimates became non-significant [28]. This possible negative effect of CBZ on cognitive abilities is not observed in older children. In fact, assessment of intelligence quotient and specific studies on language development in school-aged children failed to find a significant difference between children exposed to CBZ and controls. These data are in agreement with the Cochrane database systematic review (2014) [29].

2.2 Phenytoin

PHT is associated with the foetal hydantoin syndrome, first described in 1975 [30]; *in utero* exposure to this drug may

result in a characteristic dysmorphic syndrome in the newborn, including low-set hair, short neck with pterygium colli, small nose, deep nasal bridge, epicanthus, hypertelorism, large mouth, malformed ears, hypoplastic distal phalanges of the fingers and toes and finger-like thumbs. These dysmorphic features are often associated with growth retardation and delayed psychomotor development. As with other antiepileptics, the risk of oral clefts and cardiac malformations is five times higher among hydantoin-exposed infants, but the respective roles of the epilepsy and antiepileptic drug in the aetiology of these malformations have not been clearly established. These typical birth defects have been described in the literature from case reports [31,32]. Then, PHT-exposure is associated with a higher risk for the foetus to develop MCMs: in UK epilepsy and pregnancy register, the rate of the risk of MCMs for foetus PHT exposed during pregnancy is 3.7% [23]; however, this risk is always lower than the risk of foetuses exposed to VPA (PHT 10.7 vs VPA 20.3%) [33].

Case reports suggest also an increased risk for the occurrence of benign or malignant tumours, like neuroblastoma or other neonatal tumours (ependymoma, ectodermal tumours, Wilms tumour) [25,34-37].

In the subsequent literature, in PHT-exposed pregnancies, orofacial clefts, cardiac malformations and genitourinary defects are the major anomalies described [38,39]. The rate of all malformations has been 10.7% [39].

The risk of neurological impairment, estimated at 1 – 11%, is two to three times higher than that for the general population [29]. Neurodevelopmental functioning of children exposed to PHT during pregnancy has been investigated mainly with retrospective cohort studies; only a few prospective studies are available in the literature [40].

Meta-analyses and narrative review of these studies [28,41,42] did not find differences for PHT-exposed children compared with general population controls. A delay in the motor development [27] and language abilities [43] has been reported.

2.3 Phenobarbital

The risk of foetal malformation in the women exposed to phenobarbital (PB) during pregnancy is higher than in the general population. Children exposed to PB during foetal life have increased risk at birth of heart, orofacial or urogenital tract defects [34,44]. Findings from the North American AED Pregnancy Registry found a 5.5% incidence of major malformations (cardiac defects and oral clefts) among 199 pregnancies associated with PB use [45]. These data are in agreement with the observational study EURAP (2011), indicating the rate of MCMs in newborns PB exposed during pregnancy is 5.4% (for doses <150 mg per day) [7].

Surely the foetal toxicity of PB is enhanced when administered in combination with other AEDs. A recent study evaluated the teratogenicity of PB and CBZ co-administered to a pregnant woman;

this report highlights the possibility that PB/CBZ therapy during foetal organogenesis can induce sirenomelia, by a synergistic teratogenic effect and support the recommendation to use only one drug in pregnant epileptic women [46].

PB exposure during early development can have long-term deleterious effects on cognitive performance [47].

2.4 Valproate

VPA is the most teratogenic antiepileptic drug on the market: among the various studies, the teratogenic risk for MCMs ranges from 9.3 to 11% of pregnancies VPA-exposed [34,37]. Women whose last pregnancy resulted in a foetal malformation have a substantially increased risk of having further malformed foetuses if they become pregnant again while taking the same AEDs, particularly VPA. This suggests that maternal factors, perhaps genomic, predispose to at least VPA-associated malformations. This knowledge, together with information about the outcome of any previous pregnancy, should help in advising women with AEDs-treated epilepsy who plan further pregnancies [48].

Of foetuses, 1 – 2% exposed to VPA *in utero* develop neural-tube-like defects (spina bifida aperta, open lumbosacral myelocele), a 10- to 20-fold increase over the general population [49,50]. There may also be a pattern of MCMs consisting of meningomyelocele, cardiovascular and urogenital malformations with minor craniofacial, skeletal and genital anomalies [50]. One retrospective review of children exposed to VPA *in utero* examined by expert dysmorphologists found that higher VPA doses are associated with more frequent and more severe dysmorphia [7,51,52].

First trimester maternal exposure to VPA increases the risk of MCMs, independent of any contribution of the epilepsy syndrome itself [53-56].

The North American AED Pregnancy Registry followed VPA-exposed pregnancies to completion [24]. The prevalence of major birth defects in the offspring of women who received VPA monotherapy was 9.3%, as compared with 2.9% in the offspring of women receiving other AEDs [45]. Thus, the relative risk of major malformation in VPA-exposed women was 9.0 (95% CI 3.4 – 23.3). An increased dose of VPA was also associated with increased risk (OR = 3.7 for VPA ≤1500 mg/day vs OR = 10.9 for VPA >1500 mg/day) [45].

A case-control study using the European Surveillance of Congenital Anomalies database (registering a combined total of 98,075 MCMs) found that VPA was associated with an increased risk for several congenital malformations [57].

The effect of VPA on malformation risk is dose-dependent [58], but a lowest safe dose has not been established [35,48,58]. In the Australian registry of AEDs in Pregnancy, 17% of 110 infants exposed to VPA had malformations. VPA doses ≤1400 mg per day were associated with lower rates of malformations than higher doses. Data from the same registry also suggest that while the risk of spina bifida and hypospadias decreases with lower doses, the risk of other malformations (cleft lip/palate, atrial septal defects) does not [59].

In few patients, neonatal coagulopathy, due to hypofibrinogenaemia caused by VPA, has been reported [59,60].

If possible, VPA should be avoided in the first trimester of pregnancy due to the risks; however, a recent review by Mole *et al*. illustrates the therapeutic benefits of VPA and underlines that indiscriminate avoidance of VPA needs to be recognised as a misinterpretation of current epilepsy guidelines as it may harm young people [61].

With only a few exceptions, almost all studies assessing cognitive abilities in children exposed to VPA *in utero* found poorer outcomes in respect to control populations. Studies range from neurodevelopmental deficits found in early case reports [9,10,40,62] to works with recent prospective studies [28].

The degree of cognitive involvement has been assessed and it has been found as a mean difference in respect to a control population ranging from eight to nine points lower in the developmental quotient and in the intelligence quotient [28]. This degree of cognitive involvement should be of clinical relevance and it has been suggested that it may convey real-life implications for educational attainment.

Specific cognitive domains, although less often investigated, can also be compromised. For example, there is evidence of poor motor and language development [14,41] and of an increased prevalence of autistic spectrum disorders with prevalence estimates ranging from 8 to 15% [63,64].

A dose–effect relationship has also been investigated with the majority of studies reporting an increase in risk with doses above 800 – 1000 mg [28].

Although the risk of poor cognitive and behavioural functioning may also depend on genetic and behavioural factors, there is evidence of a drug effect and this should be communicated to women in fertile ages who start a treatment with VPA.

3. New antiepileptic drugs

3.1 Gabapentin

The literature about the safety of GBP during pregnancy reports limited and inconclusive data [16].

A study comprising 51 infants shows no increased risk for foetal malformations [65].

No information is available on neurodevelopmental delay.

3.2 Lamotrigine

LTG is one of the safer AEDs in pregnancy, presenting less teratogenic effects on the foetus, especially with regard to the effects on cognitive development [66].

The rate of malformations in the newborn of LTG monotherapy mothers is between 2% and 5.6%, compared to the general population, where the rate of risk is 1.1 – 3.6% [67].

A lower rate of malformations was associated with exposure during pregnancy at doses of LTG below 300 mg per day (2%) [7,68].

Therefore, it is not clear if LTG monotherapy increases the risk of MCMs above background rates found in the general population [69]. Early studies focused on rates of any MCMs were negative [26,69], while other individual reports have suggested possible small increases in the risk of oral clefts, hypospadias and gastrointestinal defects [70,71]. Other registry studies reported lower rates of oral clefts that fall generally within the range for offspring with no drug exposures [26,72]. This includes results of a population-based cohort study of nearly 838,000 live births in Denmark, which found no increased risk of major birth defects with *in utero* exposure to LTG (1019 exposed deliveries) compared with no drug exposure (OR 1.18, 95% CI 0.83 – 1.68) [73]. As mentioned earlier, some studies have suggested a higher risk of congenital malformations with higher maternal daily doses of LTG [23,74]; however, the majority of reports have shown no dose-related effect [69,71,74,75]. Congenital malformation rates have been shown to be lower with *in utero* exposure to LTG than VPA, and slightly lower than CBZ [75]. Data from the International LTG Pregnancy Registry have shown that rates of MCMs were substantially higher with LTG when combined with VPA compared with LTG alone (10.7 vs 2.8%) [76]. In that study, 35 infants with MCMs were observed among 1558 LTG exposures during the first trimester over an 18-year period. No consistent patterns of specific malformations of dose-dependent increases in malformation risk were observed [76].

Results of the few studies which investigated the neurodevelopmental abilities of young children exposed to LTG indicate that there is not a significant difference with the control population [14,15].

3.3 Levetiracetam

In the literature, in a meaningful number of exposed pregnancies, a low risk for MCMs with LEV monotherapy use in pregnancy is shown. MCMs risk is higher when LEV is taken as part of a polytherapy regimen, although further work is required to determine the risks of particular combinations. With respect to MCMs, LEV taken in monotherapy can be considered a safer alternative to VPA for women with epilepsy of childbearing age [69].

LEV has a widespread use by women in their childbearing years but data on the effect of this drug on cognitive development are very scarce. In one study, no difference was found in children exposed to LEV *in utero* and cognitive development at 2 and 4 years of age [76,77].

3.4 Oxcarbazepine

No adverse effects are reported in the newborns of OXC-treated mothers [78,79].

In a study, MCMs at birth were found in 11 of 393 (2.8%) children exposed to OXC, a rate that was not significantly higher than non-exposed infants [80].

A recent innovative study had shown that the encapsulation of OXC into nanoparticles may offer promise for treating pregnant women with epilepsy by improving brain delivery and limiting the transplacental permeability of AEDs to avoid foetal exposure and its consequent undesirable adverse effects. The physical properties of the developed nanoparticles were

determined with subsequent evaluation of their permeability across *in vitro* models of the blood–brain barrier (hCMEC/D3 cells) and human placental trophoblast cells (BeWo b30 cells). In this work, the authors have encapsulated OXC into biodegradable and biocompatible nanoparticles to reduce the placental transfer of the drug, maintaining the passage of the blood–brain barrier. Future developments in enzyme-prodrug therapy and targeted delivery are expected to provide improved options for pregnant patients with epilepsy [81].

3.5 Topiramate

In TPM-exposed pregnancies, the rate of all malformations is 4.2 – 4.9%, with an increase in MCMs (mostly oral cleft and hypospadia); prenatal exposure to TPM has been associated with an elevated frequency of small size for gestational age newborns [82].

In a very small study in which mothers were taking TPM with heterogeneous indications, some differences were found between cognitive abilities of children exposed to this drug *in utero* and controls [73].

3.6 Zonisamide

The teratogenic effects of Zonisamide (ZNS) were reported in one study with 26 children exposed to ZNS *in utero*. Malformations were found in two cases where ZNS was combined with first-generation AEDs, but not in the four cases treated with monotherapy [83].

3.7 Other new AEDs

The other second-generation drugs such as Tiagabine, Vigabatrin, Felbamate, Stiripentol, Rufinamide and the third-generation drugs Retigabine and Lacosamide are used in combination with other antiepileptic treatments for the difficult-to-control epileptic patients or in specific syndromes (Vigabatrin: West syndrome; Stiripentol: Dravet syndrome; Rufinamide: Lennox–Gastaut syndrome). In the literature, data about their teratogenic potential effects are limited or nonexistent [84,85].

4. Folic acid supplementation and other issues

The mechanism underlying MCMs is a characteristic illustration of the role of gene–environment interactions in the aetiology of birth defects [36]. In fact, on one side there are various genetic factors and on the other side the detrimental effect of AEDs is essential; this effect can be due to several post-replication epigenetic changes of genome through DNA methylation. Anyway, data are currently insufficient to clearly confirm this risk. Because of the incremented risk of sirenomielia, careful ultrasound monitoring of women with epilepsy is mandatory due to the teratogenic risk of both seizures and therapy [46].

Folic acid supplementation reduces the number of spontaneous abortions in women using AEDs and protects the foetuses exposed to AEDs *in utero* against cognitive impairment [1].

Epileptic women who are taking AEDs and in particular PHT, CBZ and VPA and are planning to get pregnant should receive folic acid supplements (5 mg per day), before conception, as a preventative measure against malformations [86].

In conclusion, physicians should prescribe folate supplementation because this treatment can reduce the risk of teratogenicity of AEDs [86,87].

5. Expert opinion

The risk of MCMs, growth retardation, heart defects, hypoplasia of the midface and fingers, is increased in newborns exposed to AEDs during pregnancy. Although the exact mechanism of their teratogenicity is not clear, a variety of mechanisms have been suggested, for example, folate-related actions, ischemia, reactive intermediates and genetic susceptibility [88].

Morever, when older children were assessed with an intelligence quotient measure, children exposed to VPA had significantly poorer scores than children exposed to CBZ, PHT and LTG [26]. Whether results from animal models indicate that exposure to AEDs during foetal development is associated with altered neuronal development [42], results of clinical studies are conflicting.

The explanation for some inconsistent findings may be at least in part justified by methodological differences of clinical studies. A first point is the retrospective nature of some studies which may be a possible cause of a selection bias [10]. A second point is that the control population was different in different studies. In fact, comparisons have been made versus women with epilepsy who do not take AEDs, women without epilepsy, or between women taking different AEDs to enable treatment comparisons. Finally, the assessments of cognitive function were performed in different ages of children and with different techniques of assessment. Although the most frequently reported measure of global cognitive functioning is the intelligence quotient, in younger children global ability assessments include assessment of motor and social skills and produce an outcome reported as the development quotient. More specific cognitive skills such as attention, language and memory abilities have also been investigated in some studies and the proportion of children who experience autistic spectrum disorders, attention deficit-hyperactivity disorder and dyspraxia have been signalled by some investigators.

The recent increase in information concerning AEDs teratogenesis improved our ability to care for women of childbearing potential, but it also complicated therapeutic decisions. Previous guidelines have simply recommended that physicians choose the most effective AED for the individual woman. Now, physicians must consider factors related to teratogenetic risks for specific AEDs, although the evidence for some risks and many AEDs remains uncertain. The choice of treatment for girls and women of childbearing potential

should be based on a shared decision between clinician and patient, and where appropriate, the patient's representatives. The informed consent process must include a discussion of these various factors as they relate to the individual woman [89]. The discussion should occur when the AED is first prescribed and should provide advice concerning the certainty of the information available so that the patient can participate fully in the decision process [89].

When possible, VPA should be avoided in women of childbearing potential, in accordance with the recommendations present in the Task Force of the Commission on European Affairs of the International League Against Epilepsy and the European Academy of Neurology [90]. For epilepsy types where VPA is the most effective treatment, the risks and benefits of VPA and other treatment alternatives should be discussed. While teratogenic potential of VPA has long been confirmed, information on teratogenicity of the newer generation AEDs are quite reassuring [91]. Evidence from the recent literature suggests that LTG and LEV have low risk for teratogenesis, but that TPM exposure early in pregnancy may be associated with dose-related anatomical teratogenesis [92].

The only AEDs presently approved by European Medicine Agency for monotherapy treatment of primary generalized tonic–clonic seizures, mainly in the context of idiopathic (genetic) generalized epilepsies, are LTG, PHT, PB, TPM and VPA; of these, treatment with PB and PHT is nowadays rarely initiated in Europe, and cannot be considered reasonable treatment alternatives to VPA. The results about the safety of newer AEDs require validation and further investigation [93].

In conclusion, there is convincing evidence that VPA is associated with neurodevelopmental disorders. CBZ and, perhaps, PHT might have some negative effects on some specific cognitive abilities. For all other drugs, there is no evidence for a detrimental effect but data are too scarce to exclude such effects. Newer AEDs appear to be associated with malformations risks similar to those of the general population. Even the definite increased risk of VPA has to be balanced against considerations of efficacy [94,95]. Neither teratogenesis nor efficacy for seizure control can be predicted on an individual patient basis. Literature analyzed shows VPA is the most teratogenic among old AEDs, while new drugs have a greater safety profile; so, we have previously recommended that VPA not be used as a first-line AED in women of childbearing potential, because the failure to control seizures may be corrected by altering the AED, but the occurrence of teratogenesis is frequently irreversible and results in lifelong disability [31]. If VPA is used in a woman of childbearing potential, the lowest effective dose should be employed, as VPA teratogenic risk is dose dependent.

More studies are needed as regards the safety of new AEDs, especially to provide more information to the women with epilepsy. Thus, making women more aware about the risk-benefit of therapy antiepiletic during pregnancy, we can obtain greater compliance to treatment [89].

Declaration of interest

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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