Review Articles

Old and new anti-epileptic drugs in pregnancy

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ABSTRACT

During the recent years, a significant number of anti-epileptic drugs have been approved for prescription in different countries. In addition, some other promising drugs are in various stages of development. Soon after each drug has found its place in the therapeutic arsenal, pregnancies with exposure occur, with an increased risk of birth defect and developmental disturbances. As regards the possible teratogenic effect of the new anti-epileptic drugs, apart some individual reports we have only the results of pre-clinical toxicological studies which are difficult to extrapolate to the human situation, because of the well-known interspecies differences in pharmacokinetics and pharmacodynamics. Furthermore, combinations of anti-epileptic drugs are not tested pre-clinically while these new drugs are prescribed as add-on medication. So, metabolic interactions between individual components of such drug combinations may induce unexpected teratogenic effects. Also as for the teratogenic effects of the "old" drugs many questions have still to be defined. The most common and more important are which anti-epileptic drugs or combination of drugs is most safe for a particular woman with epilepsy and if there is an association between single anti-epileptic drugs and specific malformations. The reason is that none of the available reports to date have studied a sufficient number of women with epilepsy exposed to anti-epileptic drug monotherapy during pregnancy. Other questions concern dose-effect relationships, a universally accepted definition of major and minor malformations, and the lack of a thorough, exhaustive evaluation of the other risk factors, apart from the drugs. All these questions need to be ascertained for both the old and the new anti-epileptic drugs. Owing to these considerations, in 1998 an European Register of anti-epileptic drugs and pregnancy was instituted. The primary objective of the study is to evaluate and determine the degree of safety, with respect to the human foetus, of anti-epileptic drugs with reference to both old and new, and to individual drugs and drugs in combination. Secondary objectives are to establish the pattern of abnormalities, if any, associated with anti-epileptic drugs individually and in combination, to delineate drug-specific syndromes, if any, to evaluate dose-effect relationships. Tertiary objectives are to provide references data for use in pre-pregnancy counselling, and for development of guidelines. The evaluation of other etiological risk factors is also considered.

Keywords: Epilepsy, pregnancy, anti-epileptic drugs, teratogenic effect, assessment.

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Currently, many new anti-epileptic drugs (AEDs) including felbamate, gabapentin, lamotrigine, vigabatrin, topiramate, tiagabine and zonisamide have been approved for prescription in different countries. In addition, some other promising drugs including levetiracetam, losigamone, remacemide and stiripentol are in the various stages of development. By the analogy with previous experiences with the AEDs of the first and second generation, soon after each drug has found its place in the therapeutic arsenal pregnancies with exposure will occur. In fact, exposed pregnancies do occur already during clinical trials before marketing, despite attempts to avoid pregnancy during exposure or to exclude pregnant women or women with child wish from such trials. Many of such unplanned pregnancies are followed by induced abortion, probably because of lack of information about the

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safety of the new compound. Concern is mainly about pre and postnatal growth, major congenital abnormalities, minor anomalies, psychomotor and mental development. This article will focus on the relationship between treatment with AEDs in pregnancy and the risk of congenital malformations. Existing informations on the teratogenic effect of the old AEDs and the scanty experimental and clinical findings on the new AEDs will be analyzed. An European Project aimed to establish a surveillance system in order to improve pregnancy outcomes of women with epilepsy will be described briefly. When one is dealing with the above mentioned matter the first arising question is: what we really know about the teratogenic effects of the old AEDs? In 1964 Janz and Fuchs[1] for the first time raised the question and four years later a letter to the Editor of the Lancet by Meadow[2], in which he reported on six observations of cheilo and palatoschisis among children of mothers treated with AEDs, initiated an unending flood of investigations and publications dealing with the pathogenetic evaluation of the three conditions which may be found among children of epileptic parents: congenital malformations, minor anomalies, and developmental disturbances. However, congenital malformations remain the most commonly reported adverse outcomes in the pregnancies of mothers with epilepsy. Malformation rates in he general population range from 2% to 3%.[3] Reports of malformation rates in various populations of infants of mothers with epilepsy range from 1.25% to 18.6%. At the end of the 1970s there were many retrospective inquiries but they produced contradictory results as regards the risk of assuming AEDs during pregnancy. So, prospective studies started in various parts of the world (Germany, Italy, Japan, Finland, France, USA and Canada). These groups met for a workshop in West Berlin in 1980[5] to discuss the various problems of epilepsy and pregnancy and one of the main issues was to which extent AEDs have teratogenic effects and which single AED is the safest. The results of the workshop and of that subsequently held in Santa Monica[6] led to some conclusions concerning the treatment of pregnant women with epilepsy, summed up in Consensus Guidelines. Summarizing, the risk for congenital malformations may be indicated as twofold to threefold that of the non-epileptic population. It has become common practice to quote a risk for major malformations (defined as defects of medical, surgical or cosmetic importance) of 4 to 6% to women with epilepsy. However, in spite of the conclusions of these two workshops, many points remain to be cleared up considering the complexity of the problem. In fact, malformations are not only due to the effect of AEDs but also to a possible genetic predisposition, to adverse effects of seizures during pregnancy, to demographic factors associated with epilepsy and finally to both paternal and maternal epilepsy. But of all the suggested risk factors proposed, epidemiologic and experimental studies have provided strong evidence that the teratogenic effect of AEDs is the main risk[7], even if family history for malformations, older age at delivery, and low socio-economic status are other factors that increase the risk.[8] Evidence of support the association between the increased rate of malformations and AED exposure in utero comes from four observations: malformation rates are consistently higher than those in untreated epileptic mothers[9,10], plasma AED concentrations are higher in mothers with malformed infants than in mother with healthy[11], infants of mothers receiving polytherapy have higher malformation rates than infants exposed to monotherapy[10,12], maternal seizures during pregnancy do not appear to increase the risk of congenital malformations.[13] As regards this last statement, although Majewski et al[14] described increased rates of malformation and central nervous system injury in infants exposed to maternal seizures, the majority of investigators have found no impact of maternal seizures during pregnancy on the frequency of malformations or development of epilepsy or febrile convulsions.

Which types of congenital malformations are related to AEDs? Virtually every type of congenital malformation has been observed and every AED has been implicated in their development, even though carbamazepine and valproate are the only AEDs uniquely associated with spina bifida. Cleft lip or palate (or both) and congenital heart disease account for most reported malformations.[9,15] Orofacial clefts are relatively common malformations in the general population, occurring with a frequency of 1.5 per 1000 live births[15]; for infants of mothers with epilepsy the rate of orofacial clefting is 13.8 per 1000, a ninefold increase.[15,16] On this subject some investigators have suggested that epilepsy and clefting are genetically linked. Israeli researchers[17] have found that children with cleft lip or palate are four times as likely to have a mother with epilepsy as are children in the general population, and that mothers with epilepsy are six times as likely to bear a child with an orofacial cleft as are women without epilepsy. Friis et al[18] studying the prevalence of facial clefts in the siblings and children of 2072 persons with epilepsy found no evidence supporting the belief that this factor alone contributes to the development of orofacial clefts.

Mechanisms of AEDs teratogenesis. Many mechanisms have been postulated in the past. To day three are recognized: fetal accumulation of toxic intermediary AED metabolites, induction of folate deficiency, predisposing genetic factors. These different hypothesized mechanisms may be interconnected in some cases. Several AEDs are metabolized to arene oxide intermediates by the hepatic cytochrome P450 enzyme system. These

intermediary metabolites are highly reactive. They are postulated to bind to embryonic macromolecules, disrupting normal developmental processes.[19] The enzyme epoxide hydrolase metabolizes the biologically active epoxide metabolites of AEDs to compounds that are less toxic. Experimental observation have suggested a genetic defect in the detoxification of potentially teratogenic AED metabolites by epoxide hydrolase.[20] On the other hand there is no doubt that genetic factors must play a role, since not everyone exposed to AEDs has adverse outcome.[21] Three phenotypes of epoxide hydrolase have been described, with low enzyme activity being associated with fetal hydantoin syndrome.[22] This recessive trait may be responsible for differences in metabolism of AEDs and accounts for differences in teratogenic susceptibility. For the same reason some drug combinations show altered risk profiles. When carbamazepine, phenobarbital and valproic acid are combined, with or without phenytoin, 58% of infants have birth defects.[23] This is a higher rate than for the other three or four drug combinations, suggesting metabolic interactions. Valproic acid inhibits epoxide hydrolase, which increases the presence of epoxide metabolites of aromatic AEDs and consequently the potential for teratogenicity. On the other hand folate may be a cofactor for epoxide hydrolase, so folate deficiency could further increase epoxide concentrations of aromatic AEDs. Anti-epileptic drugs may be particularly dangerous in women predisposed to give birth to infants with neural tube defects.[24] These women may not utilize folate as efficiently as other women and AED use diminishes serum folate concentrations. Besides, declines in serum folate are related to the number of AEDs taken, therefore, drug combinations should be minimized. Since a dose-response relationship has been reported for red blood cell folate and risk for neural tube defects, any decrease in folate may be significant. Folic acid supplementation has been shown to prevent low folate concentrations caused by AEDs use and should therefore be prescribed early in pregnancy.[25] The optimal dosage is unclear, as supplementation has varied between 0.36 and 5 mg/day in different studies, but protective effects of folate are maximal with high levels.[19,26] As far as this problem is concerned, little information on the folate effects of the newer anti-convulsants is available. Lamotrigine is a modified anti-folate compound that may have anti-folate effects, although at least one study indicated no effect on serum folate.[27] The incidence of folate deficiency with the new AEDs remains to be determined, as well as their ability to exacerbate the teratogenesis of other drugs through drug interactions. Felbamate might act as an inhibitor of epoxide hydrolase as does valproic acid.[28] Vigabatrin and gabapentin may be useful as add-on therapy, since neither compound is aromatic nor affects the cytochrome P450 enzyme system. No information is available until now on the folate effects of gabapentin, vigabatrin, topiramate, and tiagabine. More recently a different and common pharmacological mechanism has been hypothesized for phenytoin, carbamazepine, trimethadione and phenobarbital, related to their pharmacological properties: blockage of ion channels in the developing heart in early embryo resulting in bradyarrhythmias, hemodynamic alterations and hypoxia/reoxygenation damage.[29] So, and this is the point to underline, AEDs of first generation (e.g. phenobarbital, phenytoin, and primidone) and second generation (valproate, carbamazepine) are all more or less teratogenic. However, many questions still remain to be solved. The most common and most important is which AED or combination of drugs is most safe for a particular woman with epilepsy. If we look at the results of prospective studies[30], the incidence of major anomalies seem to depend rather more on the type of drugs than on their combination (Table 1). The figures for the main AEDs given in monotherapy do not differ greatly from each other and from those for the polytherapy group. The incidence of malformations after exposure to valproate as the only drug is however significantly increased and is even higher than in children of mothers who have taken multiple drugs during their pregnancy. As for the type of malformation seen in infants of epileptic mothers, cardiac defects are the most frequent. However, the conclusions of the

Table 1 - Types of malformations and type of anti-epileptic therapy.

Anti-epileptic drugs in monotherapy					**In polytherapy**	**Total**
N	**Pht**	**Phb**	**CBZ**	**VPA**		
	202	209	295	242	546	1530
Cleft lip/palate	0.5	0.5	1.6	0.4	2.0	1.2
Heart defects	1.0	2.7	0.3	2.1	1.6	1.5
Clubfoot	-	-	0.3	0.4	0.5	0.3
Hip dislocation	-	0.5	0.3	-	0.2	0.2
Polydactily	0.5	-	-	0.4	-	0.1
Scheletal aplasia	-	0.5	-	1.7	-	0.3
Hypospadia	0.5	-	1.0	-	0.5	0.5
Spina bifida aperta	-	-	0.3	2.9	0.4	0.5
Percentage (%)	2.5	4.1	3.9	7.9	5.2	4.6

Pht = Phenytoin CBZ = Carbamazepine
Phb = Phenobarbital VPA = Valproate

previously cited workshop of Santa Monica are still valid: "none of the available reports to date have studied a sufficiently large number of women with epilepsy exposed to AED monotherapy during pregnancy. Consequently, inadequate power has skewed the statistical analysis of risk estimates for specific forms of major birth defects associated with specific AEDs. The denominator used for analysis of each AED combination in polytherapy is even smaller". Indeed, the conclusions of the recent Joint European Prospective Study[31] are similar: " Larger prospective population-based studies are needed to evaluate the risks of many other less frequently prescribed treatment regimens, including newly marketed AEDs". This uncertainty is due not only to the lack of sufficiently large denominators for the various medication options, but also to very different types of epilepsy, seizure pattern, etc. Adding to this complex problem is the fact that many women with epilepsy, as already outlined, just like general patients with epilepsy, need to be treated with more than one AED. This increases the number of different treatment regimens, and decreases the denominators for each medication regimen considerably. On the other hand, the results of pre-clinical toxicological studies are difficult to extrapolate to the human situation, because of the well-known interspecies differences in pharmacokinetics and pharmacodynamics. Furthermore, combinations of AEDs are not tested pre-clinically, whereas metabolic interactions between individual components of such drug combinations may induce unexpected teratogenic effects. Apart from this, other important questions are still unsolved: standardized definition of major malformations, minor anomalies, and abnormal growth development, association between single AED and specific malformations, dose-effect relationships, prenatal diagnosis for specific risks. Since no agreement on the definition of major malformations has been achieved up to now, the results of the various studies are often difficult to compare. Still more difficult is the definition of minor anomalies, further complicated by the fact that for most of them the confounding existence of an inherited factor is highly probable. The issue regarding the existence of a fetal hydantoin or phenobarbital or carbamazepine syndrome is matter of debate. Nothing is known about the dose-effect relationship of the different AEDs. Current prenatal diagnostic means include trans-abdominal and trans-vaginal ultrasound examination, measurement of alpha-1-feto-protein in maternal serum and amniotic fluid, and cytogenic and molecular genetic analysis of cultured amniotic cells or cells obtained through chorionic villi sampling. These examinations may be performed where a priori genetic or teratogenic risk exists for the foetus, but also because of direct or indirect fetal signs presenting already during early pregnancy, or observed coincidentally during routine ultrasound scanning. Then, instead, have they to be done routinarily? Other points to be cleared are the evaluation of etiological risk factors, such as: medication parameters, e.g. type, dose, and administration scheme of each AED; pharmacokinetic parameters, type of etiology of maternal epilepsy, type and frequency of maternal seizures during pregnancy, intake of comedications, dietary or voluptuary substances, other chronic or intercurrent maternal diseases, family history of congential abnormalities, known hereditary diseases and epilepsy. All this we need to know about conventional AEDs and we also need to ascertain for the new AEDs. After introduction into the market, these new AEDs have been prescribed as add-on medication, which implies polytherapy, usually consisting of two-three, but sometimes of four to five different drugs; therefore, very large number of pregnancies have to be evaluated in order to establish the safety of each regimen. Large denominators are also needed because of the qualitative diversity of one of the main endpoints of outcome, i.e. major congenital malformations. Experimental studies have yielded conflicting evidence on the teratogenic effects of new AEDs. In reproductive studies, felbamate did not show birth defects in rats or rabbits.[32] Gabapentin administration in one study[33] did not result in any significant malformation, while in another study[34] at high doses was toxic to the fetus of rodents. Delayed ossification of bones was also noticed. Vigabatrin administration resulted in a high incidence of exomphalos and in a lesser percentage of other malformations in mouse fetuses suggesting that VGB should be used in pregnancy with extreme caution.[35] Lamotrigine is a weak inhibitor of dihydrofolate reductase, and may have a teratogenic potential. In animal studies with topiramate, growth retardation and limb agenesis have been demonstrated.[36] This latter toxicity may be species-specific to rats and not relevant to humans. In animal studies with tiagabine, growth retardation has been demonstrated. As regards clinical studies, in the last few years, some pharmaceutical industries have set up registries to collect data on exposure to the new AEDs during pregnancy (e.g. Lamotrigine pregnancy registry; Neurontin pregnancy registry). The data collected are both retrospective and prospective. Obviously, these studies have great limitations regarding, first of all, the limited number of collected cases, the type of collecting (frequently by phone interview) and the modality (exclusion of the abortion from he denominator); furthermore, most of the pregnancies are exposed to AED polytherapy. As reports of exposure are voluntary, they are subject to numerous selection biases (possibility of non-representative selection of women into registry). Preliminary data from the Lamotrigine Pregnancy Registry (1997)[37] showed a

proportion of births with defects following first trimester exposure not different from the expected proportion of the general population or in women with epilepsy and no consistent pattern of defect. In a study regarding zonisamide[38], the data do not indicate that the risk of teratogenicity is greater than that of other conventional AEDs. No malformation was detected in monopharmacy cases. The North American Registry for Epilepsy and Pregnancy (NAREP) has been established as a surveillance system to identify adverse pregnancy outcomes associated with exposure to AEDs.[4] All these studies demonstrate the great interest in this debate. In Italy, in 1997, we proposed to institute an Italian Register for pregnant women taking AEDs. This led to the setting up of an adhoc committee by the Italian League Against Epilepsy. It was soon decided to adhere to a forming international consortium in order to elaborate an European project. Data from all participating groups will be shared in a European Register of AEDs and Pregnancy (EURAP). This will be facilitated by use of the same protocol and the same data dictionary by all groups, and will allow for a much earlier meaningful evaluation. The primary objective of the study is to evaluate and determine the degree of safety, with respect to the human foetus, of AEDs with reference to both old and new, and to individual drugs and drugs in combination. Secondary objectives are to establish the pattern of abnormalities, if any, associated with AEDs individually and in combination, to delineate drug-specific syndromes, if any, to evaluate dose-effect relationships. Tertiary objectives are to provide references data for use in pre-pregnancy counselling, and for development of guidelines. The evaluation of other etiological risk factors is also considered. In practice, there is an European Project Commission whose functions include: co-ordination of the activities of regional commissions, creation of EURAP, periodic evaluations of data achieved in EURAP, mailing semestral relations to regional groups, publications of the results of the study. The regional commissions are responsible for the organization and local co-ordination of the study. At present, there are six identified areas: Italy, Benelux, Central Europe, France, British Isles, and Scandinavia. In the next phase, other areas will be included. For each pregnancy, all the data recruited will be recorded on a case record form that will be sent to the regional co-ordinators and included in the regional registry than shifted to the European Registry. The study is focused on pregnancies with maternal anti-epileptic drug use, and does not include controls, or pregnancies of spouses of epileptic man. The study includes pregnancies with maternal anti-epileptic drug use for other indications than maternal epilepsy, like trigeminal neuralgia, and psychosis. It is expected that the number of disorders other than epilepsy, for which some of the AEDs are effective, will increase in the near future. Inclusion of such pregnancies will provide valuable information in determining the role of AEDs irrespective of the type of maternal disease. This project will allow, we hope, to reach some definite conclusions and in any case, it will constitute a work in progress and a model for further studies.

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