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Epilepsy and Anticonvulsant Therapy During Pregnancy

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1. Introduction

Epilepsy is one of the most common chronic diseases accompanying mankind for centuries. Approximately 1% children in Europe have been born to the women suffering from epilepsy. For epileptic women is important to obtain appropriate information about possibility to have children and about risks connected with their pregnancy. A population-based cohort study in Finland (Artama et al., 2006) suggested decreased birth rate among patients with epilepsy. As both, disease and treatment, may induce inborn defect, it is essential to diminish their negative effects. Every chronic treatment during pregnancy increases estimation of the risk to offspring. Risk perception during pregnancy is individual, however almost 35% of women according to the study (Helbig et al., 2010) investigating factors important in the family planning decided to have fewer children. They were afraid about transfer epilepsy onto the offspring or disability to care for a child. Another factor having effect on their decision is teratogenicity of drugs used for treatment. Women with epilepsy may benefit from discussion with their healthcare provider about the impact their epilepsy may have on children. As almost 50% pregnancies in women with epilepsy in USA (Davis et al., 2008) are not intended, relevant information in right time may decrease the number of elective abortion.

Every physician should be informed about risk to the fetus that is associated with seizures and drugs used for treatment during pregnancy. Drug used in girls and young women should be chosen with the respect to the future reproduction, because the use of anti-epileptic drugs (AED) in women with epilepsy is in fact a balance between seizure control and adverse effects of drugs.

2. History

Modern treatment of epilepsy started during the19th century. The first drug introduced for treatment of epilepsy was potassium bromide that was widely used in USA and Europe during the second half of the 19th century. Another drug that was introduced at the beginning of 20th century was phenobarbital. Hydantoins has been used since 1938. Many new drugs were discovered subsequently. Apart from the fact, that anticonvulsant drugs have been used for many years, their embryotoxicity was not be described before 60th, when first case reports were published (Meadow, 1968; Müller-Küppers, 1963; Centa & Rasore-Quartino, 1965; Massey, 1966). Fetal hydantoin syndrome was described in 1975 by

Hanson and Smith. Similar inborn defects were described for all older anticonvulsant drugs (primidone, valproate, phenobarbital, phenytoin, carbamazepine, trimethadion). The frequency and severity of defects associated with use trimethadion were so high to warrant consideration of early elective termination of pregnancy. The teratogenic mechanism of AEDs is only partially understood.

2.1 Fetal anticonvulsant syndrome

Fetal anticonvulsant syndrome is associated with exposure to dilantin, diphenylhydantoin, phenytoin, hydantoin, and valproic acid during 1st trimester of pregnancy, in lower degree also with other (carbamazepine). The abnormalities include (Jones, 1997; Žižka, 1997; Ornoy, 2009):

a. An increase of major congenital anomalies: congenital heart defects (septal defects, tetratology of Fallot, aortic coarctation etc.), cleft lip and palate, limb defects with hypoplasia of nails and distal phalanges, finger-like thumbs, abnormal palmar creases, dislocation of hip, malformation of brain, especially neural tube defects.
b. Specific syndrome including facial dysmorphy with wide anterior fontanel, ocular hypertelorism, broad, depressed nasal bridge, short nose with bowed upper lip, midface hypoplasia, epicantus, often also malformation of external genitalia and neural tube.
c. Intrauterine growth retardation.
d. Developmental disorders mainly affecting cognitive functions and behaviour.

Small variations were noted according to the drug used. A significant association was seen between maternal use of valproic acid and spina bifida, and a weaker, non-significant one between carbamazepine and spina bifida. Facial clefts were associated with both diphenylhydantoin and phenobarbitone use and also with polytherapy (Källén et al., 1989). As AEDs have effect also on cognitive development, children exposed to valproate have increased risk of delayed early development in comparison to the control group (Bromley et al., 2010). It seems, that a distinctive pattern of abnormalities in infants is associated with the use of anticonvulsant drugs during pregnancy rather than with epilepsy itself (Holmes et al., 2001).

3. Embryotoxicity and its evaluation

3.1 Animal studies

How embryotoxic potential of drug may be detected? The first opportunity is an animal study. Every drug has to be tested in animal studies with a respect to protect the unborn child from adverse effects. Animal studies can, but do not always, predict whether a drug will be teratogenic in humans. Unfortunately, animal studies have shown as poor predictors in the case of thalidomide that did not produce malformations in rats and mice. On the other hand, some drugs have been found teratogenic in animals and not in humans. Therefore, minimally two different animal models are required for routine testing. Animals are often given far higher doses of drugs than humans would ever receive. Interspecies differences regarding the teratogenicity of drugs, that can increase doubts about results, result from differing pharmacokinetic processes, different metabolites, concentration-time relationships in an embryo, placental transfer and elimination rate. The only way to ascertain the ultimate risk or safety of drugs during pregnancy is to verify them in human studies (Einarson & Koren, 1999).

3.2 Epidemiological studies

As pregnant women cannot be enrolled in randomized, controlled studies from obvious ethical reasons, the teratogenicity have to be established in prospective or retrospective epidemiological studies. Data have been collected in a registry of birth defects (CDC- The International Clearinghouse for Birth Defects Monitoring Systems, EUROCAT - A European Network of Population-based Registries for the Epidemiological Surveillance of Congenital Anomalies), by specific registry collecting data about AEDs exposure (EURAP- European and International Registry of Antiepileptic Drugs in Pregnancy, NAAPR - North American AED Pregnancy Registry) or by services offering consultation about drug safety (OTIS - Organisation of Teratology Information Specialists, and ENTIS - European Network of Teratology Information Services). Criterion for inclusion enrolment in prospective studies is AED use at time of conception or during first trimester, however before ultra-sonographic examination of normal development of child. Registry data can be used for monitoring that can identify specific risk.

Retrospective studies using data from registry are utilized for case-control studies, where drug use among mothers whose babies express a specific malformation is compared with that of mothers whose babies do not. This method has a high sensitivity, but is more prone to bias. It is difficult to identify all concomitant factors those may affect development of birth defect. There is the evidence of partial memory and bias in the way women recall the drugs they took during pregnancy. Women suffering from chronic disease tend to recall their treatment better than women who took an over-the-counter drug.

Prospective, controlled, epidemiological studies of the pregnancy outcomes of women who were treated by a particular drug during pregnancy are another possibility how is possible to evaluate risk. Even this type of research is not ideal, because the limited size of the studies means they do not have the statistical power to detect increased risk of rare malformations. Moreover indications for treatment and concurrent exposures are not standardized.

The information received by drug manufactures is often a mix of prospective and retrospective case reports. The quality of the information about exposure is usually poor, reports of adverse fetal outcomes are more frequent as uneventful ones.

The group of exposed pregnancies is usually compared to the control group performed by the pregnancies with normal outcome. The second possibility is the use of baseline risk of major malformation in population, that is 2.75% in USA (according to CDC) and 2-3% in Europe (according to EUROCAT). Finally, the group of pregnant women exposed to drugs with minimal or no risk, represents the third type of control group.

To monitor malformations, the statistical approach is used, that compares number of observed infants with specific type the inborn defect born during a specific time period with the number of infants expected to be born during that period. However, difference between the observed and the expected number can have many explanations: real change caused by introduction of a teratogenic agents, changes in detection and registration, fluctuation of specific malformation in time, wrong estimation of expected number of malformation etc. Therefore only limited number of conditions and set of standard malformations may be monitored.

Teratological approach is focused on occurrence of specific malformations or their combinations (syndromes) those are present in exposed population or in all pregnant women. If malformation is very specific as phocomelia in thalidomide exposure, no baseline level of birth defects is needed (Källén & Hay, 1991).

Published case-reports have only limited significance, because causality between malformation and exposure can be only accidental. We need large exposed group for risk evaluation. The international cooperation is useful, because it allows collect many cases in relatively short time. For example, if the risk of major malformations in a given population is 3 percent, then at least 220 pregnancies with specific exposure and similar number of control pregnancies will be required to show that is increased risk by factor of 2.5, with a power of 80 percent (Koren, 2001). More than one thousand of cases are needed for risk assessment lower than 1%.

It is generally accepted that assessing the risk of a substance to humans we need today:

Case reports describing repeatedly a typical malformation pattern (syndrome).

At least two large and well controlled epidemiological studies.

Results of testing in laboratory mammals following the Good Laboratory Practice and WHO criteria, that serves only for confirming biological plausibility (Jelinek, 2005).

FDA classification dividing drugs in 5 groups according to its impact to fetus is greatly simplifying. Merlob and Stahl (2002) concluded that this classification of drugs for teratogenic risk must be considered as anachronistic and misleading way of approach and counselling, because the causation of inborn defects is multi-factorial and could not be limited to the qualification (if known) of a single factor, only. It is necessary perform the separate analysis of any individual case collecting as much relevant data as possible.

3.3 Genetic background as a factor for inborn defect

Drug metabolising enzymes and the genetic variants they carry are one of the factors that might be responsible for the efficacy and side effect of AED treatment in individual patients. They also modulate development and induce embryotoxicity. The speed and differences in metabolic inactivation may increase plasma level of AEDs up to embryotoxic threshold. Polymorphy in genes for enzymes involved in metabolic pathways for detoxification is suspected cause for development of birth defect in certain cases. For example, phenytoin toxicity is dependent on epoxide hydrolase activity, i.e. arena oxidase (Strickler et al., 1985) or on CYP2C19 specific cytochrome P-450 isoenzyme deficiency (Maier & Mayer, 1987). Valproate toxicity is increased in ornithine trans-carbamylase deficiency. Drug competition or the induction of microsomal enzymes may change AED plasma level and increase the risk. Higher risk for neural-tube defects such spina bifida and anencephaly after valproate or carbamazepine exposure has been assigned to the deficiency in folate dependent homocystein metabolism. Polymorphism of MTHFR (methylenetetrahydrofolate reductase) is associated with higher risk for anticonvulsant syndrome. Mothers who are homozygous for MTHRF genotype 677T were found to have three to four higher risk compared with those, that were homozygous for allele 677C. Other genes, for example MTR 2756, are involved in susceptibility to embryotoxic impairment (Steinlein, 2010). In present, we may conclude those woman having a child with vaproate fetal syndrome is in higher risk of malformed child for the next pregnancy (Tripp, 1981; Malm et al., 2002). In future, the genetic profile will be a goal for the optimal treatment of epileptic patients.

3.4 Ischemia and re-perfusion injury

The role of ischemia and re-perfusion producing tissue damage linked for example to neural tube defect has to become more evident in the past years. During an ischemic event, intracellular xantin dehydrogenase is converted to xantin oxidase. When the ischemia resolves,

xantin oxidase metabolised purines in uric acid. By-products of this reaction are super-oxide radicals. They produce tissue damage directly or indirectly. As convulsions results in anoxia, higher rate of malformation was demonstrated in epileptic women without treatment and without seizure control in comparison with healthy population. Combination anoxia with teratogenic potential of drug even increases risk (Verrotti et al., 2006).

4. Embryotoxicity of antiepileptic drugs (AEDs)

4.1 First generation of antiepileptic drugs

4.1.1 Phenytoin

Phenytoin is the most widely used hydatoin derivate with antiepileptic effect. The teratogenic potential of hydantoin and its derivatives is known since 1968 (Meadow). The anomalies observed were described as "fetal hydantoin syndrome" (see above). In the case of phenytoin, it appears that fetal susceptibility correlates with the fetal level of the microsomal detoxifying enzyme epoxide hydrolase (Buehler et al., 1994). Developmental toxicity is probably caused by concentration-dependent bradycardia and hypoxia related damage of embryonic tissue (Azarbayjani & Danielson, 1998; Danielsson et al., 2000) resulting in alteration of gene expression minimally, if not everywhere, in craniofacial region (Gelineau-van Waes et al., 1999). In comparison with other AEDs, phenytoin produced higher incidence of fetal defects (20,9%) in animal study (Sullivan & McElhatton, 1977), however risk occurring in epidemiological studies was lower.

The risk of phenytoin exposure during pregnancy has been well documented. It has been estimated to be two to three folds higher that than of mothers without treatment as has been confirmed in several studies (Kluger & Meador, 2008; Schaefer et al., 2001). The prospective observation study made by 25 epilepsy centres in USA and UK from 1999 to 2004 determine risk of adverse outcomes for phenyltoin on 10.7% (including fetal death), and major malformation on 7.1% (Meador et al., 2006). Phenytoin mono-therapy increases the risk for cleft palate, but it has not been associated with microcephaly (Almgren et al., 2009).

4.1.2 Barbiturates

Barbiturates used for epilepsy treatment are phenobarbital, methylphenobarbital, and primidone, the pro-drug of phenobarbital to which is largely metabolized. In higher doses (50 mg/kg/day and more) primidone was teratogenic in mice increasing the incidence of cleft palate, other defects as exencephaly, fused ribs, and undescended testes were observed less frequently. The incidence of major malformation was dose dependent in primidone as well as phenobarbital (McElhatton & Sullivan, 1975; McElhaton et al., 1976; Fritz et al., 1976). After exposure to primidone, the malformation typical for AEDs have been described in many case reports and studies (Rating et al., 1982; Battino et al., 1998; Akšamija et al., 2009). Increased risk for major malformations associated with primidone exposure was demonstrated in large prospective study (Jones et al., 1992). North American Registry demonstrated a 6.5% risk after phenobarbital mono-therapy in comparison with 1.6% for control population (Kluger & Meador, 2008).

4.1.3 Ethosuximide

Ethosuximide is recommended drug for petit mal treatment, only. In animal studies the risk of major malformation was approximately as high as in primidone (Sullivan & McElhatton, 1977). There are only a few report of the ethosuximide therapy during pregnancy. Study

reporting on pregnancy outcome in ten women described two major malformation cleft lip in mothers treated ethosuximide in combination with primidone or phenobarbital (Kuhnz et al., 1984).

4.2 Second generation of antiepileptic drugs

4.2.1 Valproic acid (VPA)

Valproic acid is widely used for treatment of a broad spectrum of epilepsy types, migraine as well as bipolar disorder. In utero exposure results in higher incidence of major and minor malformations. Proposed mechanism of action is related to the changes in methylation of histones (Tung & Winn, 2010). Epigenetic modification of them with hyperacetylation is accompanied with induction of apoptosis (Menegola et al., 2005; Di Renzo at al., 2010). Malformations occurred not only after valproic acid but also after valproate conjugates with anticonvulsant activity in animal model with different intensity (Spiegelstein et al., 2003; Okada et al., 2009).

Fetal valproate syndrome was described in 1968 (Meadow, 1968). Drug teratogenicity was documented in many studies (Arpino at al., 2000; Bromfield et al., 2008). Dansky and Finnel (1991) summarized the knowledge on the reproductive outcome of patients treated with antiepileptic drugs during pregnancy that covered over 30 years in their meta-analysis. They demonstrated twofold to threefold increased risk of congenital malformation in epileptic women as compared with the general population. Similar finding, i.e. 2.5 times higher risk of having baby with malformation after valproic acid mono-therapy, was published in another large meta-analysis (Koren at al., 2006). Prospective observation study (Meador et al., 2006) that enrolled mother-child pairs from USA and UK demonstrated 17.4% malformations and 20.3% of serious adverse outcomes, that included fetal death in addition to malformations. Chong and Bazil (2010) published meta-analysis including 59 studies and more than 65 000 pregnancies. They demonstrated high rate (10.73%) of malformations after VPA mono-therapy and after poly-therapy even 16.78%. Meador et al. (2009) published similar findings, i.e. 10.73% (95% CI: 8.16-13.29). The most frequent malformations were hernia, ear/neck/face malformations, cleft lip, and spina bifida. Nowadays, the studies have been focused on the correlation between dose and teratogenic effect. Higher doses than 1400 mg/day have been proved to be more teratogenic (Vajda & Eadie, 2005). The evidence for higher risk is lacking for doses that are lower than 600mg per day, and risk gradually increases (Tomson & Battino, 2009; Diav-Citrin et al., 2008) and becomes more prominent at doses above 1000mg (Koren et al., 2006). EUROCAT study published in 2010 reveals significantly higher risk for those malformations after valproic acid mono-therapy. The adjusted odds ratios were as follows: spina bifida 12.7, atrial septal defect 2.5, cleft palate 5.2, hypospadia 4.8, polydactyly 2.2., craniosynostosis 6.8 (Jentink et al., 2010).

4.2.2 Carbamazepine (CBZ)

Carbamazepine is efficacious in treatment of a variety of CNS disorders, as well as epileptic seizures. CBZ is usually well tolerated and therefore is also used in pregnant women. Carbamazepine in dose that is corresponding to the therapeutic range in humans was not associated with negative pregnancy outcome in mice. It had no effect on fertility. Higher number of resorptions or higher risk of malformation was not detected (Christensen et al., 2004). Similar findings were found in study after the exposure to higher doses (1.000, 1.500 and 2.000 mg/kg). In those doses no specific pattern of malformation and no correlation between detected anomalies and dose were found (Finnel et al., 1986). The finding was supported also

by following studies (Wray et al., 1982; Fritz et al., 1976). On the other hand, Sullivan and McElhatton (1977) demonstrated higher frequency of malformation in exposed mice (4.7% compared with 1.3% in controls). Afshar end co-workers (2010) described specific eye malformations in mice after carbamazepine exposure at clinically comparable doses.
Exposure to the carbamazepine was found to increase malformation rate in several studies (Diav-Citrin et al., 2001). Ornoy and Cohen (1996) described typical carbamazepine syndrome characterized by facial dysmorphic features and mild mental retardation, that did not seem to be related to presence of maternal convulsions but more to the hereditary factors. Rosa (1991) found higher (1%) risk for spina bifida in women used carbamazepine, that is ten times higher than in unexposed population. Many case reports describing occurrence of spina bifida or eye malformation may support the opinion (Akšamija et al., 2007; Källén, 1994; Sutcliffe et al., 1998). Meta-analysis using 16 prospective studies compared the risk of major malformation for CBZ mono-therapy and CBZ with other antiepileptic drugs, both in comparison to matched control pregnancies and to untreated epileptic pregnancies. It included 1255 CBZ exposed pregnancies. Study proved 2.89 fold-increased risks of major congenital anomalies in children treated with CBZ as compared with children of healthy control. Rate of malformations was 2.34% in control population. The rate of major malformations was further increased in cases of women treated with combination of CBZ and other antiepileptic drugs, that was about 2-fold higher. Anomalies that risk was increased were neural tube defects, however cleft lip and cardiac defects were found, too. Decrease in gestational age at delivery was also revealed (Matalon et al., 2002). Case-control study published by Jentink et al. (2010) using literature review and EUROCAT database demonstrated higher risk for spina bifida, only (odds ratio 2.6; 95% confidence interval 1.2 to 5.3). Difference was in classification of major malformations and exclusion of cases as compared with meta-analysis mentioned above.

4.2.3 Oxcarbazepine (OCZ)

Oxcarbazepine is similar to carbamazepine in chemical structure, but it is metabolized in different metabolic pathway. A monohydroxy-derivative (MHD) is responsible for its clinical efficacy. Premarketing studies showed an increase in congenital malformations in the offspring of rats treated with oxcarbazepine at doses similar to those used in humans on a surface area basis. The abnormalities in the offspring included craniofacial, cardiovascular, and skeletal abnormalities. In rabbits, an increase in fetal mortality was noted at similar doses (Micromedex® 2.0, 2011). Higher frequency of malformation was found also in mice (Bennet at al., 1996).
In one report, mother using oxcarbazepine during all pregnancy gave birth to normal healthy girl and second pregnancy on the same therapy resulted also in healthy infant (Eisenschenk, 2006). Data from Argentina register revealed 35 pregnancies exposed to oxcarbazepine in mono-therapy resulted in the delivery of healthy infants. Of the 20 pregnancies exposed to oxcarbamazepine in combination with other AEDs only one malformed child was reported: a cardiac malformation in a newborn exposed to phenobarbital and oxcarbamazepine (Meischenguiser et al., 2004). An analysis of 248 published pregnancies involving maternal exposure of oxcarbamazepine in mono-therapy and 61 in poly-therapy did not find an increased incidence of malformations in exposed infants. Malformation rate was 2.4%, the same as malformation rate reported in the general population. In poly-therapy the risk was 6.6% (Montouris, 2005). The author notes that the available data are not sufficiently large to draw definitive conclusions.

4.2.4 Benzodiazepines

Benzodiazepines are widely used as tranquilisers, hypnotics as well as AEDs. For epilepsy treatment are used currently diazepam, clonazepam, clobazam, and sultiam. Diazepam cross easily placenta and it is present in blood in three time higher level than in mother. Case control studies indicate higher risk of major malformation, especially oral cleft, however meta-analysis demonstrated no association between benzodiazepine exposure and major malformations. Short exposure is possible, however long term treatment is associated with withdrawal symptoms (Robert-Gnansia & Schaefer, 2007). Shepard and Lamire (2004) refer that clonazepam in animal studies demonstrated no fetal effect. There are only few epidemiological studies. Ornoy et al. (1998) found no increase of malformation in 69 women. No relevant information was published about clobazam and sultiam.

4.3 Third generation of antiepileptic drugs

4.3.1 Lamotrigine (LTG)

The manufacturer (GlaxoSmithKline, Research Triangle Park, NC, USA) reported teratology testing in mice, rats, and rabbits at oral doses. There was no increase in congenital malformations in any of these species. Top doses were 1.3 (mice), 0.5 (rats), and 1.1 (rabbits) times the maintenance dose recommended for humans on a mg/m^2 basis. Maternal and fetal toxicity (delayed ossification and decreased weight) were seen at the high doses in the rodent studies (Micromedex® 2.0, 2011). Lamotrigine in reproductive toxicity study given intravenously in the mouse did not produce malformation except for highest doses that were toxic for mother (50 - 300 mg/kg/day). Resorption and reduction of fetal weight were seen both being dose dependent. Skeletal malformation found in these studies were assigned to the maternal toxicity, however neural tube defects (anencephaly), malformation related to the cranial crest cells, and caudal dysgenesis were probably induced by lamotrigine (Padmanabhan et al., 2003). Prenatal exposure to LTG induced altered brain structure in a dose-dependent manner at maternal plasma concentrations within the clinically occurring range (Manent et al., 2008).

The manufacturer set up a registry to collect information on pregnant women exposed to lamotrigine. A report from this registry extending till 31 March 2009 included 1439 pregnancy outcomes after first trimester exposure to lamotrigine mono-therapy. There were 35 pregnancies with congenital malformations, for a rate of 2.4% (95% CI 1.7- 3.4%). Among the defects reported were cleft lip and palate, clubfoot, hydronephrosis with megaureter, anencephaly, anal atresia, cardiac defects, limb defects, and an esophageal malformation. No relationship of malformation rate to lamotrigine dose was evident, and an evaluation of exposure level and malformation did not suggest a dose-response relationship. The Advisory Committee noted that the registry did not replicate a signal for orofacial clefts such as that reported from the AED Pregnancy Registry (discussed below) and that with more than 1000 pregnancies enrolled, the confidence was sufficiently narrow to exclude an appreciable increase in malformation risk (Cunnington & Messenheimer, 2007). Australian Pregnancy Register of Antiepileptic Drugs included 243 pregnancies exposed to lamotrigine. The analysis did not show statistically significant difference between the risk of fetal malformation and exposure to lamotrigine mono-therapy (Vajda et al., 2010). UK Epilepsy and Pregnancy Register enrolled 647 pregnancies exposed to lamotrigine. Malformation rate was 3.2%. When adjusted for age, parity, family history of malformations, periconceptional folic acid exposure and sex of infant odds ratio was 1.71 (95%CI 0.88 - 3.32). This study revealed positive dose response with malformation rate of 5,4 (95% CI 3.3-8.7%) for total

daily doses more than 200mg. Results of five registries and one large prospective study were published up to 2007. The prevalence of major malformations in North American AED Pregnancy Registry (NAAPR) was 2.7%, however higher prevalence of cleft lip and palate than that observed in control group (Holmes et al., 2006). In contrast the EUROCAT did not find an increased risk of orofacial clefts for mono-therapy, but for poly-therapy it was increased (OR: 1.43; 95%CI: 1.03-1.93). However, observed rate was low and absolute risk is minimal (Shor et al., 2007; Meador & Penovich, 2008). Later, Miskov et al. (2009) did not find an increase of birth defect in their small prospective study (23 pregnancies).

4.3.2 Levetiracetam

In preclinical studies presented by the sponsor, levetiracetam did not produce fertility impairment in male and female rats given up to 1800 mg/kg/d, which is six times the recommended human dose on a surface area basis. Pregnant rats given levetiracetam at doses similar to the human dose were born fetuses with an increased incidence of intrauterine growth retardation and minor skeletal abnormalities. No maternal toxicity was noted at this dose (Micromedex® 2.0, 2011). Saillenfait et al. (2007) described higher incidence of resorptions in rats at dose 500mg/kg/day and dose related decrease in fetal weight. They demonstrated malformations as super-numerable ribs, absent tail, anal atresia, cardiovascular defects, and impairment of ossification at dose 250mg/kg /day and higher, that was six fold higher than therapeutic dose for human and that was toxic for mother. Study in a mouse model did not reveal higher incidence of major malformations after levetiracetam treatment up to dose 2000mg/kg/day. There was higher frequency of resorptions at high doses (Isoherranen et al., 2003).

Case reports on 3 pregnancies exposed to levetiracetam (Long, 2003) showed no adverse outcome. French et al. (2001) reported 23 women became pregnant during clinical trials. Eight pregnancies results in nine healthy offspring. Two babies had malformations, but both mothers were exposed also to other AEDs. Seven pregnancies resulted in spontaneous abortion and three women had voluntary termination. Prospective study (Johannessen et al., 2005) described 7 children (2 pregnancies with mono-therapy, 5 pregnancies with poly-therapy) without any malformation. EURAP in Netherlands (ten Berg et al., 2005) reported 11 pregnancies exposed to levetiracetam: one woman had the spontaneous abortion, and one pregnancy was elective terminated from social reasons. Nine live born children were without any malformations. The UK Epilepsy and Pregnancy Register (Hunt et al., 2006) identified 39 pregnancies exposed to levetiracetam mono-therapy and 78 in combination with at least one other AED. There were no congenital malformations in group with mono-therapy. Longo et al. (2009) summarized accessible data revealing 147 patients. Of these patients 2% experienced a major malformation, 4.8% a minor anomaly. All of them were receiving poly-therapy.

4.3.3 Topiramate

As reported by the manufacturer (Janssen-Cilag), topiramate is teratogenic in mice, rats and rabbits. Similar findings revealed a study describing an adverse effect of topiramate (100mg/kg/day) on developing embryos in rats increasing number of resorptions (Khouri, 2005).

Gentile (2009) reported on one pregnancy with normal outcome. Ornoy et al. (2008) reported on the outcome of 52 pregnancies where the mothers used topiramate at least during the

first trimester of pregnancy. The rate of spontaneous abortions (11.3%) was significantly higher in comparison to controls (2,8%). Although rate of major malformation was higher (9.8%), two cases were genetic in origin. One case from non-genetic was a baby whose mother used also valproic acid and clonazepam. Another case report (Vila Cerén et al., 2005) described the case of a neonate whose mother treated with topiramate during pregnancy at doses of 300 mg per day was born malformed child with oligodactyly and syndactyly. Prospective study (Hunt et al., 2008) following 203 pregnancies exposed to topiramate resulted in 178 live birth babies, 16 had major malformations. Three occurred in 70 pregnancies in which the drug was in mono-therapy. Two other newborns were exposed to the drug as poly-therapy. Overall, the rate for oral clefts was 11 times the background rate. Hernandez-Diaz and co-workers (2010) reported 3.8% major malformations among 289 women taking the drug in the first trimester that were enrolled by the North American AED Pregnancy Register. Risk ratio for major malformation was 2.8. They found also higher risk for cleft lip and lower birth weight. FDA now alerts on higher risk of cleft lip and palate.

4.3.4 Other new antiepileptic drugs

Risk assessment for following new antiepileptic drugs is not possible due to lack of experience. Information on few case reports was hardly even published. Only preclinical studies on animals performed by producer have been accessible for some of them.

Gabapentin: Small ENTIS study identified five normal infants after exposure to gabapentin (De Santis et al., 2004).

Vigabatrin (VGB): The animal experiments demonstrated significant teratogenic effect when drug was administered to mice during organogenesis (Padmanabhan et al., 2010). Lower doses were associated with disturbance of motor-cognitive behaviour and lower weight of pups, however higher caused abortions (Lombardo et al., 2005). Since vigabatrin exposure has been associated with retina damage, two small studies examined children exposed in utero to drug demonstrated no clear ophthalmic abnormalities, However, sample was to small to be able to confirm safety for fetus (Sorri et al., 2005; Lawthom et al., 2009). According to the FDA recommendation, the treatment may be only short-term (Chong & Bazil, 2010).

Zonisamid teratogenicity was evaluated in six pregnant women. Five patients, two on mono-therapy and three on poly-therapy delivered healthy children. Malformed child with anencephaly was reported after zonisamid in combination with phenytoin. Together with above mentioned, there were 26 pregnancies reported, only. Two of them had malformations (7.7%) The other child was born with an atrial septal defect to the woman treated poly-therapy that included phenytoin and valproate (Ohtahara & Yamatogi, 2007).

Pregabalin is a GABA analogue that inhibits with high affinity and selectivity the voltage dependent calcium channels. Animal study revealed increasing incidence of a specific tumour type (Selak, 2001)

No information about **rufinamide, lacosamide, stripentol** and **tiagabin** embryotoxicity has been published, yet.

5. Trends in epilepsy treatment and our experience

Study characterizing trends in prescribing antiepileptic drugs in Czech Republic in comparison with European countries and Australia compared used drug spectra from 1987 to 2000. Utilization of barbiturates and succimide derivatives was decreasing. Hydantoins,

that utilization in Australia was steady, were in Europe decreasing, too. The valproic acid consumption was increasing as well as utilisation of third generation AEDs (Kořístková & Grundmann, 2005). The trends in usage corresponds to recommendation for general population, however valproic acid is the most teratogenic AEDs. Studies focused on girls or women in childbearing age demonstrated also changes in prescribed drugs and increase of lamotrigine prescribing in female (Ackers et al., 2009; Vajda et al., 2007). Proportion of women that were exposed to topiramate and levetiracetam was increasing, too (Vajda et al., 2010). We recorded the same trends in treatment of epilepsy during pregnancy in our ten years experience of Czech Teratology Information Service (CZTIS) with inquiries about epilepsy treatment during pregnancy (Maňáková et al., 2006).. Lamotrigine was used in almost 30% of pregnant women, carbamazepine in 23.4%, and valproic acid in 21.3%, that correspond with above mentioned studies. New drugs as levetiracetam and topiramate were used for treatment of pregnant women in last years, too.

6. Conclusions

The management of the pregnant women suffering from epilepsy requires close cooperation between the neurologist and obstetrician. Women with epilepsy have a low complication rate except of that related to AEDs exposure (Borthen et al., 2009). All of them in childbearing age should be informed about the rates of teratogenicity of AEDs, possibility of increased seizure frequency during pregnancy, and the risks of the pregnancy and labour. If almost half of pregnancies are not planned, the optimalization of treatment and consultation should be discussed with girls on beginning of their childbearing age. Since unplanned pregnancy is very often diagnosed after the most sensitive period of embryo development, when malformations are already developed, it makes no sense to change treatment. Exposure to antiepileptic drugs is not an indication for therapeutic abortion, even if they are teratogenic. Counselling is very important, because it helps to gain a realistic perspective of risk.

The frequency of seizures is essentially the same as before pregnancy, however tonic-clonic convulsions should be avoided, because they are risky for mother and fetus. Seizures can cause trauma leading to ruptured fetal membranes or abruptio placentae (Pennell, 2003). Fortunately, with close monitoring and proper management, more than 90 percent of pregnancies in women with epilepsy will be uncomplicated.

6.1 Optimization of treatment

Optimization of treatment should be made before pregnancy. Diagnosis of epilepsy should be confirmed and indication for treatment with AEDs re-assessed. The possibility of AED gradual withdrawal should be considered in appropriate clinical setting prior to conception. The AED treatment should be optimized also prior to conception. Selection should be made the most appropriate for patient. Changing during pregnancy is rarely justified, risk probably overweight potential gain (Tomson & Hiilesmaa, 2007). To ascertain whether epilepsy remains in remission enough time before conception is required.

Drugs of choice during pregnancy are considered lamotrigine and carbamazepine. Drugs should be given in mono-therapy with the lowest effective dose. Poly-therapy should be avoided because of proved increase of risk. Effective dose and optimal concentration of the drug before pregnancy should be documented. Monitoring of drug plasma concentration have to be more frequent, minimally once during trimester. Good compliance with

treatment is essential. Lamotrigine, levetiracetam, and topiramate plasma levels are changing (decreasing) during pregnancy, so adjustment of therapeutic dose during pregnancy is needed. Valproic acid should be avoided, if it is possible. However, adequate seizure control is the primary goal. If it is only drug giving satisfactory control of seizures, valproic acid should be used of the lowest possible day dose (optimum under 600mg/day) divided into three doses to minimize negative influence to fetus. Pregnancy should be considered of high risk and must have appropriate follow up (Ornoy, 2009).
The second level (expert) ultra-sonography may justified normal development or detect most neural tube defects and about two third of other major malformations.

6.2 Folic acid supplementation and its profit

Low serum folic acid level in epileptic mothers is associated with an increased risk of congenital malformations in their offspring (Ogava et al., 1991). Population studies demonstrate benefit from fortification of cereal products by folic acid (De Walls et al., 2007) or supplementation before planed pregnancy. Daily consumption of supplements containing 400 micrograms of folic acid in the periconception period may reduce the risk of neural tube defects in general population by as much as 70% (Morin et al., 2002). If risk of malformation is higher in women with low plasma level of folic acid, periconceptional supplementation with minimally 0.4 mg folic acid per day in AEDs exposed population is considered prophylactic. The measurement that determines intra-erythrocythal level of folic acid may help with definition of optimal dose. Results suggest, that 5 mg/day folic acid as preconception supplementation in women with epilepsy is effective to balance the impact of AEDs on folate metabolism (Bauer et al., 2010). Folate profylaxis is recommended to all women taking antiepileptic drugs. Treatment with dose up to 5mg/day should start before planned pregnancy and continued minimally to the end of first trimester.

6.3 Vitamin K supplementation

Management strategies include also the prenatal use vitamin K. Vitamin K 10 mg per day orally should be administered in the last 4 weeks of pregnancy for women taking hepatic enzyme-inducing AEDs (phenytoin, phenobarbital, primidone, carbamazepine, topiramate, and oxcarbazepine). The newborn should receive vitamin K 1 mg intravenously or intramuscularly regardless of maternal AED exposure.

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8. References

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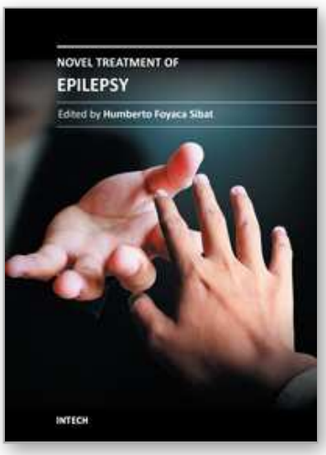

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Epilepsy continues to be a major health problem throughout the planet, affecting millions of people, mainly in developing countries where parasitic zoonoses are more common and cysticercosis, as a leading cause, is endemic. There is epidemiological evidence for an increasing prevalence of epilepsy throughout the world, and evidence of increasing morbidity and mortality in many countries as a consequence of higher incidence of infectious diseases, head injury and stroke. We decided to edit this book because we identified another way to approach this problem, covering aspects of the treatment of epilepsy based on the most recent technological results â€œin vitroâ€ from developed countries, and the basic treatment of epilepsy at the primary care level in rural areas of South Africa. Therefore, apart from the classic issues that cannot be missing in any book about epilepsy, we introduced novel aspects related with epilepsy and neurocysticercosis, as a leading cause of epilepsy in developing countries. Many experts from the field of epilepsy worked hard on this publication to provide valuable updated information about the treatment of epilepsy and other related problems.

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