Available online on 15.08.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Review Article

Antiepileptics Use in Pregnant Women

P. Arshida, K. Sreejith*, M.T. Nadiya Banu, K. ShabanaThehsin, S. Sulaikha, K. P. Midhun

Department of Pharmacy Practice, College of Pharmaceutical Sciences, Govt. Medical College, Kozhikode, Kerala, 673008, India

ABSTRACT

Epilepsy is a common neurological condition in women of reproductive age. Being careful in antiepileptic treatment during pregnancy can avoid birth defects in off springs. Valproic acid, Carbamazepine, phenytoin, phenobarbital, lamotrigine, oxcarbazepine is some of the antiepileptics used even during pregnancy.

Keywords: antiepileptics, congenital malformation, teratogenicity

Article Info: Received 16 June 2019; Review Completed 23 July 2019; Accepted 29 July 2019; Available online 15 August 2019

Cite this article as:

Arshida P, Sreejith K, Nadiya Banu MT, Thehsin KS, Sulaikha S, Midhun KP, Antiepileptics Use in Pregnant Women, Journal of Drug Delivery and Therapeutics. 2019; 9(4-s):705-708 **http://dx.doi.org/10.22270/jddt.v9i4-s.3287**

***Address for Correspondence:**

K. Sreejith, Asst. professor, Department of pharmacy practice, College of pharmaceutical sciences, Govt. Medical College, Kozhikode, Kerala - 673008, INDIA.

Introduction

Epilepsy is a chronic disease experienced by millions and distributed in all age groups. Unpredictable seizures which cause other health problems are the characteristic of Epilepsy. These spectrum conditions have a wide range of seizure types. Seizure control is different for different patients. On earth between 2.7 and 17.6 per 1000 people are suffering with active seizures. Prevalence of epilepsy in women of reproductive ageisbetween 0.3% and 0.7%, from record based studies [1].

If women take precautions, most women with epilepsy can give birth to normalbabies.There are increased risks. Higher seizure frequency was seen in 15% to 30% of women especially in first or third trimester [2]. The seizure frequency is unpredictable based on type of seizures. Even in case of Catamenial epilepsy. That is seizures with menstrual cycle. Hormoneact changes, water and sodium retention, stress and decreasing levels of antiepileptic drug are underlying causes of higher seizure frequency. Uncontrolled seizures may harmful for mother and foetus. Also it is obvious that antiepileptic drugs are a class might cause major congenitalmalformations and adverse effects of cognitive development after prenatal exposure [3].

Prior to Pregnancy

An epileptic patient who taking an AED have a risk of hormonal contraceptive failure.The reason behind it isinducement of hepatic microsomal enzymes and followed by decreasing the production of estradiol[4]. Children born to women having epilepsy possess a small risk for the inheritance of epilepsy, but the risk is increased for women whose epilepsy is genetically originated [5, 6]. Women who are seizure free for nine months prior to pregnancy have a very high chance of remaining seizure free during pregnancy. Several complications are there in pregnancy of an epileptic patient. The first one is the fact of potential teratogenicity of AED. The next one is women taking AEDs have a greater risk of miscarriage. Chance of giving birth to a child having congenital malformation is 4-8%. Because these agents can be transferred to the foetus via placenta. Also higher drug clearance during pregnancy can lower circulating AED concentration. It may results in loss of seizure control. Earlier studies suggest that folic acid consumptionbefore pregnancy can possibly decrease the baby's risk of birth defects [7].

Risk of Seizure Medication during Pregnancy

Risk for the foetus from AED taken during pregnancy is primarily that of congenital malformation or birth defects. Risk may increase with increasing no of AEDs and also with higher dose. The most common malformations are cleft lip, cleft palate which can be corrected surgically, cardiac and uro-genital defects [8]. Older generation antiepileptics have been linked to specific birth defect, such as spina bifida. Harmful effects not only manifest as structural defects but many include growth restrictions and effects on cognitive development and behaviour [9, 10].

Antiepileptic Drug Which Causes Harm

Data collected from North American AED Pregnancy Registry suggests that risk of major malformations for valproate was 9.3%, for phenobarbital 5.5%, for topiramate 4.2%, for carbamazepine 3%, for phenytoin 2.9%, for levetiracetam 2.4%, and for lamotrigine 2% [11].

The data pointing thatlevetiracetam, topiramate and lamotrigine were extensively used AED monotherapies during the first trimester. Nintytwo percentage of AEDs were used for treating epilepsy, six percentage for mood disorders, and one percentage for migraine.

The rate of major malformationriskwas raised with increasing valproate dose. Pregnancies with malformations had a 1000mg median average daily dose during the first trimester .And median average daily dose of pregnancies without malformations was 750mg per day. The similar dose trend didn't see in any other AEDs.Both malformed and non-malformed infants exposed to topiramate, phenobarbital, or lamotrigine had same median average daily dose. Also AED groups possessing lower risks of major malformations were had a burden of higher seizure frequency [11].

1. *Valproate*

Valproic acid shows an established teratogenicity that is a dose dependent risk for malformations [12, 13, 14]. A dose of 1000 mgwas lead to increased risk [15]. This is generally approved, when a woman exposed to valproic acid in first trimesterdefinitely leads to neural tube defects with a risk of 1 per 1000 or 10 per 1000 births. Recent studies also suggests an association with oral clefts, limb defects, hypospadias and cardiac septal defects.Effects of exposure to valproic acid in uterus also leads to autism and neurodevelopmental delay. Even with these established confirmation for foetal harm,t he reason behind advising valproic acid in pregnant women is its effectiveness in the treatment of idiopathic generalized epilepsy and, especially, juvenile myoclonic epilepsy [16, 17, 18].

2. *Carbamazepine*

By analysing European prospective studies, the relative risk of carbamazepine monotherapy for having major congenital malformations was found to be 4.9.While studying the frequency of major congenital malformations the most commonly reported were cleft palate, neural tube defects cardiovascular and urinary tract anomalies. Microcephaly and growth retardation were mostly reported with carbamazepine monotherapy. Polytherapy combinations show highest risk for major congenital malformations. Despite of these data the large UK Pregnancy Register study showed no increased risk for congenital malformations for carbamazepine. Carbamazepine was in association with the least risk of major congenital malformationsin all conditions, when exposed as a monotherapy. Analysis of data from the EURAP epilepsy and pregnancy registry suggests that the lowest rate of malformation was with a dose less than 400mg per day [17, 18].

3. *Phenobarbital*

Phenobarbital has been associated with oral clefts. Although less common, cardiovascular defects, and urogenital defects have also been reported .While going through prospective data from the North American AED Pregnancy Registry, out of 77 women who treated with Phenobarbital monotherapy, the number of confirmed major congenital malformations was five. A cleftpalate, cleft lip and four heart defects. The report of another two studies point out the increased incidence ofcardiac malformations was correlated with in-utero exposure of phenobarbital. Risk of malformation is higher with phenobarbital at all doses [19, 20].

4. *Phenytoin*

Loughman et al and Hanson et al were described Foetal hydantoin syndrome. These infants displayed distal digital hypoplasia, mental growth retardation, facial dysmorphism and intrauterine growth retardation.Among clinicians and scientists the teratogenicity of phenytoin has been well recognized.With respect to Australian Pregnancy Registry reports major congenital malformation rate for phenytoin is 4.7%. For phenytoin comparatively a poor number of outcomes have reported in other studies. Those studies show the range ofmajor congenital malformation rate lying between 3.4 and 10.7%. One of the study revealed a greater risk for cleft palate with [21, 22].

5. *Lamotrigine*

The North American AED Pregnancy Registry reports exposure to lamotrigine monotherapy in first trimester showing greater risk for cleft palate or cleft lip. Major congenital malformation rate was found to be 2.3%. The major congenital malformation rate of lamotrigine monotherapy according to UK pregnancy register was 3.2%. In case of Lamotrigine also a positive dose response was seen in major congenital malformation rate [22]. The researcherscurrently clarified their results to establish that the greater risk showed above 400 mg/day in first trimester. Controversially, LTG dose and major congenital malformation rate did not demonstrated any relation between them among 802 exposures reported in the International Lamotrigine Pregnancy Registry. Only 1.0% of lamotrigine pregnancies committed in serious adverse outcomes which includes foetal death and/or major congenital malformations.This supportsthe low risk of LTG use and which also supported by The UK studywhich compared with untreated women having epilepsy [23].

6. *Oxcarbazepine*

Animal studies have proved increased incidences of foetal structural abnormalities and other manifestations of developmental toxicity (embryo lethality, growth retardation), foetal malformations (craniofacial, cardiovascular, and skeletal), embryofoetal death, decreased foetal body weight, and maternal toxicity. There is no evidence to suggest that teratogenicity in these studies was preceded by maternal toxicity. Oxcarbazepine is structurally related to carbamazepine, which is considered to be a human teratogen. Due to this fact and the results of animal studies, it is likely that oxcarbazepine is a human teratogen.

New-borns having in utero exposure to oxcarbazepine was not given any evidence for an increased risk for malformations. However, there is a very small number of pregnancies containingin utero exposure to oxcarbazepine. There forit is insufficient to draw definitive findings. It is necessary to gather additional information from large-scale pregnancy registries to establish the safety profile of oxcarbazepine both as monotherapy and adjunctive therapy during pregnancy [24].

7. *Levetiracetam*

Several recent studies in a sufficient number of exposed pregnancies, establish levetiracetam monotherapy in pregnancy possess a decreased risk for congenital malformations. If levetiracetam is a part of any polytherapy regimen the risk will be increased. However more researches are required to manifest the risks of particular antiepileptic drug combinations. Women with epilepsy of child bearing

age can consider levetiracetam monotherapy as a safer alternative for valproate. There is no correlation between risk and levetiracetam dose. Not only is its efficacy in focal epilepsy but also it a better antiepileptic to use in myoclonic epilepsy [25].

8. *Topiramate*

The North American Antiepileptic Drug (NAAED) Pregnancy Registry points out a high risk of oral clefts in infants who have an utero exposure to topiramate monotherapy during the first trimester of pregnancy. The prevalence of oral clefts was 1.4% compared to a prevalence of 0.38% - 0.55% in infants exposed to other antiepileptic drugs (AEDs). The prevalence is 0.07 % when compared with infants of mothers without epilepsy or treatment with other AEDs. According to data collected fromNAAED Pregnancy Registry the relative risk of oral clefts in pregnancies having topiramate – exposure was 21.3, when compared to the risk in a background population of women without under treatment. The UK Epilepsy and Pregnancy Register also reports higher prevalence of oral clefts that is 3.2 % among infants exposed to topiramate monotherapy. This is an increase of 16-fold in risk compared to the risk in their background population that is 0.2%.Topiramate was strongly associated with microcephaly [26, 27, 28].

Some of the Recently Approved Drugs

1. *Brivaracetam*

There are very less data from human studies regarding effect of brivaracetam in fertility, pregnancy and teratogenicity. Animal studies, did not shown any effect on male or female fertility and no teratogenic potential was demonstrated in rat or rabbit models. In rabbits embryo toxicity was seen at eight times of maximum recommended dose which is also maternal toxic dose. Studies in rats manifest that briveracetam cross the placenta and its breast milk concentrations areidenticalto plasma concentration of mother. As with all women of childbearing potential with epilepsy, those taking BRV should receive counselling about these issues throughout their management and during pregnancy [29].

2. *Bumetanide*

Bumetanide is belongs to pregnancy category C by the FDA. Animal studies did not find any evidence for teratogenicity. In rabbits at a dose range of 3.4 to 10 fold of maximum recommended therapeutic human dose, a dose-related diminishing in litter size and a hike in resorption rate were noted (on a per kg basis). Data from human pregnancy studies are not available. Bumetanidemust be given during pregnancy only if the benefit outweighs risk [30].

3. *Eslicarbazepine acetate*

Considering eslicarbazepine acetate exposure in pregnant women having epilepsy, the count of normal live birth without congenital anomalies was thirty, 18 cases ended in abortion and in five cases congenital anomalies were identified.In case of abortions 10 were spontaneous and 8 were induced. But there is no established relationship with ESL was confirmed. Concomitant use of ESL with other AEDs in 15 pregnancies resulted in 11 spontaneous abortion and congenital anomaly [31].

Available data are not sufficient to draw conclusions in ESLuse through pregnancy. However any particular safety issues were not identified, ESL use through pregnancy has to be continually monitored and evaluated [31].

4. *Everolimus*

Animal studies revealed everolimus causes embryofoetal toxicities at a dose of 10 mg daily. Toxicities are increased post implantation loss, preimplantation, resorption, malformation, retarded skeletal development decreased number of live foetuses. No controlled data are there in human pregnancy. It is unknown whether these drugs induce anyfoetal harm or cause for any adverse effects in human reproductive system.

This drug and/or its metabolites cross the placenta in rats. When orally administered to rats from early gestation to weaning at doses of 1, 3 or 10 mg/kg/day (0.8, 2 and 8 times the maximum recommended human dose [MRHD]) was associated with foetal and pup deaths at the mid and high doses (associated with maternal toxicity). In rabbits, oral administration throughout organogenesis revealed embryo lethality and maternal toxicity at the mid and high doses tested (3 and 10 mg/kg/day). There are limited amounts of data in human pregnancy (less than 300 pregnancies). There are no controlled data in human pregnancy [32].

Conclusion

Lamotrigine and levetiracetam are two antiepileptic drugs which are safe in pregnancy.Almost newer antiepileptics drugs didn't clarified their effects in pregnancy. Data from different pregnancy registries has to be continually monitored.

Conflict of Interest

Nil

References

1. Banerjee PN, Filippi D, Hauser WA, The descriptive epidemiology of epilepsy—a review, Epilepsy research, 2009; 85(1): 31-45.
2. Meador K, Reynolds MW, Crean S, Fahrbach K, Probst C, Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts, Epilepsy research, 2008; 81(1): 1-3.
3. Fairgrieve SD, Jackson M, Jonas P, Walshaw D, White K, Montgomery TL, Burn J, Lynch SA, Population based, prospective study of the care of women with epilepsy in pregnancy, British Medical Journal, 2000; 321(7262): 674-675.
4. Edey S, Moran N, Nashef L, SUDEP and epilepsy related mortality in pregnancy, Epilepsia, 2014; 55(7): e72-74.
5. Crawford P, Best practice guidelines for the management of women with epilepsy, Epilepsia, 2005; 46: 117-124.
6. Timmis A, Roobottom CA, National Institute for Health and Care Excellence updates the stable chest pain guideline with radical changes to the diagnostic paradigm, Heart, 2017; 103(13): 982-986.
7. Pennell PB, Hovinga CA, Antiepileptic drug therapy in pregnancy : gestation induced effects on AED pharmacokinetics, International review of neurobiology, 2008; 83: 227-240.
8. Veiby G, Daltveit AK, Engelsen BA, Gilhus NE, Pregnancy, delivery, and outcome for the child in maternal epilepsy, Epilepsia, 2009; 50(9): 2130-2139.
9. Harden CL, Meador KJ, Pennell PB, Hauser WA, Gronseth GS, French JA, Wiebe S, Thurman D, Koppel BS, Kaplan PW, Robinson JN, Practice parameter update: management issues for women with epilepsy—focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society, Neurology, 2009; 73(2): 133-141.
10. Rauchenzauner M, Ehrensberger M, Prieschl M, Kapelari K, Bergmann M, Walser G, Neururer S, Unterberger I, Luef G, Generalized tonic–clonic seizures and antiepileptic drugs

during pregnancy—a matter of importance for the baby?, Journal of neurology, 2013; 260(2): 484-488.
11. Hernández-Díaz S, Smith CR, Shen A, Mittendorf R, Hauser WA, Yerby M, Holmes LB, Comparative safety of antiepileptic drugs during pregnancy, Neurology, 2012; 78(21): 1692-1699.
12. Robert E, Guibaud P, Maternal valproic acid and congenital neural tube defects, The Lancet, 1982; 320(8304): 937.
13. Omtzigt JG, Los FJ, Grobbee DE, Pijpers L, Jahoda MG, Brandenburg H, Stewart PA, Gaillard HL, Sachs ES, Wladimiroff JW, The risk of spina bifida aperta after first-trimester exposure to valproate in a prenatal cohort, Neurology, 1992; 42(4 Suppl 5):119-125.
14. Diav-Citrin O, Shechtman S, Bar-Oz B, Cantrell D, Arnon J, Ornoy A, Pregnancy outcome after in utero exposure to valproate, CNS drugs, 2008; 22(4): 325-334.
15. Wide K, Winbladh B, Källén B, Major malformations in infants exposed to antiepileptic drugs in utero, with emphasis on carbamazepine and valproic acid: a nationwide, population based register study, ActaPaediatrica, 2004; 93(2): 174-176.
16. Arpino C, Brescianini S, Robert E, Castilla EE, Cocchi G, Cornel MC, De Vigan C, Lancaster PA, Merlob P, Sumiyoshi Y, Zampino G, Teratogenic effects of antiepileptic drugs: use of an International Database on Malformations and Drug Exposure (MADRE), Epilepsia, 2000; 41(11): 1436-1443.
17. Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Sabers A, Perucca E, Vajda F, EURAP Study Group, Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry, The Lancet Neurology, 2011; 10(7): 609-617.
18. Matalon S, Schechtman S, Goldzweig G, Ornoy A, Theteratogenic effect of carbamazepine: a meta-analysis of 1255 exposures, Reproductive toxicology, 2002; 16(1): 9-17.
19. Holmes LB, Wyszynski DF, North American antiepileptic drug pregnancy registry, Epilepsia, 2004; 45(11): 1465
20. Holmes LB, Wyszynski DF, Lieberman E, The AED (antiepileptic drug) pregnancy registry: a 6-year experience, Archives of neurology, 2004; 61(5): 673-678.
21. Puhó EH, Szunyogh M, Métneki J, Czeizel AE, Drug treatment during pregnancy and isolated orofacial clefts in Hungary, The Cleft palate-craniofacial journal, 2007; 44(2): 194-202.
22. Morrow J, Russell A, Guthrie E, Parsons L, Robertson I, Waddell R, Irwin B, McGivern RC, Morrison PJ, Craig J, Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register, Journal of Neurology, Neurosurgery & Psychiatry, 2006; 77(2): 193-198.
23. Sabers A, Dam M, A Rogvi, Hansen B, Boas J, Sidenius P, Laue Friis M, Alving J, Dahl M, Ankerhus J, Mouritzen Dam A, Epilepsy and pregnancy: lamotrigine as main drug use, Actaneurologica Scandinavica, 2004; 109(1): 9-13.
24. Meischenguiser R, D'Giano CH, Ferraro SM, Oxcarbazepine in pregnancy: clinical experience in Argentina, Epilepsy &Behavior, 2004; 5(2): 163-167.
25. Koubeissi M, Levetiracetam: More Evidence of Safety in Pregnancy: Levetiracetam in Pregnancy, Epilepsy currents, 2013; 13(6): 279-281.
26. U.S. National Library of Medicine. National Institutes of Health. Topiramate monograph. Available at http://www.nlm.nih.gov/medlineplus/druginfo/meds/a697012.html, Accessed on 25 July 2019.
27. SDI, Vector One®: National (VONA) and Total Patient Tracker (TPT). 2007- 2010, Data extracted 2-9-11.
28. U.S. National Library of Medicine, National Institutes of Health, Cleft Lip and Palate health topic, Available at http://www.nlm.nih.gov/medlineplus/cleftlipandpalate.html. Accessed on 25 July 2019.
29. Khaleghi F, Nemec EC, Brivaracetam (briviact): a novel adjunctive therapy for partial-onset seizures, Pharmacy and Therapeutics, 2017; 42(2): 92.
30. Ward A, Heel RC, Bumetanide: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic use, Drugs, 1984: 426-64
31. Costa R, Magalhães LM, Graça J, Vieira M, Gama H, Moreira J, Rocha JF, Soares-da-Silva P, Eslicarbazepine acetate exposure in pregnant women with epilepsy, Seizure, 2018; 58: 72-74.
32. Yamamura M, Kojima T, Koyama M,Sazawa A, Yamada T, Minakami H, Everolimus in pregnancy: Case report and literature review, Journal of Obstetrics and Gynaecology Research, 2017; 43(8): 1350-1352.