WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 11, 519-529. Review Article ISSN 2277– 7105

ANTIEPILEPTIC DRUGS: USE, SAFETY AND POSSIBLE ADVERSE EFFECT IN WOMEN WITH EPILEPSY DURING PREGNANCY AND CHILDBEARING AGE- A REVIEW

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Article Received on
17 April 2018,
Revised on 07 May 2018,
Accepted on 28 May 2018
DOI: 10.20959/wjpr201811-12572

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ABSTRACT

Epilepsy is a chronic medical disorder or condition resulting unpredictable recurrent seizures that can affect various mental and physical conditions. It is one of the most serious neurological conditions which affect 50 million people worldwide. Women with epilepsy during pregnancy and lactation suffer from various serious conditions. Choice of antiepileptic for women with epilepsy is also limited because of teratogenic effects of antiepileptic drugs. Conventional AEDs seen to be safer then newer AEDs for WWE, monotherapy seems to be safer as compared to polytherapy. Carbamazapine is the most commonly used AED found whether in monotherapy or in poly therapy. Valporic acid carbamazepine, phenytoin and phenobarbital are some conventional AEDs which are commonly used in WWE. Lamotrigine, gabapentin, felbamate oxcarbazepine, zonisamide, topiramate are some newer AEDs used in WWE. There is higher risk of major malformation among infants exposed to AEDs during pregnancy. Cleft lip, congenital heart defects, neural tube defects and other neurodevelopment risk are also associated with using AEDs during pregnancy. Folic acid and vitamin K supplement should be recommended for WWE in pregnancy and lactation. It helps in managing and reducing malformation risk in neonates and children. Management and counselling in WWE during pregnancy and lactation helps in teratogenic risk of AEDs.

KEYWORDS: Antiepileptic drugs (AEDs), women with epilepsy (WWE), monotherapy, neurodevelopment, teratogenic and major malformation.

1. INTRODUCTION

Epilepsy is defined as a condition characterized by recurrent (two or more) epileptic seizure, epilepsy is constant neurological disorder of brain which requires elongated characterized management.[1] It is characterized by the persistent manifestation of spontaneous attack owing to neuronal hyperactivity in the mind.[2] WHO has evaluated that approximately 50 million people have epilepsy and this is most common with women of childbearing age.[3] Women with epilepsy has been described as having extra complications & overstress then general inhabitants. It has shown that in women with epilepsy hyperemesis gravidarum, vaginal bleeding, premature labor, eclampsia and cesarean section rates are higher than normal pregnancy. Due to increase in seizure resulted in sleep deprivation, increased emotional stress & noncompliance with medication which resulted in declining AED concentrations throughout pregnancy. Adjustment of AED dose and proper monitoring of free AED concentration is very necessary in women with epilepsy.[4] Treatment of women with epilepsy during pregnancy always be a challenge because of risk associated with AED use for fetus and mother both. Monotherapy has shown more safer for the fetus as compared to polytherapy because of lower risk of congenital abnormality.[5] Congenital heart disease, cleft lip or palate, limb defects, genitourinary malformations, neural tube defects are most common major malformations shown in pregnant women with epilepsy using AEDs.[6]

Major congenital malformations & neurodevelopment outcomes with AEDs

In women with epilepsy need continuous treatment of AEDs during pregnancy which results one of the most frequent chronic teratogen exposure. Most women results with normal & favorable outcome having AEDs for epileptic condition but there are increased risk of maternal & fetal outcome as compared to the general population. AEDs results anatomic teratogenic & neurodevelopmental consequences on the developing offspring.[7] Women with AEDs treatment duing pregnancy must be aware of the relative risks & guided appropriately in her therapy.[8] The most common major congenital malformation about physician are generally aware of neural defects which is mostly associated with in-utro exposure to sodium valproate, carbamazepine & barbiturates (phenobarbitone, Phenobarbital, primidone). While phenytoin have been reported with congenital heart defects, facial clefts and neural tube defects. Skeletal, urogenital, abnormalities are also reported as other MCMs (Major congenital malformations).[9] Treatment of women with epilepsy during pregnancy always be a challenging because of risk for fetus and mother both. Single drug treatment has been shown safer for the fetus as compared to polytherapy because of lower risk of congenital

malformations and other deformities for the fetus. Now a day increased incidence of congenital malformation is primarily caused by AEDs and this can be reduce or prevented by suggesting switching polypharmacy to monopharmacy and minimizing AEDs dose.[10]

AEDs like Valproate & Phenobarbital were associated with major risk of malformation as compaired to newer AEDs such as Lamotrigine & Levetiracetum. Topramate was recordrd with an increased risk of cleft lip.[11,12,13]

2.1 Dose dependency of MCM (Major Congenital Malformation)

Use of AEDs in higher doses increases risk of MCMs. In EURAP (European and International Registry of Antiepileptic Drugs and pregnancy registry) the lowest rate of MCMs was found with lamotrigine <300mg/day (2%), carbamazepine <400mg/day (3.4%) & valproate <700mg/day (5.6%) at the time of pregnancy. Risk of incidence of MCM was 5% with valproate ≤600mg /day, 1.9% with carbamazepine ≤500mg/day & 2.1% with lemotrigine ≤200mg/day.[12]

2.2 AEDs used in women with epilepsy during pregnancy

The most commonly used AED was found as carbamazapine whether in monotherapy or in poly therapy. This is consistent with finding of the EURAP study. Which showed maximum of countries (over 38 countries) carbamazepine is the most commonly AED to be used during pregnancy. Valproate was the second most commonly used AED in monotherapy during pregnancy. Studies showed that whenever valproic acid used as benefit controlled seizure. It is difficult to switch to another AEDs before or during pregnancy, this explain that why women continue with valproate during pregnancy.[14]

2.3 How to care for pregnancy in WWE (women with epilepsy)[12]

1. Folic acid continues during pregnancy.
2. Continue previous dose of AEDs with same drug until it shows poor seizure control or another unacceptable side effect of AEDs.
3. No need to withdrawal of AEDs during pregnancy.
4. There is a need of high level ultrasound at 14-18 week of pregnancy for detail knowledge and imagining of foetal structure. If there is any malformation is identified detailed knowledge about the possible effects of malformation on baby should be counseled for the couple. The choice of continuation termination of pregnancy should be taken after discussion with parents.

5. It is not conform that all seizure occurring during pregnancy are due to epilepsy. Whenever there is a doubt, evaluate for proper cause of seizure & manage according to the cause.
6. Seizure occur late in pregnancy, possibility due to eclampsia and if consider appropriate, it proceed with delivery induction.
7. 1mg vitamin K intramuscularly should be given to all newly born children.
8. Key of successful outcoms in WWE during pregnancy always lies in a team approach consisting of obstetrician, neurologist & neonatologist for preconception counseling & after postpartum care.

3. Anticonvulsant drugs

3.1 Phenytoin

Phenytoin (Dilation) is a anticonvulsant drug commonly used in the treatment of partial and tonic-clonic seizure, and also in status epilepticus. Oral bioavailability is high (90%) and 90% of the circulating drug is protein bound. Half life of phenytoin is 24 hours & it is eliminated by hepatic metabolism. Usual daily dose of phenytoin is 300mg to 600mg with starting dose of 5mg/kg single dose. Phenytoin is consider under class D medication in pregnancy and lactation, which show that there is positive evidence of fetal risk in human, but its benefits makes it acceptable for use in some pregnant women.[15,16] It is shown that phenytoin excreted into breast milk but not in that much quantities to provide risk to the neonate.[17,18] It is considered as compatible with breastfeeding with rarely reported side effects and low infant serum level is available for it.[19]

Side effects- dose related side effects with phenytoin include nystagmus, vomiting, gingival hyperplasia, ataxia, nausea, drowsiness, depression, megaloblastic anemia, dysrhythmias and a paradoxical increase in seizure. Idiosyncratic side effects of phenytoin include acne, hirsutism, coarse facies, Steven- Johnson syndrome, hepatotoxicity, blood dyscrasis, rash, lupus and dupuytren's contractures.[20]

3.2 Phenobarbital

Phenobarbital comes under sedative and hypnotic drugs that are also used for epileptic condiction like partial and generalized tonic- clonic seizure and sometimes in status epileptus. Oral bioavilability of Phenobarbital is high (90%) and only 50% of the circulating drug is bound with protein. Usual daily dose of Phenobarbital is 60 mg to 240 mg once or twice a day with in lowest possible dose to minimize sedative side effects. Half life is 100 hours and

eliminated by hepatic metabolism. Phenobarbital comes under class D medication for pregnancy and lactation.[15,16] Phenobarbital is excreted into breast milk due to this sedation and severe withdrawal symptoms may occur, when breast feeding is discontinued it is considered as problematic. In breastfeeding women if it is continued there should be careful drug- level monitoring is required.[17,18] Phenobarbital has potential to accumulate during breastfeeding because of long half life, there is careful monitoring is warranted in infants is needed.[19]

Side effects- Dose dependent side effect with Phenobarbital include drowsiness fatigue, depression, ataxia and restlessness. Idiosyncratic side effect of Phenobarbital includes Dupuytren's contracture, hepatotoxicity, arthritis, exfoliation, toxic epidermal necrolysis, macrocytic anemia and maculopular rash.[20]

3.3 Valporic Acid

Valporic acid (Depakene) is anticonvulsant drug used for the treatment of all types of epilepsy as absence and generalized tonic-clonic seizure. Oral bioavailability of Valproic acid is 100% and 90% bound with protein. Normal usual daily dose of Valproic acid is 500mg to 3,000 mg in three to four divided doses. Valproic acid is considered under class D medication in pregnancy and lactation. It is excreted into breastmilk.[15,16,18] Due to theoretical risk of hepatotoxicity, there is need of monitoring of jaundice or other signs of liver dysfunctions while using valporic acid during breastfeeding.[19]

Side effect- Dose dependent side effects with valproic acid include nausea, vomiting, tremor, weight gain, dyspepsia, alopecia and partial edema. Idiosyncratic side effect with valproic acid includes hepatotoxicity, thrombocytopenia, acute pancreatitis and encephalopathy.[20]

3.4 Carbamazepine

Carbamazepine (tegretol, eptiol) is an iminosulbene used as anticonvulsant for treatment of partial and generalized tonic- clonic seizure. Oral bioavailability of carbamazepine is 80% and 70% bound with protein. Daily doses of carbamazepine is 600 mg to 2,000 mg in two to four divided dose. Half life of carbamazepine is 12 to 24 hours. Carbamazepine is considered under class C medication for pregnancy and lactation. It is excreted in breast milk in low amount measuring 25% of maternal plasma levels.[15,16,18]

Side effects- Dose dependent side effects of carbamazepine are headache, nausea, neutropenia, hyponatremia, dizziness and diplopia. Idiosyncratic side effects include steven's Johnson syndrome, hepatotoxicity, agranulation, rash and aplastic anemia.[20]

3.5 Ethosuximide

Ethosuximide (Zarontin) is commonly used to treat uncomplicated patitmal absence seizure. Oral bioavailability of ethosuximide is high 95% and minimally bound with protein. Daily dose of ethosuximide is 500mg to 2,000mg in one to two divided dose. It is considered under class C medication for pregnancy and lactation and excreted in breast milk in equal level as in maternal plasma.[15,16]

Side effects- Dose dependent side effects include vomiting, drowsiness, nausea, headache, abdominal pain, anorexia and agitation. Idiosyncratic side effects of ethosuximide include Stevens- Jhonson's syndrome, lupus, agranulocytosis, aplastic anemia, and rash.[20]

3.6 Primidone

Primidone (mysoline, primaclone, sertan) is an anticonvulsant drug used in partial and generalized tonic- clonic seizure both. Oral bioavailability of primidone is 100% and minimally bound with protein. Daily dose of primidone is 500mg to 2,000mg in two to three divided doses. Primidone comes under class D medication for pregnancy and lactation, it is excreted in breast milk and cause side effects as in mother.[15,16] It is serves as prodrug for its major active metabolite Phenobarbital it is highly excreted in breastmilk.[19]

Side effects- Dose dependant side effect of primidone include depression, nausea, psychosis, nystagmus and ataxia. Idiosyncratic side effect include rash, thrombocytopenia, macrocytic anemia, agranulocytosis and lupus.[20]

3.7 Clonazepam

Clonazepam (Rivotril, Klonopin) is a benzodiazepine mostly used for refractory myoclonic seizure. Its use is limited because of its tendency to sedate and also because of development of drug tolerance. Usual daily dose of clonazepam is 2 mg to 6 mg and also there are guidelines for plasma drug-level monitoring with clonazepam. Clonazepam is considered under class C medication for pregnancy and lactation.[15,16] These are used in the treatment of chronic epilepsy.[28]

Side effects- Dose dependant side effect of clonazepam are sedation, fatigue, dizziness. Idiosyncratic side effects include thrombocytopenia and rash.[20]

3.8 Newer anticonvulsant drugs

In newer generation of AEDs consist of a large number of structurally diverse compound such as lamotrigine (Lamicatal), gabapentin (Neuronation), felbamate (Felbatol), oxcarbazepine, zonisamide, topiramate. There is not sufficient experience of newer generation in pregnancy regarding safety. Lemotrigine is an agent which has been sufficiently tested during human pregnancy to assess safety or taratogenicity, lamotrigine is considered under class C drugs for pregnancy and lactation.[15,21]

Table 1: Effects of antiepileptics on oral contraception, fertility and pregnancy.[22]

Antiepileptic drugs	Oral contraception	Fertility	Fregnancy
Phenytoin	↓Efficacy	↑ Steroid-binding globulin ↓ Dehydroepiandrosterone	Known teratogenicity
Carbamazepine	↓Efficacy	↑Steroid-binding globulin ↓ Estradiol levels in women exposed >5 y ↓ Dehydroepiandrosterone	Known teratogenicity, neural tube defects (0.5-1%) Known teratogenicity
Barbiturates	↓ Efficacy	↑ Steroid-binding globulin	Known teratogenicity, high doses, neural tube defects (1-2%)
Valproate	No effect	↑ Dehydroepiandrosterone especially at ↑ Total testosterone associated with polycystic ovaries	No teratogenicity in animals
Gabapentin	No effect	No effect on steroid binding globulin adrenal or gonadal steroids	No teratogenicity in animals
Lamotrigine	No effect	No effect on steroid binding globulin,	Teratogenicity in rodents (limbagenesis)
Topiramate	↓ Efficacy	Not known	No teratogenicity in
Tiagabine	↓Efficacy	Not known	

Table 2: Concentration of antiepileptic drugs in breast milk expressed as percentage of maternal plasma concentration.[23]

Antiepileptic drugs	Breast milk	Reported adverse effect
Carbamazepine	l 41 ± 16.8	-
Ethoswimide	94 ± 6	-
Lamotrigine	65 (48 h postpartum)	-
Phenobarbital	36.1 ± 19.5	Sedation
Phenytoin	18.6 ± 15.7	Methemoglobinemia
Primidone	70.5 ± 29.2	Sedation, feeding difficulties
Vdproate	2.7 ± 1.5	Thrombocytopenic purpura

4. Vitamin K and folic acid role in Epilepsy

In neonates, the activity of vitamin K dependant coagulation factors is lower than adults. Severe hemorrhagic disorder in young infants has been reported who are suffering from vitamin K deficiency. It has been seen that newborns that are exposed in utero to anticonvulsants drugs are in higher risk for vitamin K deficiency.[24] Detection of (PIVKA-2) [protein induced by vitamin K absence of factor 2 discarboxylated prothrombin: precursor prothrombin] is a specific test for detection of vitamin K deficiency. In vitamin K deficiency incompletely carboxylated proteins which is funcitionally carboxylated proteins is functionally defective appear in plasma. Determination of PIVKA-2 by monoclonal antibody is very specific and sensitive method for detection of vitamin K deficiency subclinically. In some prospective studies, it is found that incidence of coagulation defects resulting from neonatal vitamin K deficiency to be high after exposure to anticonvulsant drugs.[25]

Folic acid is essential for pregnant women receiving antiepileptic therapy. Some epidemiological investigations also established relationship between malformation and defective foliate metabolism.[26] Folate deficiencies result with neural tube defects (NTD) in general population, daily supplementation of folic acid approx 0.36-4.0mg has been shown to maintain NTD risk by 60-86% in general population. In some studies it was shown that folic acid 5mg per day result no malformation, whereas 23% fetal abnormalities shown with no use of folic acid in women with epilepsy taking AEDs. 5mg/day of folic acid is recommended at least for the end of the first trimester in all women taking AEDs for epilepsy it decrease the rate of malformations and NTD.[27,28,29]

5. Management and counselling of women with epilepsy during pregnancy[27,30]

Management and counselling in women with epilepsy helps not only in managing teratognic risk of AEDs but also helps to control seizure and wider quality of life issues. All women of childbearing potential should prefer 5mg/day supplement of major malformations. Choice of treatment with necessary AEDs and withdrawal of AEDs in seizure recurrence, all these topics must be discussed during counseling.

Simple safe precautions for an epileptic mother to take when caring for her baby are as follows-

- Avoidance of excessive tiredness.

- If the mother feeling unwell in that case the convenient area for the baby should be identified.
- If there is a risk of dropping the safest way of feeding is by sitting on the floor, surrounded by cushions and by leaning against a wall.
- Safest way of changing and dressing baby to protect from fall if seizure happens by using the floor.
- When there is someone else there for support is the best way for bathing the baby.

6. CONCLUSION

The goal of treatment of WWE is to minimize risk of malformation and other neurodevelopment condition in infants. Optimal treatment and monitoring may help in balancing the seizure and epileptic conditions. Choice of drug is also help in reducing the risk of malformation in infants. Monotherapy is safer as compared to polytherapy during pregnancy. Supplement of vitamin K and folic acid reduce risk of malformation and other serious condition. Counselling and drug monitoring can also help in balancing and reducing the harmful effect of AEDs.

REFERENCES

1. Patel.PM, Shah AM, Gajjar MB. Drug Utilization Pattern of Antiepileptic Drug in Tertiary Care Teaching Rural Hospital. National Journal of Physiology, Pharmacy and Pharmacology, 2016; 6(5): 458-463.
2. Kumara P, Vijayanti S, Banerjee D. *et al.* To evaluate the anti-kindling effects of allopregnanolone alone and its intraction with sodium valporate in pentylenetrazole induced kindling model. International journal of epilepsy, 2016; 68-74.
3. Kilic D, Pedersen H, Parner ET. *et al,*. Birth outcomes after prenatal exposure to antiepileptic drugs: a population based study. Epilepsia, 2014; 55(11): 1714-1721.
4. Yerby MS. Risk of pregnancy in women with epilepsy. Epilepsia, 1992; 33(1): 523-527.
5. Kulaga S, Sheehy O, Zargarzadeh AH.*et al.,* Antiepileptic drug use during pregnancy: prenatal outcomes. Seizure, 2011; 20: 667-672.
6. Adab N, Jacoby A, Chadwik D. *et al.,* Additional education need in children born to mother with educational need in children born to mother with epilepsy. Neuronal Neurosurg Psychiatry, 2001; 70: 15-21.
7. Pennell PB. Antiepileptic drugs during pregnancy what is known and which AEDs seen to be safest? Epilepsia, 2008; 49(09).

8. Gedzelman E, Meador KJ. Antiepileptic drugs in wpmen with epilepsy during pregnancy. Therapeutic advances in drug safety, 2012; 3(2): 71-87.
9. Robertson I, Waddell R, Irwin B. *et al.* Malformation risks of antiepileptic drugs in pregnancy: a prospective study from UK epilepsy & pregnancy register. A neurol neurosurg psychiatry, 2006; 77: 193-198.
10. Kene KOS, Battino D, Andermann E. *et al.,* Congenital malformation due to antiepileptic drugs. Epilepsy research, 1999; 33: 145-158.
11. Hernandez- Diaz S, Smith CR, Mittendirf R, Hauser WA, Yerby M, Holmes LB. Comparative safety of antiepileptic drug during pregnancy. Neurology, 2012; 78: 1692-1699.
12. Bansal R, Kharbanda PS, Goyal MK. *et al.,* Maternal and neonatal outcome during pregnancy in women with epilepsy. International journal of epilepsy, 2016; 3: 80-85.
13. Crawford P, Appleton R, Betts T. *et al.,* Best practice guidelines for the management of women with epilepsy. Seizure, 1999; 8: 201-217.
14. Kulaga S, Sheehy O, Zargarzadeh AH. *et al.,* Antiepileptic drug use during pregnancy: perinatal outcomes. Seizure, 2011; 20: 667-672.
15. Fergal D, Malone and Mary E, Altoin D. Drug in pregnancy: Anticonvulsant. Seminars in perinatology, 1997; 21: 114-123.
16. Goldenberg MM. Overview of drug used for epilepsy and seizure. P&T, 2010; 35(7): 392-415.
17. Brodie MJ, Dichter MA. Antiepileptic drugs. N Engl J Med., 1996; 334: 168-175.
18. The transfer of drugs and other chemicals into human milk. American academy of pediatrics, 2001; 108(3): 776-783.
19. Veiby G, Bjork M, Engelsen BA, Gilhua N.E. Epilepsy and recommendations for breastfeeding. Seizure, 2015; 28: 57-65.
20. The transfer of drugs and other chemicals into human milk. American academy of pediatrics, 1994; 93: 137-150.
21. Pennell PB. Using current evidence in selecting antiepileptic drugs for use during pregnancy. Epilepsy currents, 2005; 5(2): 45-51.
22. Morrell MJ. Guidelines for the care of women with epilepsy. American academy of neurology, 1998; 51(4): S12-S27.
23. Zahn C.A, Morrell MJ, Collins SD, Labiner DM, Yerby MS. Management issue for women with epilepsy. American academy of neurology, 1998; 51: 949-1956.

24. Cornelissen M, Theunissen RS, Kollee L. *et al.*, supplementation of vitamin K in pregnant women receving anticonvulsant therapy prevents neonatal vitamin K deficiency. American journal of obstetrics and gynecology, 1993; 168: 884-888.
25. Cornelissen M, Theunissen RS, Kollee L, Eskes. *et al*., Increased incidence of neonatinal vitamin K deficiency resulting from maternal anticonvulsant therapy. American journal of obstetrics and gynecology, 1993; 168: 923-928.
26. Biale Y, Lewenthal H. Efect of folic acid supplementation on congenital malformations due to anticonvulsive drugs. European journal of obstetrics and gynecology, 1984; 18: 211-216.
27. Adab N, Chadwick DW. Management of women with epilepsy during pregnancy. Obstetricians and Gynecologists, 2006; 8: 20-25.
28. Asadi- Pooya AA. High dose folic acid supplementation in women with epilepsy; are we sure it is safe? Seizure, 2015; 27: 51-53.
29. Patel SI, Pennell PB. Management of epilepsy during pregnancy: an update. Rherapeutic advances in neurological disorders, 2016; 9(2): 118-129.
30. Crawford P. Best practice guidelines for the management of women with epilepsy. Epilepsia, 2005; 46(9): 117-124.