ISSN: 2279 - 0594

Journal of Biomedical and Pharmaceutical Research

Available Online at www.jbpr.in

CODEN: - JBPRAU (Source: - American Chemical Society)

Index Copernicus Value: 63.24

PubMed (National Library of Medicine): ID: (101671502)

Volume 6, Issue 2: March-April: 2017, 12-17

Review Article

ANTI-EPILEPTIC DRUGS USED DURING PREGNANCY

Saugat Dahal[1]*, Sushobhan Bhandari[1], Deepak Bhatt[1]

[1]Pharm.D, Department of Pharmacy Practice, Krupanidhi College of Pharmacy, Bengaluru-35, Karnataka, India

Received 02 Feb. 2017; Accepted 20 Mar. 2017

ABSTRACT

Anti-epileptic drugs(AED's) prescribing to the pregnant women is one of the challenging tasks to the prescribers. It may be vulnerable to the mother as well as fetus if the AED's regimen is not addressed properly during pregnancy. It could even lead to the death of the mother and fetus or injury to the fetus(resulting neural tube defects,congenital malformations). Discontinuing an AED's should be done only consulting physician or the clinician or else women with epilepsy during pregnant time should not avoid anti-epileptic drugs. During pregnancy, the metabolism of AED's may vary due to various aspects. So,the clinician must give focus to addressing the changes seen in women. Monitoring drugs levels during pregnancy is also an another important tasks for the clinician. The risk of the fetus should eliminate from the particular drugs as well as from seizure disorder itself. Many anti-epileptic drugs show teratogenic effects, some risks includes poor neonatal outcome, neural tube defects, congenital malformation and various cognitive effects on the child. These risks are also mentioned in this article along with individual AED's. Similarly, some anti-epileptic drugs like lamotrigine, levetiracetam, phenytoin are safe during pregnancy but along with folic acid supplements to minimize the risks.

Keywords: Anti-epileptic drugs, congenital malformation, epilepsy, folic acid

Introduction

Epilepsy is one of the neurological defect seen in any of the age group of population.This defect requires medical treatment. In case of pregnancy, There should be such type of treatment where the adverse effects of drugs to the mother and fetus should be minimal.[1]

Anti-epileptic drugs(AED,s) which should be prescribed to the pregnant women is one of the most challenging tasks to the physicians or prescribers.There should be good choice of drugs which shouldnot cross the placenta and harm the fetus in the future.

Fifty million people are estimated worldwide that shows the prevalence of the epilepsy.There are many types of the epilepsy,so it is slight complex to manage the drugs between the patients.[2]

The risk of seizure is maximum during the first trimester of pregnancy and during the third trimester(i.e delivery period).[3,4]

MATERNAL RISK

Maternal mortality:

In 2004, There was 13 epilepsy related death indirectly related to pregnant was reported which was confidential inquiry into maternal death. These type of enquiry was reviewed over five years and show the increase in mortality in a pregnant woman from 10-fold increase which exceeds from 2-3fold mortality rate.[5] There is chance of death if any treatment is withdrawal.

Change in seizure frequency

Some studies shows that 15-37% pregnant woman shows increase in seizure frequency.This was all because of not taking the medicine properly and sleep disturbance as well.Similarly, 1-2% of woman shows tonic-clonic seizure during the labor and first 24 hours after delivery.[6]

Implications for fetal and child development

seizure:

Different case series shows that, Tonic-clonic type of seizure is seen to many fetuses and this is

*Corresponding author: Saugat Dahal | E-mail: saugatdahal434@gmail.com

associated with fetal intracranial hemorrhage,fetal hypoxia and fetal loss.[7]
However, there is no risk compulsive seizure but because of physiological consequences of the mother,non-compulsive seizure is believed to little risk of the fetus.

Fetal loss:

Two-fold increase risk of the abortion, still birth and perinatal loss among woman with AED's, such type of evidence shows some of the studies.[7]

Intrauterine growth retardation:

There is the chance of lower birth weight if any anti-epileptic drug was used during pregnancy having doses upto 200mg per day. [8] These type of risk can also be seen because of multiple AED's.

Regarding risk of malformation due to Anti-epileptic drugs, a prospective study from UK shows that, 4.2% was found having major congenital malformation(MCM) rate after exposed to AED's. IN that study,the MCM was seen higher due to polytherapy rather than monotherapy[9].

In one of the comparative study of anti-epileptic drug in pregnancy, valproate and phenobarbital were found to be the maximum risk of major congenital malformation as compared to the newer anti-epileptic drugs like lamotigrine and levetiracetam.[10]

According to the UK based study, the ratio of taking AED,s in pregnancy is decreased as compared to non-pregnant women. Carbamazepine and valproate which might cause teratogenicity has been declined to prescribe since 1994. Lamotrigrine has been started to prescribe as a choice of drug to the pregnant woman having epilepsy.[11]

Mechanism of anatomical teratogenesis:

The exact mechanism of teratogenicity cause by AED's is not clearly known. However,there are some reasons causing teratogenicity by AED's taken during pregnancy such as deficiency of folic acid, lack of oxygen supply to the fetus,free radicals etc.There is the high risk of anatomical(i.e malformation) to the fetus during first-trimester after AED's but behavior(i.e cognitive) risk can be seen during the third-trimester.Similarly,Genetic predisposition may also play certain role to cause teratogenicity.[12]

Monitoring patients during pregnancy:

It is very important to monitor the pregnant woman also suffering from epilepsy.Drug therapy is must to control epilepsy but monitor is needed to avoid major congenital malformations.Major scan (high resolution) should be done for about 5 months but few abnormalities like neural tube defects can be seen earlier.However, increased alpha-fetoprotein in maternal serum can also detect neural tube defect.Cardiac scans should be carried out for the fetus at later stage of pregnancy.[3]

Anti-epileptic drugs:

These drugs came in the market for many decades,having the moderate cost,these all drugs are found on generics. AED,s are not only found oral formulation but also in parenteral dosage form as it also has mostly used in emergency cases.

1. **Phenobarbital:**

The oral dose of phenobarbital is 60 to 200mg per day.This drug increases synaptic inhibition by acting on the GABA (gamma-amino-butyric acid) receptor.It may also bind on the calcium channel and decreases the release of excitatory transmitter.It has broad spectrum activity and works in various types of seizures(except absence seizure). Because of some cognitive and sedative effect, some of the countries are not prescribing this drug so its popularity is getting decreased. Some study shows that, long term use of phenobarbitone causes risk of osteoporosis and degrading serum lipid profile, as it is a potent enzyme inducer. [13]

2. Phenytoin:

Phenytoin is a narrow spectrum anti-epileptic drugs having lots of unwanted side effects. The therapeutic window is narrow,so as it has complication in pharmacokinetics,regarding changes in serum level. [14] Phenytoin may cause congenital abnormalities (called phenytoin hydantoin syndrome), gingival hyperplasia, some local reaction. Furthermore, this drug also shows anti-folate property.

3. Carbamazepine:

Some of the review done in 2008 concluded that, Carbamazepine which is given monotherapy in the pregnant woman is one of the most lower a risk for

the congenital malformation. It is an enzyme inducer drug which somtimes have risk of neural tube defects, as it has narrow spectrum activity.[15]

4. Valproate(VPA):

Sodium valproate may cause birth defects(malformation) and developmental and learning problem in children (delayed walking and talking,poor speech,lower intelligence).The risk of congenital malformation using valporate is 6% to 12%. If the dose of valproate is decreased(below 1000mg per day) and folate supplement is increased, the there is less chance of congenital malformation and other cognitive impairment. [16] But for normal women(who are not pregnant) group,this valproate is a wide sprectum drug which cures many types of seizures but is highly contraindicated to pregnant woman.In 1980,the first report was published regarding teratogenic effect of valproate,than in 1984,FVS(fetal valproate syndrome) term was advised.[17]

Other newer AED,s:

1.Lamotrigine:

Lamotrigine is one of the best and most common used anti-epileptic drug in pregnancy,as this drug was studied heavily and marketed in pregnant woman as an alternative to valproic acid.This drug is metabolized to N2-glucuronide by the help of enzyme Uridine-diphosphate glucuronosyl transferase(UGT). Total serum concentration of the drug is decreased by 40-60%,the fall is due to estrogen-induced glucuronidation. [18]Some of the study shows that it is not harmful in lower dose.300 mg daily dose doesn't make any harm to the fetus or donot show any risk of malformation.In case of breast feeding infant,there was one adverse effect found in one case report having apnea at day 16,at that time,the mother used to take a daily dose of 875mg lamotrigine and she developed CNS toxicity after delivery.Allover, this drug is also safe for breast-feeding woman but some caution is required.[19]

2.Levetiracetam:

This drug is metabolized by peripheral hydrolysis and is mainly unchanged in urine.The total serum concentration get decreases by approximately 40%.This drug has very low protein binding.Two-third of the drug is unchanged in the urine while a quarter of dose is metabolized in blood.This drug is safe in monotherapy and various study shows that it doesnot show any congenital malformation.This drug can be given intravenously and orally.The pharmacokinetic of levetiracetamis linear and has fast onset of action and it doesnot interact with any drugs. [20]It doesnot show any cognitive side effects and no need of monitoring blood-level.[21]

3.Oxcarbazepine:

Oxcarbazepine involves glucuronidation and metabolized by an enzyme Uridine-diphosphate glucuronosyl transferase(UGT).The total serum concentration is decreased by 30-40%. [22]One of the case report shows that,23-year-old female patient with the history of seizure during school days and treated with phenytoin and gabapentin.Later planned pregnancy proceeds and the two drugs were switched off and was given oxcarbazepine as monotherapy.The baby girl was born healthy and normal.There are few evidence or study regarding this drug.However,this drug has no teratogenic effect and can be given to the pregnant woman with epilepsy.In case of breast feeding,there were two cases reported.In both,the child remained less serum concentration despite a breast milk maternal serum concentration which was the ratio of about 0.5-1.There was no seen of any adverse effect of nursing infants in these cases.[23]

4.Topiramate:

Topiramate is used for the treatment of epilepsy and also can be prevented from migraine headache.Many studies shows that,there is a risk of fetus when topiramate is used in the first trimester of pregnant women.This drug shows high rate of oral cleft(cleft palate and cleft lips) than other AED,s.In case of breast-feeding infants,no adverse effects were seen because of very low concentration of topiramate.This drug has 20-30% hepatic biotransformation and mainly unchanged in urine.The total serum concentration is decreased by 30-40%.Moreover,topiramate shows decreased birthweight.[24]

5.Gabapentin and pregabalin:

Very less data have been collected regarding the study of gabapentin and pregabalin.There was not sufficient evidence found,few study shows thatGabapentin and pregabalin should only be use if there are no any alternatives.As these drugs are

not metabolized and unchanged in the urine.In the study,which was carried out in 51 infants,they didn't find any risk of fetal malformation.[25]

6.Zonisamide:

Zonisamide has mainly hepatic biotransformation and found 15-30% unchanged in urine.The teratogenic risk and total serum concentration has not clearly studied.Due to unchanged in urine,this drug shows high renal blood flow which might impact the serum concentration of zonisamide.In one study,the daily dose to zonisamide have been increasedfrom 200mg to 300mg to control the seizure.[26] In one study,26 children who were exposed to zonisamide were assessed,among them two children were found malformation where zonisamide was given combined with other AED's.[27]

Pregnancy changes the pharmacokinetics of AED's:

There are so many factors that change the pharmacokinetics of the AED's during pregnancy.

- Renal blood flow and glomerular filtration rate raises by 50-80% during pregnancy.Serum drug concentration which was eliminated through kidney may be decreased.This effect shows during the second trimester.
- Estrogen level is increased which ultimately lead to increased drug glucuronidation.This increament seems throughout the pregnancy peroid (first,second and third trimester).Moreover,the activity of some enzyme such as CYP450 is also high.
- During pregnancy,there is decreased serum albumin concentration which may affect total plasma clearence and AED's protein binding.
- AED's serum concentration is reduced due to increase plasma volume, this was increase due to high amount of total body water during pregnancy.[28]

Folic acid supplementation:

The occurrence of congenital malformation and neural tube defects can be prevented by folic acid supplements.These supplements are recommended for pregnant woman or who are planning to get pregnant.Although,folate is a water- soluble B vitamin(B9) and can occur naturally.The bioavailability of folic acid supplement is higher than naturally occurred follic acid,this might be due to food is raw or cooked,host-factor,combination of food consumed etc.This supplements also prevent from the risk of early labor,similarly also from other deficiencies which can cause anaemia. [29]World Health Organization recommended using 0.4mg folic acid along with 30mg to 60mg of elemental iron to protect from complication such as neural tube defects,low birth weight,maternal anemia.[28]

CONCLUSION:

Though,discontinuing the AED's may be an option in some women with epilepsy,during the pregnancy period or prior to it.But this is quite not possible, so it is necessary to monitor women as well as fetus and should be given right choice of drug.From the above study,monotherapy is considered safe along with folic acid supplements.Some of the drugs such as lamotrigine, carbamazepine, phenytoin, oxcarbazepine, levetiracetam are found quite safe using monotherapy with lowest effective dose. AED's should not stop or discontinue by women with epilepsy without consulting physician.She should have sufficient knowledge or information regarding relative risk to the fetus.

Acknowledgement:

We would like to thank the principal, Head of Department of Pharmacy Practice of Krupanidhi college of pharmacy for guiding us through this review. Also, our sincere gratitude towards all our teachers for providing us the platform during the completion of our review.

References:

1. Bech BH, Kjaersgaard MI, Pedersen HS, Howards PP, Sørensen MJ, Olsen J, Parner ET, Pedersen LH, Vestergaard M, Christensen J. Use of antiepileptic drugs during pregnancy and risk of spontaneous abortion and stillbirth: population based cohort study. BMj. 2014 Aug 22;349:g5159.
2. Gedzelman E, Meador KJ. Antiepileptic drugs in women with epilepsy during pregnancy. Therapeutic advances in drug safety. 2012 Apr;3(2):71-87.
3. Hart Y. Management of women with epilepsy before and during pregnancy. Progress in Neurology and Psychiatry. 2008 Apr 1;12(3):6-8.

4. Thomas SV. Management of epilepsy and pregnancy. Journal of postgraduate medicine. 2006 Jan 1;52(1):57.
5. Adab N, Chadwick DW. Management of women with epilepsy during pregnancy. The Obstetrician &Gynaecologist. 2006 Jan 1;8(1):20-5.
6. National Institute for Clinical Excellence. The Epilepsies. The Diagnosis and Management of the Epilepsies in Adults and Children in Primary and Secondary Care.Clinical Guideline 20.London: NICE; 2004
7. Yerby MS. Quality of life, epilepsy advances, and the evolving role of anticonvulsants in women with epilepsy. Neurology 2000;55(5Suppl1):21–31.
8. Hvas CL, Henriksen TB, Ostergaard JR. Birth weight in offspring of women with epilepsy. Epidemiol Rev 2000;22:275–82.
9. Morrow JI, 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 Feb 1;77(2):193-8.
10. Hernandez-Diaz S, Smith CR, Shen A, Mittendorf R, Hauser WA, Yerby M, Holmes LB, Cragan J, Hauser A, Mittendorf R, Fureman B. Comparative safety of antiepileptic drugs during pregnancy. Neurology. 2012 May 22;78(21):1692-9.
11. Man SL, Petersen I, Thompson M, Nazareth I. Antiepileptic drugs during pregnancy in primary care: a UK population based study. PLoS One. 2012 Dec 18;7(12):e52339.
12. Gedzelman E, Meador KJ. Antiepileptic drugs in women with epilepsy during pregnancy. Therapeutic advances in drug safety. 2012 Apr;3(2):71-87.
13. Rossetti AO. Tailored Choice of Antiepileptic Drugs in Patients with Epilepsy.
14. Brodie MJ, Mintzer S, Pack AM et al. Enzyme induction with antiepileptic drugs: cause for concern? Epilepsia2013; 54: 11-27
15. Saetre E, Perucca E, Isojarvi J et al. An international multicenter randomized double-blind controlled trial of lamotrigine and sustainedrelease carbamazepine in the treatment of newly diagnosed epilepsy in the elderly. Epilepsia2007; 48: 1292-1302.
16. Marson AG, Al-KharusiAM, Alwaidh M et al. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblindedrandomised controlled trial. Lancet 2007; 369: 1016-1026.
17. Glauser TA, Cnaan A, Shinnar S et al. Childhood Absence Epilepsy Study G: Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. N Engl J Med 2010; 362: 790-799.
18. Ohman I, Vitols S, Tomson T. Lamotriginein pregnancy: pharmacokinetics during delivery, in the neonate, and duringlactation. Epilepsia41(6), 709–713 (2000).
19. Sabers A. Algorithm for lamotrigine doseadjustment before, during, and afterpregnancy. Acta Neurol. Scand.doi:10.1111/j.1600-0404.2011.01627.x(2011) (Epub ahead of print).
20. Patsalos PN. Pharmacokinetic profile oflevetiracetam: toward ideal characteristics.Pharmacol. Ther.85(2), 77–85 (2000).
21. Johannessen SI, Helde G, BrodtkorbE.Levetiracetam concentrations in serum andin breast milk at birth and during lactation.Epilepsia46(5), 775–777 (2005).
22. Flesch G. Overview of the clinicalpharmacokinetics of oxcarbazepine. Clin.DrugInvestig. 24(4), 185–203 (2004).
23. Lutz UC, Wiatr G, Gaertner HJ, BartelsM. Oxcarbazepine treatment duringbreast-feeding: a case report. J. Clin.Psychopharmacol. 27(6), 730–732 (2007).
24. Westin AA, Nakken KO, JohannessenSI,Reimers A, Lillestølen KM, BrodtkorbE.Serum concentration/dose ratio oftopiramate during pregnancy. Epilepsia50(3), 480–485 (2009).
25. Bockbrader HN, Wesche D, Miller R,Chapel S, Janiczek N, Burger P. Acomparison of the pharmacokinetics andpharmacodynamics of pregabalin andgabapentin.Clin.Pharmacokinet.49(10),661–669 (2010).
26. Oles KS, Bell WL. Zonisamideconcentrations during pregnancy. Ann.Pharmacother. 42(7), 1139–1141 (2008).
27. Kondo T, Kaneko S, Amano Y, EgawaI.Preliminary report on teratogenic

effects ofzonisamide in the offspring of treatedwomen with epilepsy. Epilepsia37(12),1242–1244 (1996).

28. Reimers A, Brodtkorb E. Second-generation antiepileptic drugs and pregnancy: a guide for clinicians. Expert review of neurotherapeutics. 2012 Jun 1;12(6):707.

29. Wild C, Lehner P, Reiselhuber S,Schiller-Frühwirth I. Prevention of neuraltube defects: regional policies in folic acidenrichment and supplementation. Gesundheitswesen 72(12), 875–879 (2010)