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A Review on Antiepileptic Drugs Used During Pregnancy

M.Dhivya[1], P. Deenadhayalan[2], D. Sandya[3], G. pooja[4], S.M.Prabhu roshan[5]

[1]Assistant Professor, Department of pharmacology, Tagore college of pharmacy.
[2,3,4,5]Students, Tagore college of pharmacy.

ABSTRACT

When an epileptic woman becomes pregnant, the majority do so without any incident and have a healthy baby. But it is undeniable that a pregnant woman with epilepsy having higher risk of giving birth to child who have congenital defects. The proportional contributions of the epilepsy disorder itself are, seizure frequency during pregnancy and socio-economic variables, commonly used antiepileptic medicines (AEDs) in a pregnant woman with epilepsy and the teratogenic consequences of AEDs have proved that it is difficult to determine. There are more evidences pointed to the latter's significant contribution. For instance, babies born to mothers who had treatment for their epilepsy and had a higher prevalence of abnormalities than babies born to moms who are not having. (Kaneko 1988; Rating et al,1982, Nakane 1980). The necessity to manage seizures must be weighed against these hazards. Seizure disorder, in the over past two decades, research on antiepileptic drug (AED) use and pregnancy outcomes in woman with epilepsy (WWE) has shown the relative risk for major congenital malformations (MCM) with various AEDs and theirdose dependence. The folic acid use, anti-epileptic drug (AED) use, seizures during pregnancy and the malformation rate have been changed over time. Observations can aid in medication optimization to improve seizure management and reduce MCM risk. (Milne E ,2012,343) Numerous obstetric problems including as spontaneous abortion, preterm labour, stillbirth, neonatal death, infant hemorrhagic illness, low Apgar scores and low birth weight have been documented. From 2.9% in the non-drug using group to 3.7% in patients receiving mono therapy and 6.6% in patients receiving poly therapy, the incidence of malformations rises. Congenital heart, urinary tract defects, skeletal abnormalities and spinal bifida are the most often documented congenital malformations in children of mothers whose AEDs.

KEYWORDS: Antiepileptic Drugs, Pregnancy, Folic Acid

INTRODUCTION

Each medicine and person have a unique mechanism for changing the total exposure to AEDs during pregnancy. According to the MONEAD trial, there is no discernible difference in seizure frequency between pregnant epileptic woman and non-pregnant woman in the non-pregnant epilepsy control group for any AEDs. However, compared to 31% of the non-pregnant woman in the epileptic control group, 74% of pregnant women with epilepsy had at least one dose change during pregnancy. To reduce fluctuations brought by large changes in medication clearance, such as those that occur when a patient

becomes pregnant, regular TDM is frequently used. The event Birth Control Registry examined 1144 epileptic women of reproductive age and found that 79% of them had at least one of the episodes. (Baldwin RT, 2004,678)

AED PHARMACOKINETICS IN PREGNANCY

Pregnancy-related AMS pharmacokinetics

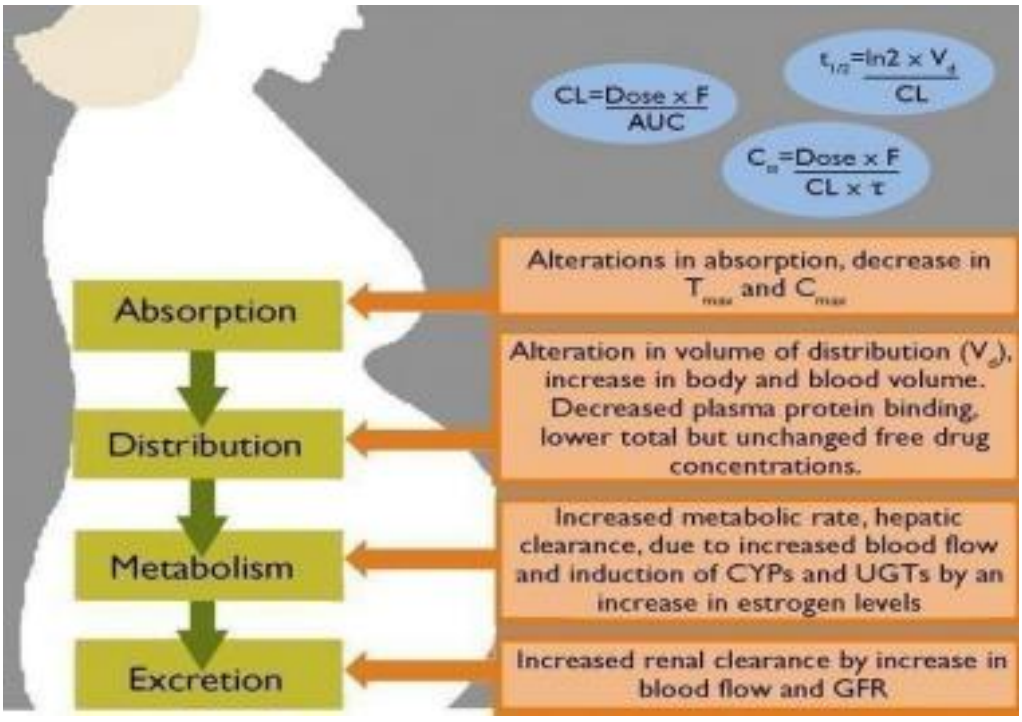
ABSORPTION

Absorption changes the patient's effective dose. Due to emesis, absorption rate can extend across people and different formulations during pregnancy. The effective dose of AEDs during pregnancy may be much lower despite their high bioavailability and broad absorption due to stomach emptying, which affects patient dose adjustments.

DISTRIBUTION

As the foetus grow, the blood volume increases during pregnancy, increasing the volume Of distribution and lowering the AED plasma concentrations . Additionally, during pregnancyalbumin and alpha-1-acid glycoprotein concentrations drop, potentially altering protein binding and the ratio of total to unbound drug concentrations. Other elements included are harmones, phenytoin and valproate.

Fig.1.Pharmaokinetic Changes In Drug Disposition During Pregnancy



METABOLISM

Both cytochrome P450 enzymes and uridine glucuronyl transferases (UGTs) are extensively metabolizedby a number of ASMs. Pregnancy-related enzyme induction causes an increase in the clearance of AEDs,which reduces seizure control.

EXCRETION

The glomerular filtration rate rises by around 50% during pregnancy, further changes mechanism of secretion and reabsorption. This process takes place throughout the first 20 weeks of pregnancy, when there is a high chance of pregnancy-related decreased serum concentrations

AIM AND OBJECTIVE

AIM

To evaluate the significance of various anti-epileptic drug and adjuvants used during pregnancy.

OBJECTIVE

1. To review the various pharmacokinetics of antiepileptic drugs used during pregnancy.
2. To analyse the importance of folic acid and its importance of preventing teratogenic effect in newborn through various literature review.
3. To analyse the underlying mechanism of folic acid as adjuvant antiepilepticdrugs during pregnancy.
4. To discuss about the futuristic scope of an alternative to folic acid in the adjuvant therapy of anti-epileptic drugs used during pregnancy.

LITERATURE REVIEW

CONGENITAL MALFORMATION:

According to Meador et al. 2007, an anatomical teratogenic mechanism of the AEDs can result in teratogenicity that is either anatomical (MCM) or behavioural (cognitive). Folatedeficiency,ischemia, neuronal inhibition, reactive intermediates (such as free radicals orepoxides) and AED-induced neuronal deaths are some of the suggested pathways. The biggest risk of physicalproblem comes from first-trimester AED exposure, whereas the highest risk appears to be predominantly from third-trimester exposure, suggesting that the mechanisms behind anatomical and teratogenic defects are distinct. Free radical generation is the prevailing theory for the mechanisms causing physical deformities, whereas AED-induced apoptosis and the malfunctions caused in surviving neurons are the major theories for the mechanisms causing behavioural and cognitive dysfunction. The genetic predisposition is at play and that multiple-liability genes may interact with teratogens. (Newman AC, 2017)

Finnell and Chernoff et al. 1987, observed that an individual variability may be partially explained byrecent developments in the teratogenic dangers of AEDs that are made possible by the establishment of numerous AEDs in pregnancy registries. Heart malformations, orofacial defects, urologic problems ,skeletal abnormalities and neural tube anomalies are the

various MCMs. The ventricular septal defect, cleftlip and palate, hypospadias, radial ray defects, phalangeal hypoplasia and spina bifida are few examples for this.

Meador et al. 2008, found that an individual anti-epileptic medication has been linked to anatomical teratogenesis. AEDs have been suspected as teratogenic potentialsince 1960s. Whencompared to other AEDs, carbamazepine has the greatest data regarding pregnancy risk. Holmesand Wyszynski et al. 2004, found an elevated risk for neural tube defects and cleft lip and palate.Jentink et al. 2010, studied the risk for spina bifida associated with carbamazepine monotherapy, validated by recent major European Surveillance of Congenital Anomalies (EUROCAT) investigation. Although it was lower than valproic acid, carbamazepine's risk was comparable to that of the other AED monotherapies.

Another study, Tomson et al. 2011, with his data taken from the EURAP epilepsy and pregnancy registry which is an observational cohort study representing a collaboration of physicians from 42 countries, prospectively monitored pregnancies exposed to monotherapy with different doseof carbamazepine, lamotrigine, valproic acid or phenobarbital, with primary endpoint of MCM detected up to 12 months after birth. This study found dose dependent effect for carbamazepine and also found that risks of malformation were significantly higher with carbamazepine than lamotrigineat doses greater than 400 mg per day. According to a meta analysis Meador et al. lamotrigine of the newer AEDs, has more data for pregnancy outcomes related to risk of MCMs. The risk of MCM is 2.91%. (Anderson DD, 2012)

Tomson et al. 2011, analysed the data from the European and International Registry of Anti epileptic Drugs in Pregnancy (EURAP) and reported the modified findings. The number of offspring with abnormalities for four monotherapies at various doses up to one year. Monotherapy samples are taken as a birth defect for up to a year. With valproic acid and phenobarbital at examined levels and with carbamazepine at doses greater than 400 mg per day, carbamazepine malformations (up to a year)were considerably higher.

Hunt et al. 2006, described about the levetiracetam-related preliminary findings from the UK Registry showing that 3 of 117 exposed pregnancies (2.7%; 95% CI 0.9-7.7%) had MCMs. Although the samplesize is modest and further researches are required to verify these results. Holmes et al. 2004, registered Phenobarbital as major abnormality which was linked to five (6.5%) of77 foetuses where phenobarbitalmonotherapy was used. Vajda et al. studied that, foetal phenytoin exposure increased the incidence of birth abnormalities by 10.5%, compared to 4.3% in those who were not exposed to AEDs. Hunt et al. studied about Topiramate that three of the 70 MCMs found in the UK Registry study of pregnancies exposed to topiramate monotherapy had MCMs. (Grupp SG, 2011).

Harden et al. 2009, made a comparative study with Valproate in comparison to phenobarbital, carbamazepine, phenytoin and lamotrigine, the AAN practice parameters found that valproate monotherapy carried a high risk of MCMs. Due to this danger, the AAN was advised against usingvalproate during the first trimester of pregnancy. Meador et al. 2008, supports meta analysis indication, an overall risk of 10.73% for MCMs in children was exposed to valproate in uterus.

According to Arta et al. 2005 and Tomson et al. 2011, the highest risk is posed by doses larger than 1000mg per day of valproate. Use of valproate monotherapy was found to be significantly associated with increased risks for six specific malformations, according to the recent large EUROCAT study. Theodd ratios were 12.7 for increased risk for spina bifida, 2.5 for atrialseptal defect, 5.2 for cleft palate,4.8 forhypospadias, 2.2 for poly-dactyl and 6.8 for craniosynostosis. Jentzink et al. 2010, estimated 38 of 1019newborns (3.7%) who were exposed to lamotrigine in the first trimester, 11 of 393 infants (2.8%) who were exposed to oxcarbazepine, and 5 of 108 infants (4.6%) who were exposed to topiramate had significant birth defects identified .(Wald NJ, 2004)

Harden et al. 2009, explained about the levetiracetam (n = 58) and gabapentin (n = 59) exposure duringthe first trimester was unusual; only 1 (1.7%) and 0 newborns respectively, were found to have birth abnormalities. Polytherapy during the first trimester is likely linked to a higher risk of MCMs. To reduce the incidence of MCMs, the AAN recommended avoiding AED polytherapy if at all possible during pregnancy. MCMs are particularly at risk from valproate (10.7%). The risk may be higher with phenobarbital (6.5%). Oral cleft risk is increased with topiramate (1.4%). Both valproate (12.7 times)and carbamazepine (2.6 times) enhance the chance of spina bifida. Numerous AEDs have showed dose-

dependent hazards, and it's possible that this is true for the entire class of AEDs.Most AEDsand particular polytherapy combinations have unknown absolute hazards.

In the previous ten years, five ASMs—ezogabine, eslicarbazepine, perampanel, brivaracetam and cannabidiol—were approved. There are no published research examining the pharmacokinetics of ezogabine, eslicarbazepine and cannabidiol in pregnant individuals. Eslicarbazepine's teratogenicity was not conclusively proved in one study. A case study of three pregnant women taking brivaracetam revealed no MCMs, but two newborns had three minor congenital abnormalities.

TABLE .1.AED'S AND IT'S PROTEIN BINDING

AED	MAJOR ROUTE OF METABOLISM	PROTEIN BINDING
PHT	CYP2C9	High
PB	CYP2C19	High
CBZ	85% CYPs (CYP3A4 major)	High
VPA	50% by glucorinide conjugation	High, but notsaturable binding
PB	CYP2C9 & 2C19	High
PRM	Renal excretion of parent drug	<20%
LTG	70-90% glucoronidation by UGT1A4	55%
TPM	60-80% excreted unchanged	15%
OXC	Keto-reduction to MHD	40%
LEV	66%renal excretion	0%
PGB	Renal excretion	0%

TABLE .2.INFLUENCE OF VARIOUS AED'S DURING PREGNANCY

	1998-2004N(%)	2005-2011N(%)	2012-2017N(%)	TOTAL N(%)	p
Age (mean± SD)	25.7±4.4	26.1±4.3	26.7±4.3	26.1±4.4	0.001
Epilepsy classification N (%)					
Generalized	299(45.0)	274(46.5)	227(46.5)	800(45.9)	0.084
Focal	366(55.0)	315(53.5)	258(52.9)	939(53.9)	

Folic acid (5mg/day) usage N (%)					
Pre-pregnancy	232(43.9)	445(68.0)	435(81.0)	1112(64.7)	0.001
First trimester	290(52.7)	506(75.5)	471(86.6)	1267(71.8)	0.001
Antiepileptic drug use in first trimesterN (%)					
Nil	118(17.4)	82(11.6)	49(8.5)	249(12.7)	0.001
Monotherapy	399(71.1)	446(71.6)	361(68.2)	1206(61.5)	0.418
Polytherapy	162(28.9)	177(28.4)	168(31.8)	507(25.8)	
Seizures during pregnancy N (%)	363(57.2)	339(50.2)	183(32.9)	885(47.4)	0.001
Major congenital malformation N (%)					
All pregnancies	51(7.5)	46(6.5)	42(7.3)	139(7.1)	0.759
Monotherapy	29(7.3)	25(5.6)	22(6.1)	76(6.3)	0.599
Polytherapy	18(11.1)	16(9.0)	16(9.5)	50(9.9)	0.802
Carbamazepine	247(36.4)	268(38.0)	208(36.0)	723(36.9)	0.917
Clobazam	32(4.7)	83(11.8)	120(40.5)	235(12.0)	0.001
Clonazepam	20(2.9)	22(3.8)	8(1.4)	55(2.8)	0.029
Oxcarbazepine	4(0.6)	44(6.2)	56(97)	104(5.3)	0.001
Levetiracetam	0	24(3.4)	10(17.5)	125(6.4)	0.001
Lamotrigine	7(1.0)	32(4.5)	32(5.5)	71(3.6)	0.001
Phenobarbitone	161(23.7)	113(16.0)	49(8.5)	323(16.5)	0.001
Phenytoin	121(17.8)	65(9.2)	31(5.4)	217(11.1)	0.001
Topiramate	4(0.6)	16(2.3)	10(1.7)	30(1.5)	0.035
Valproate	142(20.9)	153(21.7)	101(17.5)	396(20.2)	0.147

A. PHENYTOIN

According to earlier research on phenytoin Bossi et al.,1980; Chen et al., 1982; Dansky et al., 1982; Lander et al., 1980; Tomson et al., 1994, suggested that apparent clearance of the drug rises by 20–150% during pregnancy and is frequently linked to an increase in seizures. Over the first 12 weeks after delivery, PHT clearance falls back to pregestational levels. One case study (Ramsey et al., 1978) described a marked reduction in PHT absorption that resulted in status epilepticus while pregnant. Antacid usage, which can generate PHT-soluble compounds, has been linked to malabsorption on occasion. But it's likely that the enhanced hepatic metabolism by the CYP450 system, which occurs more often during pregnancy, is what's to blame for the drop in PHT concentrations. In spite of the fact that the ratio of free PHT to total plasma drug concentration rises during pregnancy in most research. Although free PHT levels only reduced by 16% relative to baseline, total PHT levels plummeted progressively throughout pregnancy and by 61% at the end. According to Yerby et al. (1990), the mean concentration of PHT dropped by 56%, with the first trimesterseeing the biggest. A hydantoin derivative called phenytoin was first used to treat tonic- clonic /focal seizuresand status epilepticus in 1939. The substance is 90–95% bound to proteins and is processed by the cytochrome P450 enzyme. Data on 125 phenytoin-treated pregnancies with daily dosages ranging from 30 to 730 mg were reported by the EURAP registry. Between the first and third trimesters, phenytoin serum levels decline by 55–61%. On the other hand, phenytoin clearance increased starting in the first trimester, perhaps as a resultof less protein binding, and reached statistical significance only during the third trimester.54, Because of thesefactors measuring free phenytoin plasma concentrations is better for AED. (Bergen Epilepsy Research Group, 2022).

B. CARBAMAZEPINE

In 1994 Thomson et al discussed that, during the third trimester, free CBZ concentrations remained steady while total CBZ concentrations very slightly decreased. When compared to before pregnancy, plasma clearance of both total and free CBZ actually reduced.to the baseline.Other investigations (Battino et al., 1985; Yerby et al., 1985, 1992) have shown low (15%) to no change in CBZ clearance during pregnancy. According to Perucca and Crema (1982), CBZ binds to both albumin and, which combined may help to withstand alterations in protein binding during pregnancy. First-generation ASM carbamazepine functions as a sodium channel blocker (SCB).45 CYP1A2, CYP2C8, and CYP3A4 are responsible for metabolizing carbamazepine, which is 75% protein bound.53 Carbamazepine-10,11-epoxide is its main active metabolite. The FDA has given it the go-aheadto treat acute mania, trigeminal neuralgia, and focal epilepsy.

C. PHENOBARBITAL

Insufficient research on PB during pregnancy leads to the conclusion that clearance rises over time (Battinoet al., 1984; Lander et al., 1981; Yerby et al., 1990).According to Yerby et al. (1990), the average total PB concentrations decreased by 55% throughout the first trimester of pregnancy. Lander et al. (1981) were ableto calculate the mean ratio of PB plasma clearance in the third trimester to clearance in the pre- or post- pregnancy condition despite prospectively examining. The first generation ASM is phenobarbital. Its primary mode of action involves attaching to GABA-Areceptors
and delaying chloride channel opening. Following oral ingestion, 80% is absorbed in the gastrointestinal tract and portion of it (25–50%) is excreted by the kidney in its original form. About 50% of the plasma

protein is bound, and in the liver, it is metabolized via N-glucosidation (25% of it) and aromatic hydroxylation (9%) catalyzed by CYP2C9.

D. PRIMIDONE

Acccording to battino et al , Primidone(PRM) concentrations tended to rise during the second trimester of pregnancy , according to a study of the drug in nine women.

E. VALPROIC ACID

According to Koerner et al. (1989), VPA clearance increased after the second trimester but free VPA clearance remained constant, which is consistent with a rise in the free percentage. The first generation antiepileptic medication is valproate. It works through a number of different methods, including the inhibitionof several tricarboxylic acid cycle enzymes and the GABAergic system. By hepatic glucuronidation, which is carried out by UDP Glucuronosyltransferase and a number of cytochrome P-enzymes (CYPs), valproate, which is 90% protein-bound, is eliminated.Unbound serum concentration does not vary throughout late pregnancy, although total serum concentrations can decrease by up to 40%. Drug dosage adjustments and monitoring (only free fraction reasonable) are not required during gestation or the postpartum period.

F. ETHOSUXIMIDE

Studies (Kuhnz et al., 1984; Tomson et al., 1990, on the metabolism of ethosuximide (ESX) during pregnancyshow variable alterations. Ethosuximide is the first-generation ASM that affects T-type calcium channels; ithas a high oral bioavailability and a low level of protein binding. Ethosuximide is metabolized by the liver. Its primary inactive metabolite, the hydroxyethyl derivative, is eliminatedby the kidneys as glucuronide.

G. LAMOTRIGINE

Other studies (de Haan et al., 2004; Tran et al., 2002; Vajda et al., 2006) have reported that, the documentedincreases in LTG clearance during pregnancy are more significant than those mentioned for AEDs that are predominantly eliminated up to 75% of women experienced seizure exacerbation during pregnancies on LTGor consequences of convulsive seizures, status epilepticus, and even foetal death. According to the second study by Pennell et al. (2004), LTG clearance increased up until 32 weeks of gestation and peaked at 230% over baseline levels before pregnancy. In a more recent Class I study, Pennell et al. (2008) found that LTG free and total clearance increased throughout all three trimesters, with peaks of 94% (total) and 89% (free) inthe third trimester, using 305 samples from preconception baseline, pregnancy, and postpartum.As acomparative study, by Ehmer et al. 2004, When compared to black patients, white patients had significantly greater levels of free LTG clearance. Significant interindividual variability was seen in these studies, which may be connected to UGT polymorphism variations. The second-generation AED is lamotrigine. More so than GABA, it prevents the release of glutamate. Lamotrigine is extensively metabolized by UDG- glucuronyl transferase and is 55% protein-bound. The FDA and EMA have approved lamotrigine for both focal and generalized seizures. During pregnancy, the levels of lamotrigine and its 2-N- glucuronide metabolite in the blood might drop by up to 70%.113,114 The dose-normalizedconcentrations during pregnancy reduced by up to 56.1%,

according to recent data from a prospective, observational cohort study of drug plasma concentrations in women taking monotherapy or in combination with noninteracting drugs.

H. OXCARBAZEPINE

According to Christensen et al, OXC monotherapy was linked to an increased risk of convulsive seizures. The FDA and EMA have approved oxycarbazepine for the treatment of focal-onsetseizures. Eslicarbazepine(or S-licarbazepine) and the inactive R-licarbazepine are produced following oral ingestion. The major method for eliminating both stereoisomers is glucuronidation. In 64-100% of oxcarbazepine pregnancies, theplasma concentration dropped from the first trimester and the lowest concentration observed after week 20was reported, and dose modifications were made in 86- 100%.141-143 Within the first 4 to 8 weeks following delivery, serum concentrations revert to normal.142 Therefore, it is advised to periodically (eg. monthly) monitor oxcarbazepine serum levels during pregnancy and daily during the first week after delivery. We can recommend using oxcarbazepine in pregnancy with caution based on all the data that is now availableregarding the risk of MCM and long-term effects. .(Olesen C, 1999).

I. LEVETIRACETAM

As per the studies by Tomson et al in (2007) Levetiracetam (LEV) is largely excreted by the kidneys (66%),with the remainder being removed through extrahepatic hydrolysis.(Thompson JR,2004) synaptic vesicle protein SV2A is the binding site for the second-generation AED levetiracetam. It has alow affinity for proteins and a high bioavailability.Levetiracetam is renally eliminated with little to no metabolization. It has approval for myoclonic jerks, generalized epilepsies, and add-on treatment for focal seizures.Although levetiracetam is primarily beneficial in the treatment of focal seizures, it also carries certain MCM-specific hazards in the treatment of bilateral tonic-clonic seizures and, to a lesser extent, myoclonic seizures.During pregnancy, serum concentrations decrease by 40–60%. According to recent studies, levetiracetam dose-normalized concentrations decreased by 36.8% during pregnancy. Levetiracetam is one of the most suitable ASMs for WWE in reproductive age due to its benign profile for despite large increasesin blood level during pregnancy.

J. BRIVARACETAM

Brivaracetam, a more recent ASM45 acting with a higher binding affinity for the synaptic vesicle protein, isthe 4-n-propyl analogue of levetiracetam. The drug is distinguished by low plasma protein binding, hydroxylation-based metabolism, and renal elimination. Only three reports of WWE athletes receiving brivaracetam during pregnancy exist as of yet. Patients 1 and 2 each exhibited focal epilepsies, while patient 1 had idiopathic generalized epilepsy. The daily doses of brivaracetam ranged from 50 to 200 mg.

K. CLOBAZAM

In 2011, the FDA and the EMA approved the 1.5-benzodiazepine clobazam. Additionally, it is applied as an adjuvant treatment for focal epilepsy, refractory status epilepticus, and Dravet syndrome. Other AEDs are frequently used alongside clobazam.Clobazam binds to the GABA-A receptor and enhances chloride conduction, which causes the postsynaptic membrane to become hyperpolarized. The medication undergoes hepatic metabolization to the active forms, N

desmethylclobazam and 4-hydroxyclobazam, and has a plasmaprotein binding of 85–91%.

L. ESLICARBAZEPINE ACETATE

Eslicarbazepine acetate is the second-generation drug that accelerates the voltage-gated sodium channel delayed inactivation. The prodrug undergoes rapid pharmacologic enantiomer conversion to S-liacarbazepine (95%) , which largely excreted by the kidneys. (Thompson JR,2004)

M. FELBAMATE

A dicarbamate derivative known as felbamate was authorized as an adjective therapy by the FAD and EMA in 1993. N-methyl-d-aspartate (NMDA) receptor antagonist , GABA agonist and sodium channel blockers are just a few of the many ways it works . It has a high oral bioavailability and a low protein binding. It is removed through oxidative metabolism and renal excretion , resulting in the production of an intermediate metabolite .(Bithell JF,1975)

N. GABAPENTIN

A second-generation calcium channel blocker is gabapentin. It binds the voltage-gated calcium channel's alpha-2-delta subunit. Due to a saturable amino-acid uptake transporter in the gut, it has a poor bioavailabilitythat declines at increasing dosage. Without being metabolized, gabapentin isserum unbound and removedby the kidneys. Only adjunctive therapy of focal seizures is FDA/EMA approved. (Lupattelli A,2019)

O. LACOSAMIDE

Lacosamide is the second-generation drugs enhancer that slows down the activation of voltage-gated sodium channels, much like eslicarbazepine acetate does. 100 lacosamide has a high oral bioavailability and linear pharmacokinetics; it is largely metabolized by demethylation in the liver (by CYP2C19 in 30% of cases)101 and is excreted unaltered in the urine in about 40% of cases.82 It is licensed by the FDA and EMA as an adjunctive treatment for focal epilepsies and seizures in adults. (D. Moher,2010)

P. PERAMPANEL

Perampanel is a third-generation ASM45 that blocks the glutamate-AMPA receptor ion channel with selectivity and non-competition. It has a high protein binding percentage (96%), is processed by the liver viaCYP3A4, and is eliminated in the urine and feces. (Czeizel AE,1992).

Q. PREGABALIN

Pregabalin has a greater and dose-independent bioavailability than gabapentin, a third- generation drug that ischemically linked to it. It is renally eliminated and not protein-bound. It is FDA/EMA approved as an adjunctive treatment for focal seizures, however it is most frequently used for neuropathic pain, anxiety, or mood problems. (Smithells RW,1980).

R. TOPIRAMATE

Topiramate is a the second-generation drugs AED with various modes of actions including blocking voltage- gated sodium channels, antagonizing the kainite and AMPA (alpha-amino-3-hydroxy methylisoxazole-4- propionic acid) receptors, and increasing GABA.15% of topiramate's protein binding

makes it renally excretedwithout significant metabolism. For migraine and both focal and generalized seizures, it has FDA and EMA approval. Data on the children's cognitive outcomes are not statistically significant. During the third trimester,serum levels might drop by 30–40%.(Daltveit DS,2020)

S. ZONISAMIDE

The FDA and EMA both approved the second-generation drugs ASM medication zonisamide in 2000 and 2005, respectively, as an adjunctive treatment for focal seizures. It works in two ways: by moderating voltage- sensitive sodium and calcium channels, it modifies GABAergic and glutamatergic neurotransmission while also weakly inhibiting enzymes. Following oral ingestion, it is quickly absorbed, has a 50% plasma protein binding rate and is primarily removed through biotransformation (GBD 2017 Childhood Cancer Collaborators).

FOLATE DEFICIENCY AS A POTENTIAL MECHANISM AED TERATOGENICITY

Folate is a coenzyme required for the formation of white and redblood cells as well as for healthy brain and spinal cord. Dr Lucy Wills, a pioneering medical researcher, discovered that, what is now known as folic acidin 1931. She treated pregnant women with macrocytic anaemia using a yeast extract employee in Mumbai. Serum values (6–20 ng/ml) and erythrocyte concentrations (160–640 ng/ml) are typically considered to be normal. The quantities needed to prevent hyperhomo cysteinemia, which is linked to low levels of folate, are 6.6 ng/ml for serum folate and 140 ng/ml for red blood cell folate.

Folate deficiency has been linked to the emergence of birth abnormalities.

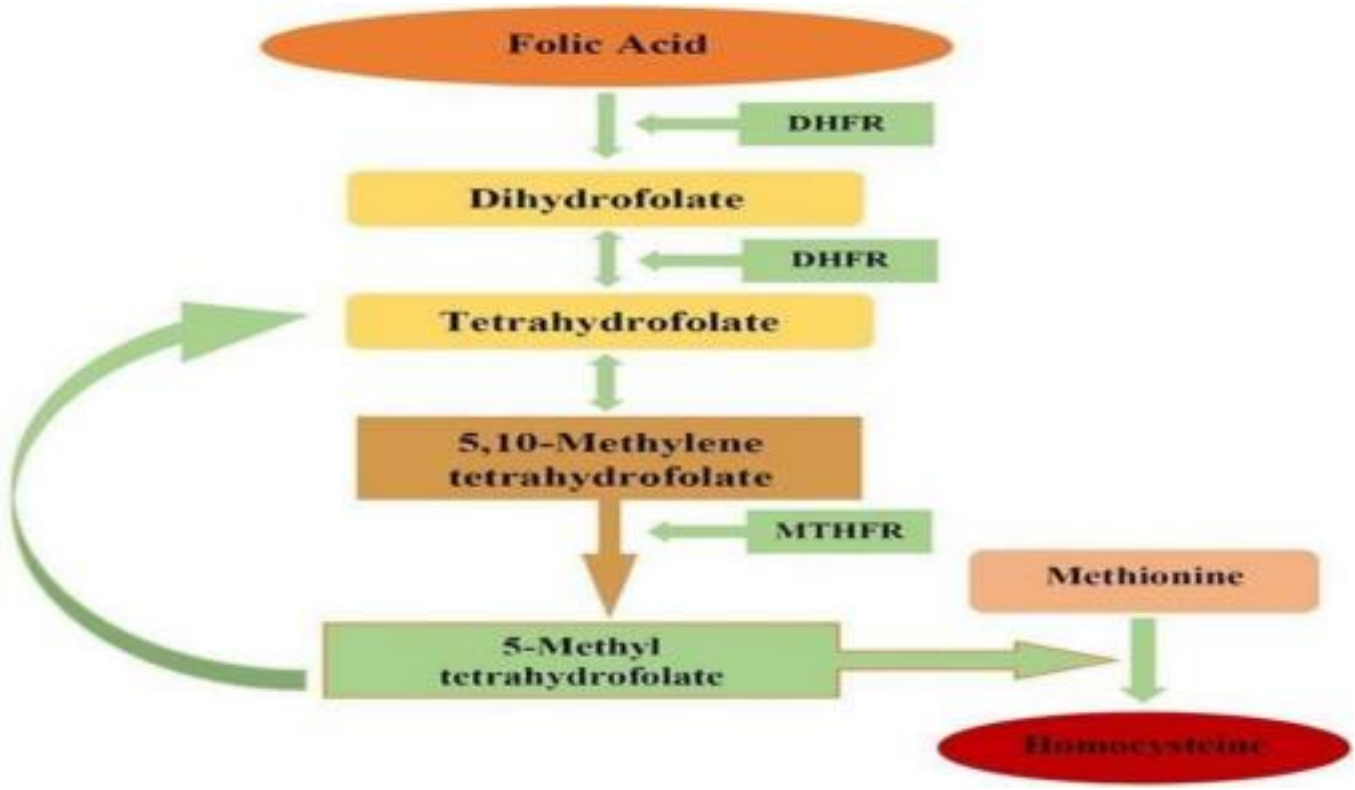
According to Dansky et al. WWE with unsatisfactory pregnancy outcomes had significantly lower blood folateconcentrations. Increasing foetal weight and length in mouse pups exposed to phenytoin (PHT) in utero and decreasing malformation rates were two effects of treating mice with folic acid, with or without vitamins andamino acids. While none of the 33 infants of moms who took folate supplements had congenital abnormalities.Biale and Lewenthal observed a 15% malformationrisk in IME without it. Eight studies have shown that periconceptional folate lowers the chance of NTD recurrence in women whose prior pregnancy was troubled.Sadly, supplementing with folate during pregnancy possibly not safe for WWE. A young woman's seizures were managed for 4 years with 2,000 mg of VPA per day, according, to a case study by Craig and colleagues.She consumed 4.0 mg of folic aciddaily for 18 months prior to become pregnant, yet the baby she gave birth had a lumbosacral NTD, a ventricular and atrial septal defect, a cleft palate, and bilateral talipes. Other investigations (46–51) were unable to decisively show that periconceptional folate has a protective effect. The small sample sizes, the absence of documentation of folate supplementation and recollection bias in the retrospective investigation made these findings dubious. There is evidence to show that variations in folate metabolism may cause women with similar folate consumption to have varied blood concentrations.

For non-pregnant men, pregnant women, and nursing women, the recommended daily limits for oxalate havebeen increased to 0.4 mg, 0.6 mg and 0.5 mg, respectively. Some have called for higher folate supplementationon the order of 0.5-0.6 mg/day due to the increased folate catabolism during pregnancy and the variance in requirements by individual woman. All women of childbearing age should take a folate supplement, even those with epilepsy. The Centres for Disease Control and Prevention (CDC) recommends 0.4 mg of folate perday, which may not be high enough for the large number of women who do not adequately metabolize folate. (EbbingM,2009).

ROLE OF FOLIC ACID

Folic acid levels in epileptic patients on enzyme-based anti-epileptic medications are too low. Foetal birth abnormalities are more likely in women who are pregnant or breastfeeding because of low serum, RBC and folic acid levels for both genders. The risk of cardiovascular disease from excessive homocysteine levels are linked to low levels of folic acid. (Smith AD,2008).

Fig.3.Mechanism Of Folic Acid



Both levetiracetam's and other medicines protein binding are not significantly affected by it. Thus the danger of medication interactions is relatively low due to its poor protein binding and absence of hepatic metabolism. Levetiracetam is extremely safe and patient-friendly in terms of metabolism and phosphatidylcholine metabolism. (Koseki K,2020)

Women were more likely to consume enough folic acid if their pregnancies were planned. This was in line with findings from earlier population-based studies and a study of pregnant women in general conducted at a hospital.A planned pregnancy was found to be the biggest predictor of an adequate consumption of folic acid in the current study. However, women with epilepsy who had planned pregnancies tended to have lesser foetal exposure to AEDs through the selection of monotherapy and by avoiding the use of valproate sodium. Another study indicated a non-significant connection between planned pregnancy and prescription of folic acid. The current study also discovered that women with planned pregnancies used valproate sodium less frequently than women with unplanned pregnancies (37.5% versus 55.7%, respectively). Despite the fact that 15% of both of these groups used AED polytherapy on a regular basis. A planned pregnancy may enhance the mother's behaviour such as folic acid intake prior to conception and AED adjustment to reduce teratogenic risk. On the other hand, a mechanism may need to be devised to direct women toward adequate folic acid intake prior to trying to get pregnant because unexpected pregnancies now make up the majority of pregnancies. [4] Potential

side effects of folic acid supplements, are numerous, in case studies regarding how folic acid and various AEDs interact with one another. In one study, four male folate-deficient individuals with epilepsy were examined to determine how folic acid (1 mg/day orally) affected the steady-state pharmacokinetics of phenytoin. Folic acid is strongly suspected to be a cofactor in the metabolism of phenytoin based on pharmacokinetic studies of this interaction. The effectiveness of phenytoin breakdown is considerably increased by higher folate levels, which seem to boost the affinities of metabolizing enzymes. In a different case report, a patient with megaloblastic anaemia who received folic acid treatment, saw an increase in seizure frequency and a decrease in the serum levels of the anticonvulsant carbamazepine and phenobarbital. The foetal levels of folic acid are typically 2-4 times greater than the maternal levels because the placenta concentrates it into the foetal circulation. The foetus needs this nutrient for rapid growth and cell division. All epileptic women should receive daily folic acid supplements before getting pregnant and throughout the pregnancy.

FOLATE's SIGNIFICANCE IN PREGNANCY

Due to the foetus, placenta and maternal tissues growing quickly during pregnancy, there is an increase in the need for folate. Pregnancy issues connected to the placenta, such as spontaneousabortions, premature births, preeclampsia and foetal growth limitation, are associated with folate insufficiency during pregnancy, along with maternal anaemia and poor placenta implantationand vascularization. Congenital abnormalities such neural tubeand heart problems, as well as neurodevelopmental diseases like autism spectrum disorder, are also linked to folate deficiency .

The precise mechanisms at play are still largely unclear, but changes in DNA and RNA synthesis, an accumulation of hazardous levels of homocysteine and altered gene methylation have all been proposed as potential culprits. Neural tube abnormalities are avoided in the general population by prenatal folic acid supplementation. As a result, the World Health Organization (WHO) advised that everyone considering a pregnancy, take 0.4mg of folic acid daily before becoming pregnant and throughout the pregnancy. According to recent research, prenatal folic acid supplementation was linked to better cognitive function and a lower risk of poor neurodevelopment in children, including autism spectrum disorders and language impairment. The recommendations are supported by high- quality research on the relationship between folate levels and neural tube abnormalities. There is strong evidence that maternal red blood cell folate concentrations >906nmol/L protectagainst folic acid- related neural tube defects in the foetus. Serum folate concentrations of >28-30nmol/L or red blood cell folate concentrations >906nmol/L have been extensively evaluated in pregnant populations. With a daily diet of 800 g of folic acid, individuals from the general population may reach a preventative red blood cell folate content of more than 906 nmol/L in 4 weeks. After 40 weeks, 35% of people had red blood cell folate concentration of less than 906 nmol/L when taking a daily folic acid supplement of 140 g and 18% when taking a 400 supplement.

ALTERNATIVE TO BETAINE FOLATE

Folate, Choline, and DMG as Betaine Determinants.

We used a Gaussian generalized additive regression (GAM), which generates dose-response curves adjusted for age, sex, and other characteristics, to study the association between betaine and indices exhibiting a straightforward correlation with betaine, such as folate, choline, DMG, creatinine, vitaminB6, and age. The relationship between serum folate, choline, and DMG and betaine was positive,

however the curves for choline and DMG peaked at 14 mol/L and 4 mol/L, respectively. In this regression model, betaine had an inverse relationship with creatinine and no relationship with vitamin B6. The relationships were found using GAM, that is largely agreed with those found using it. (spector LG , 2015)

Plasma Levels and Determinants of Betaine, Choline, and DMG

Because choline is betaine's immediate precursor, it demonstrated the linear relationship with betaine and was the best metabolic predictor of betaine. Folate and betaine also displayed a linear relationship, pointing either shared dietary sources 25 or a mutually beneficial effect of sparing. Final thought, DMG creation from betaine may be reflected in the first linear relationship between DMG and betaine at low DMG. Pathologies include cancer and cardiovascular disease, which have altered homocysteine and folate metabolism, should have their betaine status examined. (Sauter M,2021)

PREGNANCY WITH NEW AED

Since 1993, a number of new AEDs has developed the market. In the United States, you can now buy gabapentin (GBP), felbamate, lamotrigine (LTG), levetiracetam (LEV), oxcarbazepine (OXC), tiagabine, topiramate (TPM), and zonisamide (ZNS). Unfortunately, there was very few recorded pregnancies with exposure to these medicines, making it impossible to say whether there is an increased risk of negative outcomes, when foetal exposure to these substances. We are aware that the concentrations of LTG and LEV decreases during pregnancy, and we anticipate that the other novel AEDs will follow suit. (Br J Cancer. 2017)

GABAPENTIN

Dr Georgia Montouris has gathered data on 51 pregnancies involving 39 women who received GBP. Major deformities occurred at a 4.5% rate. A live birth occurred in 87% of the pregnancies, a miscarriage in 11.3%, anda therapeutic abortion in 2%.(Sauter M,2021)

LAMOTRIGINE

There have been 334 pregnancies documented in women who received LTG in the first trimester, according to the International Lamotrigine Pregnancy Registry. 166 of these were treated with polytherapy, and 166 with monotherapy. (Marcotte EL,2015)

Major structural birth defect rates varied significantly depending on whether LTG was administered as monotherapy (1.8%), polytherapy with VPA (10%), or polytherapy without VPA (4.3%). LTG penetrates the placenta, and at birth, the plasma concentrations of the mother and foetus are comparable. In babies, eliminationseems to happen gradually. The infant's plasma level is 75% that of the mother 72 hours after delivery. The average ratio of milk to plasma is 0.61.

OXCARBAZEPINE

In a recent prospective study, OXC was administered to 42 pregnant women as either monotherapy (n = 25) or polytherapy (n = 17). In the monotherapy group, no abnormalities were observed. OXC and phenobarbital (PB) polytherapy had been administered to a youngster with a ventricular septal defect. OXC crosses the placenta at levels that are the same in cord and maternal blood .

TOPIRAMATE

The number of pregnancies involving TPM exposure is not well known. There were 28 reported pregnancies in the clinical trials, one deformity, and two abnormal children. These were all polytherapy patients. 139 reports ofpregnancy have been gathered through post-marketing surveillance. 29 instances were lost to follow-up, there were five cases of hypospadias, and 87 of these resulted in live births and 23 in therapeutic abortions. TPM passesthe placenta, and at delivery, the levels in the cord and the mother's plasma are equal. Plasma to milk concentrationratios are typically 0.86. Little detectable medication was discovered in the plasma of breastfed infants 2-3 weeksafter delivery, indicating that baby elimination appears to be significant.

ZONISAMIDE

There have been 26 documented pregnancies involving ZNS. 7.7% of the 26 foetuses, or 2 of them, had congenitaldefects. Both PHT and VPA were exposed to one of these two, whereas both were exposed to the other. ZNS readily crosses the placenta as well, with 92% transfer rates. According to data from two children, the eliminationhalf-life is between 61 and 109 hours, and the ratio between breast milk and plasma concentration is 0.8.

DISCUSSION

Some AEDs, particularly those that activate cytochrome P450 enzymes, affect the absorption and metabolism of folate. Drugs including carbamazepine, phenobarbital, phenytoin, and primidone accelerated the breakdown offolate, which may obstruct the conversion of homocysteine to methionine and raise homocysteine concentrations.While there are fewer data for lamotrigine, low folate or high homocysteine concentrations have been associated with continuous use of valproate, topiramate, gabapentin, oxcarbazepine, and levetiracetam. Lamotrigine useexhibited lower folate metabolite concentrations than untreated patients with epilepsy, according to the fewresearch on folate among pregnant epileptics. Particularly high levels of homocysteine, poor DNA methylation,inhibition of folate receptors and carriers, and low quantities of folate in the brain and placenta have all beenlinked to valproate. Folic acid supplementation may therefore help to lower chances of AED toxicity in pregnancy. Authors have proposed that some of the negative effects of prenatal AED exposure in the foetus could be mediated through maternal folate deficit because many of the unfavourable outcomes in children reported after maternalfolate deficiency in the general population overlap with those seen after prenatal AED exposure. Children ofmoms who take anti-seizure medicine (ASM) are likely to benefit from folate. Optimal folate levels should bemaintained both before and during pregnancy. Although the idealdose of AED is unknown, current recommendations call for doses of 0.4–4 mg per day prior to conception and for at least the first 12 weeks of pregnancy. Supplementing more folic acid should be avoided as the safety of extra folic acid is under debate. Theideal serum folate level in expected womenwithout epilepsy is >28-30 nmol/L or >906 nmol/L for red blood cells. A feasible technique for managingpregnancy in people with epilepsy being treated with ASM is titrating the folic acid dose in accordance with the folate concentration. Vitamin B12 insufficiency should also be assessedprior to beginning folicacid therapy because folic acid supplements have the potential to disguise it. Future research should concentrate on the effectiveness and safety of adjusting the dosage of folic acid based on concentration measurements.

CONCLUSION

The influence of various kinds of antileptic drugs have been reviewed using literatures.Based on the Studies levetiracetam seems to be the most suitable drug of choice AED drug during pregnancy,due to its low affinity to protein binding.Folic acid seems to be the most essential adjuvant to pregnancy mother with AED'S.Being folic acid as one of the important precursor for homocysteine level,betaine also seems to be one of the precursor for homocysteine which is a factor responsible for congenital malformation in pregnancy.Anyhave,the role of betaine in pregnancy AED'S is concluded only through various research.

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