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Original Research Article

A Retrospective Research to Assess the Usage of Levetiracetam During Pregnancy in Epileptic Mothers

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Abstract

Aim: The aim of the present study to determine the levetiracetam use during pregnancy in women with epilepsy.

Methods: A retrospective study was conducted in the Department of Pharmacology, ICARE Institute of Medical Sciences and Research & Dr. Bidhan Chandra Roy, Hospital, Haldia, West Bengal, India for 1 year. All female cases of >18 years epileptic women with pregnancy that were included in this study. 100 women were found to have active epilepsy and were using AED before conception and through the whole pregnancy (WWAE). The other group included 100 pregnant women, in which the mother reported having seizures 5 years or more before conceiving but no need for AED at the time of pregnancy were termed non-active epilepsy cases.

Results: The mean age of patients was 24.5 years (range 18–42 years). Majority of our women (73) were multiparous (73%), 65 women (65%) were from low or rural stratum. Complete outcome data were available for 100 pregnancies. Of these 45 pregnancies had been exposed to levetiracetam in monotherapy and 55 had been exposed to Levetiracetam in combination with at least one other AED. Mean gestational age at enrolment was 14.5 weeks (standard deviation 10.55 range 5 to 38 weeks). We observed 58 (58%) women with generalized epilepsy (absence or myoclonic seizures), 37 (37%), women with focal epilepsy (localization related) and 6% with unspecified epilepsy. 61% of patients did not experience any change in seizure frequency, 20% experienced a change for better.

Conclusion: Pregnancy course is uncomplicated and neonatal outcome is good in the majority of women with active epilepsy with proper antenatal and neurologic care. Levetiracetam taken in monotherapy can be considered as safer alternative for women with epilepsy of childbearing age.

Keywords: Antiepileptic drugs, epilepsy, fetal malformation, levetiracetam, pregnancy

Introduction

Despite decades of research, choice of antiepileptic drugs (AEDs) during pregnancy in women with epilepsy (WWE) continues to be debated, the main reason being the fact that both epilepsy and its treatment (AEDs) can have deleterious effects on mother and

neonate[1]. Most of the conventional AEDs are associated with harmful teratogenic effects on the fetus. Thus, there is an urgent need of AEDs which are both (a) effective in seizure control and (b) free from teratogenic side effects. Levetiracetam (LEV) is one such AED which is supposed to be effective in controlling seizures during pregnancy and relatively free of teratogenic side effects[2]. Levetiracetam is an anticonvulsant used either in monotherapy, or as adjunctive therapy for focal or partial onset seizures with or without secondary generalisation, myoclonic seizures in juvenile myoclonic epilepsy, and primary generalised tonic-clonic seizures.

Overall, congenital malformation rates have been studied in approximately 2,000 infants prenatally exposed during the first trimester to levetiracetam monotherapy, with no evidence of any increased risk, although in some cases study methodologies limit conclusions. There are also currently no identified associations between levetiracetam exposure and a small number of specific malformations[3]. Although some studies have shown that use of levetiracetam in polytherapy may be linked to an increased risk of malformations compared to levetiracetam monotherapy, data are conflicting and, in some cases, potentially confounded by co-exposure to sodium valproate, an established teratogen. There is currently no evidence of a dose-effect. Emerging data on the teratogenic potential of antiepileptic drugs (AEDs), in particular valproate, have resulted in a prescribing shift towards lamotrigine and levetiracetam in women of childbearing age with epilepsy[4] Over the last 20 years prescription of lamotrigine to women of childbearing potential has increased tenfold in the UK, with a reduction in valproate prescription of one third.[3] However, use of lamotrigine and levetiracetam during pregnancy can be associated with other difficulties. It is widely documented that lamotrigine clearance increases by up to 330% in pregnancy[5] with studies showing an increase in seizure frequency in 39–45%of women[6,7]. Early studies have also shown that serum levels of levetiracetam fall by 40–62% during the second and third trimesters of pregnancy[8]. In contrast to lamotrigine very little is known about whether this is clinically significant. To date, the largest report of seizure control in women taking levetiracetam during pregnancy included only 19 patients[9]. Although increased seizure frequency was observed in seven women, the authors felt that no definite conclusion could be drawn between declining levetiracetam dose/concentration ratios and seizure breakthrough. Two other small studies are complicated by inclusion of women taking both lamotrigine and levetiracetam as part of polytherapy regimens[10].

Materials and methods

A retrospective study was conducted in the Department of Pharmacology, ICARE Institute of Medical Sciences and Research & Dr. Bidhan Chandra Roy, Hospital, Haldia, West Bengal, India, for 1 year, after taking the approval of the protocol review committee and institutional ethics committee. All females cases of >18 years epileptic women with pregnancy that were included in this study.

Methodology

All obstetrics parameters were studied in detail including fetal outcome. The obstetric data derived from pregnancy register were supplemented with detailed neurologic data retrieved from the medical records for the patients with epilepsy; information about the AED treatment and number and types of seizures and the course of epilepsy were obtained for WWAE. The seizures and epilepsy types were recorded according to the most recent classification of the international league against epilepsy.11 The pregnancies

were divided into two groups according to the mother's epilepsy: - 1. Those with epileptic seizures occurring less than five years before conceiving (termed active epilepsy); 2. Those with seizures five years or more before conceiving (termed Non Active Epilepsy) were excluded. We identified the type of epilepsy according to the hospital case records made by a Neurologist. We classified epilepsy as either generalized or focal and as unspecified if the woman could not be assigned to either of these two groups. All geographic prevalent regional conditions and previous studies done in addition lead to predesigned Performa to be filled by trained obstetricians to gather comprehensive data. WWAE were receiving Levetiracetam (LEV) monotherapy/polytherapy. Monotherapy was defined as exposure to LEV only, and polytherapy as exposure to LEV and at least one or more additional AED taken any time during pregnancy, whether concurrent or not. Changes in AED regimens did not affect eligibility for inclusion. In situations of seizure recurrence and/or AED toxicity, appropriate dosages adjustments were performed. Therapeutic drug monitoring of AED was not done.

Folate substitution was used before conception and during the pregnancy systematically in which the pregnancy was preplanned. During the entire study period, all new born received intramuscular injection of 1 mm vitamin K at birth to avoid coagulation affect. Premature delivery was defined as delivery before gestational week 37, and the post-term pregnancy lasting longer than 42 weeks. A small for gestational age new born were below the tenth percentile according to the normal tables of our population when adjusted to the gestational age and sex. Infants with birth weight less than 2500 grams were considered to have low birth weight.

100 women were found to had active epilepsy and were using AED before conception and through the whole pregnancy (WWAE). The other group included 100 pregnant women, in which the mother reported having seizures 5 years or more before conceiving but no need for AED at the time of pregnancy were termed nonactive epilepsy cases. This hospital caters to mainly high-risk maternal care and delivers approximately 900 babies per year.

Results

The mean age of patients was 24.5 years (range 18–42 years). Majority of our women (73) were multiparous (73%), 65 women (65%) were from low or rural stratum. [Table 1] complete outcome data were available for 100 pregnancies. Of these 45 pregnancies had been exposed to leviteracetam in monotherapy and 55 had been exposed to Levetiracetam in combination with at least one other AED.

Mean gestational age at enrollment was 14.5 weeks (standard deviation 10.55 range 5 to 38 weeks). We observed 58 (58%) women with generalized epilepsy (absence or myoclonic seizures), 37 (37%), women with focal epilepsy (localization related) and 6% with unspecified epilepsy.

Monotherapy was used in most pregnancies (45 of 100, 45%), duo therapy in 38 (38%) cases and polytherapy with three drugs in 17 (17%) cases. [Table 2]

80 of the mothers were seizure free during the pregnancy 80%), and 20 (20%) of 100 women experienced seizures during pregnancy. The number of seizures during pregnancy was 2 to 4 seizures in (6%), 1 in (12%), and 10–20 in 8% of 100 cases. 1 patient experienced an increased in seizure frequency and status epileptics during pregnancy. Another patient experienced a flurry of seizures at late stage of pregnancy, and a cesarean section was performed because of this premonitory phase of status epileptics.

Although, 61 (61%) of 100 continued to be seizure free during pregnancy, or their seizure

frequency remained the same as that before pregnancy. 11 (12%) of 100 lost their seizure freedom during pregnancy and 8 (8%) of 100 experienced an increase in their seizure number compared with the year preceding the pregnancy. Conversely, the seizure frequency was reduced in 11 (11) of 100 patients, and 9 (9%) of 100 pregnancies became seizure free during time of pregnancy.

In conclusion 61% of patients did not experience any change in seizure frequency, 20% experienced a change for better. A small but significant proportion of women (19%) experienced a change for worse in seizure control, and no specific reason could explain this exacerbation of seizures.

The mode of delivery (e.g., With regard to the complications related to pregnancy and delivery, no significant differences were noted for Forceps, vacuum) and the incidence of cesarean sections were equal. The mean gestation age of pregnancy was 37 weeks ± 4 days in women with active epilepsy. No significant interactions between parity or gestational age and epilepsy were found with respect to occurrence of induction, cesarean section and post partum hemorrhage. Regarding obstetric outcome in this study, there were 93 live births, 4 spontaneous abortions, 2 induced abortions, 1 stillbirth. [Table 3]

A significant number 18 (18%) of the children of WWAE were found to be small for gestational age (SGA). For monotherapy exposure, 6 (13.33%) infants had a low birth weight (<2500 g); these were exposed to an average dose of 1500 mg of levetiracetam per day. 5 Infants were born less than 37 weeks gestation (11.11%). For polytherapy outcomes, 12 combination of at least an antiepileptic drug in addition to levetiracetam were recorded. 8infants (14.55%) exposed to levetiracetam as part of polytherapy had a low birth weight, 2 with a very low birth weight (<1500 g) (2 of these infants were twins born at 31 weeks) and 2 (3.64%) an extremely low birth weight (<1000 g). 10 live infants exposed to levetiracetam as part of polytherapy regimen were born less than 37 weeks gestation (18.18%).

Apgar score at 5 minutes in children of WWAE was low, <7 in 7%, accordingly, the admission to the neonatal intensive Care Unit or neonatal ward were more prevalent in children of WWAE. The mean duration of follow-up in neonatal. ward and in neonatal intensive care unit for the neonates of WWAE was 8 (+ - 5.5 days). The reason for admission was suspected infection (3 of 13), hypoglycemia or other metabolic abnormality 2 of 13, respiratory distress (3 of 13), low Apgar (2 of 13) preterm (1 out of 13). 3 of these neonates needed intensive care (i.e. intubation, ventilation, surgical intervention) and others were treated only with intravenous (IV) glucose or antibiotic and monitored. Most (10 of 13, (76.92%) of the children were discharged home without any long-term diagnosis or need for follow-up. [Table 4]

The frequency of major congenital malformation was 7% percent in the children of WWAE. In the general population, the rate of major congenital malformation due to spontaneous mutations has been found around 3%. In this study, 6 infants among 93 live births had major congenital malformation resulting in 6.45% for overall prevalence. Table 5 shows detailed information about the 6 infants with major congenital malformation.

Table 1: Obstetric data for pregnancies exposed to levetiracetam

Patient characteristics	Age and Percentage
Age	24 (18-42 Years)
Age (Mean)	24.5 Years
Primiparous (%)	27%
Multiparous (%)	73%
h/o one Miscarriages	10%
>5 deliveries	40%
Mode of delivery	
Vaginal delivery	70%
Cesarean section	20%
Instrumental	10%

Table 2: Antiepileptic Therapy used during pregnancy in WWAE

AED	Frequency=100	%
Lev	45	45
Lev + Oxc	13	13
Lev + VPA	16	16
Lev + PHT	4	4
Lev + LTG	1	1
Lev + VPA + CZP	7	7
Lev + OXC + CZP	3	3
Lev + PB	2	2
Lev + PB + PHT	2	2
Lev + PB + CBZ	2	2
Lev + CBZ + PHT	2	2
Lev + CLB	2	2
Lev + CBZ + CLB	1	1

CBZ: Carbamazepine; CLB: Clobazam, CZ: Clonazepam; LTG: lamotrigine; OXC: Oxcarbazapinem; PB: Phenobarbital, PHT: phynetoin; VGB: vigabatrin; VPA: valproate

Table 3: Delivery outcomes in women with epilepsy

	Lev monotherapy	Lev polytherapy
Number of exposures	45	55
Preterm delivery (<37 weeks)	5	10
Outcome	43 live births	50 live births
	1 spontaneous abortions	3 spontaneous abortions
	1 induced abortions	1 induced abortions
	-	1 stillbirth
Mode of delivery	32 spontaneous vaginal delivery	36 spontaneous vaginal delivery
	8 Cesarean	14 Cesarean
	2 Forceps	3 Forceps
	2 Ventouse	2 Ventouse
	1 not recorded	

Table 4: Perinatal outcome

Outcome	WWAE (%)
Apgar score <7 at 5 min	7 (7%)
Small for gestation age	14 (14%)
Foetal distress	5 (5%)
Admission to a neonatal unit	13 (13%)

Table 5: Major malformations in the children of women with active epilepsy according to the medication used

Malformation	Concomitant AED	Dose, LEV during pregnancy per day	Other AED dose during pregnancyper day
Spina bifida	VPA	1000	1500-2000
Cleft palate	CBZ	1500	800-1200
Polydactyly	CBZ	1000-1500	1500-2000 (VPA)
	VPA		CBZ-800
VSD	OXC	2000	1200
B/L Club feet	VPA	1500-2000	2000 (Valproate)
	CBZ	2000	1500 (CBZ)
Hypospadias	LTG	1500-2000	800

CBZ: Carbamazepine; VSD: Ventricular septal defect; LTG: Lamotrigine; VPA: Valproate.

Discussion

Neurologist precision medicine preference the novel characteristic of new AED, (i.e. LEV), fuelling expectations that that this may be more suitable for managing difficult to treat epilepsy group.

LEV was first approved by the food and drug administration in 1999. It has several advantages over conventional AEDs, namely complete bioavailability, linear phrarmacokinetics, rapid onset of action, totally excreted by the kidneys, minimal bindings to plasma proteins, relative lack of drug to drug interactions, can be loaded intravenously or orally, is weight neutral, has no cognitive side effects, and doesn't require blood level monitoring[11].

Advantageous attributes have made LEV preferable first-line AED treatment for many neurologists, and in fact, it is one of the commonly prescribed drugs for epilepsy at our center. Currently many epileptologists try to switch to LEV during or before planned pregnancy because of its known relative safety during pregnancy. Moreover, in addition to its efficacy in focal epilepsy, LEV is an excellent AED to use in myoclonic epilepsies, whereas lamotigine which was considered to be safe in pregnancy may actually worsen the myoclonus and requires complex titration schedules and LTG level continues to drop drastically during pregnancy[12].

The percentages of patients with generalized epilepsy and focal epilepsy in our study are similar with the percentages observed in the EURAP Registry[13]. However, other studies (UK, US)[14] have not analyzed this variable, or report results that differ from ours (focal epilepsy in 48% of patients in Australian registry vs. 36.8% in this study)[15]. Such differences are very likely due to methodological reasons: the EURAP Registry gathered data recorded by Neurologists, whereas other registries gather patient-reported data[16]. Data on the type of

epilepsy is important, given that patients with generalized epilepsy are known to be more likely to remain seizure free during pregnancy than those with focal epilepsy[17,18]. Even in this study, 45% of all WWAE who were on monotherapy were taking LEV thus, it is imperative that safety profile of LEV in pregnant women should be studied in detail.

The demographic profile of study was in accordance with previous study. We were able to state the time of last seizure and hence divide the epilepsy population into active and non active groups. Women with active epilepsy and used levetiracetam monotherapy had the same obstetric risk as women with active epilepsy and used levetiracetam polytherapy in this study. The incidence of AED used in pregnancy in our study was equal to that in previous study of the total Norwegians cohort, where 0.3% of all women used AEDs during pregnancy[19]. Seizures prior to pregnancy did not seem to affect the risk in our study. In this study, we retrospective analyzed our data to determined safety profile of LEV in pregnancy.

Conflicting results may be caused by methodological limitations with recruitment bias and small sample sizes, but could also be a result of new medications giving better seizure prevention with fewer side effects[20]. In our study more than half 61% of patients did not experience any change in seizure frequency, 20% experienced a change for better. A small but significant proportion of women (19%) experienced a change for worse in seizure control, and no specific reason could explain this exacerbation of seizures. Vajda *et al.* compare use of LEV to that of VPA, finding no significant differences between these two AEDs in terms of seizure control[15]. However, that study provides no data on the percentage of patients with generalized epilepsy who received LEV or VPA, or on seizure occurrence in these patients during the year before pregnancy. Other studies directly or indirectly analyzing seizure frequency in patient receiving LEV show seizure occurrence rate no higher than those associated with the use of classic AEDs[21]. This study does not give an answer as to whether it is advisable to increase the AED doses in pregnancy having seizures controlled on antiepileptics.

However, we found that the rate of small for gestational age infants was significantly higher in WWAE. Body dimensions of infants born to mothers with epilepsy have also been studied by Wide and colleagues showing that infants exposed to polytherapy were shorter and smaller than those exposed monotharapy[22]. The incidence of low birth weight babies (i.e. <2500 grams) was higher 13.33%in our study. This can also be explained as lower mean birth weight of Indian newborn babies compared to western babies[23]. In our study, Apgar scores in children of WWAE were lower at 5 minutes. However, the need for neonatal care after birth was increased as compared to earlier studies[23]. However, the outcome was favorable in most (76.92%) of the children, because they were discharged home without any long-term diagnosis or need for follow-up.

MCM occur at a rate of 2% in the general population; reported major malformation rates in children of WWAE range from 1.25 to 11.5%, with the pooled estimates yielding 4 to 6%[24] In this study we did not find any fetal congenital malformation in WWAE who were exposed to LEV monotherapy during pregnancy. Our results of are similar to Australian pregnancy Register[25]. [no MCM in babies born to WWE on LEV; n = 22, UK and Ireland epilepsy pregnancy Registry[26]. (0.7% risk of MCM in babies born to WWAE on LEV; n = 304)], and a population-based cohort study from Denmark[27]. (no MCM in babies born to

WWE on LEV; *n* = 58). Thus, from our experience and other studies, it can be safely concluded that in utero, exposure to LEV is relatively safe in terms of occurrence of MCMs in neonates. There was a higher risk of MCMs following in utero exposure to polytherapy with LEV. In this study, 6 infants among 93 live births had major congenital malformation resulting in 6.45% for overall prevalence. The study population is too small to draw conclusions about frequency of malformations, but these results are in accordance with the previous studies[28]. In our study, children with malformations were exposed to polytherapy (reflecting difficulty to treat epilepsy) or significant confounding factors were present (genetics susceptibility). Long-term prospective Neuruo cognitive follow-up studies of children of WWAE have not been published, and therefore relatively little is known about the subsequent neurologic and cognitive development of these children. Some mainly retrospective reports have, however, suggested that a high prevalence of developmental delay and additional educational needs may exist in children exposed to AEDs in utero[29-31]. WWAE represents a particularly challenging population for Neurologists. Although guidelines on the management of pregnant women with epilepsy have been published, recent evidence suggests that antenatal care offered to women with epilepsy does not follow currently recommended optimum care practices. In this study, we confirmed that the pregnancy is uncomplicated and neonatal outcome is good in the majority of cases. Pregnancy outcome of women with earlier diagnosis of epilepsy did not differ in this study, indicating the important role of AEDs in causing the complications related to epilepsy. Re-evaluating the need for and those of AED therapy and initiating folate supplementation before conception was the cause for improvement in our outcome.

Conclusion

Pregnancy course is uncomplicated and neonatal outcome is good in the majority of women with active epilepsy with proper antenatal and neurologic care. Levetiracetam taken in monotherapy can be considered as safer alternative for women with epilepsy of childbearing age. Long-term follow-up of neuropsychological and cognitive development of the children of WWAE is still needed.

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