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Case report

Lacosamide during pregnancy and breastfeeding

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ABSTRACT

Background: The epilepsy treatment during pregnancy represents a balance between teratogenic hazard and seizure control. The aim of the study was to evaluate the safety and efficacy of lacosamide (LCS) during pregnancy and breastfeeding.

Methods: Patients referred to our Epilepsy Center for pregnancy planning who became pregnant while taking LCS were prospectively followed-up. Data on seizure frequency, side effects, pregnancy course, delivery and breastfeeding, birth outcome, congenital malformation and development of newborns were collected.

Results: Three cases of maternal exposure to LCS were reported. Treatment with LCS was continued throughout pregnancy and breastfeeding at a median daily dose of 400 mg. Lacosamide was used as monotherapy in two patients and as add-on treatment in one woman. Seizure frequency did not change throughout pregnancy and two subjects remained seizure free. The median gestational age at delivery was 39 weeks. The median Apgar scores at 1 and 5 min were 9 and 10, respectively; no major or minor congenital malformations were observed in the offspring. Normal developmental milestone were reached by all new-borns.

Conclusions: Worldwide pregnancy registries have provided consistent and increasing information about the efficacy and safety of the older antiepileptic drugs during gestation, while data are lacking for many of the newer generations. These cases could suggest a good level of efficacy and safety for LCS throughout pregnancy and breastfeeding and argue against teratogenic or toxic potentialities.

1. Introduction

Epilepsy is one of the most common neurologic disorder, and the majority of affected people are expected to participate fully in life experiences, including childbearing. Population surveys reported a prevalence of epilepsy among pregnant women up to 0.7%, and it has been estimated that from three to five births per thousand will be to women with epilepsy [1]. Worldwide prospective registries and observational studies have provided consistent findings on the teratogenic risk and clinical efficacy

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during pregnancy for many of the older antiepileptic drugs (AEDs), while there remains a large gap in the knowledge of most of the newer.

Lacosamide (LCS) (UCB, Brussels, Belgium) is a second-generation AED characterized by a novel mechanism of action which has been licensed in 2008 as adjunctive treatment for adults with partial onset seizures, with or without generalization [2], and more recently as monotherapy by the U.S. Food and Drug Administration [3]. So far, LCS has been insufficiently studied with respect to women specific issues. The aim of this study was to evaluate the safety and efficacy of LCS during pregnancy and breastfeeding.

2. Methods

2.1. *Participants selection and follow-up*

We selected study participants from consecutive women with epilepsy referred for pregnancy planning to the Epilepsy Center of the Ospedali Riuniti of Ancona. For the purpose of the study, only patients with pregnancies registered while they were taking LCS were included. Each patient underwent a clinical evaluation every 3 months from the enrolment until at least 12 months after the delivery. Data on demographics, neurologic evaluation, clinical history, types and frequency of seizures, treatment compliance, side effects, pregnancy course, delivery and breastfeeding, birth outcome, congenital malformation and development of newborns were collected.

2.2. *Standard protocol approvals, registrations, and patient consents*

The local ethical committee approved this study, and all study participants provided written informed consent.

3. Results

Three cases of maternal exposure to LCS were identified (Table 1). *Case 1* is a 25-year old, right-handed woman with a history of post-traumatic, adult-onset, localization-related epilepsy. She had previously tried and failed a variety of AEDs, including carbamazepine, oxcarbazepine, lamotrigine and topiramate. At the initial visit, she was taking valproate (1500 mg/day) and levetiracetam (2000 mg/day). Prior to conception, valproate was tapered and replaced with LCS (200 mg bid); she was placed on folic acid 1 mg daily. Despite mild nausea during the first trimester, she had no adverse effects and remained seizure-free throughout the pregnancy. Ultrasound studies did not detect any abnormality. She delivered a single-birth male at 39 weeks of gestation. Newborn weight, length and head circumference were 3450 grams, 49 cm and 35 cm, respectively; Apgar scores were 9 and 10 at 1 and 5 min postpartum. The infant was breast-fed up to 7 months postnatally. No medical problems or developmental delays were detected at calendar age of 24 months.

Case 2 is a 34-year old, right-handed woman with a history of simple and complex partial focal epilepsy with rare secondary generalization, associated to a left frontal arterio-venous malformation. After previous treatment failures with

Table 1 – Baseline characteristics and outcomes of pregnancies exposed to lacosamide.

	Patient no. 1	Patient no. 2	Patient no. 3
Age at pregnancy, years	25	34	22
Type of epilepsy	Symptomatic; post-traumatic	Symptomatic; artero-venous malformation	Cryptogenic
Type of seizure	Focal without secondary generalization	Focal with secondary generalization	Focal with secondary generalization
Pre-pregnancy seizure frequency[a]	Seizure-free	Two to four per month	Seizure-free
Body mass index, kg/m^2	23.1	20.3	20.9
AED regimen during pregnancy	Poly-therapy; LEV, LCS	Mono-therapy; LCS	Mono-therapy; LCS
LCS daily dose, mg	400	300	400
Seizure frequency in pregnancy	Seizure-free	One to four per month	Seizure-free
Generalized tonic-clonic seizures during pregnancy	None	None	None
Gestational age at delivery, weeks	39	40	39
Delivery mode	Spontaneous vaginal	Spontaneous vaginal	Spontaneous vaginal
Birth outcome	Live birth	Live birth	Live birth
Sex of newborn	Male	Female	Female
Birth weight, g	3450	2950	3650
Birth length, cm	49	46	51
Head circumference, cm	35	34	34
Apgar score[b]	9/10	9/10	10/10
Major or minor congenital malformations	None	None	None

Abbreviations: AED = anti-epileptic drug, LCS = lacosamide, and LEV = levetiracetam.

[a] Seizure frequency during the 12 months before conception was reported.

[b] Apgar score at 1 and 5 min post-partum were reported.

carbamazepine, oxcarbazepine and topiramate, at the time of conception she was on LCS at 300 mg daily as conversion-monotherapy, and the seizure frequency was two to three simple partial seizures per month. She had no adverse effects throughout pregnancy whose course was normal. She continued to experience from one to four simple partial seizures without secondarily generalization. She was kept on stable-dose LCS monotherapy since seizure frequency did not change with respect to pre-gestational time, all seizures were simple partial, and she had poorly tolerated up-titration of LCS to higher dosages trialed before pregnancy. Structural ultrasound were unremarkable and serum alfa-fetoprotein was within normal ranges. A female infant was born on pregnancy week 40 with Apgar points 9/10. The birth weight was 2950 g, the length 46 cm and the head circumference 34 cm, as appropriate for the gestational age at delivery. The mother partially breast-fed her infant up to 8 months. Normal developmental mile-stones were reached at 6, 12 and 18 months postnatally when follow-up in tertiary care was discontinued.

Case 3 is a 22 right-handed woman with a history of cryptogenic, localization-related epilepsy. The medical history was negative for smoking, alcohol consumption and drug abuse. When she referred to our Epilepsy Center for pregnancy planning, she was free from seizures since LCS had been added at the maximum recommended daily dose of 400 mg to phenobarbital. Phenobarbital was gradually tapered and folic acid supplementation was prescribed. At the time of conception, she was seizure-free on LCS monotherapy (400 mg/day). The pregnancy had a normal course with unremarkable ultrasound studies. The mother did not experience epileptic seizures throughout the pregnancy, delivery and post-partum on LCS 200 mg bid. At 39 weeks of gestation, she delivered a single-birth female with a 1st and 5th minute Apgar score of 10. The birth weight and length were 3650 grams and 51 cm, respectively; the head circumference was 34 cm. The mother breast-fed her infant up to 9 months without any feeding or alertness problems throughout lactation. No cognitive alterations or developmental delays were detected at 36 months post-natally.

4. Discussion

The pharmacological treatment of epilepsy during pregnancy represents a major clinical challenge since the potential adverse effects and teratogenic hazard of drugs should be balanced with the maternal and fetal risks related to poor seizure control [4].

The teratogenicity of AEDs is a relevant concern. The rate of major congenital malformation (MCM) in general population varies between 2% and 4%, and women with epilepsy who do not receive AEDs during pregnancy show similar rates. Instead, the risk is approximately two to three fold higher, ranging from 4% to 8%, in the offspring of epileptic mothers receiving AEDs [5]. The most common MCMs associated to AEDs exposure include congenital heart defects, cleft lip and palate, neural tube defects and urogenital abnormalities. The prevalence of congenital minor anomalies is increased, too: it ranges from 6% to 20%, and it is approximately 2.5 fold higher than expected in non-exposed [6]. Although the exacts mechanisms by which AEDs influence the structural organogenesis are not completely understood, teratogenicity is certainly related to the susceptibility of each organ according to its characteristics and specific stage of development at the time of drug exposure. In addition, the teratogenic risk is consistently higher for poli- compared to mono-therapy, and both the AED type and dose are meaningful risk variables [7,8]. A significant increase in neonatal complications, like low weight or low Apgar score at birth, has been also reported among infants from women on AEDs [1]. Studies addressing long-term psychomotor maturation are less conclusive, but meaningful, dose-dependent, associations between poor neurodevelopment and intrauterine exposure to some AEDs, like valproate, emerged [9,10].

With respect to the administration of LCS in pregnancy, there is very few available evidence. In reproductive and toxicity animal studies, orally delivered LCS did not produce teratogenic effects, but it was linked to developmental toxicity – with significant increase in either embryo-fetal and perinatal mortality and growth deficits – at maternal plasma levels corresponding to expected human exposure at the 400 mg daily dose. As concerns labor and delivery, a tendency toward prolonged gestation was observed in LCS treated rats at doses corresponding to human therapeutic plasma ranges.

In our small case-series, we did not observe any congenital malformation or obstetric complication. The exposure to LCS throughout the whole length of gestation at the maximum recommended dose has never been described. In the only available report, LCS was administered from the seventh week of gestation at the daily dose of 200 mg in conjunction with levetiracetam in a patient presenting with massive cerebral venous thrombosis and status epilepticus; the infant was born without malformations, but small for the gestational age after a cesarean section planned at the 36th gestational week [11]. Teratogenic effects were not observed, but it is noteworthy that the time of exposure to LCS did not include the most vulnerable era, which corresponds to conception and the first following weeks. The neural tube closure, for example, usually occurs between the third and fourth week of gestation. Furthermore, the small development at birth could raise concerns about the possible negative influences of the poli-therapy regimen and prolonged status epilepticus.

Beside teratogenicity, one other demanding issue to be faced during pregnancy is the control of seizures, with special regard for the major convulsive. The occurrence of seizures may have detrimental psychosocial effects on the mother and may be harmful to the fetus for the possible sequelae of maternal falls and trauma; additionally, prolonged crisis and frequent generalized tonic-clonic seizures could cause fetal hypoxia and acidosis, fetal loss, and poor development of newborns [12,13]. Wide ranges in seizure frequency variation have been reported in pregnancy, with increases occurring in approximately 15–32%, decreases in 3–25% and no significant changes in 50–83% of women [14]. Several factors may influence the seizure control, including pharmacotherapeutic compliance, sleep deprivation and physical or mental stress during labor. Furthermore, physiologic adjustments induced by pregnancy, as the increase in renal blood flow, total body water and fat stores, the raise of estrogen levels and the decrease in serum proteins concentration, could influence the

distribution and clearance of AEDs, and contribute to their different efficacy profiles [15]. With this respect, although we could not characterize the pharmacokinetics of LCS, the seizure stability may reasonably suggest drug levels within therapeutic ranges.

As concerns lactation, LCS passes over into breast milk due to its low molecular weight and minimal binding to plasma proteins; the relative infant dose of a fully breast-fed infant has been however estimated to be less than the 2% of the maternal-weight adjusted dose [11]. Accordingly, none of the breastfed infants developed side effects for indirect exposure to AEDs as sedation, apnoea, abnormal muscular tone, altered sleep patterns, hyper-excitability, poor feeding or sucking difficulty. Further, no withdrawal symptoms emerged at the end of lactation, and psychomotor development resulted normal in all children.

The cases we describe could suggest a good level of safety for LCS during pregnancy and argue against teratogenic or toxic potentialities. The lack of monitoring of serum and milk concentrations precluded any pharmacokinetic evaluation and represents the main limit of the study. The major strengths include the long lasting exposure to LCS, from conception to delivery and lactation, the long-term post-partum follow-up, the prospective assessment of both pre-gestational and gestational seizure frequency, and the absence of variations in AEDs load during pregnancy.

5. Conclusion

The teratogenic risks and the adverse cognitive effects on newborns of women treated with AEDs have come into the spotlight, but the safety of the newer drugs in human pregnancy is still largely unknown [16]. It being understood that AEDs should be prescribed if potential benefits clearly outweighs potential risks, LCS could be safe during gestation and breastfeeding. Careful prenatal diagnostics and detailed examination of the infant remained highly recommended. Further investigations and results from national and international registers are warranted to confirm the safety profile of LCS and assess the long-term effects on the offspring.

Conflict of interest

None declared.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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