Safety and Efficacy of Cenobamate in Pregnancy: A Case Report

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Abstract

Seizures remain the most frequent major neurologic complication during pregnancy, affecting 0.3% to 0.8% of all gestations. In clinical practice, the risk of seizures during pregnancy is weighed against the risks of antiseizure drug (ASD) exposure (e.g. teratogenicity, congenital malformations, developmental, and intrauterine growth). With the advent of novel ASDs, further research into the specific risks of these novel medications during pregnancy is warranted. Cenobamate, an ASD approved by the Food and Drug Administration (FDA) for focal onset epilepsy in adults, is highly efficacious, however, all trials of this ASD to date excluded pregnant and lactating subjects. Thus, we present the case of a young female patient with medically refractory epilepsy who elected to continue cenobamate throughout two of her pregnancies and lactation. Our patient had a significant reduction in the frequency of her seizures. There were no complications during either pregnancy, delivery or postpartum. While a single case experience does not establish the safety and efficacy of cenobamate during pregnancy/lactation, patients of childbearing age who are currently considering or already taking cenobamate may benefit from knowledge regarding our patient's experience.

Introduction

Half a million women suffering from epilepsy are of childbearing age.[1] One-third of pregnant women with epilepsy will have an increase in seizure frequency during their pregnancy. Epilepsy in the pregnant population confers an elevated risk of adverse obstetric outcomes. [2] These women are at higher risk of obstetric hemorrhage, spontaneous miscarriage, and hypertensive disorders. From a pediatric standpoint, five out of every thousand births will be to a mother suffering from epilepsy.[1] In the United States, roughly 25,000 children per year are born to mothers suffering from epilepsy.[3] Complications in the offspring include increased risk of stillbirth, preterm birth, small for gestational age at birth, low Apgar score at 5 minutes, neonatal hypoglycemia, neonatal infection, respiratory distress syndrome, and major congenital malformations (3x higher risk than the general population). The long-term neurobehavioral development of the child may also be significantly affected.[3,4] Despite these risks, sufficient data regarding the management of epilepsy in pregnancy is lacking.[1]

Cenobamate (YKP3089) is an antiseizure drug (ASD) that has demonstrated higher seizure-free rates than any other anti-epileptic in the last 30 years.[5] The safety and efficacy of cenobamate in the obstetric population are unknown.[6] We present the first documented use of cenobamate in a pregnant and lactating patient suffering from medically refractory, intractable focal onset epilepsy with impaired awareness.

Case Description

A patient in her early 30s, suffering from medically refractory, intractable focal onset epilepsy with impaired awareness was referred to our epilepsy clinic. At the time, she was suffering breakthrough seizures characterized by right arm stiffening, aphasia, and unresponsiveness lasting for about 60 seconds at a time. Her spells were followed by postictal confusion and occurred once a week despite being compliant with Levetiracetam 1500mg bid and Lacosamide 200mg bid. Previously, treatments including Topiramate, Lamotrigine, Carbamazepine, Oxcarbazepine, and scheduled Clonazepam were attempted, all of which failed to reduce the frequency of her seizures.

Investigations

Prior to the onset of her first pregnancy, workup with continuous EEG monitoring was remarkable for left temporal sharps and occasional lateralized periodic discharges (LPDs) localized to the left cerebral hemisphere. An MRI Brain had also been obtained **(Figure 1)**.

Treatment

Our patient was started on cenobamate and had reached 100mg daily dose (7th week of titration) when she was confirmed to be 7 weeks and 5 days pregnant in her first pregnancy. The risks and

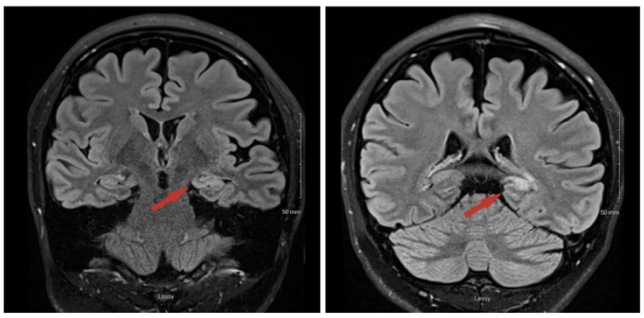

Figure 1: Magnetic resonance imaging (MRI) in our patient. The above images show coronal sections obtained via 7-Tesla MRI (Magnetic Resonance Imaging) brain in our patient. Red arrows point to areas of subtle T2-Fluid Attenuation Inversion Recovery (FLAIR) hyperintensity within the left mesial temporal lobe. These findings are consistent with left mesial temporal lobe sclerosis, a common finding seen in patients with focal epilepsy.

benefits of continuing cenobamate were discussed and the patient was informed of the lack of data regarding safety/efficacy in the setting of pregnancy/lactation. The patient expressed an adequate understanding of the same and requested to be continued on the medication throughout her pregnancy. Cenobamate was gradually titrated to 200mg daily by 12 weeks of gestation and her folic acid was increased to 4mg. Maternal and fetal monitoring was done via frequent outpatient visits.

Maternal Outcomes

During the first pregnancy, the patient's seizure frequency reduced to less than one per week and the duration of her postictal confusion was notably shorter, a notable improvement from her weekly seizures prior to initiating cenobamate. After the first delivery, her seizure frequency reduced further to one spell every other month. The patient's seizures remained well controlled approximately one year after delivery, and the patient became pregnant again. She continued cenobamate 200mg during this second pregnancy and both lactation periods. Her seizure frequency remained under one spell every other month during this second pregnancy and after delivery. Two months after the second delivery, the patient denies experiencing any complications. The patient now reports she has been seizure free for 11 months. Of note, the patient breastfed (for three and two months, respectively) and supplemented with formula for both children.

Pediatric Outcomes

For the first child, antenatally fetal heart tones were charted as within normal limits from 11 weeks to birth (143-170bpm). The patient underwent 11 antenatal ultrasounds with normal non-stress tests and biophysical profiles (10/10 or 8/8 charted), appropriate fetal growth tracking with gestational age (estimated fetal weight percentile ranging from 36th – 62nd), and appropriate amniotic fluid index (within normal limits at each ultrasound). Anatomy scan and cardiac echocardiogram were both normal. For the second child, antenatally fetal heart tones were charted as within normal limits from 11 weeks to birth (133-175 bpm). The patient underwent 11 antenatal ultrasounds with normal non-stress tests and biophysical profiles (10/10 or 8/8 charted), appropriate fetal growth tracking with gestational age (estimated fetal weight percentile ranging from 16th – 39th), and appropriate amniotic fluid index (within normal limits at each ultrasound). Anatomy scan and cardiac echocardiogram were both normal, excluding a circumvallate placenta. Since birth, both children been closely followed by a pediatrician. Their birth weights were 3.6kg and 3.7kg respectively, both determined to be within normal limits by the admitting pediatricians. At the first child's most recent well child check, they were in the 85th percentile for weight and 93rd percentile for height and met all 24-month developmental milestones. On physical exam, no neurological or cardiopulmonary abnormalities were appreciated. The second child, at the most recent well child check, was tracking at the 99th percentile for weight and length, and met all sixth month developmental milestones including: able to sit without support, able to bear weight on legs when pulled up to stand, able to roll over, able to reach for toys and pull to midline, had enjoyment, and laughs, smiles, and squeals. On physical exam, no neurological or cardiopulmonary abnormalities were appreciated.

Discussion

Current guidelines acknowledge that the management of epilepsy in pregnancy is based on observational studies.[1] Older, yet highly effective, medications such as phenobarbital and valproic acid are associated with an increased adverse risk-to-benefit ratio.[7] Lamotrigine, levetiracetam, lacosamide, and oxcarbazepine have been the preferred agents in the pregnant population due to lower rates of teratogenicity.[3] However, for medically refractory patients, there is little data regarding newer, more efficacious agents such as cenobamate.

Cenobamate is a highly efficacious anti-epileptic

that was approved by the Food and Drug Administration (FDA) in 2019 for use as adjunctive therapy in adults with focal onset epilepsy.[8] Cenobamate's efficacy was proven in 2 large randomized, multicentric, double-blind clinical trials (NCT01866111 and NCT01397968). Both trials demonstrated a dose-dependent reduction in seizure frequency by up to 55% (p-value < 0.001) when cenobamate was used as adjunctive therapy in patients suffering from medically refractory focal onset seizures. A high responder rate of >40% and a reduction of seizure frequency early in the titration of the medication attests to its potential.[9,10] The medication has since demonstrated higher seizure-free rates than any other anti-epileptic in the last 30 years.[5] Said efficacy may be secondary to cenobamate's multiple different mechanisms of action **(Figure 2)**.[11-13]

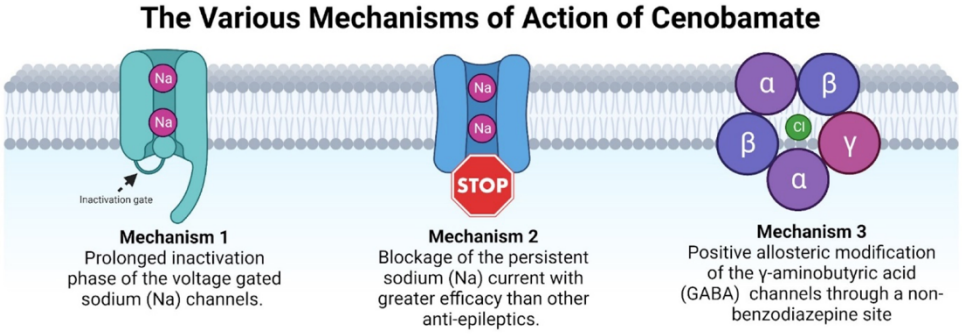

Figure 2. The various mechanisms of action of cenobamate. Cenobamate's ability to act on sodium channels and GABA receptors make it a unique anti-seizure agent.[11-13]

cenobamate, the decision to change to another anti-epileptic may be considered.[15]

There is no data regarding the use of cenobamate during lactation. The Drugs and Lactation Database, advises that the use of cenobamate is not a reason to discontinue breastfeeding, although a change to a different anti-epileptic may be considered.[16]

Our patient had a reduction in her seizure frequency after cenobamate was added to her anti-epileptic regimen. She elected to continue the medication during her pregnancies and lactation. Despite this, she had two unremarkable pregnancies, deliveries, and postpartum periods. Additionally, both children have met developmental milestones and continued to grow appropriately. This data was shared with the North American Anti-Epileptic Drug (AED) Pregnancy Registry.

Pregnant and lactating humans have been excluded from all trials involving cenobamate to date.[6] Animal studies demonstrated that the highest tested dose of cenobamate (60 mg/kg/day in rats and 36 mg/kg/day in rabbits) resulted in increased embryo-fetal mortality, reduced birth weight, incomplete ossification, and visceral malformations. Such high doses were also directly toxic to the mothers.[14] Dose-independent adverse effects on the offspring included neurocognitive and reproductive dysfunction. Per the FDA-approved cenobamate label "maternal plasma exposure at the no-effect dose for adverse effects on embryo-fetal development was less than that in humans at the maximal recommended human dose of 400 mg."[14] A large limitation of the animal studies is that the complete teratogenic potential could not be assessed due to the high rate of embryo-fetal deaths. Currently, the FDA recommends that the patient be counseled to inform the prescribing physician if they are pregnant or intend to become pregnant.[14] An expert panel led by Steinhoff et al further advised that if a patient becomes pregnant while on

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Moving forward, a larger study population involving pregnant and nursing humans is needed to definitively establish the risk-to-benefit ratio of cenobamate in the obstetric population. Furthermore, it is important to recognize that the levels of ASDs during pregnancy are highly dynamic. Future studies should aim to define better how the plasma levels of cenobamate fluctuate across trimesters. Lastly, Patients who use ASDs during pregnancy should be encouraged to submit their experiences to large databases such as the North American AED Pregnancy Registry such that it may be used to establish trends and develop a robust cohort.

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Statement of Ethics

Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

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Data Availability Statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

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