Case Report

Rare but life-threatening aspiration pneumonia related to initiation of clobazam therapy

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Abstract

Clobazam (CLB) was approved in October 2011 by the United States FDA as an adjunctive therapy for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients older than the age of 2. Due to its unique chemical design and selective binding to the alpha-2 GABA-receptor, CLB has a decreased tendency for sedation compared to other benzodiazepines. A recent literature review shows that sedation, hypersalivation (drooling), and behavior changes are the most common side effects of CLB. It has also been shown that a patient’s level of consciousness is indirectly related to the risk of aspiration. Hypersalivation is too is a significant predisposing factor for aspiration. In this report, we present three adult patients with epilepsy who had aspiration pneumonia during treatment with CLB. We would like to raise awareness of increased drooling and somnolence in patients with predisposing factors such as treatment with CLB and emphasize vigilance in this regard.

1. Introduction

Clobazam (CLB, Onfi™; Lundbeck Inc., IL, USA) was approved in October 2011 by the United States FDA as an adjunctive therapy for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients older than the age of two [1]. CLB is a benzodiazepine with a unique chemical design, with nitrogen atoms are located in the 1st and 5th positions of the diazepine ring. This configuration makes CLB a partial agonist of a GABA-A receptor; concurrently, it potentiates a higher selective affinity for the α2 subset of GABA-A receptor, which yields its antiseizure activity. Simultaneously, the compound has less affinity toward the α1 subset of the GABA-A receptor, which is responsible for adverse effects such as sedation [2,3]. CLB’s efficacy as an adjunctive therapy for LGS has been notable with sustained improvement in drop- and total seizures [4,5]. Clobazam retention rate is reported at around 80% in first two years, indicating overall treatment satisfaction and therapy compliance for most patients [4]. CLB’s main adverse effects are generally similar to those of other benzodiazepines, but with less frequent occurrence. These adverse effects include somnolence, lethargy, sedation, hypersalivation (drooling), constipation, aggression, hypomania, and insomnia [5–9]. In an open-label trial, most common adverse effects of CLB were upper respiratory infections (18.4%), falls (14.2%), pneumonia (13.9%), and somnolence (12.7%) [4]. However, upper respiratory infection and pneumonia were predominately reported in the pediatric population [4]. In this report, we present three adult patients with drug-resistant epilepsy who developed aspiration pneumonia after initiation of clobazam. Of those three, one patient passed away from complications directly related to aspiration pneumonia.

2. Methods

In this study, we report three cases of CLB related aspiration pneumonia. Clinical data were obtained from retrospective review of clinical documentation consisting of outpatient clinic notes and inpatient reports for the three patients, followed at our Comprehensive Epilepsy Clinic at Barrow Neurological Institute (Phoenix, Arizona).

3. Results

Case #1: The first patient is a 28-year-old man with a history of infantile spasms, severe developmental delay, and drug-resistant focal epilepsy manifest as bitemporal seizures in the setting of a left-sided temporal cystic lesion. His first seizure occurred at 15 months of age. The patient underwent left anterior
temporal lobectomy with amygdalohippocampectomy at the age of 8 years and revision at age of 11 years. One of the complications of surgical intervention was right-sided hemiplegia. Consequently, he underwent (vagus nerve stimulator) VNS placement at the age of 17. The procedure was complicated by recurrent retching leading to hiatal hernia and upper gastrointestinal bleeding requiring gastric tube (G-tube) placement. Previously tried antiseizure medications included phenobarbital, valproate, levetiracetam, phenytoin, zonisamide, carbamazepine, lamotrigine, gabapentin, vigabatrin, felbamate, topiramate, lorazepam, and clonazepam. He also failed ketogenic diet. Several seizure types, such as generalized tonic-clonic (GTC), atonic, and tonic seizures, were reported. On average, GTC and tonic seizures occurred every one to three days, and atonic seizures every one to two days. His longest seizure-free period lasted two days. On examination, the patient was nonverbal with a prominent dense right-sided hemiparesis, needing assistance for daily activity. Before starting CLB, the patient was taking rufinamide 1000 mg twice a day, pregabalin 200 mg every morning/400 mg every afternoon, oxcarbazepine 1200 mg twice a day, and rectal diazepam 20 mg as needed for breakthrough seizures. The patient was started on CLB 5 mg twice daily with titration up to 10 mg twice a day over the next two weeks. Approximately three weeks after the initiation of CLB, the patient developed aspiration pneumonia prompting admission to the hospital. He was readmitted one month later due to another bout of aspiration pneumonia. CLB was initially titrated down and eventually stopped completely after the third episode of aspiration pneumonia, which was approximately six weeks later. Lacosamide was added in its stead. Cessation of CLB resolved the recurrent bouts of aspiration pneumonia. The patient has been followed at our clinic continuously for the last six years without any new reports of aspiration pneumonia. Unfortunately, his seizure control has not significantly improved with subsequent changes of his pharmacological regimen.

Case #2: The second patient is a 52-year-old-man with cerebral palsy requiring G-tube feeding, severe developmental delay, LGS, severe osteoporosis, recurrent pneumonia, and urinary tract infections. On average, 15–20 seizures were reported per month. Reported seizure types included GTC, atonic, tonic, and atypical absence seizures. At baseline, he was nonverbal and quadriplegic. Valproic acid, carbamazepine, oxcarbazepine, phenytoin, and topiramate were previously tried. Before starting CLB, the patient was taking phenobarbital 120 mg at night, zonisamide 200 mg twice a day, levetiracetam 1500 mg twice a day, lacosamide 200 mg twice a day, and rectal diazepam 20 mg as needed for breakthrough seizures. The serum levels obtained on the visit before initiating CLB were as follows: phenobarbital level was 28 μg/ml, zonisamide was 13 μg/ml, and levetiracetam was 103 μg/ml. After CLB 5 mg was initiated, both a significant reduction in the duration of his seizures and a decreasing need for rescue therapy were reported. Unfortunately, the overall seizure frequency remained the same. One month later, CLB was increased to 5 mg twice daily. A group home caregiver reported patient’s drooling got worsened. At the next monthly follow-up, a 5-day period of seizure freedom was reported, and thus, encouraging the treating team to further increase the CLB dose to 10 mg twice a day with the plan of decreasing the dose of phenobarbital on follow-up visit. Shortly after the adjustment, the patient was admitted to the hospital due to aspiration pneumonia. While in the hospital, the pneumonia was complicated by septic shock, and the patient passed away.

Case #3: The third patient is a 47-year-old man with drug-resistant multifocal localization-related epilepsy secondary to intrapartum hypoxic insult, cerebral palsy requiring gastrojejunostomy tube feeding, and severe developmental delay. His seizures started at the time of birth and demonstrated a tonic-clonic semiology. The last seizure was reportedly occurred four weeks before his initial evaluation in the outpatient epilepsy clinic, right after lorazepam was decreased from 2 mg to 1 mg per day per primary care physician. The dose change was an attempt after the patient had been seizure-free for the preceding 12 years. Unfortunately, the patient had a breakthrough seizure and was restarted on 2 mg of lorazepam per day. The patient was referred to an epileptologist. At baseline, he was nonverbal and quadriplegic. He was on several antiseizure medications in the past, with adequate seizure control for the past 15 years while on valproic acid 500 mg three times a day and lorazepam 2 mg per day. Given the excellent response of the patient’s seizures to benzodiazepine therapy, the long half-life GABA agonist CLB was introduced at 10 mg once a day, and lorazepam was decreased from 2 mg to 1 mg per day. Approximately three to four weeks after initiation of CLB, the patient was admitted to the hospital with aspiration pneumonia. CLB was then stopped, and lorazepam was increased to 2 mg with resumption of good seizure control. No more episodes of aspiration pneumonia were reported. Approximately five months later, he developed acute GI obstruction with gastrojejunostomy tube malfunction, requiring surgical intervention. His family refused surgical intervention and enrolled the patient in palliative care. He passed away a few days later.

4. Discussion

Here we present three adult patients with drug-resistant epilepsy who developed aspiration pneumonia right after initiation of CLB. Aspiration was reported as severe adverse effect in four patients in OV-1002 trial [5] and nine patients in OV-1012 trial [10]. Somnolence and drooling were also increased in frequency with increasing CLB dosage [10]. Ng et al. reported six deaths in the CLB open-label trial, three of which were due to pneumonia (with one patient developing acute respiratory distress syndrome and sepsis). These complications were not considered to be related to CLB use [4]. Patients who developed aspiration pneumonia in all above trials had common established diagnoses of gastroesophageal reflux disease (GERD), a history of drooling, prior aspirations, and G-tube placement. There is some evidence that these factors, in addition to somnolence, and developmental delay, can predispose patients to developing aspiration pneumonia [11]. Our patients had a diagnosis of epileptic encephalopathy with severe brain disorder, severe developmentally delay, and drug-resistant seizures on sedating ASM. In addition, all three patients were nonverbal and dependent on the gastric tube feedings for their nutritional needs. Thus, all our patients already had at least three or more of those predisposing factors for aspiration. In patient #1, despite frequent baseline seizures and multiple predisposing factors (such as VNS and hiatal hernia from recurrent retching), recurrent aspiration pneumonia occurred right after the initiation of the CLB. After discontinuation of CLB, no more bouts of aspiration pneumonia were reported during a 6-year follow up period. Similarly, patient # 2 had daily seizure that improved after initiation of the CLB. In this case, the caregiver reported increased drooling, but this was underestimated at the time of initial evaluation. In patient #3, aspiration pneumonia with sepsis occurred right after initiation of the CLB; after discontinuation of this therapy, no further episodes were reported for several months. Thus, despite the presence of other predisposing factors, the addition of CLB we suspect likely contributed to an increased risk of developing aspiration pneumonia. Additionally, somnolence and hypersalivation were also reported in all three patients after initiating CLB treatment.

Our patient cohort demonstrated several complicating factors that limit the establishment of a causative link between initiation of the CLB therapy and development of aspiration pneu-
nia. None of the patients had reported serum levels of CLB at the time of their clinical diagnosis of aspiration pneumonia. The reports were based on the clinical history provided by the patients’ family members and group home caregivers. Thus, it was possible that any or all of our patients might have had a seizure causing an aspiration. In our patients, initiation of the adjunct CLB therapy led to a significant decrease in their seizure burden, and discontinuation of this agent resulted in no further aspiration. These chronological relationships between introduction and withdrawal of CLB therapy as well as the appearance and resolution of respiratory symptoms reassure us of a much lower possibility of aspiration pneumonia being caused by breakthrough seizures. The risk of aspiration is indirectly related to the level of the patient’s level of arousal [11–13]. All three of our patients were simultaneously using an additional benzodiazepine formulation, which could lower the level of patient’s arousal and, in turn, increase the risk of aspiration. Both patients #1 and #2 used rescue rectal diazepam daily or every other day, while patient #3 was on daily dose of lorazepam. In addition to diazepam and CLB, patient #1 had VNS and patient #2 was taking phenobarbital. Both VNS and phenobarbital added additional risks for aspiration.

Based on our experiences with these patients, we recommend more aggressive screening of adult epileptic patients for aspiration-predisposing factors before initiating CLB therapy. We hypothesize that existing benzodiazepine therapy, adjunctive anti-seizure medications with sedation side effect (such as phenobarbital), hypersalivation, increased somnolence are additional predisposing factors for development of aspiration pneumonia in adult patients along with the previously mentioned factors such as GARD, prior history of aspirations, and existing G-tube. If the patient has one or more existing risk factors, the medication should be initiated cautiously. A lower initiation dose of CLB may need to be considered side effects of somnolence and drooling are prevalent with increasing CLB dosage. Nonetheless, we would like to acknowledge that further reports and investigations are warranted to validate this recommendation. Additionally, awareness and close attention to the early signs of aspiration, including an increase in drooling and excessive somnolence should be emphasized in education of the patient’s caregivers; as they might be warning signs prompting an escalation in the patient’s level of care.

5. Conclusion

In conclusion, CLB is widely used as adjunctive therapy for LGS and its efficacy has been prominent. The patients with epileptic encephalopathy presented here observed an association between the initiation of adjunctive CLB therapy and recurrent aspiration pneumonia. By highlighting this cohort of adult patients, we would like to increase the clinician and caregiver awareness to predisposing risk factors leading to aspiration pneumonia, before initiating the CLB therapy.

Ethics statement

No investigation or intervention was performed outside routine clinical care for the patients. As this is a case series, without experimental intervention into routine care, no formal research ethics approval is required. Patients’ anonymities were well protected.

Author contributions

Thandar Aung, MD, and Vladimir Shvarts, MD, were involved in the workup of the patient, planning and conducting investigations, and providing clinical care. They reviewed and revised the manuscript and approved the final manuscript as submitted.

Conflict of interest and source of funding statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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