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EC PHARMACOLOGY AND TOXICOLOGY
Case Report

Clobazam Induced a Rare Side Effect; Delayed Pedal Edema of the Lower Body: A Case Report

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Received: August 29, 2020; **Published:** October 07, 2020

Abstract

Introduction: Delayed pedal edema of the lower extremities is a rare side effect of Clobazam (CLB). Pedal edema is commonly the accumulation of fluid in the feet and lower extremities. It reported for other anti-epileptic medications but uncommon for Clobazam. The most likely cause of edema is heart failure, renal disease, liver disease, and drugs. Herein, we report the clinical course of the first case in the state of Qatar and through the literature as well, with a 3- year-old boy who had received CLB for two years and developed delayed pedal edema.

Methods: The patient was diagnosed with Ohtahara Syndrome and treated with CLB, developed edema which mainly in the lower extremities, other causes of edema such as cardiac, renal and hepatic causes were ruled out by different laboratory tests and images.

Results: Clobazam was stopped and the baby was observed. After 2 -3 weeks the edema was totally resolved.

Conclusion: Pedal edema is a rare side effect of Clobazam, and Health care professionals should be aware about that effect.

Keywords: *Clobazam (CLB); Pediatrics; Side Effect; Delayed Pedal Edema*

Abbreviations

CLB: Clobazam; AED: Anti-Epileptic Drug; GABA: Gamma-Aminobutyric Acid; CBC: Complete Blood Count; CRP: C-Reactive Protein; US: Ultra Sonogram; BZDs: Benzodiazepines

Introduction

Clobazam (CLB) is a commonly used oral antiepileptic drug (AED) that has been shown to be effective in various forms of epilepsy. Given its distinct 1, 5-benzodiazepine structure, rapid absorption, minimal drug interactions, and favorable safety profile, CLB displays unique properties when compared to other commonly used benzodiazepines. Clobazam is an anti-epileptic medication that is used in pediatrics and adults. Its mechanism of actions is bind to gamma-aminobutyric acid (GABA) A receptors and act by potentiating GABA-mediated action [1]. Its side effect included including drowsiness, ataxia, diplopia [1], and, rarely, hypersensitivity and hypothermia [2,3]. Pedal edema that is noticed and reported for other anti-epileptic medications [4,5] but rarely for Clobazam. The most likely cause of edema is heart failure, renal disease, liver disease, and drugs. The laboratory and radiological findings such as the fluid status; total protein, albumin, creatinine, urine routine, thyroid function tests, echocardiography, and ultrasound of the abdomen all are needed to rule out any other causes for the edema. In this case report we made a review for Clobazam side effect and mainly edema as it is a rare side effect.

Case Presentation

A 3 year-old boy. He is a case of Ohtahara syndrome secondary to migration brain anomaly with seizure disorder on multiple antiepileptic medications. He is on carbamazepine (15 mg/kg/day), phenobarbital (5 mg/kg/day) and phenytoin (6 mg/kg/day). He was started on Clobazam 2 years ago (0.5 mg/kg/day). 3 months back lower limb edema noticed.

During detailed physical examination there were lower limb pitting non painful swelling involving bilateral feet, extending up to the ankle. There is no hand edema, other no shifting dullness or abdominal distention; Pulses are felt normal in femoral and dorsal pedis arteries, capillary filling normal less than 2 seconds. Abdomen is soft, no hepatosplenomegaly. Chest examination showed good air entry. Cardiac examination showed no added sounds. S1/S2 heard. No heart murmur.

Initial laboratory work up was done to rule out other serious diagnosis such as cardiac, renal, thyroid, or respiratory disease, [CBC, total protein, CRP, albumin, creatinine, urine routine, and thyroid function tests] have been ordered and all were normal. X-ray showed no fractures. US Doppler ruled out deep venous thrombosis.

Patient seen by neurologist who suspected that edema could be related to the clobazam as Pedal edema was rarely reported as a side effect with Clobazam so he suggested holding it. Patient was observed, after 2 weeks edema improved. By the third week the edema was totally resolved.

Discussion

Drug-induced edema is not a dangerous side effect, but it would cause worries like heart, liver failure, vascular thrombosis, and or infections. That would cost the patient a long list of expensive investigations. In the literature, rare adult cases have been reported edema correlated with CLB therapy [6,7]. Mathew., *et al*. reported four patients with epilepsy who had pedal edema after starting CLB. All the cases had pitting non- painful edema [6]. The other case was described by Tanaka., *et al* [7]. He was 38 years old, male, was tread by CLB and his convulsions disappeared; however, after one month, oliguria and edema were shown in his lower extremities. After one week from discontinuation of CLB, edema disappeared. Six months later, the convulsions were frequently observed, so CLB was re-administrated again, and his convulsions significantly decreased, however, edema was manifested again. Two weeks after discontinuation of CLB, again, his edema disappeared. These findings suggested the correlation between CLB treatment and edema.

In pediatric, there was only one case has been reported in Turkey, 11-year-old boy, had bilateral hand and leg edema [8]. The seizures were ceased, after starting CLB at a dose of 0.5 mg/kg/day, and then dose was increased to 1 mg/kg/day. After Six weeks, edema was manifested in his lower extremities initially, Then edema evident on both hands and the leg. They thought CLB might be the cause of this edema, so CLB was discontinued, and his edema disappeared within two weeks. All Characteristics of patients with Clobazam-induced edema were mentioned in the table below.

Table: *Characteristics of patients with clobazam-induced edema.*

	Reported cases	Type of Epilepsy	Age	Sex	Duration of CLB before onset of Edema	Time to resolution of pedal edema after stopping CLB	Concomitant medications
Our case	Case 1	Generalized tonic-clonic seizures	3	Boy	2 years	2 weeks	Carbamazepine, phenobarbital, phenytoin
Epilepsy Study 20.3 (2002): 180-184.	Case 2	Intractable generalized epilepsy	38	Male	4 weeks	2 weeks	Sodium Valproate and phenytoin
Epilepsia 57.3 (2016): 524-525	Case 3	Complex partial seizure	66	Male	4 weeks	3 weeks	Locasamide, Phenytoin
	Case 4	Simple partial seizure	55	Female	12 weeks	6 weeks	Sodium Valproate
	Case 5	Complex partial seizure	35	Female	8 weeks	4 weeks	Oxcarbazepine, Topiramate
	Case 6	Complex partial seizure	58	Female	4 weeks	6 weeks	Levetiracetam, Telmisartan, Atorvastatin
Acta Neurologica Belgica 118.3 (2018): 521-522.	Case 7	Intractable epilepsy	11	Boy	6 weeks	2 weeks	Levetiracetam, carbamazepine, phenobarbital

In our case, the baby had lower limb edema only. The novelty in our case, he developed the edema after two years from initial start for Clobazam, while all the previous cases in the literature developed edema within 1 - 3 months of starting clobazam. Also, we do not know if the age can affect as a risk factor for the time for edema to appear (early versus delay), because the age of our case is only three years old while the other pediatric case was adolescent 11 years old and the rest of other cases all of them were adults. This report will shed more light to increase the awareness among physicians and care givers for that side effect. Pedal Edema is noticed as a swelling of hands and feet are noticed with antiepileptic medications as gabapentin, pregabalin, and valproate [4,5]. It is not considered as an allergic reactions, the exact cause is not known but presumed that antagonistic action of gabapentin, pregabalin on the calcium channels in the peripheral vasculature, the exact mechanism in the case of valproate is not yet known. Clobazam is a 1, 5-benzodiazepine derivative that is a relatively safe antiepileptic drug with reported side effects including drowsiness, ataxia, diplopia, and, rarely, hypersensitivity. Benzodiazepines (BZDs) are a class of antiepileptic's that bind to c-aminobutyric acid (GABA) receptors and act by potentiating GABA-mediated action. The mechanism by which Clobazam causes pedal edema has not yet been evaluated. However, there is evidence that BZDs have an inhibitory influence on vagal tone [9]. Probably by a similar effect on peripheral vasculature, clobazam may cause pedal edema.

Conclusion

Our case highlights this rare side effect of Clobazam and even could be delayed. Resolution of the edema after withdrawal of the drug will happen in few weeks. Health care professionals prescribing Clobazam should be aware about that effect.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

This case report received ethical approval from the medical research committee at Hamad Medical Corporation (MRC-04-18-413).

Funding

This study did not receive any specific funding.

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Volume 8 Issue 11 November 2020