

Contents lists available at ScienceDirect

Epilepsy & Behavior Case Reports

journal homepage: www.elsevier.com/locate/ebcr

Case Report

Hypothermia associated with clobazam use in adult epilepsy



Angela C. Gauthier*, Imran H. Quraishi, Richard H. Mattson

Yale Comprehensive Epilepsy Center, Department of Neurology, New Haven, CT 06510, United States

ARTICLE INFO

Article history:

Received 30 November 2015
Received in revised form 19 December 2015
Accepted 9 January 2016
Available online 20 January 2016

Keywords:

Antiepileptic drug
Benzodiazepine
Clobazam
Epilepsy
Hypothermia

ABSTRACT

Clobazam, a 1,5-benzodiazepine FDA-approved in 2011, is commonly used to treat anxiety and epilepsy. It has not been associated with hypothermia until very recently, in a case report involving two pediatric patients. Here, we report the first case of hypothermia development in an adult patient with epilepsy associated with clobazam use. A couple months after starting clobazam, the patient started developing episodes of hypothermia every several weeks, with temperatures ranging from 90 °F–95 °F. Normothermia was achieved with Bair Hugger therapy. Thyroid-stimulating hormone and cortisol levels were normal, and there was no evidence of infection in most instances. After 11 total episodes of hypothermia over a year of clobazam use, the drug was discontinued. It has now been 7 months after discontinuation, and the patient has not experienced any more episodes of hypothermia. Early recognition of the link between clobazam and hypothermia may prevent avoidable Emergency Department visits and hospitalizations.

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1. Introduction

Clobazam is a 1,5-benzodiazepine that has been used to treat anxiety and epilepsy since the 1970s [1]. It works by activating the GABA_A receptor, increasing the frequency of chloride channel opening [2]. Although clobazam is only approved for Lennox–Gastaut syndrome in the USA, it is regularly prescribed as an adjunctive therapy for refractory epilepsy [1]. Clobazam usually has only mild side effects such as sedation, dizziness, and ataxia [3]. However, a recent case report linked clobazam to the development of hypothermia in two pediatric patients [4]. Here, we describe the novel finding of hypothermia associated with clobazam use in an adult patient.

2. Case report

A 58-year-old male with severe developmental delay, convulsive seizure disorder since the age of three, left hemiparesis, recurrent aspiration pneumonia, and urinary retention presented for evaluation of hypothermia. Over the preceding year, he had experienced nine hypothermic episodes, with temperatures ranging from 90 °F–95 °F (Fig. 1). The hypothermia was usually thought to be secondary to infection. Upon presentation, his temperature was 92 °F at his group home and 95 °F in the office.

The patient, who was noncommunicative at baseline, was hospitalized and on examination appeared awake with no distress, calmly sitting in his wheelchair. He is normally hyperactive, but his caregivers noticed he would become listless during his hypothermic episodes. His blood pressure was 138/74 mmHg, pulse was 59 beats per minute, and oxygen saturation was 96%. The patient's lungs were clear to auscultation, and his heartbeat had a normal rate and rhythm, with no murmurs. He had full visual fields, intact extraocular movements, no nystagmus, pupils equal and reactive to light, and a midline tongue. He also had a left facial droop, increased spastic tone in the left arm and leg, and intact reflexes, but sensation and strength could not be tested.

Bair Hugger therapy, a forced air warming blanket, successfully raised the patient's temperature to 97 °F, which was maintained after it was removed. Empiric cephalexin and ciprofloxacin were started to treat any potential infectious etiology of temperature dysregulation. However, a urinalysis and chest X-ray were both unremarkable, and cultures remained negative, so antibiotics were discontinued on hospital day two. TSH and cortisol levels were normal.

Additional past medical history included hyponatremia, hypertension, cyclothymia, renal cell carcinoma, iron deficiency, thrombocytopenia, osteoporosis, and gastroesophageal reflux disease. The patient was taking phenytoin (200 mg/day), levetiracetam (3000 mg/day), and clobazam (10 mg bid) for seizures, amlodipine (10 mg/day) for hypertension, quetiapine (100 mg/day) and fluoxetine (30 mg/day) for cyclothymia, clonazepam (1 mg/day) for behavior, and aspirin (81 mg/day). He had previously taken oxcarbazepine for epilepsy but switched to clobazam because of hyponatremia. Clobazam had been started one year prior, and it was the last drug added. Because of this and the fact

* Corresponding author at: Yale Comprehensive Epilepsy Center, Department of Neurology, Yale School of Medicine, PO Box 208018, New Haven, CT 06520-8018, United States.

E-mail addresses: angela.gauthier@yale.edu (A.C. Gauthier), Imran.quraishi@yale.edu (I.H. Quraishi), Richard.mattson@yale.edu (R.H. Mattson).

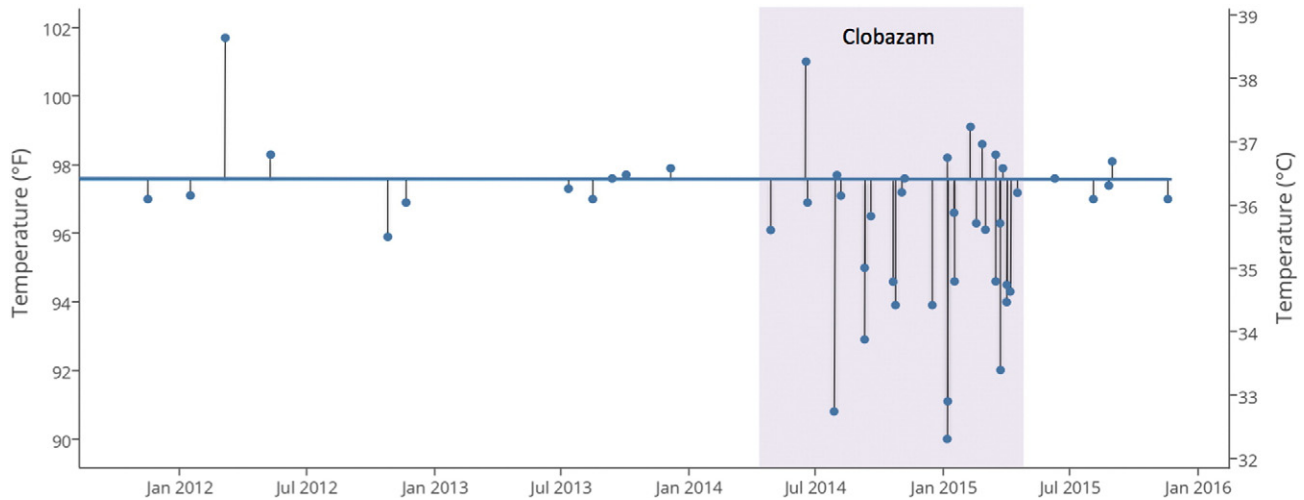


Fig. 1. Episodes of hypothermia during clobazam use. The patient experienced 11 total episodes of hypothermia during one year of clobazam use, resulting in many Emergency Department visits and a couple hospitalizations. There were no hypothermic episodes before clobazam use, and there have not been any after its discontinuation for 7 months. The horizontal line represents the patient's average temperature.

that clobazam had been recently linked to hypothermia [4], the drug was tapered from 10 to 5 mg bid over one week. During this period, the patient experienced one more hypothermic episode. Clobazam was then discontinued after this week, and since then, there have been no episodes of hypothermia for over half a year.

3. Discussion

This report describes an adult patient taking clobazam who experienced multiple episodes of hypothermia, which stopped after the drug was discontinued. Many patient populations are predisposed to developing hypothermia, including the young, the old, the mentally or physically disabled, and those taking certain medications [5]. Our patient had some of these risk factors. However, hypothermia occurred soon after clobazam was initiated and stopped immediately after the drug's discontinuation, leading us to conclude that clobazam played a primary role in the temperature dysregulation.

Benzodiazepines have been known to cause hypothermia through central thermoregulatory failure [5]. Normally, cooling of the peripheral circulation stimulates cold receptor afferents and the preoptic nucleus, triggering vasoconstriction, shivering, and other responses to conserve heat [5]. Tonic GABAergic signals inhibit the preoptic nucleus, preventing it from excessively raising body temperature [6]. If this tonic activity is increased, it could lower the set point temperature. Clobazam and other benzodiazepines allosterically activate GABA_A receptors, potentially causing this response [1]. There are many other

possible mechanisms of clobazam-induced hypothermia [4]. Although the exact mechanism remains unknown, future studies of patients with less comorbidities and known serum drug levels could further investigate this association.

Regardless of the mechanism, early recognition of the link between clobazam and hypothermia could allow for rapid reversal of the problem, preventing unnecessary visits and hospitalizations.

Conflict of interest

The authors declare that there are no conflicts of interest. This study was not funded. Written consent was obtained from the patient's guardian.

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