Seizure 23 (2014) 234–236

Contents lists available at ScienceDirect

Seizure

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

Short communication

Carbamazepine treatment of generalized tonic–clonic seizures in idiopathic generalized epilepsy

Katharine Kenyon [a,b], Scott Mintzer [b], Maromi Nei [b,*]

[a] School of Medicine, University of North Carolina, Chapel Hill, NC 27599, United States
[b] Jefferson Comprehensive Epilepsy Center, Department of Neurology, Thomas Jefferson University Hospital, 901 Walnut Street, Suite 400, Philadelphia, PA 19107, United States

ARTICLE INFO

Article history:
Received 19 September 2013
Received in revised form 25 November 2013
Accepted 25 November 2013

Keywords:
Idiopathic generalized epilepsy
Carbamazepine
Refractory epilepsy
Generalized tonic–clonic seizure
Juvenile myoclonic epilepsy

ABSTRACT

Purpose: Evaluate the efficacy of carbamazepine in the treatment of idiopathic generalized epilepsy (IGE).
Method: The response of five patients with IGE, who experienced primarily generalized tonic–clonic seizures which were refractory to multiple antiepileptic drugs, is reported.
Results: Carbamazepine controlled multiple seizure types and did not induce or increase the frequency of myoclonic or absence seizures in these patients. Many family members also responded favorably to carbamazepine.
Conclusion: Carbamazepine can be used with caution as an alternative treatment option for refractory IGE, especially in cases in which the main seizure type is generalized tonic–clonic.
© 2013 British Epilepsy Association. Published by Elsevier Ltd. All rights reserved.

1. Introduction

Idiopathic generalized epilepsy generally responds well to treatment with antiepileptic drugs (AEDs), with 80–90% achieving seizure-freedom.[1] Commonly used AEDs to successfully control IGE include valproate (VPA), ethosuximide (ESX), lamotrigine (LTG), and levetiracetam (LEV).[1,2] Topiramate (TPM) and zonisamide (ZNS) are also often considered "broad spectrum" AEDs, with activity against primary generalized seizure types.[2,3] The antiepileptic drug carbamazepine (CBZ) has been reported to increase or induce seizures in patients with IGE.[1,4,5] CBZ has been shown to exacerbate myoclonic and absence seizures and is therefore not typically used in the treatment of IGE.[6,7]

Other than a case report suggesting that the addition of CBZ to VPA in refractory juvenile myoclonic epilepsy (JME) treatment may control tonic–clonic seizures only, we are not aware of any other literature documenting successful treatment of IGE with CBZ.[8] Additionally, we are not aware of any reported cases of IGE being completely controlled with CBZ alone, or of CBZ controlling the multiple seizure types that characterize IGE. Here we report five patients with refractory IGE, mainly experiencing generalized tonic clonic seizures, whose seizures were controlled or dramatically reduced in frequency due to treatment with CBZ.

2. Case histories

2.1. Patient 1

A 36-year-old woman had a 19-year history of JME characterized by generalized tonic–clonic seizures and myoclonus, but had been seizure-free for 18 years on CBZ. Due to excessive daytime sleepiness and a polysomnogram showing frequent persistent generalized 4 Hz spike-wave activity, her CBZ had been discontinued by in favor of VPA. She had recurrent generalized tonic–clonic seizures, which were resistant to VPA (up to 1500 mg/day), LEV (3000 mg/day), and TPM (100 mg/day). A brain MRI was unavailable, but video-EEG monitoring verified both interictal and ictal activity typical of JME, with 4 Hz spike-wave discharges and non-localized generalized tonic–clonic seizures without aura. Due to repeated seizures, CBZ was finally restarted, and she has once again been seizure-free for five years on CBZ monotherapy.

2.2. Patient 2

A 26-year-old woman presented with JME at age 13 years with myoclonus, generalized tonic–clonic seizures, normal brain MRI,

* Corresponding author at: Jefferson Comprehensive Epilepsy Center, Department of Neurology, Thomas Jefferson University Hospital, 901 Walnut Street, Suite 400, Philadelphia, PA 19107, United States. Tel.: +1 215 955 1222; fax: +1 215 955 0606.
E-mail address: Maromi.Nei@jefferson.edu (M. Nei).

1059-1311/$ – see front matter © 2013 British Epilepsy Association. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.seizure.2013.11.016

and an EEG showing a photoparoxysmal response with generalized spike wave activity. She had been unable to tolerate multiple AEDs, including phenytoin (PHT), TPM, LTG, and valproate due to side effects or allergic reactions. Her seizures, occurring every 4–6 months, were refractory to several other AEDs, including ZNS (300 mg daily), LEV (1250 mg), primidone (PRM) (500 mg), and phenobarbital (PB) monotherapy (160 mg). CBZ was then added to PB, and she became seizure-free. An attempt was made to wean her PB, which resulted in recurrent myoclonic jerks with falls. She has since been maintained on CBZ XR (1000 mg) and PB (90 mg) and has remained seizure free for the past six years. She has three family members with epilepsy, all of whom have been evaluated at our epilepsy center. Her father, who has had myoclonus and generalized tonic–clonic seizures since college and isolated bursts of generalized spike-wave on EEG, has been seizure free since 2004 on a combination of PHT and PRM. Her sister and a paternal cousin have also responded well to CBZ. Her sister is currently seizure-free off AEDs, and her 56-year-old cousin has been seizure-free on CBZ since adolescence. Both had normal routine EEGs.

2.3. Patient 3

A 46-year-old man presented with a 26-year history of epilepsy. An interictal EEG near the time of presentation demonstrated 4–5 Hz generalized spike and wave and polyspike and wave activity. He began having generalized tonic–clonic seizures at age 7, but these were controlled on PHT until age 20 when status epilepticus occurred following head trauma. After this, his seizures became refractory to multiple AEDs, including PHT (400 mg), LEV (2000 mg), VPA (3000 mg), LTG, ZNS (300 mg), and TPM (800 mg). He was unable to tolerate clonazepam or gabapentin. Several EEGs performed during this time period continued to reveal generalized 4–5 Hz spike wave discharges, as well as generalized tonic–clonic seizures beginning with generalized polyspikes. Generalized tonic–clonic seizure frequency ranged from several per week to one every 2–4 weeks, myoclonic seizure frequency was less than one per month, and absence seizures occurred occasionally (3 in one year). After CBZ XR (1200 mg) was added to PHT (400 mg), his seizure frequency decreased to 2 GTC seizures in 10 months, with occasional myoclonus, and no absence seizures. The CBZ was subsequently replaced by oxcarbazepine (1800 mg) in addition to PHT(300 mg) and has not had any seizures for 1.5 years. He has two brothers with epilepsy (records unavailable), one controlled on CBZ and LEV, and the other controlled on PHT. His head CT was normal prior to head trauma. Subsequently, he had additional head trauma with a subsequent MRI brain showing only a subdural hematoma but no intraparenchymal abnormalities.

2.4. Patient 4

A 51-year-old man with a history of generalized tonic–clonic seizures beginning at age 14 years had experienced approximately one generalized tonic–clonic seizure per year for many years while treated with PHT. Due to gingival hyperplasia and continued seizures, his PHT was tapered and replaced by LEV (1500 mg), but his seizure frequency increased to once per month. Seizures continued on ZNS (400 mg). EEG testing revealed 4-Hz generalized spike wave discharges and a brain MRI was normal. He was thus begun on VPA but continued experiencing frequent seizures with 3 seizures within one month, despite a therapeutic level (82 mg/L). VPA was tapered, and CBZ XR (600 mg) was begun. He has been seizure-free for 7 months. Of note, his sister, who is also treated at our epilepsy center, has idiopathic generalized epilepsy and has been seizure-free for two years on VPA.

2.5. Patient 5

A 51-year-old woman with history of generalized tonic–clonic seizures beginning in childhood and EEG with generalized 4 Hz spike wave pattern had seizures refractory to TPM, LTG, VPA, LEV, and ESX, with seizures occurring once every two to several months on these medications. She was additionally unable to tolerate PHT due to side effects. Her brain MRI showed nonspecific periventricular white matter changes. She had been seizure-free on CBZ monotherapy for 4.5 years, but this had been tapered (due to alopecia) and replaced by oxcarbazepine (OXC). However, due to continued seizures on oxcarbazepine (1050 mg), CBZ was restarted and OXC tapered. She has been seizure-free for the past two years.

3. Discussion

Prior to treatment with CBZ, multiple AEDs had failed to provide adequate seizure control for these patients. After starting CBZ, these patients achieved full or significantly improved seizure control. Rather than exacerbating or increasing absence and myoclonic seizure frequency in these patients, a phenomenon which has been documented as a potential consequence of CBZ use in IGE treatment, CBZ also increased control of absence and myoclonic seizures in one patient and of myoclonic seizures in two patients. Notably, one patient also had improved seizure control on OXC, a closely related compound. Additionally, two patients had family members with epilepsy who achieved seizure control on CBZ or PHT, which also affect the sodium channel and have been reported to exacerbate seizures in IGE.[5,6]

As with all case histories, it is conceivable that the change in seizure frequency in these patients was coincidental, rather than being due to the introduction of CBZ, as spontaneous improvements in epilepsy appear to be at least as common as medication responses, at least in focal epilepsy.[9] However, two patients experienced recurrence of seizures upon CBZ withdrawal, regular seizures on other drugs, and then regained long-term seizure-freedom once "rechallenged" with CBZ, supporting that this was indeed a drug-specific response.

These cases suggest that carbamazepine may offer an effective treatment option for IGE that fails to respond adequately to AEDs which are typically used as first-line treatment in this syndrome, particularly when generalized tonic–clonic seizures are the primary seizure type. However, it should be emphasized that CBZ, particularly in monotherapy, should be used only with caution, as it may also exacerbate seizures in some individuals with IGE.

The response to atypical AEDs in family members with epilepsy suggests that there may be a genetically predisposed response to specific AEDs in some families. The existence of patients with IGE that is specifically CBZ-responsive suggests that there is genetic heterogeneity within the IGE syndromes, even those as well-defined as JME. Further investigation is needed to determine why some IGE cases respond well to CBZ, as well as whether a genetic marker may be identified to indicate which patients may benefit from treatment with CBZ.

Conflict of interest statement

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

References

1. Benbadis S, Tatum W, Gieron M. Idiopathic generalized epilepsy and choice of antiepileptic drugs. *Neurology* 2003;**61**:1793–5.

2. Mantoan L, Walker M. Treatment options in juvenile myoclonic epilepsy. *Current Treatment Options in Neurology* 2001;**13**:355–70.
3. Marinas A, Villanueva V, Giraldez BG, Molins A, Salas-Puig J, Serratosa JM. Efficacy and tolerability of zonisamide in idiopathic generalized epilepsy. *Epileptic Disorders* 2009;**11**(1):61–6.
4. Beydoun A, D'Souza J. Treatment of idiopathic generalized epilepsy—a review of the evidence. *Expert Opinion on Pharmacotherapy* 2012;**13**(9):1283–98.
5. Osorio I, Reed R, Peltzer J. Refractory idiopathic absence status epilepticus: a probable paradoxical effect of phenytoin and carbamazepine. *Epilepsia* 2000;**41**(7):887–94.
6. Thomas P, Valton L, Genton P. Absence and myoclonic status epilepticus precipitated by antiepileptic drugs in idiopathic generalized epilepsy. *Brain* 2006;**129**:1281–92.
7. Perucca E, Gram L, Avanzini G, Dulac O. Antiepileptic drugs as a cause of worsening seizures. *Epilepsia* 1998;**39**(1):5–17.
8. Knott C, Panayiotopoulos CP. Carbamazepine in the treatment of generalised tonic clonic seizures in juvenile myoclonic epilepsy. *Journal of Neurology Neurosurgery & Psychiatry* 1994;**57**:503–6.
9. Wang SP, Mintzer S, Skidmore CT, Zhan T, Stuckert E, Nei M, et al. Seizure recurrence and remission after switching antiepileptic drugs. *Epilepsia* 2013;**54**:187–93.