PharmacologyOnLine
April 30, 2013
Archives • 2013 • vol.1 • 7 - 11

THE EFFECT OF ZONISAMIDE IN PROPHYLAXIS THERAPY IN EPISODIC AND CHRONIC CLUSTER HEADACHE

V. Pizza*, V. Busillo° and A.Capasso^
*Neurophysiopatology Unit, Headache Centre, S. Luca Hospital, Vallo della Lucania (SA), °Neurology Unit, Headache Centre Maria SS Addolorata Hospital, Eboli (SA) and ^Department of Pharmacy, University of Salerno, Italy

Abstract

The prophylactic therapy of the episodic (ECH) and chronic cluster headache (CCH) is based on verapamil and carbolithium. Besides several patients are not responders at this drugs.

To evaluate the efficacy and tolerability of zonisamide in prophylaxis therapy of ECH and CCH.

11 patients (pz), (4 F,7 M) mean age 42.8 years (SD 5.8), range 36-56 years, suffering from ECH (8pz) and CCH (3 pz) (ICDH '04 criteria) were studied. In all patients with ECH prophylaxis therapy with verapamil, carbolithium and valproic acid was failed in the past and patients with CCH continued therapy with carbolithium (2 pz) and verapamil (1 pz). During the three months evaluation period zonisamide was administered (starting dose 25mg/die, target dose 100 mg/die).

In patients with ECH the basal frequency of attack/days and 1, 2, 3 months respectively was 4.2 (SD 1.9): 2.4 (SD 0.9), 1.6 (SD 0.9), 0.8 (SD 1.1) [P<0.0001]. In patients with chronic CH the basal frequency of attack/days and 1, 3, 6 months respectively was 2 (SD 0.8): 0.2 (SD 0.08), 0.06 (SD 0.04), 0.01 (SD 0.01) [P<0.05] (T-test analysis). In all patients zonisamide was well tolerated (5 patients complained somnolence, lack of concentration, vertigo and nausea but not withdrew the study).

These data showed a good efficacy in reduction of frequency of attacks. Still, the drug is tolerable, in fact none patients withdrew the study. Our study suggests that zonisamide could be an alternative or complementary prophylaxis therapy for ECH and CCH.

Key words: episodic cluster headache, chronic cluster headache, prohylaxis therapy, zonisamide

Introduction

Cluster headaches are excruciating unilateral headaches [1] of extreme intensity [2]. The duration of the common attack ranges from as short as 15 minutes to three hours or more. The onset of an attack is rapid, and most often without the preliminary signs that are characteristic of a migraine. However, some sufferers report preliminary sensations of pain in the general area of attack, often referred to as "shadows", that may warn them an attack is lurking or imminent. Though the headaches are almost exclusively unilateral, there are some documented as cases of "side-shifting" between cluster periods, or, even rarer, simultaneously (within the same cluster period) bilateral headache [3]. Trigeminal neuralgia can also bring on headaches with similar qualities. However, with trigeminal neuralgia the pain is mostly located around the facial area and is described as being like stabbing electric shocks, burning, pressing, crushing, exploding or shooting pain that becomes intractable. Cluster headaches have been classified as vascular headaches. The intense pain is caused by the dilation of blood vessels which creates pressure on the trigeminal nerve. While this process is the immediate cause of the pain, the etiology (underlying cause or causes) is not fully understood. A wide variety of prophylactic medicines are in use, and patient response to these is highly variable.

Current European guidelines suggest the use of the calcium channel blocker verapamil at a dose of at least 240 mg daily. Steroids, such as prednisolone/prednisone, are also effective, with a high dose given for the first five days or longer (in some cases up to 6 months) before tapering down. Methysergide, lithium and the anticonvulsant topiramate are recommended as alternative treatments [4]. Also, it has been reported success with sodium valproate and carbamazepine in some chronic, treatment-refractory cases. Intravenous magnesium sulfate relieves cluster headaches in about 40% of patients with low serum ionized magnesium levels [5]. Melatonin has also been demonstrated to bring significant improvement in approximately half of episodic patients; psilocybin, dimethyltryptamine, LSD, and various other tryptamines have shown similar results [6].

Zonisamide, a new antiepileptic drug, has been approved in the US as adjunctive therapy for the treatment of partial seizures in adults. [7,8]. Chemically a sulfonamide analogue, zonisamide is thought to have several mechanisms of action, including a rate-dependent blockade of voltage-gated sodium channels and reduction of ion flow through T-type calcium channels [9-11]. It is also a weak carbonic anhydrase inhibitor. Zonisamide has a favorable pharmacokinetic profile that includes high oral bioavailability and a long half life (63 hours), permitting a once- or twice-daily dosing regimen [12].

There are only a limited number of current migraine preventive medications that have proven efficacy. Their use is often limited because of adverse events (AEs) in a significant number of patients [13]. Because of its pharmacologic properties, zonisamide is potentially an effective drug for migraine prevention, and preliminary data suggest that it may be effective for this indication [14-16]. The long half life of the drug makes it a good candidate for migraine patients who have poor compliance to preventive therapy that involves multiple daily dosing.

The aim of this study was to evaluate the efficacy and tolerability of zonisamide in prophylaxis therapy of ECH and CCH.

Patients and Methods

The study was performed and approved by Neurophysiopatology Service, Headache Centre, S. Luca Hospital, Vallo della Lucania (SA),Italy.

We studied 11 patients (pz), (4 F,7 M) mean age 42.8 years (SD 5.8), range 36-56 years, suffering from ECH (8 pz) and CCH (3 pz) (ICDH '04 criteria) [17] . In all patients with ECH prophylaxis therapy with verapamil, carbolithium and valproic acid was failed in the past and patients with CCH continued

therapy with carbolithium (2 pz) and verapamil (1 pz). During the three months evaluation period zonisamide was administered (starting dose 25mg/die, target dose 100 mg/die).

Demographic data, including weight, zonisamide dosage and duration of treatment, were collected and analyzed. History of patients' previous migraine treatments and their outcome was analyzed. The frequency of attack/days of ECH and CH were evaluated. The type, severity, and prevalence of side effects were also evaluated.

We used paired t-test to compare the value of each parameter before the initiation of zonisamide treatment to the corresponding value at the last follow-up after treatment initiation. The level of significance was set at $p<0.05$.

Results

Table 1 and Figure 1 report general data of the sample and the basal attack frequency/days in patients with ECH before zonisamide treatment [4.09 (SD 2.3)] and the basal attack frequency/days in patients with ECH after 1, 2, 3 months zonisamide treatments: 2.2 (SD 1.1), 1.6 (SD 0.9), 0.7 (SD 0.09) [P<0.0001] Zonisamide was able to reduce significantly and in time-related manner the attack frequency without inducing significative side effects.

Table 2 and Figure 2 report general data of the sample and the basal attack frequency/days in patients with CH before zonisamide treatment [3.6 (SD 0.9)] and the basal attack frequency/days in patients with CH after 1, 2, 3 months zonisamide treatments: 2.2 (SD 1.1), 1.6 (SD 0.9), 0.3 (SD 0.04) [P<0.05] Zonisamide was able to reduce significantly and in time-related manner the attack frequency without inducing significative side effects.

Discussion

In this retrospective study of ECH and CCH patients, zonisamide treatment was able to decrease significantly the attack frequency/days without significative side effects thus confirming previous studies suggesting that zonisamide may be effective in headache prevention.

Drake et al. [14] conducted an open label study to examine the effect of zonisamide on headache in 34 refractory migraine patients.8 Zonisamide treatment was initiated at a dose of 100 mg/day and titrated up to 400 mg/day as tolerated. Significant improvement in headache frequency, severity, and duration was evident one month after initiation of zonisamide therapy, which continued throughout the three-month study period.

Also, Smith [15] conducted an open label study to evaluate the efficacy of zonisamide, given at a dose of 100-200 mg/day, on 16 patients with refractory chronic daily headache.9 Three months after initiation of zonisamide treatment, both average headache frequency and average headache duration decreased (by 34% and 24%, respectively). Zonisamide also decreased headache-related disability in this study, and was well-tolerated.

Finally, Krusz [16] examined the effect of zonisamide on 33 patients who had refractory migraine with or without tension type headache. The zonisamide dose range was 100-600 mg/day. Of the 23 patients who had been evaluated, 14 had a decrease in headache frequency of 25%-65%. [17,18].

Our study shows a statistically significant beneficial effect of zonisamide on ECH and CCH patients, however, it should be noted that our study population consisted of patients who had failed multiple migraine preventive drugs prior to zonisamide therapy

The limitations of this study include a small sample size, a retrospective, open label, noncontrolled design, and variability among patients in zonisamide dosing regimen.

Controlled studies are needed to evaluate the role of zonisamide in ECH and CCH prevention therapy.

References

1. Beck E, Sieber WJ, Trejo R (February 2005). "Management of cluster headache". Am Fam Physician 71 (4): 717–24.
2. Capobianco DJ, Dodick DW (April 2006). "Diagnosis and treatment of cluster headache". Semin Neurol 26 (2): 242–59.
3. Meyer EL, Laurell K, Artto V, Bendtsen L, Linde M, Kallela M, Tronvik E, Zwart JA, Jensen RM, Hagen K (June 2009). "Lateralization in cluster headache: a Nordic multicenter study". J Headache Pain 10 (4): 259–63.
4. May A, Leone M, Afra J, Linde M, Sándor P, Evers S, Goadsby P (October 2006). "EFNS guidelines on the treatment of cluster headache and other trigeminal-autonomic cephalalgias". Eur J Neurol 13 (10): 1066–77.
5. Mauskop, Alexander; Altura, Bella T.; Cracco, Roger Q.; Altura, Burton M. (1995). "Intravenous magnesium sulfate relieves cluster headaches in patients with low serum ionized magnesium levels". Headache 35 (10): 597–600.
6. Leone M, et al. (19965). "Melatonin versus placebo in the prophylaxis of cluster headache: a double-blind pilot study with parallel groups". Cephalalgia 16 (7): 494–496.
7. Jain KK. An assessment of zonisamide as an anti-epileptic drug. Expert Opin Pharmacother 2000;1:1245-1260.
8. Frampton JE, Scott LJ. Zonisamide: a review of its use in the management of partial seizures in epilepsy. CNS Drugs 2005;19:347-367.
9. Schauf CL. Zonisamide enhances slow sodium inactivation in Myxicola. Brain Res 1987;413:185-188.
10. Suzuki S, Kawakami K, Nishimura S, et al. Zonisamide blocks T-type calcium channel in cultured neurons of rat cerebral cortex. Epilepsy Res 1992;12:21-27.
11. Leppik IE. Zonisamide: chemistry, mechanism of action, and pharmacokinetics. Seizure 2004;13 Suppl 1:S5-S9
12. Elan Pharmaceuticals I. ZonegranTM (zonisamide) capsules product information. San Francisco, CA 2000
13. Silberstein SD, Goadsby PJ. Migraine: preventive treatment. Cephalalgia 2002;22:491-512.
14. Drake ME, Jr., Greathouse NI, Renner JB, Armentbright AD. Open-label zonisamide for refractory migraine. Clin Neuropharmacol 2004;27:278-280.
15. Smith, T. R. Treatment of refractory chronic daily headache with zonisamide: a case series. Poster presentation at the American Epilepsy Society Annual Meeting in Philadelphia, PA December 4th. 2001.
16. Krusz JC. Zonisamide in the treatment of headache disorders. Cephalalgia 2001;21:374-375.
17. Headache Classification Committee. The International Classification of Headache Disorders, 2nd Edition. Cephalalgia 2004;24:1-160.
18. Silberstein SD, Lipton RB, Sliwinski M. Classification of daily and near-daily headaches: field trial of revised IHS criteria. Neurology 1996;47:871-875.

N° patients	sex	age	D. Y.	F. A.	F.A. > 1month	F.A. >3months	F.A. >6months	C. D.	S. E.
1	f	36	10	2	1	1	0	N	sleepy, vertigo, nausea
2	m	49	12	2	1	1	0	N	N
3	m	56	26	8	2	0	0	N	N
4	M	34	9	5	2	1	1	Y	N
5	F	44	12	4	4	2	1	Y	N
6	M	40	3	6	3	2	0	Y	N
7	M	40	2	4	3	3	3	N	N
8	M	42	3	3	3	3	2	N	sleep

Table 1: EHC Patients: data

Legend:
D.Y.: disease years
F.A.: frequency years
C.D.: concomitant disease
S.D.: side effects

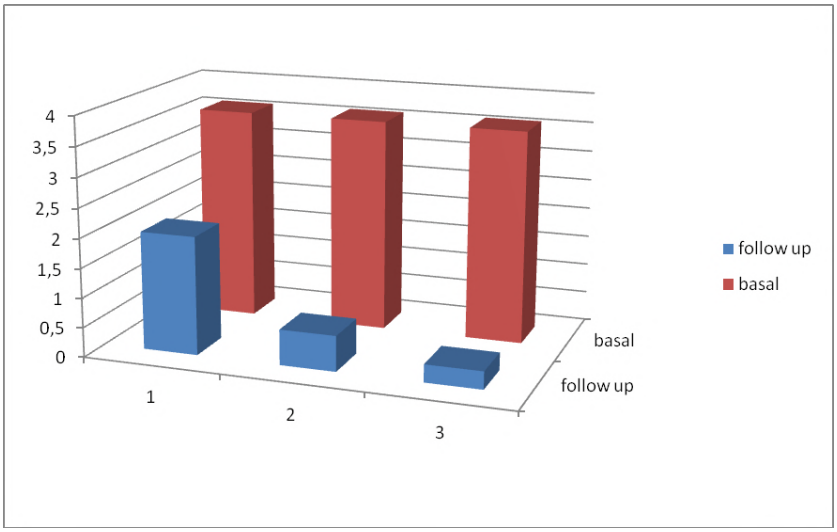

Fig. 2: Frequency attacks basal vs follow up at 1, 3 and 6 months in patients with CCH
Legend: 1= 1 month; 2= 3 months; 3= 6 months