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Avi Ashkenazi
Thomas Jefferson University, avi.ashkenazi@jefferson.edu

Adam Benlifer
Thomas Jefferson University

Jason Korenblit
Thomas Jefferson University

Stephen D. Silberstein
Thomas Jefferson University

Zonisamide for Migraine Prophylaxis in Refractory Patients

Avi Ashkenazi, M.D., Adam Benlifer, B.S., Jason Korenblit, B.S.,

Stephen D. Silberstein, M.D., F.A.C.P

Jefferson Headache Center

Philadelphia, PA

Zonisamide, a new antiepileptic drug, has been approved in the US as adjunctive therapy for the treatment of partial seizures in adults.[1,2] 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.[3-5] 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.[6]

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.[7] 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.[8-10] 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.

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The aim of this study was to evaluate the efficacy and tolerability of zonisamide for migraine prophylaxis in refractory patients attending a tertiary headache center.

Methods:

The study was approved by the Jefferson University Hospital Institutional Review Board. We reviewed the charts of adult patients (18 years of age or older) who had a diagnosis of episodic migraine (EM) with or without aura, as defined by the International Headache Society (IHS), or with transformed migraine (TM) according to the Silberstein-Lipton criteria.[11,12] Included patients had been treated with zonisamide at the Jefferson Headache Center from January 2001 to June 2003 for a minimum of 60 days. 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 following disease-related parameters were evaluated: number of headache days per month, average headache severity (measured using an 11-point verbal scale), average headache attack duration, and headache-associated disability, as measured by the number of missed days from school/work per month. Data on these parameters before initiation of zonisamide treatment and at the last office visit after treatment initiation were abstracted and compared. The type, severity, and prevalence of AEs were abstracted.

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Statistical analysis:

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:

Thirty-three patients (27 women and six men) were included in the study. Their average age was 43.9±8.4 years (range: 20-61 years). Twenty-three (70%) had transformed migraine and 10 (30%) had episodic migraine. The average duration of disease was 23.8±12.1 years (range: 2-51 years). Twenty four patients (72%) had psychiatric co-morbidity, including depression (15 patients), anxiety (four patients), adjustment disorder (four patients) and bipolar disorder (two patients). The patients had failed an average of 6.2 migraine prophylactic drugs prior to zonisamide. The headache-preventive medication class most commonly used prior to zonisamide therapy was anticonvulsants (30 patients, 91%), followed by antidepressants (22 patients, 66%), herbal medications, vitamins and minerals (18 patients, 54%) and anti-psychotic drugs (16 patients, 48%) (Table). Seventeen patients were on zonisamide alone and sixteen were on polytherapy (i.e. on zonisamide and at least one other migraine preventive drug). The patients used a variety of acute pain medications during the study evaluation period, including triptans, NSAIDs, neuroleptics, and, rarely, opioids. In accordance with our clinical practice, the

use of these medications was limited to no more than three days per week total, and no more than two days/week for triptans and opioids.

Zonisamide treatment was started at a dose of 100 mg/day and, in the majority of patients (18/33, 55%) was titrated up by 100 mg/day every week to an initial target dose of 300 mg/day. In 12 (36%) patients, the rate of zonisamide titration was slower, and in 3 (9%) it was more rapid. In 16 (48%) patients, the zonisamide dose was increased above 300 mg/day, up to a maximum of 600 mg/day, in an attempt to achieve headache control, while 9 (27%) patients remained on less than 300 mg/day because of decreased tolerance. The average zonisamide daily dose was 337.9±146.3 mg (range: 100-600 mg). The average total duration of treatment was 186.4±174.0 days (range: 61-780 days), and the average duration of treatment on the maximal maintenance dose of zonisamide was 159±210 days.

The average number of days with headache per month was reduced from 20.7±9.5 before the initiation of zonisamide treatment to 18.0±11.3 after treatment initiation (p=0.06) (figure). The corresponding median values were 24 and 18 days. Data stratification showed that the number of days with headache per month was reduced from 24.7±7.3 before initiation of zonisamide treatment to 21.0±10.7 after treatment initiation in patients with TM (p=0.06). The corresponding values for patients with EM were 11.6±7.6 and 11.0±9.7 (p=n/s) (figure). No significant changes in headache severity, headache duration, or the number of missed days from school or work occurred after zonisamide treatment was initiated.

Fourteen patients (42.4%) reported AEs, the most common of which was fatigue (4 patients, 12%). Other AEs included irritability, anxiety, concentration difficulties, dizziness, gastrointestinal upset, foot edema, and renal calculi. Most patients (12/14, 85.7%) rated AEs as mild or moderate. There was no significant change in weight with zonisamide therapy (the average weight before treatment initiation was 80.0 ±25.5 kg vs. 80.9±25.9 kg at the last office visit after treatment initiation).

Discussion:

In this retrospective study of refractory migraine patients, zonisamide treatment was associated with a small, non-statistically significant, decrease in the number of headache days per month.There was no significant effect of zonisamide on any of the other headache parameters. Interestingly, the mild beneficial effect of zonisamide was seen in TM, but not in EM, patients.

Other studies have suggested that zonisamide may be effective in migraine prevention. Drake et al. 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.

Zonisamide was well-tolerated. Smith 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. Krusz examined the effect of zonisamide on 33 patients who had refractory migraine with or without tension type headache.[10] 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%. Our population of patients may have been more refractory than these. This might be due to differences in various demographic and disease-related factors, including age, disease duration, attack frequency and severity and co-morbidity.

Our study did not show a statistically significant beneficial effect of zonisamide on headache or on any of the other evaluated parameters. It should be noted that our study population consisted of refractory patients who had failed multiple migraine preventive drugs prior to zonisamide therapy. They also had a high prevalence of depression and anxiety, rendering their management more challenging.

The limitations of this study include a small sample size, a retrospective, open label, non-controlled design, and variability among patients in zonisamide dosing regimen. Additionally, study patients were taking various doses of other preventive and acute pain medications at the time of study, potentially confounding the results.

Controlled studies are needed to evaluate the role of zonisamide in migraine prevention.

Medication Class	**Number (%) of Patients**
Anticonvulsants (gabapentin, lamotrigine, levetiracetam, topiramate, valproic acid)	30 (91%)

Antidepressants (amitriptyline, nortriptyline, fluoxetine, paroxetine, venlafaxine, mirtazapine, phenelzine)	22 (66%)
Herbal medicines, vitamins and minerals (feverfew, riboflavin, coenzyme Q10, magnesium)	18 (54%)
Anti-psychotics (quetiapine, olanzapine, ziprasidone)	16 (48%)
NSAIDs (indomethacin, celecoxib)	10 (30%)
Calcium channel blockers (verapamil, diltiazem)	8 (24%)
Anxiolytics (buspirone)	5 (15%)

Table: Headache preventive medications used unsuccessfully by patients prior to zonisamide treatment

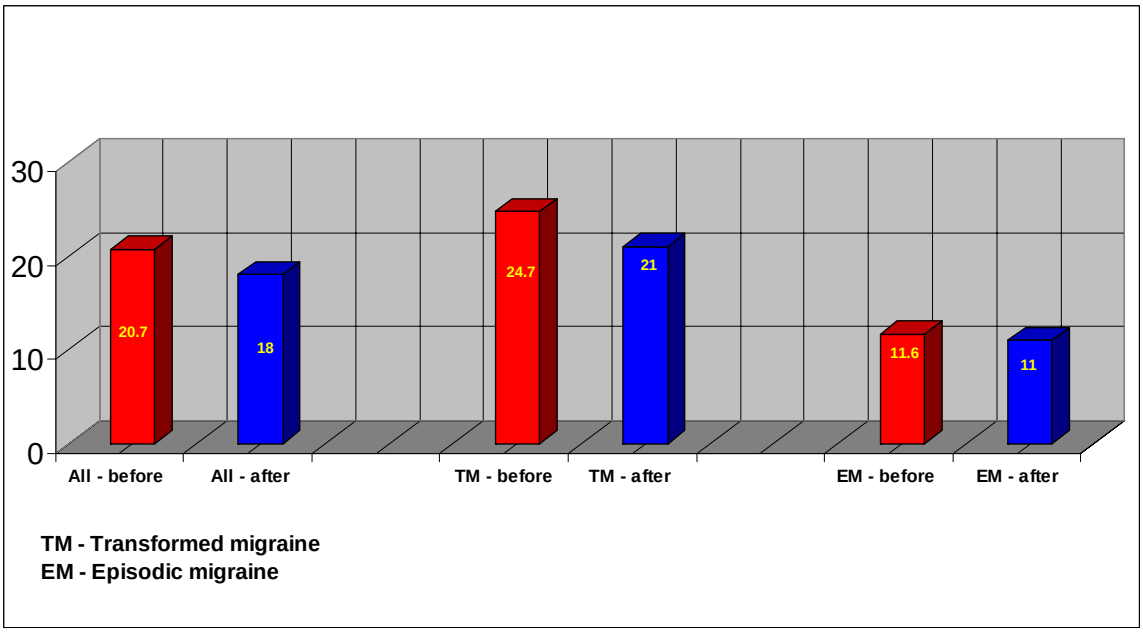

Figure: Average number of headache days per month before and after treatment with zonisamide

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