Epilepsy & Behavior 17 (2010) 455–460

Contents lists available at ScienceDirect

Epilepsy & Behavior

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

A prospective audit of adjunctive zonisamide in an everyday clinical setting

Linda J. Stephen *, Kevin Kelly, Elaine A. Wilson, Pamela Parker, Martin J. Brodie

Epilepsy Unit, Division of Cardiovascular & Medical Sciences, Western Infirmary, Glasgow, Scotland, UK

ARTICLE INFO

Article history:
Received 21 October 2009
Revised 13 January 2010
Accepted 15 January 2010
Available online 5 March 2010

Keywords:
Epilepsy
Zonisamide
Seizures
Antiepileptic drug
Side effects

ABSTRACT

This audit examined outcomes for 203 patients prescribed zonisamide (ZNS) for various uncontrolled seizure types at a specialist outpatient service. Forty-two (20.7%) patients achieved 6 months of seizure freedom, and an additional 37 (18.2%) had a ⩾50% seizure reduction for 6 months on a stable ZNS dose. Seizure freedom was more likely in patients with primary generalized (24/61, 39%) than in those with partial-onset (18/141, 12.7%) seizures ($P < 0.001$). Eight patients (5 seizure free) were maintained on ZNS monotherapy. More patients became seizure free with ZNS as monotherapy or first add-on, compared with those in whom ZNS was the second, third, or fourth adjunctive drug ($P = 0.001$). Seizure freedom was less likely in patients treated with hepatic enzyme-inducing agents (13/113, 11.5%) than in those receiving noninducing AEDs (24/82, 29.3%) ($P = 0.002$). ZNS was discontinued in 72 (35.5%) patients largely because of side effects ($n = 58$, 28.6%). Commonest complaints leading to withdrawal were sedation ($n = 14$), nausea and vomiting ($n = 13$), neuropsychiatric symptoms ($n = 12$), rash ($n = 6$), and weight loss ($n = 6$). Around 80% of patients who became seizure free on ZNS or had the drug withdrawn did so on a dose ⩽200 mg. ZNS is an effective broad-spectrum AED that can also produce a range of dose-dependent and idiosyncratic side effects.

1. Introduction

Zonisamide (ZNS) is a synthetic 1,2-benzisoxazole derivative. The drug is licensed in Europe as adjunctive treatment for partial seizures with or without secondary generalization. ZNS blocks the repetitive firing of voltage-sensitive sodium channels, and reduces voltage-sensitive T-type calcium currents without affecting L-type calcium currents [1,2]. It has been shown to inhibit excitatory glutamate-mediated synaptic transmission [3], as well as to have effects on γ-aminobutyric acid (GABA) function [4]. Facilitation of dopaminergic and serotonergic transmission and neuroprotection have also been demonstrated [5–7], although whether these properties are linked to the antiepileptic effects of the drug is unclear.

Four randomized studies have demonstrated the efficacy and safety of ZNS in adults with partial and/or secondarily generalized seizures [8–11]. A systematic review concluded that the drug is effective as add-on treatment for drug-resistant localization-related epilepsy [12]. Controlled and open-label studies suggest ZNS may also have efficacy against idiopathic generalized epilepsies in patients with primary generalized tonic–clonic, tonic, typical and atypical absence, atonic, myoclonic, and clonic seizures [13–18]. Patients with Lennox–Gastaut syndrome may benefit from ZNS introduction [19], and efficacy against infantile spasms has also been demonstrated [20].

Although double-blind randomized controlled studies are important in establishing the efficacy and safety of AED treatment, strict entry and dosing criteria limit the amount of useful data that can be derived to allow decision making in routine practice. Pragmatic studies in clinical practice are increasingly recognized as providing information that complements that derived from regulatory trials [21,22]. Hence the aim of this prospective audit was to examine the pros and cons of adjunctive ZNS for patients with a variety of seizure types in an everyday clinical setting.

2. Methods

At the Epilepsy Unit at the Western Infirmary in Glasgow, Scotland, ZNS was added to the antiepileptic drug (AED) regimens of 203 patients ⩾12 years (82 men, 121 women, aged 15–80 years [median 39 years]) with uncontrolled seizures of any type in an attempt to improve their seizure control. Of these patients, 142 had partial seizures with or without secondary generalization, and 60 had primary generalized seizures (27 juvenile myoclonic epilepsy [JME], 23 tonic–clonic seizures, 4 typical absence seizures, 5 tonic–clonic/absence seizures, 1 tonic–clonic/myoclonic/akinetic). One patient had Landau–Kleffner syndrome. In total, 15 patients had learning disabilities. Seizure types were classified according to the clinical description of the event, as well as the EEG pattern [23]. Epilepsy syndromes were classified taking into account fac-

* Corresponding author. Address: Epilepsy Unit, Western Infirmary, Glasgow G11 6NT, Scotland, UK. Fax: +44 141 211 2072.
E-mail address: linda.stephen@ggc.scot.nhs.uk (L.J. Stephen).

1525-5050/$ - see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.yebeh.2010.01.016

tors including seizure type, age at onset, clinical and EEG characteristics, presence or absence of an underlying neurological lesion, and presumed genetic etiology [24]. Patients had already failed treatment with a median of two AEDs (range: 1–12). Prior to the introduction of ZNS, 3 were taking no AEDs, 57 were taking one, 87 were taking two, 52 were taking three, and 4 were taking four drugs. Of the 3 patients taking no AEDs, all were having seizures, but had chosen to stop previous AED treatment, one because of side effects and two because of lack of efficacy.

As do all patients attending the Epilepsy Unit, patients and/or caregivers kept a written record of their baseline seizure frequency prior to the addition of ZNS. Retrospective analysis revealed the median monthly seizure frequency to be 5 (range: 1–210) in the 3 months prior to the addition of ZNS. Where possible, patients were reviewed by the same clinician every 6–8 weeks or sooner if required. Clinical data were recorded in a structured casesheet and entered into a computerized database. All patients and/or caregivers kept a record of seizure frequency on standard charts. Adverse effects were inquired about by asking: "Are you having any problems with your medication?" Other AEDs were withdrawn or doses reduced in an effort to improve tolerability or reduce drug burden as necessary. Weight was measured prior to the addition of ZNS and was monitored at each clinic visit thereafter.

Two ZNS dosing schedules were employed. Patients taking hepatic enzyme-inducing AEDs took 25 mg twice daily in week 1, increasing to 50 mg twice daily in week 2. Thereafter, dosing was adjusted as clinically indicated in two weekly increments of up to 100 mg, with target dosing of 300–500 mg/day. Patients not taking hepatic enzyme-inducing AEDs took 25 mg twice daily in weeks 1 and 2, increasing to 50 mg twice daily in weeks 3 and 4. Thereafter, dosing was adjusted as clinically indicated in two weekly increments of 50 mg, with target dosing of 200–300 mg/day. Patients becoming seizure free on any given dose remained on that dose. The optimal maintenance dose was identified for each patient according to efficacy and tolerability. Other AEDs were withdrawn where possible in an effort to minimize side effects or reduce drug burden.

Patients were kept under observation until one of the following primary endpoints was established: seizure freedom for at least 6 months on a given dose of ZNS; $\geqslant$50% reduction (responder) in seizure frequency over a 6-month period compared with baseline on the highest tolerated dose of ZNS; <50% seizure frequency reduction (marginal effect) compared with baseline in patients wishing to continue ZNS treatment; or withdrawal of ZNS for lack of efficacy, side effects, or both. The χ^2 test was used for comparisons of categorical data. All statistical tests were two-tailed. Calculations were computed using Minitab for Windows (Release 13.32) software.

3. Results

All 203 patients started on ZNS have reached an endpoint (Fig. 1). Overall, 42 (20.7%) patients have been seizure free for $\geqslant$6 months on an unchanged ZNS dose. Of these, 18 have partial-onset seizures, and 24 have primary generalized seizures (10 JME, 8 tonic–clonic seizures, 4 absence seizures, 2 primary generalized tonic–clonic/absence seizures). Patients with primary generalized seizures (24/60, 40%) were significantly more likely to become seizure free than those with partial-onset seizures (18/142, 12.7%) ($P < 0.001$). Of the seizure-free patients, 13 were also taking hepatic enzyme-inducing AEDs (median ZNS dose = 100 mg/day, range: 75–300 mg/day); 24 were taking non-enzyme-inducing AEDs (median ZNS dose = 100 mg/day, range: 50–400 mg/day). Patients taking non-enzyme-inducing AEDs were significantly more likely to attain seizure freedom than those who took hepatic enzyme-inducing agents ($P = 0.003$). AED combinations resulting in seizure freedom are listed in Table 1. Five seizure-free patients (2 with primary generalized tonic–clonic seizures, 1 with JME, 1 with absence seizures, 1 with partial-onset seizures) took ZNS monotherapy (2 on 100 mg/day, 1 on 200 mg/day, 1 on 225 mg/day, 1 on 350 mg/day).

A $\geqslant$50% reduction in seizure frequency for 6 months was achieved by 37 (18.2%) patients. Of these, 21 had partial-onset seizures, 15 had primary generalized seizures (9 JME, 5 tonic–clonic seizures, 1 tonic–clonic/absence seizures), and 1 patient had Landau–Kleffner syndrome. Characteristics of patients who continued taking ZNS are outlined in Table 2. A marginal reduction (<50%) in seizures was reported by 52 (25.6%) patients who experienced a

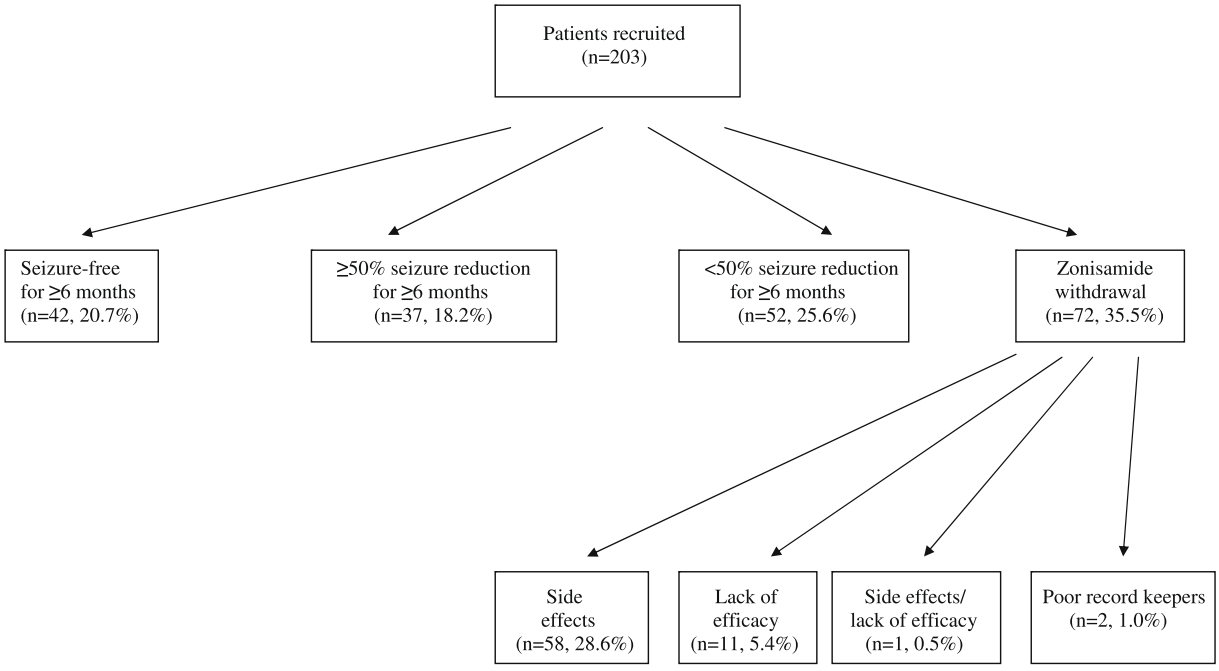

Fig. 1. Outcomes in patients treated with adjunctive zonisamide.