ELSEVIER

Epilepsy Research 68S (2006) S17–S24

Epilepsy Research

www.elsevier.com/locate/epilepsyres

Practical prescribing and long-term efficacy and safety of zonisamide

Ilo E. Leppik *

University of Minnesota and MINCEP Epilepsy Care, College of Pharmacy, 308 Harvard St. SE, 7-115 WDH, Minneapolis, MN 55455, USA

Received 22 September 2005; received in revised form 4 November 2005; accepted 4 November 2005
Available online 9 January 2006

Abstract

Long-term efficacy, tolerability and safety of antiepileptic drug (AED) therapy is essential given the chronic nature of epilepsy. Zonisamide (Zonegran®), a novel AED with a broad range of mechanisms of action contributing to its antiseizure efficacy, has been evaluated extensively for the long-term management of epilepsy. Open-label extension studies in the United States and Europe suggest continued efficacy of zonisamide in long-term treatment without development of adverse events further to those seen in registration studies. Baseline seizure frequency is reduced by approximately 40–70% during long-term treatment for up to 2 years, and 30–50% of patients attain ≥50% reduction in seizure frequency across all categories of seizure and durations of treatment. Preliminary data indicate a progressive decline in seizure frequency with continued zonisamide treatment. Zonisamide is well tolerated in long-term use, with a trend towards decreasing incidence of generally mild adverse events over time and a low rate of withdrawal during chronic use. Nephrolithiasis and other serious adverse events are infrequent, and can be minimised by appropriate management and patient education. This profile of maintained efficacy, tolerability and safety during sustained administration in combination with other AEDs supports zonisamide as a valuable adjunctive agent in the long-term management of refractory partial epilepsy.

Keywords: Long-term treatment; Partial seizures; Review; Tolerability; Zonisamide

1. Introduction

Zonisamide (Zonegran®) is a novel antiepileptic drug (AED), structurally unrelated to existing AEDs. It has a unique combination of modes of action that contribute to its antiepileptic efficacy (Leppik, 2004; see also Baulac, this issue). Zonisamide was licensed in the United States (US) in the year 2000, and has been studied extensively within clinical programmes in the US and Europe. There has been widespread use of zonisamide in Japan since 1989, which has added considerably to our knowledge base. More than 2 mil-

* Tel.: +1 612 625 7139; fax: +1 612 624 6695.
E-mail address: leppi001@umn.edu.

0920-1211/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.eplepsyres.2005.11.006

lion patient-years of exposure have accrued over zonisamide's 15 years of clinical use.

An appreciation of the long-term efficacy, tolerability and safety of AED therapy is essential because of the chronic nature of epilepsy. Extensive experience with zonisamide has included the evaluation of long-term treatment in patients in the US and Europe who had progressed from placebo-controlled and uncontrolled studies into open-label, long-term studies. This paper describes the efficacy and long-term safety of zonisamide demonstrated in clinical studies, outlines the application of this profile to clinical practice in the US, and presents the author's current approach to practical prescribing to optimise the benefits for patients.

2. Long-term efficacy in US and European clinical trials

Long-term open-label extension studies have provided evidence for the continued efficacy of zonisamide against complex partial seizures (CPS), all partial seizures and all seizures in patients with refractory partial epilepsy. Following completion of short-term placebo-controlled and open-label studies, more than 1000 patients have been evaluated in eight open-label, long-term studies conducted in the US and Europe assessing zonisamide treatment for up to 9 years (Table 1). The characteristics and demographics of patients evaluated in these long-term extension studies were consistent with those in double-blind studies, and were representative of the refractory epilepsy population. These studies included slightly more males than females (overall ratio 54:46) and mean patient age was 34 years (range 2–79 years). Analyses of these extension studies indicate that zonisamide continues to be efficacious and well tolerated during long-term treatment (Faught, 2004; Brodie, 2004; Wroe and Brodie, 2005; Eisai, data on file), a finding confirmed during personal experience with zonisamide in clinical practice.

2.1. Long-term seizure reduction

Data from four completed extension studies, 922 Ext (US), 912 Ext (US), 912 Ext (EU) and 912-39 (US), and 1 ongoing study, 353 (EU) (see below), show that zonisamide provides effective seizure control in long-term administration of up to 2 years. Median baseline frequency of complex partial seizures (CPS), all partial seizures and all seizures (all seizures, excluding partial seizures) decreased 42–65% in the four completed studies during continued treatment with zonisamide 400–600 mg/day for up to 2 years (Fig. 1A). The corresponding data from the four completed studies indicates that up to 45% of patients achieve ≥50% reduction in seizure frequency across all categories of seizure (Fig. 1B). A further extension study (921

Table 1
Open-label long-term studies (n = 1041) examining the efficacy, safety and tolerability of zonisamide

Study (location)	Number of patients	Duration (mean)	Zonisamide exposure
922 Ext (US)[a]	145	2 years	0–81 μg/ml serum[*]
912 Ext (US)[a]	123	4–173 (57) weeks	0–1100 (median 500) mg/day[**]
912 Ext (EU)[a,b]	115	1–149 (54) weeks	33–900 (median 400–500) mg/day
920 (US)[a]	103	≤2 years	0–600 mg/day
921 Ext (US)[a]	147	≤5 years	100–900 (median 600) mg/day
912-39 Ext (US)[c]	137	17–104 (56) weeks	100–1100 (median 400–500) mg/day
912-99[c] (US)	28	0.4–9.1 years	<20 mg/day/day or <40 μg/ml
353 (EU)[d,e]	243	≤2 years	100–600 (median 500) mg/day

EU, Europe.
[a] Faught (2004).
[b] Brodie (2004).
[c] Unpublished (Eisai data on file).
[d] Wroe and Brodie (2005).
[e] Ongoing.
[*] Doses were adjusted to target serum levels of 20–30 μg/ml.
[**] Final dose range, some patients discontinued.