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Introduction to zonisamide

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Abstract

Zonisamide (Zonegran®), a novel antiepileptic drug (AED) approved recently in Europe as adjunctive therapy for refractory partial seizures in adults, has been used extensively in Japan and the United States. A substantial body of clinical experience has accumulated over a 14-year period, allowing the properties and pharmacologic/clinical profiles of zonisamide to be clearly defined. Zonisamide is structurally distinct from other AEDs and has multiple and complementary mechanisms of action, which likely contribute to its efficacy across a broad range of epilepsy types. Zonisamide has a long $T_{1/2}$ enabling once-daily dosing, linear pharmacokinetics and minimal interaction with other drugs; plasma levels of commonly administered AEDs and oral contraceptives are unaffected by concomitant zonisamide. Effective control of partial seizures (up to 51% decrease in seizure frequency) is attained at doses of $\geq$300 mg/day, and optimal titration and maintenance dosing schedules have been established. The adverse event profile is well defined; in common with most AEDs, most adverse events are central nervous system-related (e.g. somnolence, dizziness, tiredness). Adverse events may be minimised with appropriate patient management. Zonisamide therefore has many characteristics considered desirable in an AED and represents a valuable addition to the therapeutic options for treating epilepsy in Europe.

Keywords: Antiepileptic drug; Clinical development; Pharmacokinetics; Pharmacodynamics; Zonisamide

1. Introduction

Zonisamide (Zonegran®) is a new generation antiepileptic drug (AED), which provides highly effective adjunctive treatment of refractory partial seizures in adults (Schmidt et al., 1993; Faught et al., 2001; Sackellares et al., 2004; Brodie et al., 2005). Although only recently approved in Europe, zonisamide has benefited from an extended development programme leading to approval in Japan in 1989 and the United States (US) in 2000. This extensive clinical experience, equivalent to more than 2 million patient-years, has provided a particularly well-defined profile for zonisamide in European-approved licensed indications.

Drugs developed for adjunctive therapy of partial seizures should aim to provide long-term clinical efficacy, safety and ease of use in routine patient manage-

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ment. The wealth of data available on the characteristics, clinical efficacy and safety of zonisamide indicate that it offers many of these desirable properties. Zonisamide has multiple modes of action, a favourable pharmacokinetic profile and few drug–drug interactions, and is highly efficacious and well-tolerated across a broad range of seizure types. These characteristics are reviewed briefly and the dosing schedule and precautions included in the European licence are outlined. These features demonstrate zonisamide to be a valuable new choice in the adjunctive treatment of refractory partial seizures.

2. Pharmacology of zonisamide

2.1. Structure and mode of action

Zonisamide is a benzisoxazole derivative with a non-arylamine sulphonamide group (Fig. 1) and is chemically unrelated to other AEDs. Zonisamide is further differentiated from other AEDs by multiple modes of antiepileptic action, including ion channel modulation and effects on neurotransmitter systems to enhance neuronal inhibition and attenuate excitatory transmission. These effects are likely to be complementary in mediating effective seizure control.

Zonisamide blocks sodium channels, binding preferentially to inactive channels producing use- and voltage-dependent blockade and slowing the rate of recovery (Schauf, 1987; Rock et al., 1989; Macdonald, 2002). Zonisamide is thereby effective at inhibiting high-frequency repetitive firing (and limiting epileptiform activity) rather than influencing normal physiological function. Other AEDs, including phenytoin, carbamazepine and sodium valproate exert a similar effect on high-frequency repetitive firing (McLean and Macdonald, 1983, 1986a,b). In addition, zonisamide reduces low-threshold T-type calcium channel current, thereby suppressing inward calcium currents, reducing

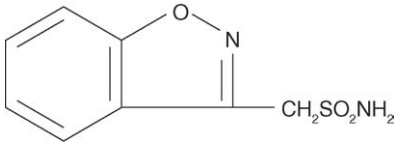

Fig. 1. Zonisamide.

cellular bursting and therefore, the spread of seizure discharge (Suzuki et al., 1992; Kito et al., 1996; Macdonald, 2002).

Zonisamide also enhances neuronal inhibition via modulation of neurotransmitter systems, including dopaminergic, GABAergic and serotonergic systems. Zonisamide may enhance GABA function through interaction at allosteric or other binding sites and/or by influencing GABA transport (Mimaki et al., 1990; Ueda et al., 2003). It also facilitates dopaminergic and serotonergic transmission by increasing extracellular levels of these monoamines (Kaneko et al., 1993). Zonisamide-mediated inhibition of excitatory glutamate-mediated transmission (Okada et al., 1998; Zhu and Rogawski, 1999) may be secondary to effects on voltage-gated sodium or calcium channels or may be through direct effects on neuronal transport (Ueda et al., 2003).

Zonisamide is also reported to be a weak inhibitor of carbonic anhydrase. It is thought to be 100–200 times less potent in this effect than acetazolamide (Masuda and Karasawa, 1993). This mechanism is not thought to contribute to its antiepileptic effects.

The multiple modes of action of zonisamide are consistent with its efficacy in a range of preclinical models. Zonisamide is highly effective in models of partial seizures in vivo (limbic-kindled seizures in rats and cats) and also has broad-spectrum activity across a range of models of generalised seizures (Macdonald, 2002). Zonisamide is effective against maximal electroshock seizures in rodents, tonic–clonic and myoclonic seizures in a gerbil genetic model of reflex epilepsy, tonic seizures in spontaneously epileptic rats, and spontaneous seizures of the EL mouse (a genetic model of multifactorial idiopathic epilepsy) (Macdonald, 2002). Zonisamide also reduces spiking activity and contralateral spread in vitro (Macdonald, 2002). This broad range of pre-clinical efficacy indicates that zonisamide may be efficacious over a wide range of epilepsies.

2.2. Pharmacokinetic properties

Zonisamide exhibits a favourable pharmacokinetic profile (Shah et al., 2002). It is absorbed rapidly following oral administration (peak plasma concentrations 2–6 h after dosing) and has high bioavailability (95%) that is unaffected by food. There is low to moderate