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CLINICAL RESEARCH

Efficacy and safety of adjunctive zonisamide therapy for refractory partial seizures

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Summary An approach to the selection of appropriate antiepileptic drugs (AEDs) for inclusion in polytherapy is to take into account both the efficacy of a drug and also its mechanism of action and pharmacokinetic profile. The AED zonisamide is licensed in Europe and the USA for use as adjunctive therapy in adult patients with partial onset epilepsy. Four pivotal clinical studies in patients with refractory partial seizures demonstrated that zonisamide as an add-on was most effective at doses of ≥300 mg/day, with responder rates (≥50% reduction from baseline in seizure frequency) ranging from 28 to 47% for all seizures. In addition, zonisamide has a unique combination of multiple mechanisms of action that are potentially complementary with concomitant AEDs. Zonisamide has no clinically relevant effects on the pharmacokinetics of other commonly used AEDs, however, co-administration with cytochrome P450 3A4 (CYP3A4) inducers or inhibitors may change zonisamide's pharmacokinetic profile. Zonisamide is well tolerated with the majority of adverse events being mild-to-moderate and generally manageable. The tolerability of zonisamide has also been shown to improve with slower drug titration and duration of drug treatment. These characteristics suggest that zonisamide may be suitable as a key adjunct in rational polytherapy.

Contents

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Introduction

Localisation-related (partial onset) epilepsy is manifested by simple partial seizures, complex partial seizures and secondarily generalised seizures. More than 60% of patients with epilepsy, including the most difficult-to-treat cases, have partial onset epilepsy (Semah et al., 1998).

The first-line choice of antiepileptic drugs (AEDs) for partial onset epilepsy varies geographically, and the wide range includes carbamazepine, sodium valproate, phenytoin, lamotrigine and oxcarbazepine. US guidelines promote tailoring first-line AED treatment to individual patient characteristics, using the full range of available AEDs; whereas European guidelines recommend using the older AEDs, such as sodium valproate and carbamazepine, as first-line treatments, with the newer AEDs being used only if the patient is unresponsive or if the older AEDs are unsuitable (French et al., 2004; Beghi, 2004; NICE, 2004). Furthermore, lamotrigine and oxcarbazepine are increasingly being used as first-line choices for adults with partial seizures (Karceski et al., 2005). However, up to 30% of patients with partial seizures do not respond to AED therapy (Brodie, 2001). Should a patient not respond to the first AED, the common practice is to titrate upwards with a second AED while tapering off the first to establish the patient on an alternative monotherapy (NICE, 2004). Some patients not responding to initial AED treatment have been shown to achieve freedom from seizures by switching to an AED with an alternative mode of action (Brodie and Mumford, 1999). Further clinical observations have suggested that when two appropriate AED monotherapy regimens have failed that there is very limited success with the third (Kwan and Brodie, 2006).

The preferred strategy in the management of refractory epilepsy is combination therapy (Perucca and Levy, 2002). The recent introduction of several new AEDs for use as adjuncts in refractory partial epilepsy has considerably increased the number of potential combinations. However, practice recommendations for when and how to combine drugs remain empirical (Kwan and Brodie, 2006). Although randomised controlled studies in refractory patients might help to determine guidelines on optimal combinations of AEDs, the size and cost involved in obtaining such data may be prohibitive.

There are a number of considerations when selecting appropriate adjunctive agents for polytherapy. These include mode of action, efficacy and tolerability profile, lack of interaction with concomitant AEDs and other drugs (e.g. oral contraceptives), and ease of administration.

The theoretical approach of rational polytherapy based on mode of action suggests that patients respond favourably to drug combinations with complementary modes of action (Macdonald, 1996; Brodie and Mumford, 1999). There is an absence of controlled data to inform the situation and currently, there is no consensus as to whether any particular drug combination can improve prognosis in a given patient/seizure type (Leppik, 2000). Therefore, a pragmatic approach to the selection of drug combinations should include an appraisal of each drug's mechanism of action, spectrum of efficacy, drug interaction potential and side effect profile (Brodie, 2001).

Zonisamide has been available in the USA since 2000 and in Japan since 1989 and worldwide experience now exceeds 2 million patient-years. It has been widely used in Japan and the USA as an adjunct for refractory partial seizures, and is now approved in Europe for this indication in adults. Zonisamide possesses a number of properties likely to confer antiepileptic activity, including: blockade of voltage-dependent T-type calcium channels (Suzuki et al., 1992) and voltage-sensitive sodium channels (Schauf, 1987), blockade of potassium-evoked glutamate response (Okada et al., 1998), reduction of glutamate-mediated synaptic excitation (Zhu and Rogawski, 1999) and increased GABA release (Kawai et al., 1994). In line with these findings, clinical observations suggest that zonisamide may be effective in a diverse range of seizure types, from partial onset seizures and their secondary generalisations to generalised epilepsy syndromes including both primary (idiopathic) and symptomatic generalised epilepsies (Seino and Fujitani, 2002).

Furthermore, zonisamide is reported to be a weak inhibitor of carbonic anhydrase and is generally accepted to be 100—200 times less potent in this effect than acetazolamide (Masuda and Karasawa, 1993). However, this mechanism is not believed to contribute to the antiepileptic effects of zonisamide.

This paper reviews the efficacy and safety of zonisamide in refractory partial seizures, based on extensive clinical experience from registration studies and open-label evaluations, relevant to the topics covered in this review. The authors conducted a Medline literature search for all full paper publications on zonisamide clinical trials in partial epilepsy (no date limit applied), and a manual search of congress abstracts for the key epilepsy congresses (includ-

ing the American Academy of Neurology [AAN], American Epilepsy Society [AES], International Epilepsy Congress [IEC] and European Congress on Epileptology [ECE]) from 2000 to 2006. In line with its licensed indication, the review discusses zonisamide in the context of its potential as a key adjunct for inclusion in the rational therapy of refractory partial seizures in adults.

Pharmacokinetics and pharmacodynamics

The pharmacokinetic profile of zonisamide has shown it to have rapid absorption, good bioavailability (not affected by food), and a long elimination half-life ($t_{1/2}$) of approximately 63 h in healthy volunteers. This long $t_{1/2}$ permits once- or twice-daily dosing of zonisamide in the USA (Eisai Pharma International Ltd., 2004), although twice-daily dosing is more commonly used for convenience of co-administration with other AEDs. The long $t_{1/2}$ also minimises the risk of break-through seizures should the patient miss a dose. The European licence also allows for once- or twice-daily dosing following titration—allowing flexibility in the choice of dosing regimen (Eisai Ltd., 2006).

Zonisamide has no clinically relevant effects on the pharmacokinetics of other commonly used AEDs (e.g. carbamazepine (Ragueneau-Majlessi et al., 2004), phenytoin (Levy et al., 2004), valproate (Ragueneau-Majlessi et al., 2005) and lamotrigine (Levy et al., 2005)). However, zonisamide is metabolised in part by cytochrome P450 3A4 (CYP3A4), and co-administration with CYP3A4 inducers or inhibitors may change its pharmacokinetic profile. For example, the $t_{1/2}$ of zonisamide is reduced to 27 h when given concomitantly with phenytoin and 36 h when given with carbamazepine, but since the $t_{1/2}$ remains above 24 h this should not affect the zonisamide dosing interval. Indeed, titration of zonisamide when added to a regimen containing these AEDs may be achieved more rapidly as a result of this effect, although, conversely, care should be taken when withdrawing the original AED. However, overall, the combination of zonisamide with phenytoin or carbamazepine is well tolerated (Greenblatt, 1993; Levy et al., 2004).

Results from a pharmacokinetic study in 33 paediatric patients receiving treatment with two AEDs other than zonisamide, 16 of whom were taking AEDs with enzyme-inducing activity (Levisohn, 2005), were consistent with those reported in adults; concomitant administration of enzyme inducers was associated with lower zonisamide exposure than in non-induced paediatric patients.

Efficacy of zonisamide

Placebo-controlled studies

Four randomised, double-blind, placebo-controlled studies involving a total of 850 patients with refractory partial epilepsy have demonstrated significant efficacy with zonisamide at doses of ≥300 mg/day, compared with placebo (Schmidt et al., 1993; Faught et al., 2001; Sackellares et al., 2004; Brodie et al., 2005). In these studies, significantly greater reductions from baseline were achieved in the median number of seizures experienced per month compared with placebo, as shown in Fig. 1 for complex

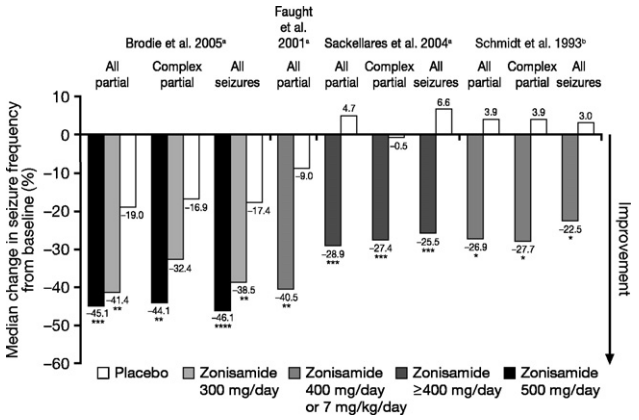

Figure 1 Median percentage reduction in seizure frequency from baseline with adjunctive zonisamide or placebo from four placebo-controlled trials (intent-to-treat [ITT] population). $^{*}p < 0.05$ vs. placebo; $^{**}p < 0.01$ vs. placebo; $^{***}p < 0.001$ vs. placebo; $^{****}p < 0.0001$ vs. placebo. [a]All patients who received at least one dose of study drug or placebo. [b]All patients who received at least 7 days of treatment.

partial, all partial (i.e. simple partial and complex partial) and all seizures (i.e. simple partial, complex partial and secondarily generalised). Similarly, the responder rates (defined as the proportion of patients achieving ≥50% reduction from baseline in seizure frequency) were greater for patients treated with ≥300 mg/day zonisamide than for those treated with placebo. Responder rates ranged from 30 to 45% for complex partial seizures, 27 from 44% for all partial seizures and 28 from 47% for all seizures (Table 1). In addition, patient and investigator global assessments of efficacy, whilst varying between studies, were greater in subjects receiving ≥300 mg/day zonisamide compared to those receiving placebo (Schmidt et al., 1993; Sackellares et al., 2004; Brodie, 2004).

In addition, seizure freedom data were analysed for the most recent European placebo-controlled study in 351 patients with refractory partial epilepsy (Brodie et al., 2005). In this analysis up to 9% of patients shown to remain free of seizures for at least 28 days with the highest dose of zonisamide (500 mg/day), despite the highly refractory nature of this patient population (Hirsch and Duncan, 2005).

A Cochrane review of these placebo-controlled clinical trials confirmed the significant efficacy of zonisamide ≥300 mg/day over placebo on responder rates (relative risk ratio 2.44) (Chadwick and Marson, 2005). A Chi-squared test for heterogeneity also indicated that the response to zonisamide was statistically consistent between the trials. The reviewers concluded that zonisamide was effective as an add-on treatment in patients with refractory partial onset epilepsy.

Dose—response relationship

While zonisamide doses of ≥300 mg/day have been shown to be the most effective, lower doses may be efficacious in some patients. Indeed, Faught et al. (2001) reported that zonisamide at 100 and 200 mg/day was significantly more efficacious than placebo, both in terms of responder

Table 1 Responder rates for zonisamide (≥300 mg/day) from four placebo-controlled trials (intent-to-treat [ITT] population)

Study	Zonisamide dose (mg/day)	Responder rates per seizure type (%)		
		All seizures	All partial seizures	Complex partial
Brodie et al. (2005)[a]	300	34.5	34.6	30.3
	500	46.6**	44.3**	45.1**
	Placebo	17.6	20.2	22.3
Sackellares et al. (2004)[a]	≥400	28.2	26.9	30.8*
	Placebo	16.2	16.2	13.9
Faught et al. (2001)[a]	400	43.0*	—	—
	Placebo	22.2	—	—
Schmidt et al. (1993)[b]	7.0 mg/(kg day)	29.9*	30.3*	30.3*
	Placebo	9.4	10.9	12.7

[a] All patients who received at least one dose of study drug or placebo.
[b] All patients who received at least 7 days of treatment.
* $p < 0.05$ vs. placebo.
** $p < 0.001$ vs. placebo.

rates and changes in seizure frequency. This is an important attribute for inclusion in rational polypharmacy, whereby the dose of each treatment is individualised during titration at the initiation of therapy, and will vary between patients depending on other AEDs already received, and also on intrinsic factors affecting individual drug sensitivity.

In the recent pivotal study, analysis of effects with 100, 300, 500 mg/day zonisamide showed that seizure frequency decreased and responder rate increased in a dose-dependent manner (Brodie et al., 2005). In this study the highest dose of zonisamide (500 mg/day) was significantly superior to placebo in reducing all seizures, complex partial seizures and all partial seizures. The 300 mg/day dose also produced significantly greater reductions in all seizure frequency and all partial seizures (Fig. 2).

Open-label and active comparator studies

Although randomised controlled trials provide the most robust evidence to demonstrate efficacy, they are rarely practical or ethical for assessing response over a longer term. Whilst uncontrolled extension studies can provide valuable data over prolonged treatment periods, their results should be interpreted with caution. In particular, such studies are subject to drop out over time and a consequential enrichment of the subjects who remain. Therefore, where available, it is helpful to report efficacy in the context of the percentage of remaining subjects. Long-term assessment of adjunctive zonisamide (≥300 mg/day) in partial seizures has been reported in several such studies, evaluating treatment durations of up to 16 years (Alapati et al., 2000; French and Ruelle, 2002; Brodie, 2004; Faught, 2004; Wroe and Brodie, 2005; Tosches and Tisdell, 2005a,b). The results suggested that at least for the subgroup of ''responders'' who remained in the trials over such periods efficacy is maintained over time. Specifically, in the extension of the main pivotal trial (Brodie et al., 2005), treatment response (≥50% reduction in seizure frequency) was maintained in 43, 45 and 46% of subjects at 1, 2 and 3 years, respectively, with 65, 45 and 29% of subjects remaining in the study at these timepoints [Wroe SJ, Personal Communication].

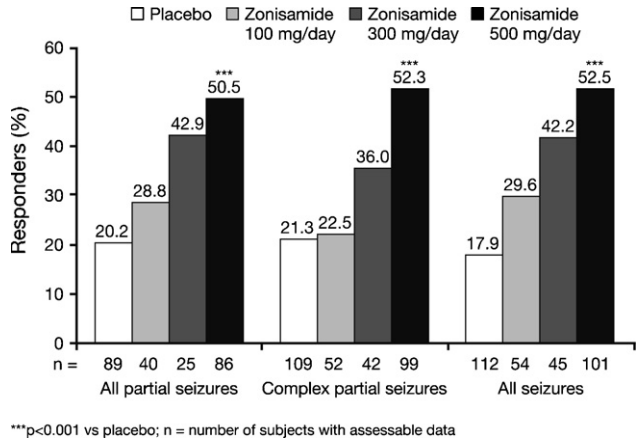

Figure 2 Proportions of patients experiencing $a \geq 50\%$ reduction in seizure frequency (responders) with adjunctive zonisamide or placebo (primary efficacy-analysis population) (Reproduced from Brodie et al., 2005, with permission from Blackwell Publishing).

These response rates are in line with those reported in earlier small-scale open-label and retrospective studies in adults with refractory partial seizures, which reported responder rates of 35–57% (Ono et al., 1988; Leppik et al., 1993; Schacht et al., 2002; Saleh et al., 2003; Yagi and Seino, 1992). However, many of these studies have not been reported in full, making further interpretation of their findings difficult.

Data using active comparators are limited. One randomised, double-blind trial has compared zonisamide and carbamazepine as an adjunctive therapy over 16 weeks of treatment (including a dose titration phase of 4–8 weeks followed by maintenance treatment) in patients with refractory partial seizures (Seino et al., 1988). This study, conducted in Japan, evaluated efficacy data in 56 patients treated with zonisamide (mean maintenance dosage 330 mg/day) and 52 patients treated with carbamazepine (mean maintenance dose 600 mg/day). The frequency of partial seizures without secondary generalisation decreased during the study, with mean changes at

Week 16 of −68.4% with zonisamide versus −46.6% with carbamazepine, accompanied by responder rates (defined by ≥50% reduction in total seizure frequency) of 82% for zonisamide and 71% for carbamazepine. These differences did not reach statistical significance ($p > 0.10$). There were also slightly more early discontinuations in the carbamazepine group (5 versus 2 in the zonisamide group, all within the first 3 weeks, due to adverse events) but treatment groups were comparable in all other respects (baseline characteristics, effects of treatment on other seizure types, concomitant medications and tolerability). However, the interpretation of these findings, particularly the effects on other seizure types, is limited by the small numbers of patients involved.

Studies in children

Zonisamide is currently indicated for use in adolescent (aged 12−17 years) and adult patients with partial epilepsy in the US, and only adults in Europe. The inclusion of low numbers of adolescents in the registration trials, and the exclusion of children prevented determination of efficacy in these subpopulations. Evaluation of the recent pivotal placebo-controlled trial (Brodie et al., 2005), which included a small number of adolescent patients ($n = 39$) relative to adults (total $n = 349$), suggests similar proportions of responders to zonisamide for both age groups [Eisai Ltd., Data on file(a)].

Open-label data from 14 Japanese studies in children have been reviewed by Glauser and Pellock (2000), including five studies of adjunctive therapy. The responder rate for these adjunctive therapy studies was 35% of children with partial seizures.

Another study concerned the retrospective analysis of 50 children with medically refractory epilepsies treated with zonisamide, of whom eight had partial seizures and 42 generalised seizures. Results reported a responder rate of 44%, although the level of response declined after 2−6 months in 10/22 responders (Henning and Eriksson, 2004). In a further small retrospective study, three responders were reported out of six children treated with adjunctive zonisamide therapy, including one child (out of two) with partial seizures with or without generalisation (Beitinjaneh et al., 2001). The same caveats apply to the interpretation of these uncontrolled data as was discussed previously.

Tolerability and safety of zonisamide

As with all AEDs, adverse events (AEs) occurred more frequently during treatment with zonisamide than with placebo (Sackellares et al., 2004). Across all placebo-controlled studies with zonisamide, AEs were reported for 78 and 68% of zonisamide and placebo recipients, and treatment-related AEs were reported for 61 and 49%, respectively (Brodie, 2006). However, these AEs were generally of mild-to-moderate severity and few AEs or treatment-related AEs resulted in discontinuations: 20 and 19% for zonisamide groups compared with 11 and 9% for placebo, respectively [Eisai Ltd., Data on file(b)]. In addition, the incidence of severe AEs was no greater than placebo in patients treated with zonisamide (Brodie et al., 2005). Furthermore, the tolerability of zonisamide improves with duration of drug treatment and a slower drug titration reduces the incidence of AEs (Faught et al., 2004). Table 2 summarises the AEs reported most frequently across the four placebo-controlled adjunctive zonisamide therapy trials [Eisai Ltd., Data on file(b)].

CNS-related adverse events

The most commonly reported treatment-related AEs with zonisamide are of CNS origin but these are generally of mild-to-moderate severity (Brodie, 2006). Across all placebo-controlled trials, the CNS-related AEs which occurred more frequently with zonisamide than with placebo were somnolence; dizziness; agitation/irritability; fatigue; tiredness; and ataxia (Eisai Pharma International Ltd., 2004). Similarly, the Cochrane review of four trials reported that ataxia, dizziness, somnolence and agitation were associated with zonisamide therapy (Chadwick and Marson, 2005). As with other AEs, CNS events are generally reported early during treatment, and are more common during dose titration than at steady-state (Brodie et al., 2005).

Renal calculi

Carbonic anhydrase inhibitors have been linked to an increased risk for renal calculi, and since zonisamide weakly inhibits carbonic anhydrase activity *in vitro*, the potential for renal calculi to occur during zonisamide therapy warrants investigation. However, no renal calculi were reported in the US and European placebo-controlled trials (Faught et al., 2001; Sackellares et al., 2004; Brodie et al., 2005), while a review of 1008 patients in Phase II and III trials in Japan showed only two patients who developed renal calculi, both of whom had a family history of nephrolithiasis (Yagi and Seino, 1992; Lee, 2002).

Renal calculi may be associated with high doses and long-term treatment (Faught, 2004). In a long-term extension of an early US trial (median zonisamide dose 500 mg/day), four cases of symptomatic renal calculi were reported amongst 113 patients receiving up to 96 weeks of continuous treatment (3.5%) (Leppik et al., 1993). However, in an open-label extension of the early European placebo-controlled trial, only one patient developed renal calculi (Brodie, 2004). The overall incidence of renal calculi, calculated from clinical studies and post-marketing surveillance, is reported as uncommon and occurring in ≤1% of patients receiving zonisamide (Eisai Ltd., 2006).

Although renal calculi may occur at a higher rate with zonisamide treatment than in the general population, careful patient management (e.g. appropriate fluid intake) reduces the risk. Treatment discontinuation may not be necessary for patients who develop asymptomatic renal calculi. In a follow-up study, three patients who developed renal calculi all remained asymptomatic with continued zonisamide therapy (Richards et al., 2005).

Weight change and appetite decrease

Weight loss and appetite decrease (anorexia) are commonly encountered as a result of zonisamide treatment. The Cochrane review of four placebo-controlled trials reported a

Table 2 Summary of adverse events occurring in >5.0% of patients from four placebo-controlled trials [Eisai Ltd., Data on file(b)]

Adverse events	Percentage of patients	
	All doses of zonisamide ($n = 498$)	Placebo ($n = 350$)
Total	77.9	67.7
Body as a whole		
Abdominal pain	7.2	3.4
Headache	12.4	12.6
Infection	8.0	8.0
Digestive		
Appetite decrease (anorexia)	10.8	4.3
Diarrhoea	5.8	3.7
Nausea	9.6	8.0
Nervous system		
Agitation/irritability	7.4	4.9
Ataxia	5.6	2.3
Confusion	5.6	2.6
Depression	6.2	2.9
Difficulty concentrating	6.4	2.0
Dizziness	15.5	8.3
Fatigue	6.6	6.3
Insomnia	5.4	3.1
Somnolence	16.1	8.3
Tiredness	8.6	6.9
Special senses		
Diplopia	7.0	3.7

significant association of appetite decrease with zonisamide treatment compared with placebo (99% confidence interval 3.0) (Chadwick and Marson, 2005). However, the majority of patients in placebo-controlled trials lost less than 5 kg (Faught et al., 2001; Sackellares et al., 2004; Brodie et al., 2005). In one review of clinic experience, mean weight significantly decreased ($p < 0.001$) following zonisamide treatment (mean duration 11 months), mean weight before zonisamide was 76.8 kg compared with 73.76 kg after treatment (Tran et al., 2002). This review also showed that weight loss was greater for women than for men. These results contrast with those of several other AEDs, including two of the most common first-line therapies, carbamazepine and sodium valproate, which are associated with weight gain (Biton, 2003). As the effect of weight loss appeared to be independent of concomitant AEDs (Tran et al., 2002) combination therapy with zonisamide may be helpful to offset the weight gain associated with these drugs.

Oligohydrosis in paediatric patients

Oligohydrosis and secondary fever have been reported in children treated with zonisamide but these are rare (Racoosin and Knudsen, 2004; Glauser and Pellock, 2002). A recent review of available data in the USA identified 11 cases of oligohydrosis and/or hyperthermia in patients aged ≤18 years, considered to be related to zonisamide. The reporting rate was estimated at 1 case per 4590 patient-years of exposure, during the first 3 years of zonisamide marketing in the USA. In all these cases, oligohydrosis was reversible on discontinuation of zonisamide (Low et al., 2004). Although a rare event, awareness of the potential of oligohydrosis in the paediatric population, particularly during the summer and in warm climates, should help prevent morbidity (Knudsen et al., 2003).

Rash

Drugs containing sulphonamide moieties are associated with skin rash but these are most commonly reported in patients receiving sulphonamide antimicrobials (Tilles, 2001). Although an association between hypersensitivity to treatment with antibiotic sulphonamide drugs and subsequent treatment with a nonantibiotic sulphonamide drugs has been noted, this is believed to be more related to a predisposition to allergic reactions rather than to cross-reactivity (Strom et al., 2003). Zonisamide is a benzisoxazole derivative, which contains a sulphonamide group. In placebo-controlled trials of adjunctive zonisamide therapy, the incidence of rash as an AE was 3% (Eisai Pharma International Ltd., 2004), although an additional study indicated that less than half the cases of rash reported in zonisamide studies could be attributed to the drug (Penovich et al., 2003). No apparent relationship has been discerned between zonisamide dose and occurrence of rash (Eisai Pharma International Ltd., 2004).

Furthermore, post-marketing experience from Japan has reported low rates of serious skin reactions, such

as Stevens—Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), at 46 per million patient-years of exposure (Eisai Pharma International Ltd., 2004).

Teratogenicity

Despite the availability of zonsiamide in Japan since 1989, there is an unfortunate paucity of data to inform the rates of congenital malformation when administered to women who are or who become pregnant. However, preclinical studies demonstrated a teratogenic potential, and consequently, as for all other AEDs, the use of zonisamide is contra-indicated in pregnancy. Outcome data from pregnancy registers of all AEDs generally suggest a two- to three-fold increase in the risk of malformation compared to no usage, and further increased risk when multiple AEDs are administered (Beghi et al., 2001; Adab et al., 2004; Breen and Davenport, 2006). Pregnancy outcome data specific to zonisamide is being added to European registers as it accumulates and will be reported in due course.

Conclusion

Most patients with partial epilepsies that are refractory to monotherapy are likely to receive adjunctive AED therapy. However, at present guidelines for the combination of AEDs remain empirical. When selecting appropriate adjunctive agents, the theoretical approach to rational polypharmacy may allow early identification of the most appropriate drug combination. This should include consideration of the spectrum of efficacy, tolerability, modes of action and potential for interactions between concomitant AEDs.

In this context addition of zonisamide may be worth consideration in that it has multiple mechanisms of action that are potentially complementary with other AEDs, predictable pharmacokinetic profile allowing convenient once- or twice-daily dosing, and no clinically relevant interactions with the most commonly administered first-line AEDs (e.g. carbamazepine).

In placebo-controlled studies in partial seizures, zonisamide has demonstrated efficacy at doses of 300—500 mg/day. Furthermore, a substantial body of supporting evidence exists from retrospective reviews and open-label studies. Zonisamide can be titrated to an optimum dosage according to clinical effect, with some patients benefiting from treatment at relatively low doses.

In addition to its effects on partial onset seizures, uncontrolled data suggest beneficial effects as adjunctive therapy that extend across a range of seizure types and syndromes, including generalised epilepsy (Thomas and McCabe, 2005; Conry et al., 2005), juvenile myoclonic epilepsy (O'Rourke et al., 2005), progressive myoclonic epilepsy (Welty et al., 2003; Vossler et al., 2002; Seino et al., 2002; Mullin et al., 2001; Valeriano and Lane, 2001).

Although side effects are a feature of all AED therapies, those associated with zonisamide treatment are generally of mild-to-moderate severity and diminish with continued treatment. The incidence of AEs during zonisamide therapy can be reduced by careful patient management, such as slow dose titration and appropriate hydration.

In conclusion, zonisamide is an efficacious AED that is a potentially useful component in the adjunctive therapy of partial onset seizures.

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