1-4-2007

Potential efficacy of zonisamide in refractory juvenile myoclonic epilepsy: retrospective evidence from an Irish compassionate-use case series.

Deirdre O'Rourke
Beaumont Hospital, Dublin

Cora Flynn
Beaumont Hospital, Dublin

Maire White
Beaumont Hospital, Dublin

Colin P. Doherty
Trinity College Dublin

Norman Delanty
Royal College of Surgeons in Ireland, normandelanty2@rcsi.ie

Citation

O'Rourke D, Flynn C, White M, Doherty C, Delanty N. Potential efficacy of zonisamide in refractory juvenile myoclonic epilepsy: retrospective evidence from an Irish compassionate-use case series. Irish Medical Journal. 2007;100(4):431-3.

Potential Efficacy of Zonisamide in Refractory Juvenile Myoclonic Epilepsy: Retrospective Evidence from an Irish Compassionate-Use Case series

Deirdre O''Rourke,C Flynn,C Doherty,Maire White,N Delanty

Ir Med J. 2007 Apr;100(4):431-3

Abstract

To retrospectively evaluate the efficacy of zonisamide as adjunctive therapy in the treatment of refractory juvenile myoclonic epilepsy. We retrospectively reviewed the records of seven patients with refractory juvenile myoclonic epilepsy, commenced on a compassionate-use basis on zonisamide as adjunctive treatment between October 2001 and September 2004. We found significant response rates (>50% reduction in seizure frequency) of 83.3%, 100% and 100% for generalised convulsions, myoclonus, and absence seizures respectively. These results were sustained over more prolonged follow-up in five of seven patients, with one patient improving further over time. Two patients became seizure free with the introduction of zonisamide. Two patients were able to reduce the number of anti-epileptic medications and maintain >75% and 100% reduction in seizure frequency respectively. Four patients initially had minor side-effects that resolved during the maintenance period. In this retrospective study, zonisamide was effective and well-tolerated as adjunctive therapy in patients with refractory juvenile myoclonic epilepsy.

Introduction

Juvenile myoclonic epilepsy (JME) is a genetic, idiopathic generalised epilepsy syndrome found in 7-10% of all patients with epilepsy.[1] Accurate diagnosis is important as it responds well to treatment with appropriate anticonvulsants, while inappropriate therapy may be ineffective or aggravate certain seizure types.

Valproate has traditionally been the drug of choice in the treatment of JME, with case series reporting seizure-free rates of between 63% and 86%.[2] A subset of patients with JME are resistant to treatment despite careful lifestyle and treatment with adequate doses of valproate - approximately 15 % patients at a specialised epilepsy referral centre.[3] Predictors of pharmacoresistance include 1) the co-existence of all three seizure types, and 2) the existence of associated psychiatric problems.[3] Recent studies indicate that topiramate, lamotrigine and levetiracetam are also effective in JME[2,4,5], although the effect of lamotrigine appears to be variable. Vagal nerve stimulation has also been used in refractory JME.[1]

Zonisamide (ZNS) is a novel anti-epileptic drug with multiple mechanisms of action, and a possible broad-spectrum of anti-epileptic activity. This study aimed to evaluate the efficacy of ZNS as adjunctive therapy in treatment of refractory JME, in a cohort of Irish patients treated on a compassionate-use basis.

Methods

We retrospectively reviewed the records of all patients in our institution with refractory JME who were commenced on ZNS as adjunctive treatment between October 2001 and September 2004. ZNS was kindly provided on a compassionate-use basis by Elan Pharma and subsequently by Eisai Pharmaceuticals. The diagnosis of JME was based on the criteria of the International Classification of Epilepsies.[6] Refractory JME was defined as failure to respond to two or more appropriate broad-spectrum AEDs. Demographic data was reviewed including: age, sex, age at first seizure, seizure types, family history of epilepsy, history of febrile convulsions, presence of psychiatric comorbidity, and number of AEDs at baseline.

Seizure frequency pre- and post- treatment with ZNS was assessed by chart review and follow-up patient interview. Significant response was defined as greater than or equal to 50% reduction in seizure frequency. Any adverse effects were recorded.

Results

A total of seven patients with refractory JME receiving treatment with compassionate use ZNS were identified. All seven patients were female, age range 18-32 years. Five patients had a history of all three seizure types. The other two patients had a history of convulsions and myoclonus. Three patients had psychiatric co-morbidity, with depression of varying severity. Zonisamide was titrated according to tolerability and seizure control. The ZNS dose range was 200-600mg/day. Patients were followed regularly in the clinic. Duration of follow-up was 7 - 42 months (mean 19 months).

Table 1 Demographics	
Age (mean 26.4)	18-32 years
Sex	7 Female, 0 Male
Age at first seizure (mean 10.6)	8 - 15 years
Seizure types	
GTCSz + MJ + AS	5 patients
GTCSz + MJ	2 patients
Family history epilepsy	5 patients
History febrile convulsions	3 patients
Psychiatric co-morbidity	3 patients
Number of AEDs prior to ZNS	1 - 4 (mean 2.7)
Number of current AEDs	2 - 4 (mean 2.6)

Seizure frequency rates were compared for the six months prior to initiation of treatment with ZNS and the first six months once optimum dose of ZNS was achieved. Five of six patients had a significant reduction (>50% reduction) in frequency of generalised tonic-clonic seizures, with two patients becoming free of generalised tonic-clonic seizures. One patient was unchanged with regard to generalised convulsions. One patient had no generalised tonic-clonic seizures at initiation of ZNS, but had refractory myoclonus, and therefore was not included in analysis of generalised tonic-clonic seizure response.

All six patients with active myoclonus prior to initiation of ZNS had >50% reduction in myoclonus, and two of these patients became free of myoclonus on ZNS. One patient noted worsening of her myoclonus initially, at doses of 400mg/day, which improved with dose reduction to 200mg/day. One patient had achieved control of myoclonus prior to introduction of ZNS, but had refractory generalised convulsions, and therefore was not included in analysis of response of myoclonus. Of the five patients with a history of absence type seizures, one had achieved control prior to introduction of ZNS, and four noted >50% reduction in frequency, with one of these patients having complete resolution of absence seizures.

Table 2 Percentage reduction in seizure frequency					
	100%	**75-99%**	**50-74%**	**25-49%**	**<25%**
GTCSz	n=2 (33.3%)	n=3 (50%)			n=1 (16.7%)
Myoclonus	n=2 (33.3%)	n=1 (16.7%)	n=3 (50%)		
Absence	n=1 (25%)	n=1 (25%)	n=2 (50%)		
"n" represents number of patients					

These results were sustained over more prolonged follow-up in five of seven patients, with one patient improving further over time. Two patients who showed initial improvement at six month follow-up - one with regard to myoclonus only and one with regard to all three seizure types - have not maintained this improvement in seizure control. The latter patient responded well over the first six months of treatment at optimum dose of zonisamide, but deteriorated again over the subsequent nine months. We have recently commenced her on felbamate after discussing all potential risks in detail.
The average number of AEDs on initiation of ZNS was 2.7 (range 1-4). Two patients were able to reduce the number of anti-epileptic medications and maintain >75% and 100% reduction in seizure frequency. ZNS was well tolerated and all seven patients remain on treatment with the drug. Four patients had initial side-effects (fatigue, light-headedness, anxiety, tremor, paraesthesia, weight loss/anorexia), which settled during the maintenance period.

Discussion
JME is a common idiopathic generalised epilepsy syndrome. It is characterised by myoclonic jerks in 100% of patients, generalised tonic-clonic convulsions in 90-95%, absence seizures in 40% and an abnormal photo-paroxysmal response in 40%. Sleep deprived EEG typically shows generalised discharges of bilaterally symmetrical and synchronous 4-6/Hz polyspike and wave complexes.[1] JME remains under-diagnosed due to lack of awareness of the syndrome. It is important to ask about myoclonic jerks and precipitating factors, as symptoms may not be reported, as highlighted by a recent case report of myoclonic seizures dismissed by the patient as an after-effect of ecstasy use.[7]

Although valproate is usually very effective in JME, up to 15% of patients may have refractory JME. Newer antiepileptic drugs (AEDs) with efficacy in JME will be useful in expanding therapeutic options for these difficult-to-treat patients, in addition to those patients who do not tolerate valproate due to adverse effects, or those in whom there are concerns over teratogenicity.

Zonisamide (ZNS) is a new anti-epileptic drug (AED) with potential efficacy in JME. It has been available in South Korea and Japan since 1989 and has been licensed in the United States for adjunctive treatment of partial onset seizures since 2002. It was approved in Europe for adjunctive treatment of partial seizures in adults in early 2005, and prior to that had been available on a compassionate use basis in Ireland. It is a sulphonamide AED with multiple mechanisms of action, including blockade of voltage-dependent T-type calcium channels, blockade of voltage-gated sodium channels, blockade of potassium-evoked glutamate response, reduction of glutamate-mediated synaptic excitation, and increase in GABA release.[8] It is not highly protein bound (40%), has a long half-life (T1/2= 50-68 hours), and steady state conditions may be achieved within two weeks of reaching a stable dose.[9] It is generally well tolerated. Side effects include somnolence, ataxia, anorexia,

confusion, abnormal thinking, nervousness, fatigue and dizziness, which are dose-related. Renal calculi may develop in a small percentage of those treated.[10]

While ZNS is thought to be a potentially broad-spectrum agent due to its multiple mechanisms of action, recent review articles have found insufficient evidence to date for efficacy of ZNS in idiopathic generalised epilepsy (IGE).[2,11] However, open-label data from Japanese pre- and post-marketing clinical studies suggest efficacy of ZNS in IGE.[12,13] A recent retrospective study, in the USA, of 15 patients showed ZNS to be effective as first-line treatment for JME, with 80% of patients on ZNS monotherapy as initial AED achieving significant seizure control.[14] In particular, there is little evidence available to date for the use of ZNS in refractory JME. A recent case report described a patient with refractory JME who had complete resolution of convulsions, myoclonus and absence seizures, and had a dramatic reduction in epileptiform discharges on ambulatory EEG with introduction of ZNS.[15] Two small studies of ZNS in refractory JME, presented at recent American Epilepsy Society meetings, with follow-up periods of fifteen and eight weeks have also shown promising results.[16,17]

In this retrospective, open-label study, we found significant response rates (>50% reduction in seizure frequency) of 83.3%, 100% and 100% for generalised convulsions, myoclonus, and absence seizures respectively. Two patients became seizure free with the introduction of ZNS. Two patients were able to reduce the number of AEDs and maintain >75% and 100% reduction in seizure frequency respectively. These improvements were sustained, in five of seven patients, over a mean follow-up period of 19 months. The medication was well tolerated by all patients, with minor side effects only, which settled during the maintenance period.

This is a retrospective study with inherent difficulties in quantifying myoclonus and absence seizures more specifically than seizure-freedom, greater than 50% reduction in seizure frequency. Despite this, the effects of add-on therapy are promising, and use of ZNS in JME deserves further study. Most of the existing evidence in drug therapy of JME, in particular with valproate - the drug of choice - is based on clinical experience, retrospective series and open-label studies. This is partly due to common methodological difficulties with designing trials in IGE, including lower prevalence than localisation-related epilepsies, efficacy of available treatments precluding enrolment of many patients in trials and difficulties in precisely quantifying myoclonus and absence seizures.[18] There is a need for further well-designed trials, in particular for the newer broad-spectrum AEDs in treatment of IGE.

In conclusion, in this case series ZNS was effective and well tolerated as adjunctive therapy in patients with refractory JME. This study supports the case for efficacy of ZNS in idiopathic generalised epilepsies, and in particular in the difficult-to-treat cohort of patients with refractory JME. Further multi-centre randomised controlled trials would be valuable in confirming these observations.

References

1. Renganathan R, Delanty N. Juvenile myoclonic epilepsy: under-appreciated and under-diagnosed. Postgrad Med J 2003;79:78-80.
2. Sullivan J, Dlugos D. Idiopathic generalized epilepsy. Curr Treat Options Neurol 2004 ;6:231-242.
3. Gelisse P, Genton P, Thomas P, Rey M, Samuelian JC, Dravet C. Clinical factors of dr ug resistance in juvenile myoclonic epilepsy. J Neurol Neurosurg Psychiatry 2001; 70:240-243.

4. Wheless JW, Sankar R. Treatment strategies for myoclonic seizures and epilepsy syn dromes with myoclonic seizures. Epilepsia 2003;44 (suppl 11) 27-37.
5. Grunewald R. Levetiracetam in the treatment of idiopathic generalized epilepsies. Epi lepsia 2005; 46 (suppl 9) :154-160.
6. Commission on Classification and Terminology of the International League Against E pilepsy. Proposal for Revised
Classification of Epilepsies and Epileptic Syndromes. Epilepsia 1989; 30 : 389-399
7. Carmondy J, Delanty N. Juvenile myoclonic epilepsy masquerading as ecstasy withdr awal. Ir Med J 2005; 98:281.
8. Brodie MJ, Duncan R, Vespignani H, Solyom A, Bitenskyy V, Lucas C. Dose-dependent safety and efficacy of zonisamide: a randomised, double-blind, placebo-controlled study in patients with refractory partial seizures. Epilepsia 2005; 46: 31-41.
9. Mimaki T. Clinical pharmacology and therapeutic drug monitoring of zonisamide. The r Drug Monit 1998; 20: 593-597
10. Wallace SJ. Myoclonus and epilepsy in childhood: a review of treatment with valproate, ethosuximide, lamotrigineand zonisamide. Epilepsy Res 1998; 29: 147-154.
11. French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepilep tic drugsII: Treatment of refractory epilepsy. Neurology 2004 ; 62: 1261-1273.
12. Glauser TA, Pellock JM. Zonisamide in pediatric epilepsy: review of the Japanese exp erience. J Child Neurol 2002;17: 87-96.
13. Yagi K. Overview of Japanese experience – controlled and uncontrolled trials. Seizure 2004;13(suppl 1): 11-15.
14. Kothare S, Valencia I, Khurana DS, Hardison H, Melvin JJ, Legido A. Efficacy and tole rability of zonisamide in uvenile myoclonic epilepsy. Epileptic Disord 2004; 6: 267-270.
15. Szaflarski JP. Effects of zonisamide on the electroencephalogram of a patient with ju venile myoclonic epilepsy.Epilepsy Behav; 2004;5:1024-1026.
16. Mullin P, Stern JM, Delgado-Escueta AV, Eliashiv D. Effectiveness of open-label zonisamide in juvenile myoclonic epilepsy. Epilepsia 2001; 42 (suppl 7) 184.
17. Biton V, Bebin ME. Multicenter, open-
label assessment of the efficacy and safety of zonisamide as adjunctive
therapy for primary generalized epilepsy. Epilepsia 2002; 43 (suppl 7) 190.
18. Faught E. Clinical trials for treatment of primary generalized epilepsies. Epilepsia 200 3; 44 (suppl 7) 44 – 50

Author's Correspondence
Dr. Norman Delanty,
Department of Neurology and Clinical Neurological Sciences, Beaumont Hospital and Royal College of Surgeons in Ireland, Beaumont, Dublin 9, Ireland.
Telephone number: +35318093000 Fax number: +35318092302 E-mail address: normandelanty@eircom.netN Delanty & D O'Rourke, Beaumont Hospital, Beaumont Road, Beaumont, Dublin 9
normandelanty@beaumont.ie & deirdreorourke@beaumont.ie

Acknowledgement
No Acknowledgement

Other References
No References