Seizure (2006) **15**, 387–392

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Predicting drug-resistant patients who respond to add-on therapy with levetiracetam

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Received 9 March 2006; received in revised form 4 April 2006; accepted 1 May 2006

KEYWORDS
Levetiracetam;
Response;
Seizure free;
Interactions

Summary

Introduction: Levetiracetam (LEV) is approved for use as add-on therapy in adult patients with partial epilepsy. It is apparent from clinical trials that up to 8% of previously drug-resistant patients may be rendered seizure-free by adding-on levetiracteam. As yet there is no way of predicting these unexpectedly responsive patients. We set out to identify our previously refractory patients who had demonstrated unexpected responsiveness to add-on therapy with levetiracetam, and compared these to patients who had not responded to the drug. We then attempted to characterise any clinical features that differentiated these groups of patients.

Methods: We included all patients with a history of present or previous exposure to levetiracetam who had been unresponsive to at least two other prior anti-epileptic drugs (AEDs) and recorded their demographic and clinical data. We divided response into (a) 'seizure-free' (seizure-free for a minimum of 6 months after commencing LEV); (b) 'partial >50%' (greater than 50% reduction in seizures for a minimum of 6 months after commencing LEV); (c) 'honeymoon' (seizure-free for less than 6 months after commencing LEV and then returned towards baseline frequency); and (d) 'no-response'. For the purpose of analysis we considered the 'seizure-free' and 'partial >50%' groups as 'responders', and the 'no response' group as 'non responders'.

Results: 344 patients were included in the analysis. Fifty-six patients (16.3%) were rendered seizure-free on levetiracetam. Idiopathic generalised epilepsy and post-traumatic partial epilepsy were more common in the responder than the non-responder group ($p = 0.005$ and 0.05 respectively). Lamotrigine was used significantly more often in combination with levetiracetam in responders than non-responders ($p = 0.003$). The mean daily dose of levetiracetam was lower in responders than non-responders.

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1059-1311/$ – see front matter
doi:10.1016/j.seizure.2006.05.001

Discussion: A higher than expected number of previously drug-resistant patients was rendered seizure-free by add-on therapy with levetiracetam. Those who respond best appear to do so at relatively low doses and our data suggest the possibility of a beneficial pharmacodynamic interaction between levetiracetam and lamotrigine. We were unable to identify any clinical factors that clearly predicted which patients would become seizure-free and we hypothesise that response may be determined by genetic or molecular factors. All drug-resistant patients, including those being assessed for surgery, should be considered for a trial of levetiracetam, regardless of their epilepsy classification.

Introduction

Levetiracetam, the S-enantiomer of alpha-ethyl-2-oxo-1-pyrrolidine acetamide, is approved for use as add-on therapy in adult patients with partial epilepsy.[1] The effectiveness of the drug in this regard was established in three pivotal multi-centre, randomized, double blind placebo-controlled trials, comprising a total of 904 patients.[2–4] At the 3000 mg dose, a maximum of 8% of patients became seizure-free in these trials. The drug is currently undergoing trials as monotherapy for new-onset partial epilepsy and for the treatment of idiopathic generalised epilepsy (IGE) where preliminary data suggest it has efficacy.[5–7] The drug appears to have a unique mechanism of action, binding to the synaptic vesicle protein SV2A. Although the exact effect of this is unclear, it is believed to involve modulation of the synaptic release of neurotransmitters.[8] The drug has a favourable pharmacokinetic profile with rapid oral absorption, bioavailability of nearly 100%, linear pharmacokinetics at oral dosing of 500—5000 mg and less than 10% protein binding. It is excreted two-thirds unchanged by the kidney.[9]

It is apparent both from the initial clinical trials of the drug and from post-release clinical experience that some, previously drug-resistant patients, are exquisitely sensitive to add-on therapy with levetiracetam and may be rendered seizure-free.[2–4,10] Indeed, in a small pilot study of 11 patients on the waiting list for epilepsy surgery at our institution, the addition of levetiracetam resulted in four patients being removed from the waiting list due to dramatic improvement in seizure control.[11] There is currently no way of predicting these potentially responsive patients. The ability to do this would be of particular clinical benefit as early recognition of these patients might prevent unnecessary trials of other anti-epileptic drugs and potential drug toxicity. It might also obviate the need for epilepsy surgery in some patients.

In this study, we therefore set out to identify previously drug-resistant patients who had demonstrated unexpected responsiveness to add-on therapy with levetiracetam, resulting in seizure freedom, and compared these to patients who had not responded to the drug. We then attempted to identify any predictors of response by characterising the clinical features that differentiated these groups of patients.

Methods

Patients were selected from the epilepsy clinic at our institution. We included all patients with a history of present or previous treatment with levetiracetam who had failed at least two other prior anti-epileptic drugs (AEDs), appropriate for their epilepsy classification, due to non-responsiveness. We defined non-responsiveness as a failure to substantially improve seizure-control despite treatment with the maximum tolerated dose of that drug, necessitating the addition or substitution of another AED. Data were collected using a combination of patient interview and review of patient records. We recorded demographic data including age and sex of patient; epilepsy diagnosis including cause if known; duration of exposure and maximum dose of levetiracetam; combination of AEDs while on levetiracetam and all other AEDs; average seizure frequency in the 6-months prior to commencing levetiracetam; response to treatment and any side effects experienced. We divided response into (a) 'seizure-free', if patients were rendered seizure free for a minimum of 6 months after commencing therapy; (b) 'partial >50%', if patients had a greater than 50% reduction in seizures for a minimum of 6 months after commencing therapy; (c) 'honeymoon', if patients had been rendered seizure free for less than 6 months after commencing therapy and then returned towards baseline frequency; and (d) 'no-response', if patients had (i) a less than 50% reduction in their seizures; (ii) no improvement; or (iii) a worsening of their seizure control, despite taking the maximum tolerated dose. Seizure rates were estimated using a combination of patient report and review of seizure diaries. For the purpose of analysis we considered the 'dramatic' and

Table 1 Summary of patient data

Response	*n*	M/F	Diagnoses	Average no. of current drugs (inc. LEV)	Average seizures prior to LEV (per month)	Drug used most frequently in combination	Average no. of previous drugs	Average daily dose (g)	Average exposure time (months)	% with adverse effects (%)
Seizure-free	56	26/30	12 IGE (21%) 4 SGEK (7%) 2 SGEU (3%) 16 SLREK (28%) 20 SLREU (36%) 2 Unclassified (3%)	2.3	6.8	LTG (24/56) VAL (15/56) CBZ (11/56)	2.6	2.2	29.3	4
Partial >50%	46	22/24	4 IGE (9%) 0 SGEK (0%) 3 SGEU (7%) 23 SLREK (50%) 13 SLREU (28%) 3 Unclassified (7%)	2.6	7.1	LTG (21/46) VAL (10/46) PHY (8/46)	2.3	2.65	29.2	16
Honey-moon	18	10/8	2 IGE (11%) 0 SGEK (0%) 2 SGEU (11%) 8 SLREK (44%) 6 SLREU (33%) 0 Unclassified (0%)	2.8	5.7	LTG (8/18) VAL (5/18) PHY (5/18)	2.4	2.7	27.3	19
No-response	224	102/122	16 IGE (8%) 6 SGEK (3%) 16 SGEU (7%) 86 SLREK (38%) 92 SLREU (41%) 8 Unclassified (4%)	2.7	7.4	VAL (54/224) LTG (49/224) PHY (40/224)	4.0	2.95	34.6	18

IGE, idiopathic generalised epilepsy; SGEK, symptomatic generalised epilepsy cause known; SGEU, symptomatic generalised epilepsy cause unknown; SLREK, symptomatic localisation related cause known; symptomatic localisation related cause unknown. (LTG, lamotrigine; VAL, valproate; PHY, phenytoin)

Table 2 Summary of known etiologies in responders and non-responders

	Hippocampal sclerosis	Cortical dysplasia	Tumour	Trauma	Other
Responders	10 (10%)	5 (5%)	7 (7%)	7 (7%)	9 (9%)
Non-responders	29 (13%)	9 (3%)	12 (5%)	6 (2%)	31 (14%)
Honeymoon	4 (22%)	0 (0%)	1 (5%)	1 (5%)	3 (16%)

Figures are shown as the absolute number and as a percentage of the total number of responders and non-responders. Note the similar percentages in each group. ('Other' includes CNS infection, strokes, haemorrhage, vascular malformations and congenital anomalies.)

'partial >50%' groups as 'responders', and the 'no response' group as 'non responders'.

Results

In total 364 drug resistant patients were identified who had been exposed to levetiracetam. Twenty patients were excluded because they had either stopped the drug due to intolerable side effects ($n = 14$) (psychosis in three, mood changes in six, severe fatigue in three and dizziness in two) and hence response could not be judged, or had not been on the drug for a sufficient period to make a reliable assessment of response ($n = 6$). A summary of patient data for the remaining 344 patients is shown in Table 1.

Fifty-six patients (16.3%) were rendered seizure-free for a minimum of 6 months following the addition of levetiracetam therapy. If we include only those with localization-related epilepsy, the seizure-free percentage is 13.6% (36/264). The mean duration of seizure freedom was 29.2 months (range 7—59 months). Fifty-one of the fifty-six patients had follow-up data for at least 1 year. As can be noted from Table 1, the group consisted of essentially equal numbers of males and females and featured a range of epilepsy types, most commonly localisation-related epilepsy of unknown cause (36%), followed by localisation-related epilepsy of known cause (28%), idiopathic generalised epilepsy (21%) and symptomatic generalised epilepsy (10%). The mean number of drugs that patients had been exposed to prior to commencing levetiracetam (including previous and concurrent drugs) was four (range 2—7). All patients were on a polytherapy regimen that included levetiracetam and at least one other drug (mean 2.3 drugs, range 2—4, including levetiracetam). The commonest drug used in combination with levetiracetam in these patients was lamotrigine, in 43%. The mean daily dose used in these patients was 2.2 g (range 500 mg to 3 g).

The 'partial responder', 'honeymoon' and 'no-response' groups were broadly similar to the seizure-free group in terms of patient demographics, epilepsy diagnoses and drug history. Males and females were present to a similar degree in each group. The various epilepsy syndromes were represented in each group to a similar extent, except for IGE, which was significantly less common in the no-response group than in the seizure-free group ($\chi^2 = 7.73$, $p = 0.005$). Apart from one individual in the 'no-response' group, all patients in these three groups had taken levetiracetam as part of a polytherapy regimen. For patients with a partial response of >50% reduction in seizures, the drug used most commonly in combination with levetiracetam was again lamotrigine (46%). By contrast, in patients that had no response to levetiracetam, lamotrigine was used concomitantly in only 22%. When compared to the seizure-free and >50% responder groups, this difference was statistically significant ($\chi^2 = 8.82$, $p = 0.0029$). The most frequently used concomitant drug in the no-response group was valproate (24%). The average daily dose of levetiracetam was higher in these groups compared to the seizure-free group, averaging almost 3 g per day in the no-response group.

Among the patients with partial epilepsy due to a known cause, the distribution of aetiologies was similar between responders and non-responders (see Table 2), although patients with post-traumatic epilepsy were more commonly represented in the responder group ($\chi^2 = 3.87$, $p = 0.05$). However, the number of patients with post-traumatic epilepsy was small in each group. Hippocampal sclerosis was the commonest known aetiology in both responders and non-responders.

Discussion

In this study 16% of previously drug-resistant patients were rendered seizure-free for at least 6 months with the addition of levetiracetam, and 15% were seizure-free for at least 1 year. 13.5% of patients with drug-resistant partial epilepsy were rendered seizure-free. This figure is higher than the maximum 8% observed in initial clinical trials using levetiracetam as add-on therapy in partial epilepsy,[2–4] and 8.8% observed in a post-licensing surveillance study.[10] It also considerably higher than the remission rates

reported for patients who have previously failed two (7%) and three drugs (3%).[12] Our figures are not based on prospective, placebo-controlled trials but are relevant nonetheless. Patient selection was based solely on a history of failure to respond to at least two appropriate anti-epileptic drugs prior to the addition of levetiracetam. Patients typically attend our clinic every 3—6 months and we are therefore confident that good follow-up data was achieved over the study period.

The principle aim of the study was to determine if these responsive patients were somehow predictable. We were unable to identify any clinical factors that clearly predicted whether drug-resistant patients would become seizure-free with the addition of levetiracetam. A diagnosis of drug-resistant IGE and post-traumatic partial epilepsy were statistically associated with a better response but, although interesting, the overall numbers are too small to draw any firm conclusions. Of note hippocampal sclerosis was present to a similar extent in both responders and non-responders. In fact, based on this data, patients with hippocampal sclerosis who had failed at least two prior AEDs, had a better than one in three chance of having at least a 50% reduction in seizures on levetiracetam.

In terms of drug-exposure, the combination of levetiracetam and lamotrigine was used significantly more often in responders than in non-responders. This raises the possibility of a beneficial pharmacodynamic interaction between the two, although there is currently no experimental evidence to support this. Alternatively, it may simply represent a prescribing bias in our department. Also of note, the mean daily dose of levetiracetam was lowest in the seizure-free group suggesting that patients who respond best do so at relatively low doses and that increasing to the maximum dose in patients who have shown no response at lower doses may not be worthwhile.

If clinical features do not reliably predict patients who are likely to respond to add-on therapy with levetiracetam, what other factors are likely to play a role? Levetiracetam is a compound with a unique mechanism of action among antiepileptic drugs. It binds to an integral membrane protein, SV2A, present on synaptic vesicles and also present in endocrine cells.[13] It has been demonstrated that compounds with increasing affinity for this protein have increasing anti-seizure properties in animal models of epilepsy, suggesting that the drug exerts its anti-seizure effect through this mechanism.[8] The protein is believed to interact with the presynaptic protein synaptotagmin, and affect calcium-dependent fusion of synaptic vesicles to the plasma membrane and release of neurotransmitters.[14,15] Its precise action is unknown but one theory is that binding of levetiracetam may enhance a function of SV2A that inhibits abnormal bursting in epileptic circuits.[8] Even more interesting is that the drug appears to have no effect on either the electrophysiology or standard amino acid neurotransmitter release of normal neuronal tissue.[16—18] This suggests that the drug may modulate a function of SV2A present only under pathophysiological conditions, as might be found in epileptic brain tissue. It is possible therefore that those patients who respond best to levetiracetam have an alteration in either the expression or function of SV2A, for example up-regulation of the protein. Alternatively, patients who respond to levetiracetam may have genetic variation in SV2A or related proteins that results in a higher affinity for the drug, a hypothesis we are currently examining in pharmacogenetic studies. Until such data becomes available, it seems reasonable to suggest that all drug-resistant patients, including those being assessed for surgery, should be considered for a trial of add-on therapy with levetiracetam, regardless of their epilepsy classification.

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