Seizure 34 (2016) 1–5

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Clinical experience with adjunctive perampanel in adult patients with uncontrolled epilepsy: A UK and Ireland multicentre study

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ARTICLE INFO

Article history:
Received 27 May 2015
Received in revised form 22 October 2015
Accepted 27 October 2015

Keywords:
Epilepsy
Perampanel
Antiepileptic drug
Responder rate
Tolerability
Efficacy

ABSTRACT

Purpose: To derive clinically useful information about the efficacy and tolerability of adjunctive treatment with perampanel for refractory epilepsy in an outpatient setting.
Method: We pooled retrospective casenotes data of adult patients with refractory epilepsy prescribed perampanel from 18 hospitals throughout UK and Ireland.
Results: Three hundred and ten patients were included (mean age 40.9 [SD = 12.0], 50% women, 27.7% with learning disability). The mean duration of epilepsy was 26.7 years (range 2–67 years, SD = 13.5) and 91.9% were taking two or more anti-epileptic drugs at the time of perampanel initiation. Mean retention was 6.9 months (range 1 day–22.3 months, SD = 4.5). The retention was 86% at 3 months, 71% at 6 months, 47.6% at 12 months and 27% at 18 months. At final follow-up a >50% reduction in seizure frequency was reached in 57.5% of tonic–clonic seizures, 57.4% of complex partial seizures and 43.8% of simple partial seizures. Eleven patients (3.5%) became seizure free. Two hundred and nine patients (67.4%) experienced adverse effects and of these 67% withdrew treatment due to their effects. The most common were sedation, behaviour/mood disturbance, dizziness, and unsteadiness.
Conclusion: Perampanel appears a safe and effective antiepileptic drug when used as adjunctive therapy in patients with uncontrolled partial epilepsy (including those with learning disability), although few patients achieved complete seizure control. Long-term retention was slightly lower than reported rates for other anti-epileptic drugs, potentially due to the highly refractory population. Monitoring for adverse effects on energy levels, mood and behaviour is recommended.

1. Introduction

Perampanel is a new first-in-class non-competitive AMPA (a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) antagonist licensed as an adjunctive treatment for partial-onset seizures in patients with refractory epilepsy aged twelve or above. It was licensed for use in the UK in September 2012 and in the US in October 2012.

Three randomised, multi-centre, double-blind, placebo-controlled trials of perampanel have demonstrated a major reduction in seizure frequency at four different doses, with >50% responder rates varying from 20.6% at 2 mg/day, 28.5% at 4 mg/day, 33.3–37.6% at 8 mg/day and 33.9–36.1% at 12 mg/day. In these studies, the placebo responder rates varied from 14.7 to 26.4% [1–3]. Two post-marketing studies have been published, also showing high response rate and good tolerability [4,5]. Here, we present the clinical experience with perampanel in a large patient cohort from fifteen centres around the UK and Ireland.

2. Method

Data were obtained from case notes from eighteen secondary and tertiary epilepsy centres in the UK and Ireland between February 2014 and December 2014. Cases were identified from the

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http://dx.doi.org/10.1016/j.seizure.2015.10.017
1059-1311/

electronic medical and pharmacy records of patients who had been prescribed perampanel. Those included were adults attending their usual epilepsy clinic and the decision to use perampanel was based upon the treating clinician's recommendation. Data were obtained by reviewing medical notes and clinic letters, then entered on to an electronic database.

All adult patients who had been prescribed perampanel were included, irrespective of the length of time they took the drug. The only exclusion criterion was a lack of follow-up. Data included: patient demographics, clinical features, history and treatment details; such as concomitant antiepileptic drugs (AEDs), maximum dosage of perampanel, length of exposure to perampanel, adverse effects and withdrawal rates.

Patients were typically seen in clinic every three to six months. Frequencies of seizures were obtained from medical notes or seizure diaries when available. Clinicians usually documented the number of seizures each month or provided a monthly average since their previous review of the patient. If numerical recordings of seizure frequency were not provided yet the clinician felt improvement had been achieved, patients were recorded as demonstrating a less than 50% reduction in seizure frequency.

Outcomes following treatment were defined as follows:

- Seizure free: a terminal remission of seizures for three months or more.
- 50% or more reduction: a reduction in seizure frequency of 50% or more in the last three months of follow-up compared with a pre-treatment three month baseline. Only cases where seizure frequency was accurately recorded were placed in this group.
- Less than 50% reduction: a reduction of between 1% and 49% in seizure frequency in the last three months of follow-up compared to the three month baseline period. A minority of cases deemed to show improvement but lacking accurate frequency data were also placed in this group.
- No reduction or worsening of seizures: this was based either on numerically recorded frequencies or on qualitative clinical impression.

Two response rates were determined, the first based upon the seizure frequency in the first three months after commencing perampanel and the second upon the three months prior to last follow-up. Those with less than three months exposure were excluded from the first response rate. The second response rate was only determined for patients with a minimum of six months follow-up. Inferential statistical tests were used to describe the dataset. Retention time on perampanel was estimated using Kaplan–Meier survival curves and compared using a Tarone–Ware test.

3. Results

Case notes were reviewed for 522 patients. A total of 310 patients (155 female) undergoing perampanel treatment who had at least one follow-up were included in analysis. 230 patients were classified as having symptomatic or cryptogenic partial epilepsy, 15 symptomatic generalised epilepsy, 8 idiopathic generalised epilepsy and 57 patients were either unclassified or their form of epilepsy was unknown. The following analyses were ran separately for those patients with partial epilepsy, however, as no differences were apparent between these patients and the sample as whole, data for the overall cohort have been reported here (Table 1).

Ages of the patients ranged between 18 and 75 years old (mean 40.9, SD = 12.0). The mean duration of epilepsy for this patient group was 26.7 years (SD = 13.5) and mean number of concomitant anti-epileptic drugs was 2.6 (range = 0–6, SD = 0.9). 91.9% of these patients were taking two or more AEDs at the time of perampanel initiation.

Table 1
Clinical features of all 310 patients that underwent perampanel treatment.

Characteristic		Total number/number with ≥6 months FU
Age	18–30	74.0/33.0
	31–50	166.0/87.0
	51–75	70.0/41.0
Learning disability	Yes	86.0/40.0
	No	177.0/96.0
Gender	Male	155.0/81.0
	Female	155.0/80.0
Syndrome	SPE/CPE	230.0/122.0
	IGE	8.0/6.0
	SGE	15.0/7.0
	U	57.0/14.0
Concomitant AEDS	1	22.0/13.0
	2	131.0/66.0
	>3	154.0/80.0
Length of treatment (months)	<3.0	60.0
	3.0–5.9	87.0
	6.0–8.9	71.0
	9.0–11.9	47.0
	>12.0	40.0

3.1. Titration

The initial starting dose was typically 2.0 mg. This was then titrated up by a further 2 mg/2 weeks in 64.2% of patients without LD, although these increments varied between 2 mg/1 week and 2 mg/6 weeks according to the judgement of the clinician (Table 2). The mean maximum dose reached was 7.1 mg (SD = 2.9), ranging between 2 mg and 16 mg. Patients were divided into 'fast' (≤2 mg/2 weeks) and 'slow' (>2 mg/2 weeks) titration groups. There was a trend towards a significant difference between the length of treatment in the two titration groups; $t(150) = 1.7$, $p = 0.090$, 95% CI [−0.3,3.6]. Fisher's exact test revealed a significant difference in the prevalence of dizziness in the fast and slow groups; $p = 0.025$.

3.2. Follow-up and outcome

The duration of perampanel treatment ranged from one day to 22.3 months with a mean of 6.9 months (SD = 4.5). The probability of remaining on treatment with perampanel was assessed using

Table 2
Impact of titration rate on patients without learning disability (LD).

	≤2 mg/2 weeks	>2 mg/2 weeks
No. of patients	131.0	22.0
Mean max dose (95%CI)	7.1 (6.9–7.7)	6.6 (5.5–6.9)
No. experienced AEs (%[CI])	94.0 (75 [66.9–82.0])	13.0 (61.9[40.8–79.3])
Sedation (%[CI])	34.0 (27 [20.3–35.9])	6.0 (30 [14.3–52.1])
Behavioural/mood disturbance (%[CI])	26.0 (21 [14.7–29.0])	3.0 (15 [4.1–35.5])
Unsteadiness (%[CI])	21.0 (16.9 [11.3–24.6])	1.0 (5 [<0.1–25.4])
Dizziness (%[CI])	25.0 (20.1 [14.0–28.1])	0.0
Mean length of treatment; months (CI)	7.1 (6.3–7.4)	5.5 (4.1–5.9)
No. withdrew (%[CI])	55.0 (42 [33.6–50.2])	4.0 (18[6.7–39.1]
No. withdrew due to adverse effects (%[CI])	37.0 (29.1 [22.0–37.6])	3.0 (13.6 [3.9–34.2])
Seizure free	7.0	1.0
>50% reduction TCS at final FU (%[CI])	25.0 (56.8 [39.2–66.7])	4.0 (50 [21.5–78.5])
>50% reduction CPS at final FU (%[CI])	39.0 (47 [36.6–57.6])	4.0 (28.5 [1.5–12.1])