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Prospective audit with adjunctive perampanel: Preliminary observations in focal epilepsy

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ABSTRACT

Purpose: Perampanel (PER) was first licensed in the United Kingdom in 2012 for the adjunctive treatment of focal seizures with or without secondary generalization in adults and children over 12 years of age. It has recently also been approved for use as add-on therapy for patients with primary generalized tonic–clonic seizures. This prospective audit reports preliminary outcomes with adjunctive PER in patients with focal-onset seizures in everyday clinical practice using a standard design.

Methods: To date, 54 patients (38 males, 16 females; 21–65 years, median: 48 years) have completed the study. The median monthly seizure frequency was 4 (range: 1–60). At baseline, patients were taking a median of 2 other antiepileptic drugs (range: 1–4 drugs), with their seizures having previously failed to improve on a median of 3 schedules (range: 1–15 schedules). After 12 weeks of stable dosing, PER was added, aiming at a target range of 6–12 mg/daily. Review took place every 6–8 weeks until one of 4 endpoints was reached: seizure freedom for ≥6 months on a given PER dose, ≥50% (responder) or <50% (marginal effect) seizure reduction over 6 months, compared with the prospective baseline, on the highest tolerated PER dose, or withdrawal of PER due to a lack of efficacy or side effects.

Results: Three (5.6%) patients have remained seizure-free, with 8 (14.8%) demonstrating a ≥50% response and a further 17 (31.5%) reporting a marginal effect. Of the 26 (48.1%) dropping out of PER treatment, 21 (38.9%) did so because of side effects. The commonest problems were nausea, vomiting, ataxia, dizziness, and sedation. Overall, 6 (11%) patients developed neuropsychiatric problems, with 3 reporting irritability and/or aggression. Two patients had substantial weight gain, and another patient suffered recurrent falls. Treatment with enzyme-inducing AEDs had no effect on PER dosing in patients responding to PER or withdrawing due to side effects.

Significance: These data support the value of adjunctive PER in some patients with pharmacoresistant epilepsy in everyday clinical practice.

1. Introduction

Despite the introduction of more than 15 new antiepileptic drugs (AEDs) over the past 25 years, around 30% of adolescent and adult patients with epilepsy still have uncontrolled seizures [1]. During the last decade, a range of new AEDs, some with unique mechanisms of action, have been developed as adjunctive therapy for pharmacoresistant focal epilepsy [2]. Perampanel (PER), a selective noncompetitive AMPA-type glutamate receptor antagonist [3], was the latest AED to be licensed as adjunctive treatment for focal seizures with or without secondary generalization in adults and children over 12 years of age in the United Kingdom following successful completion of the regulatory trial program [4]. More recently, given positive results in a phase III study, its license has been extended for use as add-on therapy for primary generalized tonic–clonic seizures [5]. After its approval for use by the Scottish Medicines Consortium in early 2013, a prospective audit of adjunctive PER usage in patients with pharmacoresistant focal epilepsy was undertaken at the Western Infirmary Epilepsy Unit using a standard design [6]. Enzyme-inducing AEDs, such as carbamazepine, oxcarbazepine, and phenytoin, accelerate PER clearance [7] and reduce its dose-related exposure [8]. This audit, therefore, also examined PER dose requirements of enzyme-induced patients in everyday clinical practice. Most of the side effects of this agent mirror those occurring with other AEDs with the exception of falls and aggression [9]. The effect of its introduction in producing or exacerbating neuropsychiatric symptoms was specifically explored in this prospective outcome study.

2. Materials and methods

Patients 12 years of age and prescribed one or more AEDs for uncontrolled focal epilepsy with or without secondary generalization were recruited into the audit. Those who were intermittently nonadherent to their drug regimen or had poor clinic attendance and those who did not document their seizure frequencies and descriptions appropriately were excluded. Each patient recorded their baseline seizures for

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12 weeks on an unchanged AED regimen prior to starting PER. All were then prescribed 2-mg PER in the evening with most increasing by 2 mg every 2 weeks, aiming for a daily maintenance dose of 6–12 mg. Some patients on high doses of enzyme-inducing AEDs were initially given weekly PER increments. Where necessary, doses of other AEDs were reduced or occasionally withdrawn to minimize side effects. Endpoints included seizure freedom for at least 6 months on a given PER dose, ≥50% seizure reduction (responder) for 6 months, compared to baseline, on the highest tolerated PER dose, <50% seizure reduction (marginal effect) in patients wishing to continue taking the drug, and withdrawal of PER due to a lack of efficacy or side effects.

As this was a clinical audit project it did not require ethics approval.

3. Results

To date, 54 patients have reached an endpoint (38 males, 16 females; 21–65 years, median: 48 years). At baseline, median monthly seizure frequency was 4 (range: 1–60). Patients were taking a median of 2 other AEDs (range: 1–4), having already failed to improve on a median of 3 schedules (range: 1–15). Following the addition and titration of PER, 3 (5.6%) patients have remained seizure-free, with 8 (14.8%) demonstrating a ≥50% seizure reduction. A further 17 (31.5%) patients remained on PER at their behest despite documenting a seizure reduction of <50% versus baseline. The median dosing in patients continuing on PER was 8 mg/day, ranging between 4 and 14 mg/day. Perampanel doses and concomitant AEDs are listed for each of these patients in Table 1. Three of these patients had one AED withdrawn, and dosage reduction was undertaken in a further 2 patients.

Overall, 26 (48.1%) patients discontinued PER treatment, 21 due to side effects and 5 due to a lack of efficacy. Mean PER dosage in these patients was 4 mg/day with a range of 2 to 12 mg/day. Individual side effects are listed in Table 2. The commonest problems were nausea, vomiting, ataxia, dizziness, and somnolence, with some patients reporting more than one symptom. Three patients withdrew because of depression, 2 of whom had received previous treatment with antidepressants. A further 5 patients with a history of depression tolerated PER without problem. Another 3 patients reported increased irritability and/or aggression. They were taking PER 4 mg, 6 mg, and 8 mg daily. Overall, therefore, only 6 (11.1%) patients reported neuropsychiatric symptoms sufficiently severe to result in PER discontinuation. Two further patients stopped treatment because of weight gain (5.1 and 7.9 kg), and another discontinued because of recurrent falls.

Table 1
Antiepileptic drug combinations and perampanel doses in responders.

No.	Seizure control	Concomitant antiepileptic drugs	Perampanel daily dose (mg)
1	Seizure-free	Eslicarbazepine	4
2		Lacosamide/levetiracetam	8
3		Phenytoin/levetiracetam	12
4	≥50% reduction	Sodium valproate	8
5		Lacosamide	10
6		Carbamazepine/levetiracetam	4
7		Lamotrigine/vigabatrin	10
8		Carbamazepine/topiramate/levetiracetam	8
9		Carbamazepine/levetiracetam/gabapentin	4
10		Carbamazepine/clobazam/levetiracetam	8
11		Valproate/lamotrigine/levetiracetam/zonisamide	4
12	<50% reduction	Sodium valproate	10
13		Lamotrigine	6
14		Lamotrigine	6
15		Carbamazepine/clobazam	8
16		Carbamazepine/clobazam	12
17		Carbamazepine/pregabalin	12
18		Carbamazepine/zonisamide	6
19		Valproate/levetiracetam	6
20		Valproate/zonisamide	6
21		Lamotrigine/zonisamide	6
22		Levetiracetam/eslicarbazepine	4
23		Levetiracetam/lacosamide	8
24		Carbamazepine/levetiracetam/lacosamide	4
25		Valproate/levetiracetam/eslicarbazepine	6
26		Valproate/gabapentin/levetiracetam	12
27		Topiramate/levetiracetam/eslicarbazepine/clobazam	8
28		Carbamazepine/gabapentin/levetiracetam/zonisamide	14

Table 2
Side effects leading to perampanel withdrawal.

Side effect	n
Nausea/vomiting	4
Ataxia	4
Depression	3
Dizziness	3
Somnolence	3
Aggression	2
Fatigue	2
Irritability	2
Weight gain	2
Falls	1
Confusion	1
Abdominal pain	1
Dysarthria	1
Lethargy	1

Some patients reported more than one side effect.

Perampanel daily doses in all 54 patients completing the audit are highlighted in Fig. 1. The 3 seizure-free patients took 4-, 8-, or 12-mg PER daily. The doses in responders and those reporting a marginal effect tended to be higher, since PER was titrated to the maximally tolerated amount while the patient still reported seizures. Sixteen of the 21 patients withdrawing from treatment due to side effects did so at PER doses of 4 mg or less daily. Failure at higher doses usually indicated a lack of efficacy rather than poor tolerability.

Overall, 29 of the 54 recruited patients took enzyme-inducing AEDs. Of the 28 patients who responded to PER, 15 were established on enzyme-inducing AEDs (dosing range: 4–14 mg/day; median: 6 mg/day) and 13 were on noninducers (dosing range: 6–12 mg/day; median: 6 mg/day). Of those patients discontinuing PER, 14 were receiving enzyme inducers (dosing range: 4–12 mg/day; median: 4 mg/day), and 12 were on noninducers (dosing range: 4–12 mg/day; median: 4 mg/day). Thus, enzyme induction did not appear to influence dosing or outcome in this audit.

4. Discussion

As PER has a unique mechanism of action [10], it has the potential for efficacy in patients whose seizures have failed to improve from treatment with other AEDs [11]. However, its long elimination half-life of 2–6 days presents a challenge in everyday use as it may take 3 weeks

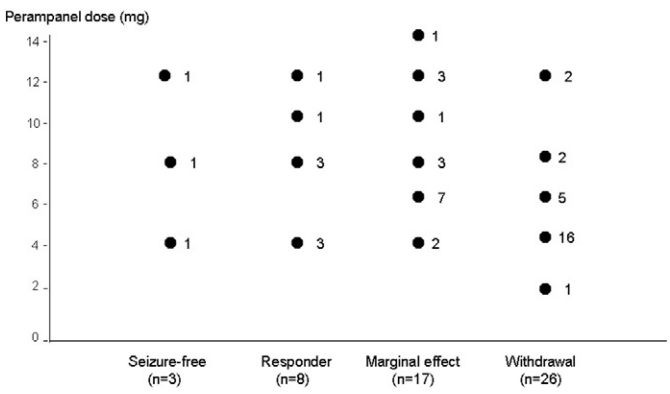

Fig. 1. Final daily perampanel doses in all outcome groups.