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Effectiveness and tolerability of Perampanel in children, adolescents and young adults with refractory epilepsy: A UK national multicentre study

N. Swiderska[a,*], H.J. Tan[a], A. Rajai[b], A. Silwal[c], A. Desurkar[d], T. Martland[a]

[a] Paediatric Neurology, Royal Manchester Children's Hospital, Manchester, United Kingdom
[b] Institute of Population Health, Faculty of Medical and Human Sciences, University of Manchester, Research & Innovation, Central Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom
[c] Paediatric Neurology, Great Ormond Street Hospital, London, United Kingdom
[d] Paediatric Neurology, Sheffield Children's Hospital, Sheffield, United Kingdom

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ABSTRACT

Purpose: Perampanel is one of the latest antiepileptic drugs (AEDs) approved for the treatment of focal and generalised epilepsy in individuals with epilepsy aged 12 years and older. There is sparse data on the use of Perampanel in children under 12. We conducted a study amongst paediatric neurologists in the United Kingdom to investigate its effectiveness and tolerability as an adjunctive therapy in children of all ages with refractory epilepsy.

Methods: Data was collected via an online questionnaire sent to paediatric neurologists in the UK. Data gathered, prospective in 62 (64.5%) and retrospective in 34 (35.5%) patients, included changes in seizure frequency from baseline and unwanted effects at 3, 6 and 12 months follow-up. Only patients with a minimum follow-up of six months were included.

Results: Ninety six patients (48 females) with refractory epilepsy from 11 of 29 tertiary centres were included. Median [IQR] (range) age was 14 years 11 months [12 years, 16 years 6 months] (11 months–24 years 5 months). Seventy three (76%) had focal epilepsy, sixteen (17%) generalised, and seven (7%) patients both generalised and focal epilepsy. The responder rate, ≥50% seizure reduction from baseline, was 19% for all seizure types at both 6 and 12 months, 19% and 24% for focal seizures, and 25% and 7% for generalised seizures at these time points respectively. The retention rate was 42% at 12 months. Treatment was discontinued due to unwanted effects in 29 (36.7%) of the 79 patients with follow-up data available up to 12 months: 30% due to challenging behaviour, 14% dizziness, and 7.6% somnolence.

Conclusion: Perampanel was fairly effective in a heterogeneous group of 96 children and adolescents with very refractory epilepsy. The rate of adverse events leading to discontinuation was considerable in this group.

1. Introduction

Since the introduction of Phenobarbital in 1912 as a treatment for epilepsy, there has been an expansion in the numbers of antiepileptic drugs. The pharmacological advances over the past 20 years have led to the discovery of many new AEDs, although the mechanism of action in some is still poorly understood [1]. Clinicians have national guidelines to help them with the choice of AEDs in the management of epilepsy [2]. However, the problem of intractability in childhood epilepsy persists despite appropriate medical treatment. A recent Dutch study of 413 patients with childhood-onset epilepsy with a mean follow-up period of fifteen years showed that at least 12.1% patients had a period of intractability [3]. Earlier studies had shown higher rates (23.2%–37%) of drug resistance in patients with epilepsy [4,5]. This highlights the need for the development of new antiepileptic treatments with alternative targets.

Perampanel (PER) is the first AED in the class of selective non-competitive AMPA-type glutamate receptor antagonists with a novel mechanism of action. AMPA receptors are ligand-gated ion channels activated by glutamate, a major excitatory neurotransmitter. They have an important role in excitatory neurotransmission in the CNS and are involved in the generation and spread of

* Corresponding author at: Paediatric Neurology Department, Royal Manchester Children's Hospital, Oxford Road, Manchester M13 9WL, United Kingdom.
E-mail address: ninaswiderska@doctors.org.uk (N. Swiderska).

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seizure activity [6,7,8]. In an in vitro study, Perampanel was shown to inhibit the increase of intracellular free calcium influx following AMPA receptor activation, which in turn reduces neuronal excitation [9]. Perampanel was found to have non-competitive antagonism at AMPA receptors as it did not compete with glutamate for binding to AMPA receptors [9]. Preclinical studies in vivo, based on the studies on rat amygdala-kindling model, showed that PER significantly reduced motor seizure duration and severity and demonstrated inhibitory properties in both focal, secondary generalised seizures and in status epilepticus [8,9,10].

There have been three phase III trials, studies 304, 305, and 306, assessing the efficacy and tolerability of Perampanel as an adjunctive AED in adults and adolescents with focal epilepsy with or without secondary generalisation [11,12,13]. Overall, 1480 adults and adolescents lacking seizure control despite two to three AEDs were recruited to these studies. Of these, 143 patients were between 12 and 17 years of age. Perampanel was proven to be effective in reduction of focal seizures and focal seizures with secondary generalisation as an adjunctive treatment at daily doses of 4 to 12 mg [11,12,13,14]. Perampanel has been approved by the Food and Drug Agency (USA) and European Medicines Agency (EMA) for adjunctive treatment of partial-onset seizures for patients from age 12 years in 2012. The license was further extended by EMA for PER to be used as an adjunctive treatment for primary generalised tonic-clonic seizures (GTCS) in idiopathic epilepsy from age of 12 years in May 2015, following a multicentre, double-blind, placebo-controlled study [15].

Perampanel is orally administered and has a long half-life of 105 h, allowing it to be administered once daily. The recommended dose at the start of treatment is 2 mg/day, which can be increased by increments of 2 mg/day to a maximum dose of 12 mg per day. There is significant reduction in PER concentration when it is combined with three commonly used enzyme-inducing AEDs (EIAEDs); Carbamazepine, Oxcarbazepine and Phenytoin [16].

There were a few multicentre surveys of clinical experience with Perampanel in adults and in children of different ages [17–23]. The open label pilot study on pharmacokinetics, efficacy, and safety of Perampanel oral suspension on seizure frequency in 50 children $\geq$2 years to $<$12 years as an add on therapy has been recently completed by Eisai Limited. The results of the study are currently being analysed [24].

2. Methods

2.1. Data collection

This was a prospective and retrospective study of Perampanel use in children with epilepsy. All consultant paediatric neurologists, members of British Paediatric Neurology Association (BPNA), were sent an online link to complete questionnaires about patients treated with Perampanel between January 2014 and April 2016. Overall, there were four questionnaires for each patient, obtaining information on demographic details, changes in seizure frequency, and unwanted effects at 3, 6 and 12 months follow-up. Patients, who were given a prescription of PER between December 2012 and December 2015, were identified by a local clinician from hospital and pharmacy records. Medical and clinical records were reviewed by local paediatric neurologists and the anonymised clinical information was submitted online. All patients included in the survey had a minimum of six months follow-up once the treatment

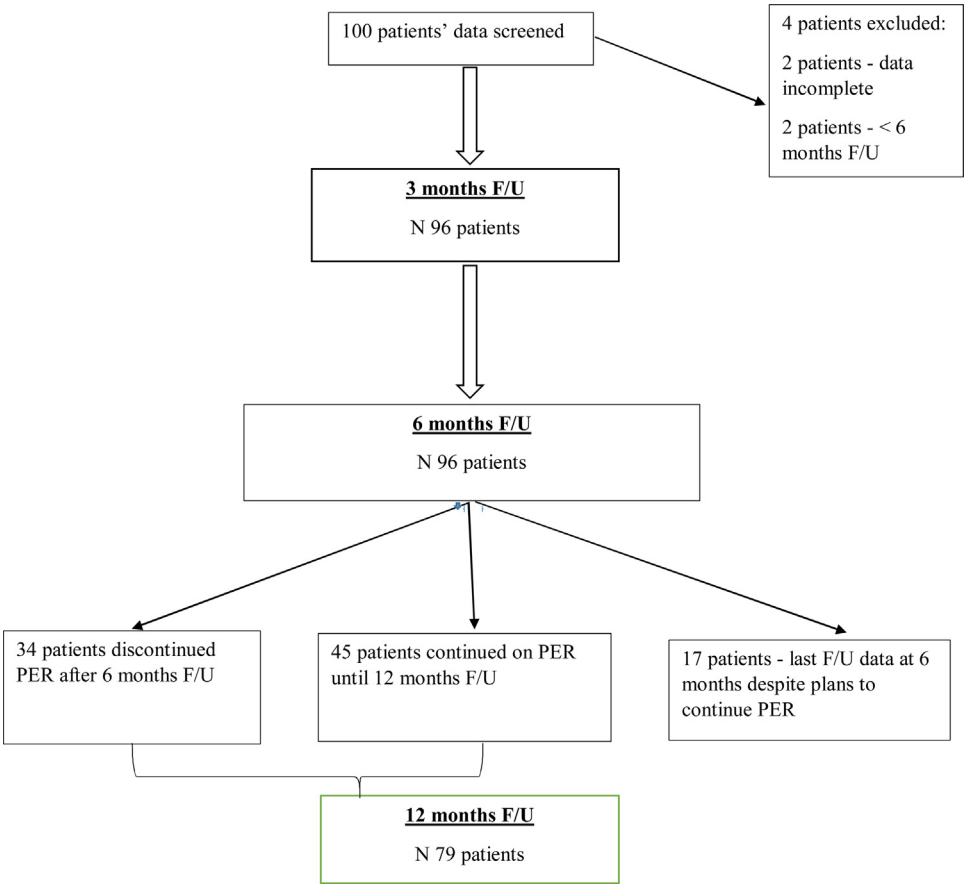

Fig. 1. Flow chart of all 96 patients included in the Perampanel (PER) survey at 6 months follow-up; data from 79 patients eligible for further analysis at 12 months follow-up (F/U).