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Brief Communication

Use of perampanel in children and adolescents with Lennox–Gastaut Syndrome

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ABSTRACT

Aim: Report the use of perampanel treatment in children with Lennox–Gastaut syndrome (LGS).
Method: We conducted a prospective study of 13 LGS patients (seven male; mean age, 12.8 years) treated with adjunctive perampanel therapy. Perampanel was initiated at 2 mg/day and titrated to a median maximum dose of 6 mg/day.
Results: After a mean follow-up duration of 10.8 months (range, 1–24 months), nine patients (69.2%) were responders (≥50% reduction in total seizure frequency) and nine (69.2%) were rated by their physician as "much improved" or "very much improved". Four patients (30.8%) discontinued perampanel due to the lack of efficacy (n = 2) and seizure aggravation (n = 2). No patients discontinued due to other adverse events (AEs). AEs were reported for six patients (46.2%) and comprised decreased activity/social interaction (n = 3), behavior disturbance with agitation (n = 2), and/or fatigue (n = 2). All AEs became manageable after perampanel dosing was decreased. Improvements in cognitive function and/or behavior were reported for seven patients (53.8%). Introduction of perampanel allowed the dose reduction and/or discontinuation of other treatments in seven patients (53.8%).
Interpretation: Perampanel was efficacious and generally well tolerated as an adjunctive treatment for seizures associated with LGS, supporting further research in this area.

1. Introduction

Lennox–Gastaut syndrome (LGS) is an epileptic encephalopathy that typically begins between the ages of 1 and 7 years (most commonly 3–5 years), but it may also be diagnosed during adolescence or adulthood [1,2]. The syndrome is associated with considerable morbidity and mortality, and is characterized by multiple seizure types, pharmacoresistance, abnormal electroencephalogram features with slow spike–wave discharges, and cognitive impairment (often accompanied by behavioral problems) [1,2]. Antiepileptic drugs (AEDs) with effectiveness in LGS are typically used in combination, increasing the risk of adverse effects and aggravation of co-morbidities [1]. AEDs with a broad range of efficacy have been recommended to help control the multiple seizure types associated with the condition [1].

Perampanel is an orally active, selective, non-competitive antagonist at the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor [3]. It is approved for the adjunctive treatment of partial-onset seizures, with or without secondarily generalized seizures, in epilepsy patients aged ≥12 years, and primary generalized tonic–clonic seizures in patients with idiopathic generalized epilepsy aged ≥12 years [4,5]. The effectiveness of perampanel in these settings has been established in a series of phase III trials, [6,7] supported by open and real-world studies [8–12].

Reports on the use of perampanel in children are currently scarce [13–15] and only two studies have included a limited number of children with LGS [13,14]. Here, we report our center's experience of using perampanel specifically to treat pediatric patients with LGS.

2. Patients and methods

A cohort study was conducted at the Department of Pediatric Neurology at Robert Debré University Hospital, Paris, France. This prospective cohort has been approbed by local ethical committee. Data were collected prospectively for all LGS patients, and the departmental database and cohort files were used to identify patients with LGS treated with perampanel between July 2014 and July 2016. All patients treated with perampanel are reported. All patients with LGS have the following criteria: 1. multiple types of seizures including at least tonic seizures, and atonic seizure or atypical absence; 2. EEG abnormalities

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including at least slow (1–2 Hz) spike-and-wave complexes and fast rhythm activities; and 3. cognitive involvement. Medical History, clinical data, concomitant treatments and perampanel treatment data were collected (Tables 1 & 2).

Efficacy was evaluated after 1, 3, 6, 9, and 12 months of perampanel treatment and at the last follow-up. Seizure count analysis was based on the seizure diary used by all patients in this cohort. Responders were defined as patients experiencing a ≥ 50% reduction in the frequency of generalized tonic–clonic seizures and drop seizures compared with baseline (before perampanel treatment). In addition, the Clinical Global Impression (CGI) of the physician was assessed at each visit and rated as "very much improved", "much improved", "minimally improved", "no

Table 1
Patient demographics, baseline characteristics, and treatment details.

Patient	Sex	Age at onset of epilepsy (years/months)	Epilepsy prior to LGS	Cognitive delay before epilepsy	Age at LGS diagnosis (years/months)	Etiology	Previous treatment[a]	Concomitant treatment[a] at perampanel initiation	Age at perampanel initiation (years/months)	Maximum perampanel dose (mg/day)
1	F	4/1	Multifocal	Yes	14/0	Unknown (probably genetic)	VPA, CLB, CBZ, LEV, TPM, ZNS, LTG, RUF, ETX	VPA, CLB	15/0	6
2	M	3/8	Multifocal	No	5/9	Multifocal injury due to encephalitis	VPA, CLB, OXC, TPM, LTG, LEV, FLB, RUF KD	VPA, LTG VNS	10/6	6
3	F	0/3	Unknown; including epileptic spasm	Yes	11/2	Unknown (probably genetic)	VGB, LCM, FLB, RUF, TPM, LEV, CLB	VPA, LTG	15/3	8[b]
4	F	2/6	Epileptic encephalopathy with late-onset spasms	No	10/6	Unknown	VGB, OXC, VPA, LTG, TPM, FLB, RUF, CBZ, ZNS HC, ACTH KD	VGB, TPM	14/0	4
5	M	0/6	West syndrome and focal seizures due to FCD	No	12/0	Developed LGS 5 years after frontal lobectomy for FCD	VGB, NZP, LTG, VPA, LCM, LEV Surgery	VPA, LEV, RUF	13/0	8[b]
6	M	6/2	Focal	Yes	9/0	Unknown	VPA, CLB, LEV, STM, TPM, RUF, FLB KD	VPA, LTG, CLB	13/0	8[b]
7	M	0/9	Multifocal	No	7/8	Traumatic brain injury with brain hemorrhage	VPA, TPM, OXC, PB, LEV, CLB KD	LTG, LEV	13/0	8[b]
8	M	0/6	West syndrome	No	6/7	Unknown	VGB, NZP, OXC, VPA, LTG, TPM, LEV ACTH	VPA, LTG, CLB	11/0	6[c]
9	F	0/8	Unknown	Yes	14/0[d]	Unknown (probably genetic)	CBZ, CLB, TPM, LTG, LEV, ZNS KD	LTG, RUF	18/6	4
10	M	1/0	Focal	Yes	6/8	Possibly malformative (bilateral frontal subependymal heterotopia)	VPA, CBZ, LEV, LTG, RUF, FLB VNS	VPA, LTG	13/6	4
11	F	0/9	Dravet syndrome; acute encephalopathy (5 years)	No	6/0	Brain injury after acute encephalopathy	VPA, TPM, CLB, STP, RUF, ETX	VPA, TPM, CLB	10/0	4
12	F	2/5	Unknown	Yes	2/8	Multifocal infectious lesion including left frontal porencephaly; tyrosinemia	LEV, LTG, RUF, TPM, VPA, CLB KD	VPA, LTG, CLB	6/0	4
13	M	2/0	Multifocal	No	9/5	Meningitis (2 years); multiple stroke; sickle cell disease	VPA, LEV, CBZ, CLB, LTG[e], OXC	VPA, TPM, RUF	13/0	8[c]

ACTH, adrenocorticotropic hormone; AED, antiepileptic drug; CBZ, carbamazepine; CLB, clobazam; ETX, ethosuximide; F, female; FCD, focal cortical dysplasia; FLB, felbamate; HC, hydrocortisone; KD, ketogenic diet; LCM, lacosamide; LEV, levetiracetam; LGS, Lennox–Gastaut syndrome; LTG, lamotrigine; M, male; NZP, nitrazepam; OXC, oxcarbazepine; PB, phenobarbital; RUF, rufinamide; STP, stiripentol; TPM, topiramate; VGB, vigabatrin; VNS, vagus nerve stimulation; VPA, valproate; ZNS, zonisamide.

[a] AEDs and non-pharmacological treatments.
[b] Subsequently decreased to 6 mg/day.
[c] Subsequently decreased to 4 mg/day.
[d] Referred to the Department of Pediatric Neurology at Robert Debré University Hospital, Paris, France at this age.
[e] Developed Stevens–Johnson syndrome with LTG.