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Utility and Safety of Perampanel in Pediatric FIRES and Other Drug-Resistant Epilepsies

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Abstract

Perampanel is a novel antiepileptic drug, which antagonises AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) glutamate receptor. We describe perampanel as an adjunctive treatment for FIRES (febrile infection-related epilepsy syndrome) and other drug-resistant epilepsies. A single-centre, observational, retrospective study involving 20 pediatric patients was conducted. Perampanel was started for three patients with FIRES, achieving seizure cessation in two patients within a day and on days 19 and 32 of illness. Doses used ranged from 4 to 12 mg/day, without any adverse effects reported or discontinuation of therapy. Responder-rate for other drug-resistant epilepsies is 25%. Median time to achieve ≥50% seizure reduction was 80 days (range: 26-326 days). Adverse effect reported in 47% of the patients includes central nervous system-related, and thrombocytopenia. Eight patients discontinued perampanel, because of ineffectiveness or adverse effects. The median time on perampanel before discontinuation was 179 days (range: 94-345 days). Perampanel may be of benefit in pediatrics FIRES and is of utility in other drug-resistant epilepsies.

Keywords

antiepileptic drugs, antiseizure drugs, children, epilepsy, pediatric, seizures

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Introduction

Perampanel is a novel antiepileptic drug (AED) and a noncompetitive antagonist of the ionotropic alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor on postsynaptic neurons.[1-3] AMPA receptor blockade inhibits excitatory discharges and seizure propagation.[2,3] It is efficacious and safe in drug-resistant epilepsy and has a long half-life, of approximately 105 h.[1-3] Perampanel has efficacy in focal-onset seizures with or without secondarily-generalized seizures in phase III studies, has established safety and tolerability profile at doses up to 12 mg/day, and is approved by the US Food and Drug Administration (FDA) in the adjunctive treatment of focal-onset seizures with or without secondarily-generalized seizures for patients aged four or older.[4-8] Febrile infection-related epilepsy syndrome (FIRES) is a rare catastrophic epilepsy syndrome of unknown etiology in previously healthy children.[9,10] It is characterized by a febrile illness prior to the onset of refractory status epilepticus.[9,10] Treatment remains challenging and is associated with a low success rate.[9,10] Direct inhibition of the postsynaptic excitatory AMPA receptor has been hypothesized to potentially interrupt the pathogenic mechanism in FIRES.[11]

There is a paucity of information on the utility and safety of perampanel in FIRES and the management of drug-resistant epilepsy in multiethnic, Asian, pediatric populations. Seizure control may be improved by using multiple AEDs with different mechanisms of action.[12-17] Pharmacokinetics studies of perampanel are described in children aged 12-years and older, and safety and efficacy in Asian children aged eight and older.[18-20] Ethnicity and age may affect treatment response to perampanel in pediatric patients.[18,19] We report our experience with

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perampanel in multiethnic, Asian pediatric population aged 1 to 19 years with a focus on FIRES and drug-resistant epilepsies.

Methods

Patients

Patients who were started on perampanel from January 2015 to April 2020 in the pediatric neurology service in KK Women's and Children's Hospital (KKH) were included. Inclusion criteria included: a diagnosis of FIRES or other drug-resistant epilepsies as defined by the International League Against Epilepsy (ILAE), aged below 19-years when they newly started on perampanel and were in adequate compliance to it. Patients allergic to perampanel or components of the formulation, with a currently implanted vagus-nerve stimulator, with any existing renal, hepatic impairment, or haematological disorders were excluded.

ILAE defines FIRES as a sub-category of new-onset refractory status epilepticus (NORSE), with a febrile episode starting between one to 14 days before the onset of refractory status epilepticus.[21] Drug-resistant epilepsy is defined as the failure to achieve seizure control with adequate trials of two or more AEDs as monotherapy or as combination therapy, which is well tolerated by the patient at therapeutic doses and appropriately chosen for the seizure type.[22]

This study was approved by SingHealth Centralised Institutional Review Board. Informed consent was obtained from all patients and caregivers.

Table 1. Demographics Data of 20 Patients Who Were Initiated on Perampanel in KKH.

	Total (N = 20)
Mean age (±SD), years	11.0 (±5.1)
Age group, years, n (%)	
<6	4 (20)
6 to 11	6 (30)
12 to 19	10 (50)
Age of seizure onset, years n (±SD)	5.1 (±4.5)
Gender, n (%)	
F	7 (35)
M	13 (65)
Ethnicity, n (%)	
Chinese	12 (60)
Malay	1 (5)
Indian	3 (15)
Others	4 (20)
Starting dosage of PER	
Median dosage, mg	2 (2-12)
Median dosage, mg/kg (range)	0.05 (0.03-0.49)
Maximum dosage PER	
Median dosage, mg	9 (4-12)
Median dosage, mg/kg (range)	0.2 (0.1-0.5)
Abnormal brain CT/MRI scans, n (%)	8 (40)
Seizure types, n (%)	
Focal only	12 (60)
Generalized onset tonic–clonic	1 (5)
Progressive myoclonic epilepsy	1 (5)
Lennox-Gastaut syndrome	1 (5)
Febrile Infection-Related Epilepsy Syndrome	3 (15)
Unknown	2 (10)
No. of concomitant AEDs at baseline, n (%)	
2	2 (10)
3	11 (55)
4 or more	7 (35)
Enzyme-inducing AEDs, n (%)	
PB	4 (20)
OXC	3 (15)
CBZ	4 (20)
PHE	1 (5)
Non-enzyme-inducing AEDs, n (%)	8 (40)

Abbreviations: AEDs = antiepileptic drugs; CBZ = carbamazepine; CT = computerised tomography; F = female; M = male; MRI = magnetic resonance imaging; OXC = oxcarbazepine; PB = phenobarbitone; PHE: phenytoin; PER = perampanel.

Data Collected

Patient data collected comprised of demographics, diagnosis, concomitant antiepileptic drugs, perampanel dispensing records, seizure frequency before and after perampanel initiation, laboratory results (full blood count, renal panel, and liver function test) before and after perampanel initiation, starting and highest dose of perampanel achieved, duration of perampanel use, and reported clinical adverse drug reactions deemed to be secondary to its use. Perampanel dispensing records were identified from pharmacy dispensing records and electronic or hardcopy case notes were reviewed to obtain clinical information.

Treatment compliance was assessed by reviewing the medication refill rates and the documentation by the neurologist during the outpatient review. Medication compliance in the inpatient setting was deemed to be 100%.

Responder-rate was defined as ≥50% reduction in focal seizures with or without focal to bilateral tonic-clonic (FBTC) seizures and generalized tonic-clonic (GTC) seizures.[5-7] The efficacy of perampanel was assessed by comparing the seizure frequency before and after treatment with perampanel. Seizure frequency was abstracted from the clinical inpatient and outpatient electronic notes. Seizure freedom was defined as no seizures upon reaching the maximum tolerated dose of perampanel. Exacerbation of seizures was defined as an increase in seizure frequency, length of seizure duration, or worsening severity of seizures. The safety profile of perampanel was evaluated by reviewing the documented adverse effects reported by the patient or caregivers.

Dose and Titration of Perampanel

Patients were started on perampanel at usual doses ranging from 2 mg to 4 mg once daily.[3] For most patients, perampanel was initiated at 2 mg once nightly and titrated up to 4 mg at night in 1 to 2 weeks, then in 2 mg increment every 2 weeks to a maximum of 12 mg at night or age-appropriate maximum. If adverse effects were noted, the titration rate was reduced.

Perampanel was started at a lower dose in the outpatient setting, as compared to the inpatient setting. In the patients with FIRES, perampanel was started directly at the maximum therapeutic dose for age and weight. It was weaned off when considered ineffective by the prescribing neurologist—if there were worsening seizures or adverse effects were intolerable.

Data Reporting

Quantitative data were generated using Microsoft® Excel® 2019 MSO (16.0.14228.20216). Categorical variables were reported as frequencies and percentages.

Results

Demographics

Three patients with FIRES and 17 patients with other drug-resistant epilepsies met the inclusion criteria and were recruited. One patient had lesionectomy of the frontal lobe, shortly after starting perampanel, and was only included in the safety reporting. Baseline demographic and clinical data of the 20 patients were summarized below (Table 1).

Clinical Summary

The clinical information of the patients recruited into the study is summarised below (Table 2).

Efficacy of Perampanel in FIRES

Perampanel was initiated in three patients with FIRES. Two had been in thiopentone coma and had seizure recrudescence on the reduction of thiopentone infusion. Perampanel was started as a full therapeutic dose and was associated with the cessation of seizures. The responder-rate (≥50% reduction) for FIRES patients after initiating perampanel was 67% (2/3 patients). Complete seizure control (100% reduction) was achieved in both of them. The median time on perampanel to achieve ≥50% reduction in seizures from baseline was one day.

Case 1. A 5-year-old Bangladeshi boy was transferred to KKH Children Intensive Care Unit (CICU) for refractory status epilepticus, and was managed as FIRES. He presented with fever for six days and recurrent generalised seizures for two days. He received acyclovir, ceftriaxone, vancomycin, phenobarbitone, phenytoin, and midazolam in Bangladesh, and was air evacuated to Singapore in view of refractory seizures. Clinical seizures ceased on day 19 of illness with phenobarbitone, phenytoin, levetiracetam, midazolam, and clobazam, although multiple electrographic seizures were recorded. Ketamine and topiramate were then started for the patient and the doses of the AEDs were optimised, with discontinuation of phenytoin. Magnetic resonance imaging of the brain on day 24 of illness showed hippocampal hyperintensities, likely secondary to postictal state. Autoimmune and infective panels were unremarkable. The patient received pulsed methylprednisolone and intravenous immunoglobulin as part of the immunotherapy.

Persistent electrographic seizures were seen on electroencephalogram (EEG) monitoring and perampanel was started at 4 mg once daily on day 31 of illness. Seizures ceased on day 32 of illness. No clinical adverse effects attributed to perampanel were reported. The patient was eventually discharged with carbamazepine, clobazam, lorazepam, levetiracetam, perampanel, and topiramate, with no reported seizures.

Case 2. A 16-year-old Chinese girl presented with seven days of fever, headache, bilateral retro-orbital pain, diarrhea, and vomiting, with new onset of altered mental status. She developed left-sided focal seizures on day 8 of illness. The patient was given lorazepam, loaded with phenytoin and levetiracetam, and transferred to CICU. Midazolam infusion and topiramate were started, but EEG monitoring showed generalised periodic epileptiform complexes with burst suppression patterns, despite treatment with levetiracetam, midazolam infusion, and topiramate. Magnetic resonance imaging of the brain on day eight of illness, autoimmune and infective panels were unremarkable. The patient was cultured and covered empirically with ceftriaxone, ciprofloxacin, metronidazole, and acyclovir. She received pulsed methylprednisolone and intravenous immunoglobulin against possible inflammatory meningoencephalitis. The infective screen was negative and the clinical impression was FIRES. Thiopentone coma was commenced on day 10 of illness and clinical seizures ceased. On switching from thiopentone to phenobarbitone on day 13 of illness, breakthrough status epilepticus occurred. Thiopentone coma was restarted and AEDs were further optimised.

Perampanel was started on day 18 of illness at 12 mg once daily, and the seizures ceased 24 h after the initiation of perampanel. The patient remained intubated and no clinical adverse effects were reported. Phenobarbitone and thiopentone were gradually weaned as no clinical seizures were reported. The patient was eventually discharged with clobazam, lorazepam, topiramate, phenobarbitone, and perampanel, with no reported seizures.

Case 3. A 3-year-old Chinese girl presented with three days of fever, vomiting, abdominal pain, and lethargy. She had two seizures in the ward and was transferred to CICU for a persistent low Glasgow Coma Scale score. Following lorazepam bolus, phenobarbitone loading and thiopentone infusion clinical seizures ceased, though electrographic seizures were recorded on EEG monitoring. She was diagnosed with FIRES and thiopentone coma was initiated on day five of illness, the infusion rate of midazolam was increased, and topiramate was started.

Magnetic resonance imaging of the brain on day five of illness showed gyral areas of restricted diffusion in the right temporal lobe and inferior right parietal lobe. The patient was empirically managed with acyclovir and ceftriaxone, and received pulsed methylprednisolone. The autoimmune and infective panels were unremarkable.

On day six of illness, she had persistent electrographic seizures and perampanel was initiated at 4 mg twice daily. However, no improvement in electrographic seizures was observed. The patient was subsequently started on levetiracetam, oxcarbazepine, ketamine, and rituximab. She underwent right temporal lobe lobectomy with a tailored resection on day 15 of illness, with no further epileptiform activity. Low

Table 2. Summary of Perampanel Use in Patients With FIRES and Other Drug-Resistant Epilepsies.

Case Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Age (y), Gender	5, M	16, F	5, F	9, M	16, M	17, F	13, M	6, M	19, F	12, F	9, M	17, M	5, F	16, M	9, M	14, M	14, M	18, F	10, M	1, M
Age of epilepsy onset	5	15	4	5	10	8	0	2	10	8	6	9	1	3	0	12	0	0	8	1
Ethnicity	B	C	C	I	C	I	C	Ca	C	C										
Others	C	C	C	C	C	C	I	A	Ma											
Weight, kg	16	51	16	27	101	58	47	24	66	50	49	51	37	66	32	54	75	21	46	12
Diagnosis	FIRES	FIRES	FIRES	LGS	PME	FE	FE	FE	FE	FE	FE	E	FE	E	FE	FE	FE	TS	PTE	AE
Brain CT/MRI	N	N	GRD	N.A.	N.A.	CD	N.A.	N.A.	V	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	CD	N.A.	ST	DAI	PDS
Seizure frequency change	100% ↓	100% ↓	↑*	No change	No change	25 to 50% ↓	>50% ↑	N.A.	>50% ↓	No change	25 to 50% ↓	No change	No change	>50% ↓	>50% ↓	>50% ↓	No change	No change	<25% ↓	No change
PER starting dose, mg	4	12	8	2	4	2	2	2	2	2	2	4	2	2	2	2	2	2	2	2
PER starting dose, mg/kg	0.3	0.2	0.5	0.07	0.04	0.03	0.04	0.08	0.03	0.04	0.04	0.08	0.05	0.03	0.06	0.04	0.03	0.1	0.04	0.2
PER maximum dose, mg	10	12	8	8	10	12	6	4	12	12	12	8	8	12	8	12	12	8	6	6
PER maximum dose, mg/kg	0.6	0.2	0.5	0.3	0.1	0.2	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.3	0.2	0.2	0.4	0.1	0.5
Concomitant AEDs	CLB, KT, LEV, MDZ, PB, TPM	CLB, LEV, MDZ, PB, TP, TPM	MDZ, TP, TPM	CLB, LTG, VPA	CLB, LEV, VPA, ZNS	CLB, TPM, VPA	CBZ, CLB	CLB, OXC	CBZ, CLB, PHE	CLB, LEV, PB, TPM	CLB, LTG, TPM, VPA	CBZ, CLB, LEV	CBZ, CLB, TPM	CLB, LTG, VPA	CLB, OXC, TPM	CLB, TPM, VPA	CLB, LEV, LTG	CLB, LEV, VPA	CLB, LEV, OXC, ZNS	LEV, MDZ, PB, TP
Adverse effects	Nil	Nil	Nil	D	T	CS	BI	T	BI, T, CS	T, U, CS	BI	BI, U	BI, S	Nil	BI	BI, S	BI, U	Nil	Th, BI, T	Nil

Abbreviations: Gender: F, female; M, male. Ethnicity: A, Arab; B, Bengali; C, Chinese; Ca, Caucasian; I, Indian; Ma, Malay.
Diagnosis: AE, autoimmune encephalitis; E, epilepsy; FE, focal epilepsy; FIRES, Febrile infection-related epilepsy syndrome; LGS, Lennox-Gastaut syndrome; PME, progressive myoclonic epilepsy; PTE, Post traumatic epilepsy; TS, Tuberous sclerosis.
Brain scan: CD, cortical dysplasia; CT, computerised tomography; DAI, diffuse axonal injury; GRD, gyriform restricted diffusion; MRI, magnetic resonance imaging; N, negative; N.A.: not applicable as it was not performed, PDS, prominent dural sinuses; ST, subcortical tubers; V, ventriculomegaly.
Drugs: AEDs, antiepileptic drugs; CBZ, carbamazepine; KT, ketamine; LTG, lamotrigine; LEV, levetiracetam; MDZ, midazolam; OXC, oxcarbazepine; PB, phenobarbitone; PER, perampanel; PHE: phenytoin; TP, thiopentone; TPM, topiramate; VPA, valproic acid; ZNS, zonisamide.
Adverse effects: BI, behavioural issues; CS, cognitive slowing; D, drowsiness; S, somnolence; T, tiredness; Th, thrombocytopenia; U, unsteadiness.
*Percentage increase in seizure frequency was not documented in the clinical notes.

amplitude electrographic seizures recurred on weaning of ketamine, adjacent to the resection margin. The patient subsequently returned to her home country by air ambulance. No adverse effects associated with perampanel were identified.

Efficacy of Perampanel in Other Drug-Resistant Epilepsies

The responder-rate (≥50% reduction) for our patients with other drug-resistant epilepsies after initiating perampanel was 25% (4/16 patients). None of the patients achieved complete seizure control (100% reduction). The median time on perampanel to achieve ≥50% reduction in seizures from baseline was 80 days (range: 26-326 days). One patient (case 8) had frontal lobe lesionectomy shortly after starting perampanel and was only included in the safety reporting.

Overall Efficacy of Perampanel

Nineteen patients were included in the efficacy analysis, of which three patients were diagnosed with FIRES. The overall responder-rate (≥50% reduction) after initiating perampanel was 31% (6/19 patients). Complete seizure control (100% reduction) was achieved in two patients with FIRES. The median time on perampanel to achieve ≥50% reduction in seizures from baseline was 35 days (range: 1-326 days). There was no change in seizure frequency in 42% (8/19 patients) of the patients who were initiated on perampanel.

Patients aged 11-years and younger in the study had a responder-rate of 22% (2/9 patients). Four patients in this age group did not have any improvement in seizure control, while seizure freedom was achieved in one patient.

Patients aged older than 11-years in the study had a responder-rate of 40% (4/10 patients). No positive change in seizure frequency was reported in three patients. Perampanel was discontinued in four patients because of intolerable adverse effects or no change in seizure pattern. Seizure freedom was achieved in one patient.

Safety and Tolerability of Perampanel

No adverse effects attributed to perampanel were identified in the three patients with FIRES, who were sedated and intubated during their stay in CICU.

Of 20 patients included in safety outcome reporting, adverse effects were reported in 70% (14/20 patients). Eight patients reported more than one adverse effect. Adverse effects reported include behavioural issues (9/20 patients), tiredness (4/20 patients), unsteadiness (4/20 patients), cognitive slowing (3/20 patients), somnolence (3/20 patients), and thrombocytopenia (1/20 patients).

Adverse effects were transient in 10 patients. Two patients required a down-titration in the dose which resolved their adverse effects. Two patients discontinued perampanel because of intolerable adverse effects. No other laboratory abnormalities, suicidal ideation, allergic rashes, or death associated with the use of perampanel were reported in our patient population.

Discontinuation Rate

All three patients with FIRES continued perampanel.

In other refractory epilepsy, perampanel was discontinued in eight (47%); five because of no change in seizure frequency (case 5, 6, 12, 13, 18), one because of seizure exacerbation (case 7), and two because of tiredness, unsteadiness, or dizziness (case 10, 15). The median time on perampanel before it was discontinued was 179 days (range: 94-345 days).

Concomitant Drug Treatment and Doses of Perampanel Used

The median number of concomitant AEDs was three (range: 2-6). Eleven patients were on enzyme-inducing AEDs, in combination with perampanel, of which the most common enzyme-inducing AED reported was carbamazepine (4/20 patients, 20%) and phenobarbitone (4/20 patients, 20%).

The dose of perampanel used ranged from 2 mg to 12 mg daily. The median starting dose of perampanel for our study group was 2 mg/day (range: 2-12 mg/day), or 0.05 mg/kg/day (range: 0.03-0.49 mg/kg/day). The maximum dose prescribed was 12 mg/day or 0.5 mg/kg/day.

The dosing regimen in our study differed between patients on concomitant enzyme-inducing AED and the patients not on concomitant enzyme-inducing AED. The median starting dose of perampanel in those on concomitant enzyme-inducing AED (median dose: 2 mg/day, range: 2-12 mg/day) was comparable to those not on concomitant enzyme-inducing AED (median dose: 2 mg/day, range: 2-4 mg/day). The median maximum dose of perampanel in the group not on concomitant enzyme-inducing AED was 12 mg/day (range: 8-12 mg/day), while the median maximum dose of perampanel in the group on concomitant enzyme-inducing AED was 8 mg/day (range: 4-12 mg/day). The maximum dose was based on the patient's response to perampanel.

Discussion

Perampanel has been reported to be efficacious as adjunctive therapy in the treatment of pediatric drug-resistant epilepsy. Our study focused on the use of perampanel in FIRES, and other drug-resistant epilepsies in a multi-ethnic, Asian pediatric patient group aged between 1 and 19-years.

Perampanel in FIRES

Perampanel may be considered as a therapeutic option in the management of pediatric FIRES. Treatment of FIRES remains challenging, as the seizures are refractory and prolonged, and treatment is associated with a low success rate.[8,9]

Despite the use of multiple AEDs, immunotherapy, ketogenic diet, magnesium sulphate infusion, propofol, and inhalational anaesthetic treatment response remains unpredictable.[8,9,23] The sequelae include behavioural issues, learning difficulties, movement disorder and even death.[8] AMPA receptor antagonism may have the potential to interrupt the pathogenic mechanism in refractory status epilepticus and ameliorate FIRES.

Perampanel treatment was started for three patients diagnosed with FIRES for the management of clinical seizures and electrographic seizures on electroencephalography. Two of the patients (case 2 and 3) were started on treatment doses of perampanel without any titration regimen (8 mg/day for 4-year old; 12 mg/day for 15-year old) to rapidly optimise the therapeutic effect. Seizure cessation was achieved for two patients (cases 1 and 2) within a day after the initiation of perampanel. One patient (case 3) reported worsening of electrographic seizures, likely because of the ongoing progression of FIRES, requiring the use of ketamine and right temporal lobectomy. No clinical or laboratory adverse effects associated with perampanel was identified in these three patients.

Cessation of seizures following perampanel in cases 1 and 2 was rapid, within one day of initiation and on day 32 and 19 of seizures respectively. While it is possible that the cessation of seizures was coincidental and may have been caused by the natural waning of FIRES, the abrupt manner in which the seizures ceased and the temporal relationship between perampanel intiation and seizure cessation, coupled with the lack of adverse effects, make perampanel a safe and reasonable treatment option in FIRES. Our experience with perampanel suggests that it may be of utility in patients with FIRES. To our knowledge, this is the first report describing the use of perampanel for the management of FIRES in pediatric patients.

Overall Efficacy of Perampanel in our Cohort

Perampanel shows a beneficial reduction in seizure frequency in a proportion of our patients when used as adjunctive therapy in patients with drug-resistant epilepsy. Response (≥50% reduction) was reported in 31% of our patients (6/19 patients), with two patients achieving seizure freedom.

A Taiwanese study by Lin et al. reviewed 66 patients of Chinese descent, aged between 8 to 18-years, reported a responder-rate of 34.7% and seizure-free rate of 14.3% at 12 months follow-up.[20] Our study complements this data, with our patients aged younger than 8-years reporting a similar responder-rate and seizure-free rate of 14%, which suggests similar efficacy in younger children.

Our patients aged 12-years and older reported a higher responder-rate (40%) as compared to our patients aged 11-years and younger (22%). This may be attributed to pharmacokinetics, or age-related pharmacodynamic factors, such as the expression of AMPA receptors. Perampanel undergoes CYP3A4/5 metabolism and sequential glucuronidation.[3] It is subsequently excreted in the urine and feces.[3] The metabolism and excretion model may differ between the two age groups. Pharmacokinetics studies may be required in pediatrics aged 11-years and younger to investigate the pharmacokinetic properties of perampanel.

Concomitant Drug Treatment and Doses of Perampanel Used

The median starting dose of perampanel in our study group was 0.05 mg/kg/day (range: 0.03-0.49 mg/kg/day), while the maximum dose prescribed was 12 mg/day or 0.5 mg/kg/day. The common practice in pediatric AED dosing is to optimize the dose by body weight, presuming a linear relationship between body weight and dosing regimen.[24,25] This considers the pharmacokinetics parameters in pediatrics.[24,25] The doses we utilised, taking into account the weight, were higher than that reported in the literature.[26] A mean maximal dose of 6.5 mg/day or 0.19 mg/kg/day was reported by Heyman and colleagues for their pediatric patients.[26]

Enzyme-inducing AEDs have been reported to affect the serum concentration of perampanel.[5-8] Concomitant use of enzyme-inducing AEDs with perampanel increases the CYP3A-mediated metabolism of perampanel.[8] This reduces the serum concentration of perampanel, which in turn affects the efficacy and dosing regimen.[5-8] The dosing regimen of perampanel is reportedly higher with enzyme-inducing AEDs.[5-8] This was not observed in our patient group. The median starting dose was comparable between both patient groups, while the maximum dose was reportedly higher in the group not on concomitant enzyme-inducing AEDs.

Comparison With Other Reported Studies in Pediatrics

Biró and colleagues reported a study of 58 patients with drug-resistant epilepsy, aged between 2- to 17-years.[27] At least 50% seizure reduction was achieved by 31% of patients after three months of treatment, with 8.6% of patients achieving complete seizure control. An Italian observational multicentre study consisting of 62 patients by Liso et al. aged between 6- to 18-years, reported a responder-rate of 50% and seizure-free rate of 4.8% after an average of 6.6 months follow-up.[28] One Canadian study involving 24 pediatric patients reported a responder-rate of 42% over a median treatment duration of 59 weeks.[29] However, no patients achieved seizure freedom in this series. A similar responder-rate of 42% was achieved in an Israeli study by Heyman et al. over an average of 8.1 months of follow-up involving 24 patients aged between 1- to 17-years.[26] A single centre postmarking study with 16 children reported a responder-rate of 63% after an average of 8.2 months of treatment.[30] Our responder-rate of 31% and seizure-free rate of 10% were lower than other observational studies. This could be because of the placement of perampanel initiation in our practice, as it is often used after three to five other anticonvulsants have failed, and may also be attributed to our small heterogenous patient population.

Safety of Perampanel in Our Cohort

Adverse effects were reported in 70% of our patients (14/20 patients) compared to 35% to 67% in the literature.[20,26-30] Our retention rate of 60% (12/20 patients) was comparable to other reported studies which reported ranges from 47.6% to 80.3%.[20,26-30] Adverse effects were transient in 10 patients while the adverse effects of the other two patients resolved with dose reduction of perampanel. Behavioural-related adverse effects, including irritability and aggression, were higher than reported in the literature.[20,26-30] Thrombocytopenia was noted in one patient on multiple AEDs (clobazam, levetiracetam, oxcarbazepine, zonisamide) (case 19), with the platelet count decreasing from 223 ($\times 10^9$/L) to 153 ($\times 10^9$/L) when the dose of perampanel was increased from 4 mg once daily to 6 mg once daily. The platelet counts subsequently recovered to 203 ($\times 10^9$/L) after the dose of perampanel was decreased to 4 mg once daily. Polytherapy could have contributed to the haematological derangement, and closer monitoring of blood indices is warranted when perampanel is used in combination with other AEDs associated with blood dyscrasias, such as oxcarbazepine.

The adverse effects profile of perampanel differed between patients aged 11-years and younger, and patients aged older than 11-years in our study. Perampanel appeared to be better tolerated in younger patients. No unsteadiness or cognitive slowing was reported in patients aged 11-years and younger, as compared to patients aged older than 11-years. This may be contributed by the differing developmental stages of the child, as well as various pharmacokinetics factors.[1,2,18,19,31]

Limitations

This is a retrospective and observational study. The number of patients reported in this study was small and the patient population was heterogeneous.

Significance

We report the efficacy and safety of perampanel in the management of FIRES, and other drug-resistant epilepsies in our multiethnic, Asian, pediatric patients. Our data suggested that perampanel appeared to be generally safe and may be of benefit as an adjunctive treatment in the management of FIRES and other drug-resistant epilepsies. Despite the lower responder-rate reported in our study, perampanel may be considered as a therapeutic option in certain difficult-to-treat conditions, such as FIRES. Perampanel may be initiated at a higher dose in patients with FIRES to optimise the therapeutic effect.

Conclusion

Perampanel is a safe treatment option in FIRES and may aid seizure control. It is of benefit as adjunctive therapy for pediatric drug-resistant epilepsies in multiethnic, Asian patients aged 11-years and younger, and have a good safety profile in our patients. A lower perampanel starting dose and slow titration may be helpful in minimising side effects in children aged older than 11-years.

Declaration of Conflicting Interests

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Ethics Approval

Ethical approval to report this case series was obtained from SINGHEALTH INSTITUTIONAL REVIEW BOARD (2018/3183).

Informed Consent

Written informed consent was obtained from the patient(s) and or caregivers for their anonymized information to be published in this article.

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