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# Efficacy and tolerability of perampanel in pediatric patients with Dravet syndrome

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ABSTRACT

*Purpose:* In the present study, we aimed to investigate the efficacy and tolerability of perampanel in patients with Dravet syndrome.

*Methods:* We retrospectively reviewed data regarding seizure frequency and adverse effects in 10 patients (four boys, six girls) with Dravet syndrome following treatment with perampanel. Perampanel treatment was considered effective when seizure frequency had been reduced by more than 50%.

*Results:* The mean age of patients at perampanel introduction was 11.5 ± 2.2 years. Seizure types were as follows: generalized tonic-clonic seizure (n = 8), unilateral clonic seizure (n = 6), myoclonic seizure (n = 3), atypical absence seizure (n = 3), and focal impaired awareness seizure (n = 1). The average number of concomitant anti-epileptic drugs (AEDs) was 3 ± 0.9. The mean duration of perampanel use was 11.1 ± 3.8 months. Seizure frequency was reduced by more than 50% in five patients (50%). The efficacy of perampanel for each seizure type was as follows: generalized tonic-clonic seizure: 50% (4/8), unilateral clonic seizure: 50% (3/6), myoclonic seizure: 33% (1/3), atypical absence seizure: 33% (1/3), and focal impaired awareness seizure: 100% (1/1). The effects of perampanel in each patient occurred between 3 and 6 months following the initiation of treatment. Seizure reduction was observed beginning at perampanel doses of 0.1 ± 0.07 mg/kg/day. Adverse events were observed in seven of 10 patients. Although somnolence was noted in 50% of patients, most events were mild.

*Conclusions:* The results of this retrospective observational study indicate that perampanel treatment may be promising in some patients with Dravet syndrome. Additional studies are necessary to verify the actual efficacy of perampanel for Dravet syndrome.

## 1. Introduction

Dravet syndrome is a severe epileptic encephalopathy that develops within one year of age and is characterized by frequent episodes of multiple types of seizures: generalized tonic clonic, unilateral clonic, atypical absence, focal impaired awareness, and myoclonic. Psychomotor developmental delay after seizure onset and extremely intractable seizures commonly induced by fever or vaccination are also indicative of the condition (Dravet, 2011).

Perampanel is a selective, noncompetitive antagonist of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor (Hanada et al., 2011). Numerous studies have demonstrated the efficacy and tolerability of perampanel for patients with epilepsy over the age of 12 years who experience focal onset seizures, focal to bilateral tonic-clonic seizures, and primary generalized tonic-clonic seizures (Krauss et al., 2018; Steinhoff et al., 2013; Villanueva et al., 2018; French et al., 2015). Moreover, recent studies have reported that perampanel is effective for the treatment of myoclonic and absence seizures in patients with genetic generalized epilepsy (Villanueva et al., 2018; Gil-López et al., 2018), intractable myoclonic epilepsy in patients without genetic generalized epilepsy, and in those with specific epilepsy syndromes including Lennox–Gastaut syndrome

*Abbreviations:* AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AED, anti-epileptic drug; *PCDH19*, protocadherin-19; GEFS+, genetic epilepsy with febrile seizures plus; EEG, electroencephalogram

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(Auvin et al., 2017) and some kinds of progressive myoclonus epilepsy (Goldsmith and Minassian, 2016; Crespel et al., 2017; Shiraishi et al., 2017). Given its novelty as an anti-epileptic drug (AED) with antagonistic actions at AMPA receptors, perampanel may target a relatively broad range of seizure types and epilepsy syndromes (Potschka and Trinka, 2018).

A few recent studies have investigated the use of perampanel in patients with Dravet syndrome (Lin et al., 2018; Swiderska et al., 2017; Biró et al., 2015; De Liso et al., 2016). Although such studies have yielded promising results regarding the efficacy of perampanel for Dravet syndrome, the number of reported cases remains limited. Therefore, in the present study, we examined responses and tolerability to perampanel treatment in 10 patients with Dravet syndrome.

## 2. Methods

We retrospectively reviewed the medical records of all pediatric patients (under 18 years old) diagnosed with Dravet syndrome at NHO Shizuoka Institute of Epilepsy and Neurological Disorders between July 2016 and January 2019. Diagnoses of Dravet syndrome were made based on the following criteria: (a) seizure onset within the first year of age; (b) presence of clonic or tonic-clonic seizures (either generalized or unilateral) and myoclonic, absence, or focal seizures; (c) history of seizures induced by fever related to infection, vaccination, or hot water; (d) apparent developmental delay within the second year of life, followed by cognitive and motor impairments; (e) exclusion of the following diagnoses: Lennox–Gastaut syndrome, protocadherin-19 (*PCDH19*)-related epilepsy, Doose syndrome, genetic epilepsy with febrile seizures plus (GEFS + ), complex febrile seizures, and other forms of focal epilepsy.

We evaluated seizure frequency before and after initiation of perampanel treatment, as well as adverse effects of treatment. Seizure frequency was calculated every 3 months after the introduction of perampanel, and final evaluations were performed at the final observation. Seizure reduction was calculated in reference to that observed 3 months prior to the introduction of perampanel. Perampanel treatment was considered effective when seizure frequency had been reduced by more than 50%. We continued observation until the dose of concomitant AEDs had increased or until patients started taking another AED. Adverse events were determined via physical examination, laboratory testing, or based on reports from patients and family members.

This study was approved by the Ethics Committee of NHO Shizuoka Institute of Epilepsy and Neurological Disorders in Shizuoka, Japan. Informed consent was obtained from the parents of all patients. Informed consent was also obtained for off-label use of perampanel when the patient was under 12 years old.

## 3. Results

### 3.1. Clinical background

A total of 10 patients (four boys and six girls) were included in the present study. Table 1 shows the clinical characteristics of each patient. The mean age of patients at perampanel introduction was 11.5 ± 2.2 years old. Four patients had only one type of seizure, whereas the remaining six patients had two to four types of seizures. The average number of concomitant AEDs was 3 ± 0.9. The most commonly used concomitant AED was sodium valproate (n = 10), followed by topiramate (n = 8). Data collection ceased for Patient 7 at 7 months after perampanel introduction, when she started taking nitrazepam. All patients had autism spectrum disorder and moderate to severe psychomotor developmental delay. All patients except for Patient 3 underwent genetic analysis, which revealed a *de novo* pathogenic variant in *SCN1A*.

### 3.2. Efficacy of perampanel

Table 2 shows responses to perampanel in each patient. The mean duration of perampanel use was 11.1 ± 3.8 months. The mean maximum dose of perampanel was 0.14 ± 0.1 mg/kg/day. The overall seizure rate (i.e., seizure rate for all seizure types) was reduced by more than 50% in five of 10 patients (50%). The efficacy of perampanel for each seizure type was as follows: generalized tonic-clonic seizure: 50% (4/8), unilateral clonic seizure: 50% (3/6), myoclonic seizure: 33% (1/3), atypical absence seizure: 33% (1/3), and focal impaired awareness seizure: 100% (1/1).

Even in responsive patients, we observed no significant differences in interictal electroencephalogram (EEG) findings between the pre-treatment and post-treatment periods. The effects of perampanel treatment became evident at 3 months (Patients 1, 2, 3, 5) or 6 months (Patient 4) following initiation. Effective seizure reduction was observed beginning at perampanel doses of 0.1 ± 0.07 mg/kg/day.

### 3.3. Adverse effects of perampanel

Adverse events were observed in seven patients, and somnolence (50%) was the most frequent. Although most adverse events were mild and did not substantially influence patients' daily lives, severe irritability and exacerbation of autistic behavior were observed in Patient 3. In this case, the dose of perampanel was reduced due to his mother's concerns regarding the severity of his behavior, and the patient was treated with risperidone until his behavior had improved.

## 4. Discussion

In the present study, we aimed to investigate the efficacy and tolerability of perampanel in patients with Dravet syndrome. In previous studies (Lin et al., 2018; Swiderska et al., 2017; Biró et al., 2015; De Liso et al., 2016), perampanel reduced seizure frequency by more than 50% in six of nine patients (66.7%) with Dravet syndrome. Moreover, three of these patients (33.3%) remained seizure free. In our study, five of 10 patients with Dravet syndrome (50%) treated with perampanel exhibited effective seizure reduction (> 50%), although none became seizure free. If we exclude Patient 6 and 10 because perampanel doses administered to them (0.06 and 0.07 mg/kg/day, respectively) were lower than the mean effective dose (0.1 ± 0.07 mg/kg/day), the efficacy ratioin our study was 62.5% (5 out of 8), which is almost the same as that in previous studies.

Altogether, the accumulated evidence suggests that perampanel can effectively treat several types of seizure in patients with Dravet syndrome, including generalized tonic-clonic seizures and unilateral clonic seizures, and possibly myoclonic seizures, atypical absence seizures, and focal impaired awareness seizures.

Furthermore, reductions in one seizure type may lead to reductions in other types of seizures. Based on this observation, we speculate that perampanel may act in an "all-or-nothing" fashion. That is, if perampanel is effective in treating one seizure type, it is likely to be effective in treating all seizure types. Thus, the efficacy of perampanel treatment may depend not on seizure type, but on the status of individual patients.

Although severe irritability and exacerbation of autistic behavior were observed in Patient 3, almost all adverse effects were mild in other patients and did not require discontinuation of perampanel treatment. These findings are consistent with those of another recent study, which also reported severe adverse effects of perampanel among patients with Dravet syndrome (Lin et al., 2018). Average age in the present study was 11.5 ± 2.2 years (range: 7–15 years), and average patient age in the study by Lin et al. (2018) was 14.4 ± 2.3 years (range: 12–17 years). Further studies are required to determine the efficacy and tolerability of perampanel in younger children or toddlers with Dravet syndrome, as they often experience more frequent seizures than

**Table 1**
Clinical characteristics of each patient.

| Patient/Sex | Age at initiation of PER | Seizure types at PER introduction | Seizure frequency before introduction of PER | Concomitant drugs | Interictal EEG findings before introduction of PER | Developmental disorder/ Psychomotor development | Pathogenic genetic variants |
|---|---|---|---|---|---|---|---|
| Pt 1/G | 11y4m | GTCS<br>Unilateral clonic seizure | Weekly<br>Daily | VPA, STP, LEV | Diffuse SpW | ASD/<br>DQ 28 (K scale test at 4y7m) | *SCN1A* c.4476 G > C (missense mutation) |
| Pt 2/B | 13y10m | GTCS<br>Unilateral clonic seizure | Weekly<br>Weekly | VPA, TPM, CLB, STP | Diffuse SpW, diffuse polyspike | ASD/<br>IQ 20 (Tanaka-Binet test at 11y1m) | *SCN1A* c.5029C > T (missense mutation) |
| Pt 3/B | 13y4m | GTCS<br>FIAS<br>Myoclonic seizure<br>Atypical absence seizure | Monthly<br>Weekly<br>Daily<br>Daily | VPA, STP, TPM, CLB | Diffuse SpW | ASD/<br>DQ 34 (K scale test at 4y2m) | *SCN1A* c.1624C > T (nonsense mutation) |
| Pt 4 /B | 9y9m | GTCS | Weekly | VPA, TPM, CLB | Diffuse SpW | ASD/<br>DQ 51 (K scale test at 6y1m) | *SCN1A* c.1027 G > T (missense mutation) |
| Pt 5/G | 15y1m | GTCS | Weekly | VPA, TPM, DZP | Diffuse SpW, multifocal spikes | ASD/<br>Severely delayed | *SCN1A* c.342 A > V (missense mutation) |
| Pt 6/G | 10y2m | GTCS | Weekly | VPA, STP, TPM | Multifocal SpW | ASD/<br>DQ 23 (K scale test at 4y1m) | *SCN1A* c.2869 T > C (missense mutation) |
| Pt 7/G | 11y4m | GTCS<br>Unilateral clonic seizure | Weekly | VPA, ZNS, TPM, LEV | Multifocal SpW | ASD/<br>DQ 45 (K scale test at 5y2m) | *SCN1A* c.2369 A del |
| Pt 8/G | 7y7m | GTCS<br>FIAS<br>Myoclonic seizure<br>Atypical absence seizure | Monthly<br>Weekly<br>Daily<br>Daily | VPA | Diffuse SpW | ASD/<br>DQ 37 (K scale test, 5y3m) | *SCN1A* c.5734C > T (missense mutation) |
| Pt 9/G | 10y2m | GTCS<br>FIAS<br>Myoclonic seizure<br>Atypical absence seizure | Monthly<br>Monthly<br>Daily<br>Daily | VPA, KBr, TPM | Diffuse SpW, multi focal spikes | ASD/<br>DQ 33 (K scale test, 5y0m) | *SCN1A* c.4201 G > A (missense mutation) |
| Pt 10/B | 12y2m | Unilateral clonic seizure | Daily | VPA, TPM | Multifocal SpW, multi focal sharp | ASD/<br>DQ 33 (K scale test, 6y0m) | *SCN1A* c.1178 G > A (missense mutation) |

Pt: patient, B: boy, G: girl.
d: days, w: weeks, m: months, y: years.
GTCS : generalized tonic-clonic seizure, FIAS: focal impaired awareness seizure.
PER: perampanel, VPA: sodium valproate, KBr: potassium bromide, TPM: topiramate, ZNS: zonisamide, STP: stiripentol, LEV: levetiracetam, CLB: clobazam, DZP: diazepam.
EEG: electroencephalogram, SpW: spikes and waves.
ASD: autism spectrum disorder.
DQ: developmental quotient, IQ: intellectual quotient.
K scale test: Kyoto Scale of Psychological Development test.
*SCN1A*: sodium voltage-gated channel alpha subunit 1.

**Table 2**
Response to perampanel (Efficacy and adverse effects).

| Seizure reduction rate 3 months after PER introduction/ PER dose (mg/kg/day) | Seizure reduction rate 6 months after PER introduction/ PER dose (mg/kg/day) | Seizure reduction rate 9 months after PER introduction/ PER dose (mg/kg/day) | Seizure reduction rate at final observation/ PER dose (mg/kg/day) | Interictal EEG findings on PER | Adverse effects of PER |
|---|---|---|---|---|---|
| > 75%/0.08 | > 75%/0.08 | > 75%/0.08 | > 75%/0.08 | Unchanged at 2 months | Mild somnolence, irritability |
| > 75%/0.08 | > 75%/0.08 | > 75%/0.08 | > 75%/0.08 | | |
| > 50%/0.06 | > 50%/0.06 | > 50%/0.06 | > 50%/0.06 | Not performed | Transient somnolence |
| > 50%/0.06 | > 50%/0.06 | > 50%/0.06 | > 50%/0.06 | | |
| > 75%/0.08 | > 75%/0.08 | > 75%/0.11 | > 50%/0.11 | Diffuse SpW, reduced pattern induced epileptic discharge at 2 months | Mild somnolence, severe irritability, |
| > 75%/0.08 | > 75%/0.08 | > 75%/0.11 | > 50%/0.11 | | |
| > 75%/0.08 | > 75%/0.08 | > 75%/0.11 | > 50%/0.11 | | exacerbation of autistic behavior |
| > 75%/0.08 | > 75%/0.08 | > 75%/0.11 | > 50%/0.11 | | |
| Unchanged /0.08 | > 50% /0.23 | > 75% /0.31 | > 75% /0.38 | Not performed | Transient somnolence, mild lethargy |
| > 50% /0.09 | > 50% /0.09 | — | — | Not performed | Mild lethargy |
| Unchanged /0.03 | Unchanged /0.06 | Unchanged /0.06 | — | Not performed | Transient/slight irritability |
| Unchanged /0.03 | Unchanged /0.06 | Unchanged /0.06 | — | | |
| Unchanged /0.03 | Unchanged /0.12 | — | Unchanged /0.12 | Not performed | — |
| Unchanged /0.03 | Unchanged /0.12 | — | Unchanged /0.12 | | |
| Unchanged /0.16 | Unchanged /0.18 | Unchanged /0.22 | — | Unchanged at 3 months | Mild somnolence |
| Unchanged /0.16 | Unchanged /0.18 | Unchanged /0.22 | — | | |
| Unchanged /0.16 | Unchanged /0.18 | Unchanged /0.22 | — | | |
| Unchanged /0.16 | Unchanged /0.18 | Unchanged /0.22 | — | | |
| Unchanged /0.19 | Unchanged /0.19 | — | — | Unchanged at 2 months | — |
| Unchanged /0.19 | Unchanged /0.19 | — | — | | |
| Unchanged /0.19 | Unchanged /0.19 | — | — | | |
| Unchanged /0.19 | Unchanged /0.19 | — | — | | |
| Unchanged /0.07 | Unchanged /0.06 | Unchanged /0.06 | Unchanged /0.03 | Unchanged at 13 months | Moderate irritability |

Pt: patient, B: boy, G: girl.
PER: perampanel.
GTCS: generalized tonic-clonic seizure, FIAS: focal impaired awareness seizure.
(-): not yet observed.
EEG: electroencephalogram, SpW: spike and waves.

adolescents.

Our study is subject to several limitations, including its retrospective observational design and small number of cases. We cannot completely discern whether seizure reductions observed in each patient were the product of perampanel administration or the natural clinical course of Dravet syndrome. The reliability of data on seizure frequency may also detract from our findings; almost all the information concerning seizure frequency was obtained from the parents of each patient. Additionally, the efficacy of perampanel in infants and toddlers with Dravet syndrome remains unknown, as our assessment only considered patients in early adolescence. Furthermore, the duration of observation and dose of perampanel may have limited our evaluation in some patients. Nonetheless, our findings suggest that perampanel is a promising treatment for patients with Dravet syndrome. Future research should aim to more fully elucidate the efficacy of perampanel in this patient population.

## Declarations of interest

None.

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