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ORIGINAL WORK

Perampanel Treatment for Refractory Status Epilepticus in a Neurological Intensive Care Unit

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Abstract

Background/Objective: Perampanel is a novel anti-epileptic drug (AED) which acts as a non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist to reduce glutamate-mediated postsynaptic excitation. Previous animal studies and a few case reports/series have suggested that it may be effective to treat refractory status epilepticus (RSE).

Methods: We retrospectively reviewed 67 consecutive patients with RSE, of whom 22 received perampanel. The clinical features, epidemiology-based mortality score in status epilepticus, status epilepticus severity score, seizure control, functional outcome, RSE etiology, and electroencephalogram findings were collected. Responder to perampanel was defined as seizure resolution within 4 days of therapy with perampanel being the last AED used plus no recurrence during hospitalization.

Results: Eight of the 22 (36.4%) RSE patients fulfilled the definition of responder to perampanel. An additional 1 patient responded to perampanel after 4 days of treatment. In total, perampanel was the last AED in 9 (40.1%) patients. Among the 8 responders to perampanel, 5 had convulsive SE, 1 had non-convulsive SE, and 2 had focal motor SE. The responders accounted for both of the patients with focal motor SE (100%), 5 (33.3%) of the 15 patients with convulsive SE, and 1 (20%) of the 5 patients with non-convulsive SE. The ictal and inter-ictal activities also decreased after perampanel therapy, and three patients (13.6%) had preferable outcomes at last follow-up.

Conclusions: Perampanel may be an effective add-on treatment for RSE even in patients who failed multiple AEDs. Our study suggests that perampanel may be more effective for focal motor SE and convulsive SE than non-convulsive SE. As most previous studies have focused on non-convulsive SE, further studies are warranted to clarify the effectiveness of perampanel for different subtypes of SE.

Keywords: Status epilepticus, Refractory status epilepticus, Perampanel, AMPA, Intensive care unit, Prognosis

Introduction

Status epilepticus (SE) is a prolonged, self-sustaining seizure associated with high morbidity and mortality [1, 2]. The short-term mortality rate of SE has been reported to be up to 19–22% and may be as high as 30–40% in elderly patients [3]. The severity of SE is also closely related to the outcomes, and the 1-year mortality of refractory SE (RSE) has been reported to range from 16 to 31.75% and up to 35–43% for super-refractory SE (SRSE) [4–6]. It is therefore important to develop more effective therapies to improve the overall outcomes of SE patients.

Several mechanisms have been proposed to contribute to the development of RSE in animal models, including internalization of inhibitory γ-aminobutyric acid (GABA) receptors, increased excitatory N-methyl-D-aspartate receptors, and increased excitatory alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors [7–10]. Perampanel is a novel anti-epileptic drug (AED) which acts as a non-competitive AMPA receptor antagonist to reduce glutamate-mediated

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postsynaptic excitation, and hence, it is a potential effective AED for RSE. In benzodiazepine-resistant animal SE models, perampanel has been shown to successfully terminate SE when GABAergic inhibition decreases and the ratio of AMPA receptor subunits changes [8, 11].

The effect of perampanel in the treatment of SE in humans remains to be determined, as only a few case reports and small case series have been published [12–16]. Perampanel has been reported to be effective in 16.2–30% of patients with RSE [13–15], and it is typically given at a relatively delayed disease stage (as the 4th–6th drug given at an average 36–138 h after SE onset) [12–16]. The initial dose has been reported to range from 4 to 6 mg/day. To date, a total of 41 patients have been reported, most of whom have had non-convulsive SE (29/41, 70.7%) or focal motor SE (10/41, 24.4%), and only 2 (4.9%) with convulsive SE. The effectiveness of perampanel for different subtypes of SE, and especially convulsive SE, remains to be determined. Therefore, the aim of this study was to report a consecutive cohort of RSE patients treated with perampanel at our neurological intensive care unit (NICU).

Methods

Study Design

From May 2016 to December 2017, 141 adult SE patients were admitted to the NICU at Kaohsiung Chang Gung Memorial Hospital. Among them, 67 patients fulfilled the criteria of RSE. Of these 67 patients, 22 (32.8%) received perampanel treatment as an add-on AED for seizure control. All treatments were given by the attending physicians considering the patients' best interests. The definition and classification of types of SE were based on the report of the International League Against Epilepsy (ILAE) Task Force on Classification of Status Epilepticus [2]. For non-convulsive SE, the modified Salzburg Consensus Criteria were used [17]. The classification was determined according to patient's presentation upon admission or at the onset of SE during hospitalization. SE persisting despite the administration of at least two appropriately selected and dosed parenteral medications including a benzodiazepine was defined as RSE. SRSE was defined as SE persisting for at least 24 h after the onset of anesthesia, either without interruption despite appropriate treatment with anesthesia, recurring while on appropriate anesthetic treatment, or recurring after withdrawal of anesthesia and requiring the reintroduction of anesthesia [18, 19].

We retrospectively collected data on the etiology and classification of SE, AEDs used, baseline medical conditions, durations of NICU stay and hospital stay, electroencephalogram (EEG) examinations, laboratory studies, adverse effects of AEDs, and outcomes. For the etiology, we distinguished between acute symptomatic, remote, and progressive etiologies as suggested by the ILAE Task Force on Classification of Status Epilepticus [2]. Status epilepticus severity score (STESS) and epidemiology-based mortality score in SE (EMSE) were also calculated. The STESS calculated the risk of death of SE based on four parameters: seizure type, history of seizures, age, and level of consciousness [20]. The EMSE adopted a more delicate scoring system using different categories: etiology, age, comorbidity, and EEG finding [21]. The study was approved by the local Institutional Review Board of Kaohsiung Chang Gung Memorial Hospital.

Clinical Assessment

All AED adjustments were recorded. Treatment responses were assessed based on clinical seizure resolution at the following time points: day 0 (before perampanel), day 1 (6–24 h), day 2 (24–48 h), and days 3–4 (48–96 h) after the initiation of perampanel treatment. Responder to perampanel was defined as being clinically and electrographically seizure free within 4 days with perampanel being the last AED used, plus no relapse during hospitalization. A partial response to perampanel was defined when perampanel did not achieve seizure freedom within 4 days, perampanel was not the last AED used, or when seizures recurred during hospitalization.

To quantify the effect of perampanel on ictal and inter-ictal activities, we assessed the electrographic outcomes by reviewing EEG recordings at day 0 (before perampanel), day 1 (6–24 h), day 2 (24–48 h), and days 3–4 (48–96 h) after the initiation of perampanel treatment. Both continuous EEG and routine EEG were used to monitor treatment response in our NICU based on the availability of EEG facility. The duration of electrographic ictal events was calculated on routine 30-min EEG or on 2-h epochs on continuous EEG monitoring and was expressed as the percentage of the total recording. The frequency of inter-ictal discharges (IEDs) was calculated as the number of IEDs divided by the total duration and was expressed as numbers per minute. Glasgow Outcome Scale (GOS) [22] and modified Rankin Scale (mRS) were used as outcome measures. GOS 2 category 2 was described as patients who are unable to interact with the environment, which equals to the current concept of persisted vegetative state and minimally consciousness state (MCS). The follow-up period was determined from discharge to last available clinic visit.

Statistical Analysis

All statistical analyses were performed using SPSS version 24.0 for Mac (SPSS Inc., Chicago, IL, USA). Descriptive summaries were reported as the mean ± standard deviation for continuous variables and as number

(percentage) for categorical variables. For nonparametric variables, median with interquartile range and Mann–Whitney *U* test were used. A p value <0.05 was considered to indicate statistical significance.

Results

Demographic Data

Of the 67 RSE patients (Table 1), 44 (65.7%) were male and 23 (34.3%) were female. The mean age was 60.4 years (range 26–89 years). With regard to the SE type, 45 (67.1%) patients had generalized convulsive SE, 12 (17.9%) had non-convulsive SE with coma, 6 (8.9%) had non-convulsive SE without coma, and 5 (7.4%) had focal motor SE. In terms of etiology, 23 (34.3%) patients had cerebrovascular disorders, 12 (17.9%) were post-traumatic, 10 (14.9%) had an autoimmune etiology, 10 (14.9%) were due to sepsis, 4 (5.9%) were due to CNS infections, 6 (27.3%) were due to alcohol or sedative medication withdrawal, 3 (4.4%) had brain tumors, 3 (4.4%) had dural arteriovenous fistula, 2 (2.9%) had hypoxic encephalopathy, 2 (2.9%) had electrolyte imbalance, 1 (1.5%) was induced by antibiotics, and 8 (11.9%) had an unknown etiology. Twenty-two patients (32.8%) had pre-existing epilepsy, and 24 (35.8%) fulfilled the criteria for SRSE. The baseline median scores of GOS, mRS, STESS, and EMSE were 4.5, 1.5, 4 and 67, respectively. In terms of EEG patterns, 38 (57%) patients had lateralized periodic discharges (PDs), 13 (19%) had bilateral independent lateralized PDs, 2 (2.9%) had generalized PDs, 18 (26.8%) had rhythmic delta activity, and 5 (7.4%) had spontaneous burst suppression. Of all 67 RSE patients who failed first AED, 24 (35.8%) required second AED for seizure control, 19 (28.4%) responded to third AED, and 9 (13.4%) was controlled by fourth AED.

Perampanel Treatment

Of the 67 RSE patients, 22 received perampanel (Fig. 1). Perampanel was given as a median 4th AED (range 2–7, IQR 4–5), at a median 5.45 days after seizure onset (range 0.2–12.9 days, IQR 2.54–10.55 days), with a median initial dose of 2 mg (range 2–8 mg, IQR 2–3.5 mg), and with a median maximum dose of 4 mg (range 2–12 mg, IQR 4–8 mg). Perampanel was titrated up to maximum dose in a median 2 days (range 1–4 days, IQR 1–3 days). Four patients died during treatment, all of whom died during anesthesia due to sepsis. No significant side effects of perampanel treatment were observed, and no elevation in liver enzymes was recorded.

There were no significant differences in sex, age, preexisting epilepsy, baseline GOS, discharge GOS, baseline mRS, discharge mRS, mortality, and STESS between the perampanel and non-perampanel groups (Table 2). The perampanel group was more severe than the non-perampanel group as they had a higher EMSE (median 92 vs. 61, $p<0.001$), used more AEDs (median 5 vs. 3, $p<0.001$), and had a higher frequency of SRSE (59% vs. 24%, $p=0.002$).

Table 1 Demographic and clinical data of the patients with RSE in the NICU

Characteristics of the patients		
Mean age (years, mean ± SD)	60.4	±17.6
Male gender (*N*, %)	44	(52)
Preexisting epilepsy (*N*, %)	22	(32)
Baseline mRS (median, IQR)	2	(0–5)
Baseline GOS (median, IQR)	4	(2–5)
STESS (median, IQR)	3.6	(2–5)
EMSE (mean ± SD)	72.1	±32.5
No. AEDs used (median, IQR)	4	(2.5–5)
Etiology type		
Acute (*N*, %)	44	(66)
Progressive (*N*, %)	6	(9)
Remote (*N*, %)	31	(46)
Unknown (*N*, %)	8	(12)
Etiology		
Cerebrovascular (*N*, %)	24	(36)
Posttraumatic (*N*, %)	14	(21)
Autoimmune (*N*, %)	10	(15)
CNS infection (*N*, %)	4	(6)
CNS tumor (*N*, %)	2	(3)
Other (*N*, %)	13	(19)
SE type[§]		
Generalized (*N*, %)	45	(67)
Focal motoric (*N*, %)	5	(7)
NCSE without coma (*N*, %)	6	(9)
NCSE with coma (*N*, %)	12	(18)
EEG patterns[§]		
LPD (*N*, %)	38	(57)
BiLPD (*N*, %)	13	(19)
GPD (*N*, %)	2	(3)
Rhythmic delta activity (*N*, %)	18	(27)
Spontaneous burst suppression (*N*, %)	5	(7)
RSE type		
SRSE (*N*, %)	24	(36)

AED anti-epileptic drug, *BiLPD* bilateral independent lateralized periodic discharge, *CNS* central nervous system, *EEG* electroencephalography, *EMSE* epidemiology-based mortality score in status epilepticus (etiology, age, comorbidity, EEG), *GOS* Glasgow Outcome Scale, *GPD* generalized periodic discharge, *LPD* lateralized periodic discharge, *N* number, *NCSE* non-convulsive status epilepticus, *NICU* neurological intensive care unit, *PER* perampanel, *RSE* refractory status epilepticus, *SE* status epilepticus, *SRSE* super-refractory status epilepticus, *STESS* status epilepticus severity score

[§] The SE type and EEG pattern were determined on admission or at the onset of SE during hospitalization

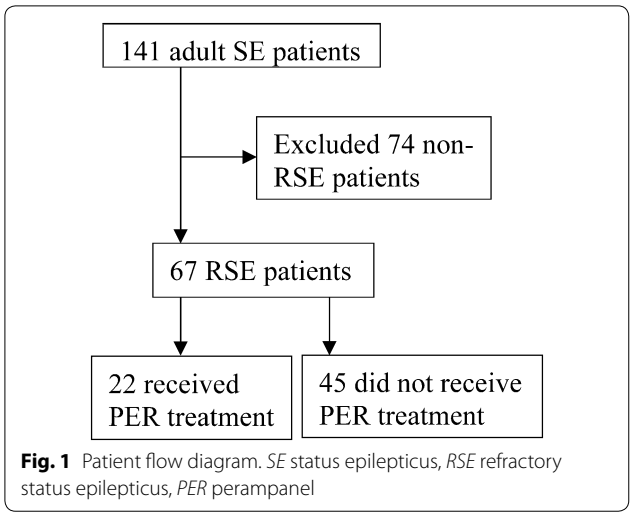

Fig. 1 Patient flow diagram. *SE* status epilepticus, *RSE* refractory status epilepticus, *PER* perampanel

Seizure Outcomes

Among the 22 RSE patients who received perampanel treatment, 16 (72.7%) were free from clinical and electrographic seizures within 4 days. Among these 16 patients, 9 initially responded to perampanel and used perampanel as the last AED to achieve SE cessation. This included 1 patient who had 1 recurrent seizure weeks after he was transferred to a ward. Therefore, only the remaining 8 (36.4%) patients were considered to be responders to perampanel. In another patient, perampanel was the last AED but he achieved seizure cessation on day 5. In addition, another 7 patients had a partial response to perampanel treatment at day 4 but required additional treatment for seizure control. Five patients (22.7%) continued to have uncontrolled seizures after perampanel therapy and other SE treatment, four of whom died during anesthesia due to sepsis.

Among the 22 RSE patients, 14 received anesthesia before PRE therapy. Five (5/14, 35.7%) were responder, while 3 (37.5%) of the 8 patients who did not receive anesthesia were responder ($p=1$).

SE Subtypes and Response to Perampanel

Among the 8 perampanel responders, 5 had convulsive SE, 1 had non-convulsive SE, and 2 had focal motor SE. This accounted for 5 of the 15 (33.3%) convulsive SE patients who received perampanel, 1 of the 5 (20%) non-convulsive SE patients, and both (100%) of the focal motor SE patients. The patient who responded to perampanel at day 5 also had convulsive SE. The other 8 patients with a partial response to perampanel all had convulsive SE. Four of the 5 non-responders had non-convulsive SE and 1 had convulsive SE. Three of the 4 non-convulsive SE patients and 1 of the convulsive SE patients died during admission.

Table 2 Clinical data of the PER and non-PER groups

	PER		Non-PER		*p* value
	N = 22		*N* = 45		
STESS (median, IQR)	3.5	(2–4)	4	(2–5)	0.264
EMSE (median, IQR)	92	(67.75–116)	61	(45–74)	**<0.001**
No. of AEDs used (median, IQR)	5	(4–5)	3	(2–3)	**<0.001**
Etiology					
Cerebrovascular (*N*, %)	8	36%	16	36%	0.764
Posttraumatic (*N*, %)	3	14%	11	24%	0.527
Autoimmune (*N*, %)	3	14%	7	16%	0.837
Meningitis (*N*, %)	2	9%	2	4%	0.454
CNS tumor (*N*, %)	1	5%	1	2%	0.205
Other (*N*, %)	5	23%	8	18%	0.431
SE type					
Generalized (*N*, %)	15	(68)	30	(67)	0.724
Focal motoric (*N*, %)	2	(9)	3	(7)	0.765
NCSE without coma (*N*, %)	1	(5)	5	(11)	0.968
NCSE with coma (*N*, %)	4	(18)	8	(18)	0.380
RSE type					
SRSE (*N*, %)	13	(59)	11	(24)	**0.002**
Discharge GOS (median, IQR)	2	(2–2)	2	(2–4)	0.058
Discharge mRS (median, IQR)	5	(5–5)	5	(2–5)	0.052

Bold values are statistically significant ($p < 0.05$)

AED anti-epileptic drug, *CNS* central nervous system, *EMSE* epidemiology-based mortality score in status epilepticus (etiology, age, comorbidity, EEG), *GOS* Glasgow Outcome Scale, *mRS* modified Rankin Scale, *N* number, *NCSE* non-convulsive status epilepticus, *No.* number, *PER* perampanel, *RSE* refractory status epilepticus, *SE* status epilepticus, *SRSE* super-refractory status epilepticus, *STESS* status epilepticus severity score

The Effect of Perampanel on Ictal and Inter-Ictal Activities

The average changes in ictal time percentage and the number of IEDs after perampanel therapy are shown in Fig. 2. Both the average IED frequency and average ictal time percentage decreased gradually with time after the initiation of perampanel therapy.

Functional Outcomes on Discharge and Long-Term Outcomes

Upon discharge, most (15/22, 68.1%) of the patients were in GOS score 2 (all in MCS). Although 2 of the 15 patients had some degree of clinical improvement after discharge, they both had severe disability (GOS score 3) at the last follow-up. Only 3 patients (13.6%) were in a non-vegetative state (GOS score > 2), 2 (9.1%) of whom had a good recovery (GOS score 5) after rehabilitation. The other patient had moderate disability (GOS score 4) at the last follow-up due to critical illness polyneuropathy. The 2 patients who had a good recovery both presented with convulsive SE on admission, and 1 evolved into focal motor SE after initiating perampanel treatment.

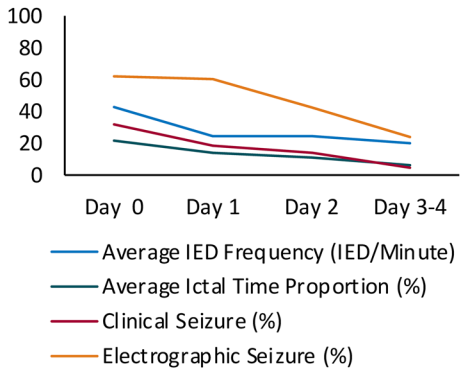

Fig. 2 Clinical and electrographic evolution. *IED* inter-ictal discharge, *PER* perampanel, *Day 0* before PER use, *Day 1* < 24 h, *Day 2* 24–48 h, *Days 3–4* 48–96 h, *EEG* electroencephalography

After discharge, 4 patients (18.2%) had recurrent seizures, 3 of whom required admission for further management. None developed recurrent SE. With regard to outcome prediction, EMSE > 40 was significantly associated with poor mRS and GOS scores ($p = 0.017$ and $p = 0.039$, respectively), while STESS > 3 was not significantly associated with either outcome measure.

Discussion

In this study, we evaluated the therapeutic effect of perampanel in the treatment of patients with RSE who failed multiple AEDs. Overall, perampanel successfully resolved RSE in more than a third of the patients within 4 days. A partial response was also observed in about 40% of the patients, and the ictal and inter-ictal activities also decreased with time after perampanel treatment. We found that different SE subtypes responded differently to perampanel, with focal motor SE and convulsive SE appearing to be more responsive to perampanel than non-convulsive SE. Even though most patients still had poor functional outcomes, 2 patients with convulsive SE who responded to perampanel had favorable outcomes.

The largest retrospective study to date investigated 30 patients treated with perampanel and reported that 17% of their cases responded to perampanel [15]. Our patients appeared to have a better response to perampanel treatment (8/22, 36.4%) compared to previous studies, which ranged from 17 to 30% [13–15]. This may be because we included more patients with focal motor SE and convulsive SE, who accounted for 74% of our cohort. In most previous studies, the SE patients treated with perampanel have had non-convulsive SE [14, 15, 23], and only 2 studies have reported 2 convulsive SE patients treated with perampanel, 1 of whom responded to treatment [15, 16]. In the current study, most of our responders (7/8, 87.5%) had focal motor SE and convulsive SE. The higher response rate in our study is likely due to the higher proportion of patients with focal motor SE and convulsive SE, which was also reflected in the subtype analysis where the patients with focal motor SE and convulsive SE responded better than those with non-convulsive SE.

In this study, the RSE patients who received perampanel had a higher frequency of SRSE, used more AEDs, and had a higher EMSE than those who did not receive perampanel. However, due to the retrospective nature of the study, we were unable to determine why the perampanel treatment group had more severe SE. It is possible that the patients with more severe SE were more likely to receive novel treatments, such as perampanel.

We also found that quantitative ictal and inter-ictal activities gradually decreased with time after the initiation of perampanel therapy. The decline in ictal and inter-ictal activities was not dramatic, which may have been due to the relatively low loading dose and long half-life of perampanel. A recent study showed that a higher loading dose of perampanel (median initial dose of 24 mg, range from 16 to 32 mg) tended to result in a shorter duration of responsiveness compared to a standard dose, although the difference did not reach statistical significant due to the small number of cases [15]. Our findings suggest that in patients with focal motor SE and convulsive SE, a lower loading dose of perampanel may be effective at least in some patients without causing severe adverse effects. It is also possible that the earlier use of perampanel may require a lower dose and result in quicker seizure control. Further studies are required to clarify the optimal loading dose and safety profiles of perampanel in patients with RSE.

Despite the good response to perampanel, the functional outcomes of our patients remained dismal, and only 2 (9.1%) had a good recovery with a GOS score of 5, which is similar to the previous largest retrospective study on perampanel [15]. This probably reflects the severity of RSE patients regardless of perampanel therapy. The major determinant of SE outcomes is the underlying etiology [24], which is not altered by perampanel treatment. Nevertheless, the 2 patients with good recovery were both responders to perampanel.

Our study is limited by the retrospective nature, and the use and dosing of perampanel were at the discretion of the treating physician, which may under- or overestimate the treatment response to perampanel due to the selection of patients who received perampanel. The average dose of perampanel in our study is less than the dose used in previous studies [12–16], which may lead to suboptimal treatment response. Moreover, some EEG recordings may not have been available at all sampling time points, which may affect the accuracy timing of SE resolution.

Conclusions

As AMPA receptor modification plays an important role in seizure perpetuation [8, 25], our preliminary findings suggest that perampanel may be an effective treatment for RSE and SRSE patients. Previous studies have mostly focused on the use of perampanel for non-convulsive SE, whereas the current study suggests that it may be more effective in patients with focal motor SE and convulsive SE. Although differences in ethnicity and patient subtypes may limit direct comparisons with previous studies, the trend of better SE control in the patients with focal motor SE and convulsive SE rather than in those with non-convulsive SE is still interesting. Further studies are therefore warranted to clarify the potential of perampanel in the treatment of SE, especially earlier use in the SE protocol, the optimal loading dose, and the effect on different SE subtypes.

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Author's Contribution
CJH, CHL, YTL, FYS, CWH, WCT, and MHT contributed to the acquisition and interpretation of the data and revising the manuscript for intellectual content. CJH and MHT contributed to the design and conceptualization of the study; analysis and interpretation of the data; drafting, revising, and final approval of the manuscript for intellectual content. This manuscript has not been published elsewhere and is not under consideration by another journal.

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Conflict of interest
The conflict of interest statement for all authors is included.

Ethical Publication Statement
The authors confirm that they have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. This study was approved by the local human research ethics committees (Chang Gung Medical Foundation Institutional Reviewer Board 103-3665B and 201800677B0).

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