Perampanel in patients with refractory and super-refractory status epilepticus in a neurological intensive care unit: A single-center audit of 30 patients

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Summary
In refractory status epilepticus (SE), γ-aminobutyric acidergic drugs become less effective and glutamate plays a major role in seizure perpetuation. Data on the efficacy of perampanel (PER) in treatment of refractory SE in humans are limited. Here, we present a single-center case series of patients with refractory SE who received PER orally in an intensive care unit. We retrospectively analyzed treatment response, outcome, and adverse effects of all patients with refractory SE in our Neurological Intensive Care Unit who received add-on PER between September 2012 and February 2018. Thirty patients with refractory SE (median = 72 years, range = 18-91, 77% women) were included. In 14 patients (47%), a high-dose approach was used, with a median initial dose of 24 mg (range = 16-32). In five patients (17%), SE could be terminated after PER administration (median dose = 6 mg, range = 6-20 mg, 2/5 patients in high-dose group). Clinical response was observed after a median of 24 hours (range = 8-48 hours), whereas electroencephalogram resolved after a median of 60 hours (range = 12-72 hours). Time to treatment response tended to be shorter in patients receiving high-dose PER (median clinical response = 16 hours vs 18 hours; electroencephalographic response = 24 hours vs 72 hours), but groups were too small for statistical analysis. Continuous cardiorespiratory monitoring showed no changes in cardiorespiratory function after “standard” and “high-dose” treatment. Elevated liver enzymes without clinical symptoms were observed after a median of 6 days in seven of 30 patients (23%; 57% high dose vs 43% standard dose), of whom six also received treatment with phenytoin (PHT). Outcome was unfavorable (death, persistent vegetative state) in 13 patients (43%; 39% high dose vs 61% standard dose), and good recovery (no significant disability, moderate disability) was achieved in nine patients (56% high dose vs 44% standard dose). Oral PER in loading doses up to 32 mg were well tolerated but could terminate SE only in a few patients (5/30).
In approximately 23%-43% of cases, status epilepticus (SE) does not respond to first and second line treatment with benzodiazepines and intravenous antiepileptic drugs (AEDs) and is therefore considered refractory.1-4 As defined recently in a new proposal of definition and classification of SE,5 time point \( t_1 \) marks the point at which self-limitation of seizures is unlikely due to “failure of the mechanisms responsible for seizure termination” or “initiation of mechanisms which lead to abnormally prolonged seizures.” The underlying pathophysiological mechanisms resulting in the state of self-sustaining seizure activity and finally refractory SE are multiple and still not completely understood.6 The imbalance of inhibitory \( \gamma \)-aminobutyric acid and excitatory glutamate plays a crucial role in the development of refractory SE. On a cellular basis, changes in receptor density on the cell surface with internalization of synaptic \( \gamma \)-aminobutyric acid type A receptors, up-regulation of extrasynaptic \( \gamma \)-aminobutyric acid receptors with \( \delta \)-subunits, and accumulation of excitatory glutamatergic \( N \)-methyl-\( \text{D} \)-aspartate receptors on the cell surface contribute to the state of increased excitability.7-9 The understanding of these changes is essential for a rational targeted treatment of refractory SE.

As morbidity and mortality increase with duration of SE,10,11 fast and aggressive treatment is necessary. Beyond time point \( t_2 \), defined as 30 minutes for generalized tonic-clonic SE and 60 minutes for focal SE with impaired consciousness,5 neuronal loss and neurotoxicity must be expected. According to the staged treatment approach, anesthetics are the treatment of choice at the stage of refractory SE, with midazolam being most widely used.12 However, use of anesthetic drugs carries potentially life-threatening risks such as immunosuppression, respiratory insufficiency, hypotension, and bradycardia, which may require controlled ventilation and the application of catecholamines, and should therefore be used cautiously.13 Thus, there is a need for better-tolerated drugs with fewer adverse events.

Perampanel (PER) is the first orally active noncompetitive \( \alpha \)-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist. It terminated benzodiazepine-resistant SE in a lithium pilocarpine rat model at a median effective dose of 5.1 mg kg\(^{-1}\) after 30 minutes. A coadministration of diazepam 5 mg kg\(^{-1}\) and PER 1 mg kg\(^{-1}\) terminated seizures in all rats at 30 minutes, with earlier recovery of central nervous system–depressant effects.14

Human data on the efficacy of PER in refractory SE is very limited. To date, there are two case reports15,16 and two small case series,17,18 altogether including 23 patients. The effective dose of PER in SE in humans is unknown so far. Our aim was to assess efficacy and safety of add-on treatment with PER in patients with refractory and super-refractory SE with special focus on safety and tolerability of higher loading doses of PER.

### Key Points
- Perampanel terminated SE in 17% of patients with refractory or super-refractory SE in this single-center case series
- Time from perampanel administration to treatment response ranged between 6 and 72 hours
- High loading doses of perampanel up to 32 mg were safe without cardiorespiratory side effects or laboratory changes
metabolic panel) and clinical examination by a neurologist at least once daily were performed as standard of care on the NICU. Diagnostic workup of SE routinely included laboratory testing (including hemogram, C-reactive protein, basic metabolic panel, and AED levels in case of medically treated preexisting epilepsy), brain imaging (computerized cranial tomography in all patients, magnetic resonance imaging according to clinical needs and in case of de novo SE), and electroencephalography (EEG; immediately for diagnosis of nonconvulsive SE, otherwise within 24 hours of admission). Cerebrospinal fluid investigation and further laboratory testing were performed if etiology was still unknown to search for less common inflammatory, infectious, or metabolic causes. Continuous EEG monitoring has been available at our center since July 2015 and was mainly used in case of nonconvulsive SE with coma. Diagnosis of SE was made either clinically in case of SE with prominent motor symptoms or using electroclinical criteria according to the Salzburg consensus criteria of SE in case of nonconvulsive SE.\(^{19,20}\) We classified status according to the International League Against Epilepsy Task Force Report.\(^5\) Treatment followed a staged approach following our in-hospital guidelines.\(^{21-23}\) The sequence and doses of administered drugs in the emergency setting were systematically documented on a standardized form established in our hospital since August 2013, and could therefore be extracted retrospectively by chart review. If seizure onset was not witnessed, the duration of SE before admission was estimated based on information from relatives and emergency doctors. Super-refractory SE was defined as ongoing seizure activity ≥24 hours after initiation of anesthetic therapy, including seizure recurrence on the reduction or withdrawal of anesthesia.\(^{24}\) PER was administered via nasogastric tube, crushed and dissolved in water. PER serum levels were not performed on a routine basis until March 2017.

Treatment response was assessed clinically and based on EEG changes and was regarded as response to PER if no further AED or anesthetic drug was added before clinical SE cessation or EEG improvement, defined as cessation of EEG pattern fulfilling the Salzburg consensus criteria of SE.\(^{19,20}\)

Outcome was assessed at discharge from hospital using the modified Rankin Scale, which was calculated retrospectively based on documented deficits in the medical report. Status Epilepticus Severity Score (cutoff level for unfavorable outcome = 3 points)\(^{25}\) and Epidemiology-Based Mortality Score in Status Epilepticus (cutoff level for unfavorable outcome = 64 points)\(^{26}\) were used to estimate mortality risk.

### 2.1 Statistics

Descriptive statistical analysis including calculation of frequencies, median (range) and mean (standard deviation) were performed using Excel (Microsoft, Redmond, WA, USA). For group comparison between the standard-dose and high-dose groups, Wilcoxon-Mann-Whitney test was used for nonparametric independent samples to compare the variables Status Epilepticus Severity Score, Epidemiology-Based Mortality Score in Status Epilepticus, Glasgow Outcome Scale, modified Rankin Scale, duration of SE, and duration of stay in the NICU. Additionally, chi-square test was used for assessing the distribution of survivors and responders between the two groups. We used exact test statistics and corrected the \(P\) values for multiple comparisons using the Holm-Bonferroni method. The resulting \(P\) values, being already corrected, were then interpreted using a threshold of \(P = .05\). For statistical analysis, we used the R-Environment (R version 3.4.1; R Core Team, 2017).

### 2.2 Standard protocol approvals, registrations, and patient consents

This is a retrospective chart review with no patient contact, which does not require ethics committee approval according to the Austrian Law on Research.

### 3 RESULTS

Thirty patients (23 women, median age = 72 years) received PER as add-on treatment in refractory (21/30, 70%) or super-refractory (9/30, 30%) SE. Twelve of these patients were reported previously.\(^17\) The most frequent SE type was NCSE without coma (13/30, 43%); in four cases (13%), NCSE followed a generalized tonic–clonic seizure. Etiology was acute symptomatic in eight patients (27%); in 12 (40%), SE arose de novo (for details on demographic data, see Table 1).

Treatment followed a staged approach, with lorazepam given as first treatment in the majority of patients (97%, 29/30), followed by levetiracetam (97%, 29/30). Patients received a median of four intravenous drugs (range = 2–7) before PER was given. For details on treatment, see Table 2.

PER was administered after a median of 2.3 days (range = 0.5-18.3). Sixteen patients (53%) received a “standard dose” of median 4 mg (range = 2-12, dose increase = 2-4 mg/d). Higher initial doses with median 32 mg (range = 16-32 mg) were used in 14 patients (47%) since April 2016.

Altogether, treatment response was observed in five patients (17%; for clinical details, see Table 3). Two responders were described previously. In one female patient aged 51 years with standard-dose treatment, who suffered from NCSE following a focal to bilateral tonic–clonic seizure, clinical response was observed 18 hours after PER.
8 mg, whereas resolution of SE on EEG could be documented after 72 hours. As no further treatment was added, this was considered a possible response to PER treatment (Figure 1A and 1B). In the high-dose group, in one male patient aged 89 years with NCSE without coma, SE was terminated within 12 hours after PER 24 mg was given, with clinical improvement after 8 hours (Figure 2A and 2B).
Furthermore, one woman aged 21 years with refractory focal motor SE due to a focal cortical dysplasia in the left parietal region showed clinical and EEG treatment response within 24 hours of administration of PER 20 mg. The patient had been admitted to the epilepsy monitoring unit for presurgical evaluation of left-sided focal epilepsy with focal motor seizures with preserved consciousness starting at the age of 15 years. Despite administration of high doses of lorazepam, levetiracetam, and valproic acid, the patient suffered from approximately 250 focal motor seizures per 24 hours with concordant EEG patterns, which were classified as focal motor SE (Figure 3A and 3B) and resolved within 24 hours after administration of PER 20 mg. There was only mild dizziness reported as an adverse effect after PER, which quickly resolved despite ongoing PER treatment. No transfer to the NICU was indicated due to preserved consciousness and unremarkable cardiorespiratory monitoring.

In a further two patients, clinical response was observed 72 hours after treatment with PER 20 and 12 mg without further changes of concomitant medication, with EEG resolution after 6 days. In one of these patients, another SE occurred while the patient was on PER treatment 1 week later, and in the other patient clinical improvement was only temporary; hence, those two patients were not considered true responders. Additionally, in two patients clinical improvement was documented 3 days after initiation of treatment with PER 16 and 24 mg, respectively, with concomitant loading of PHT. EEG improvement was observed 6 and 7 days after PER in these patients. As PHT was started simultaneously, response could not be clearly attributed to PER treatment, so those two patients were not considered responders. For details on those four patients, see Figures S1 and S2.

Serum plasma levels of PER were taken in two of the three responders after single dose PER 20 and 24 mg, respectively, and were within the therapeutic range. Altogether, serum levels of nine patients were measured and were within the therapeutic range after loading doses of PER ranging from 12 to 32 mg (median dose = 24 mg) with an observable dose dependency. In patients who

| Substance, median dose (range) | 1st Treatment, N = 30, n (%) | 2nd Treatment, N = 30, n (%) | 3rd Treatment, N = 30, n (%) | 4th Treatment, N = 28, n (%) | 5th Treatment, N = 25, n (%) | 6th Treatment, N = 14, n (%) | 7th Treatment, N = 8, n (%) | 8th Treatment, N = 6, n (%) | 9th Treatment, N = 2, n (%) |
|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| Lorazepam 4 mg (2-8)         | 29 (97)                       |                               |                               | 1 (4)                        |                               |                               |                               |                               |                               |
| Midazolam 1 (3)              |                               | 1 (4)                        |                               | 1 (7)                        |                               |                               |                               |                               | 1 (13)                       |
| Levetiracetam 3000 mg (1000-4000) |                               | 29 (97)                       |                               | 1 (5)                        |                               |                               |                               |                               |                               |
| Phenytoin 750 mg (250-1000)  |                               |                               | 4 (20)                        | 9 (32)                       | 7 (28)                        |                               |                               |                               | 1 (13)                       |
| Valproic acid 2000 mg (1000-2000) |                               |                               |                               | 1 (5)                        | 8 (27)                        | 9 (32)                        | 1(4)                          |                               | 1 (17)                       |
| Lacosamide 300 mg (200-400)  |                               |                               |                               | 3 (11)                       |                               |                               |                               |                               | 1(7)                         |
| Topiramate 50 mg             |                               |                               |                               |                               | 2 (8)                        |                               |                               | 2 (14)                       |                               |
| Eslicarbazepine 800 mg       |                               |                               |                               |                               |                               | 2 (7)                        | 1 (4)                        |                               | 1(8)                         |
| Propofol 1 (5)               |                               | 1 (4)                        |                               | 2 (8)                        | 2 (14)                        |                               |                               | 1 (17)                       |                               |
| Ketamine 2 (14)              |                               |                               | 2 (14)                        |                               |                               | 2 (25)                        | 1 (17)                       |                               |                               |
| Brivaracetam 1 (17)          |                               |                               |                               |                               |                               |                               |                               |                               |                               |
| Sevoflurane                  |                               |                               |                               |                               |                               |                               |                               |                               | 1 (50)                       |
| Perampanel 3 (10)            |                               | 4 (14)                        |                               | 11 (37)                      | 5 (36)                        | 4(50)                        |                               | 2 (33)                       | 1 (50)                       |

TABLE 2 Antiepileptic drug treatment in refractory status epilepticus
received standard doses of PER, no serum levels were available. No changes of cardiorespiratory parameters were observed with standard- or high-dose PER. Altogether, 17 patients (56%) received catecholamines throughout the stay on the NICU (11 patients receiving PHT, six patients throughout anesthesia), none of them related to treatment with PER. In seven patients (23%, 4/7 in high-dose group), an increase of liver enzymes without clinical symptoms was observed after a median of 6 days (median γ-glutamyl transferase = 457 U L⁻¹, range = 103-3300 U L⁻¹; median alkaline phosphatase = 243 U L⁻¹, range = 102-709). Six of them received PHT prior to PER treatment. No further laboratory changes occurred throughout treatment with PER, and plasma levels of concomitant AEDs were not altered.

Demographic data between the standard- and high-dose groups were comparable (see Table 1). Comparing responder rates (P = 1.0), median stay on the NICU (P = 0.9426), survival (P = 0.9405), and outcome after SE (P = 0.7238), no differences between the two groups were found. Median stay on the NICU was 9 days (range = 1-72 days), and median time in hospital was 20 days (range = 6-91). Outcome after SE was unfavorable (death, severe disability) in 13 patients (43%); good recovery was observed in two patients (7%) with preexisting epilepsy and moderate disability in seven patients (23%).

### Table 3: Clinical details of responders

| Responder 1 | Responder 2 | Responder 3 | Responder 4 | Responder 5 |
|-------------|-------------|-------------|-------------|-------------|
| Gender      | Female      | Female      | Male        | Female      |
| Age, y      | 60          | 77          | 51          | 89          | 21          |
| Preexisting epilepsy | Yes | No | Yes | Yes | Yes |
| Etiology    | Tumor       | Meningioma  | Hepatic encephalopathy, alcohol withdrawal | Remote cerebrovascular left hemispheric stroke | Focal cortical dysplasia |
| SE type     | NCSE without coma | NCSE with coma | Bilateral tonic–clonic seizure → NCSE with coma | NCSE without coma, with impairment of consciousness | Focal motor SE without impairment of consciousness |
| EEG pattern | LPD, rh SW < 2.5 Hz right temporal | Periodic SW < 2.5 Hz left temporal with fluctuation | Periodic delta + superimposed fast activity right frontotemporal | Periodic SW < 2.5 Hz left temporal with subtle clinical phenomena | >250 Evolution pattern per 24 h |
| Number of AEDs | 7       | 4           | 3           | 4           | 3           |
| STESS score | 0          | 5           | 3           | 4           | 3           |
| EMSE score  | 82         | 65          | 129         | 107         | 17          |
| Initial dose of PER | 6 mg | 6 mg | 6 mg | 24 mg | 20 mg |
| Titration schedule | Dose increase to 12 mg on the 2nd day | Daily dose increase of 2 mg up to a maximum dose of 12 mg | Dose increase of 2 mg on 2nd day | No further dose increase | No further dose increase |
| Maximum dose | 12 mg | 12 mg | 8 mg | 24 mg | 20 mg |
| Stay in NICU, d | 21 | 8 | 11 | 8 | 0 |
| Stay in hospital, d | 60 | 25 | 11 | 32 | 11 |
| GOS         | Moderate disability | Severe disability | Moderate disability | Moderate disability | Good recovery |
| AEDs        | LZP, LEV, LCM, PHT, MDZ, TPM, CBZ | LZP, LEV, PHT, VPA | LZP, LEV, PRO | LZP, LEV, VPA, PHT | LZP, LEV, VPA |

AED, antiepileptic drug; CBZ, carbamazepine; EEG, electroencephalographic; EMSE, Epidemiology-Based Mortality Score in Status Epilepticus; GOS, Glasgow Outcome Scale; LCM, lacosamide; LEV, levetiracetam; LPD, lateralized periodic discharges; LZP, lorazepam; MDZ, midazolam; NCSE, nonconvulsive SE; NICU, Neurological Intensive Care Unit; PER, perampanel; PHT, phenytoin; rh, rhythmic; SE, status epilepticus; PRO, propofol; STESS, Status Epilepticus Severity Score; SW, sharp wave; TPM, topiramate; VPA, valproic acid.
In the group of nonsurvivors (n = 12), STESS score was true positive in eight patients (sensitivity 67%, positive predictive value = 42%, negative predictive value = 75%) and Epidemiology-Based Mortality Score in Status Epilepticus in all 12 patients (sensitivity 100%, positive predictive value = 54%, negative predictive value = 100%).

4 | DISCUSSION

Treatment response to add-on PER was observed in five of 30 patients (17%) with refractory or super-refractory SE. Clinical cessation of SE was documented 6-72 hours after PER administration, with resolution of EEG pattern after 12-72 hours. Comparing the standard-dose approach with low initial doses of median 4 mg and daily up titration of 2 mg, with the high-dose approach of loading doses up to 32 mg, no significant difference in treatment response, outcome, or stay on the NICU was found. PER was remarkably well-tolerated even with high doses of PER up to 32 mg without cardiorespiratory adverse events or laboratory changes. Elevated liver enzymes without clinical symptoms were documented as the only remarkable laboratory change in seven patients (23%, 57% in high-dose group) and attributed to concomitant medication with PHT.
Although glutamate plays a major role in seizure perpetuation and glutamatergic receptors are up-regulated with ongoing seizure activity, the noncompetitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist PER could only ameliorate seizure activity in a few patients (15%). Possible reasons for the moderate response are various, as described below.

The underlying brain pathology leading to refractory and super-refractory SE is the most important predictor for SE outcome and probably also the major determinant for treatment response. Outcome was unfavorable (death, severe disability) in almost half of the patients (43%) receiving PER, mainly reflecting the severe underlying SE etiology in our series. Due to the small sample size, we were not able to perform statistical analysis of responders and nonresponders.

Another relevant factor might be the long duration of SE before administration of PER, with a median of 2.3 days. There might also be poor absorption after dissolution in water due to the poor solubility of PER, which best dissolves in mild acidic fluids. However, acidic conditions of the stomach are changed by application of proton pump inhibitors as a standard treatment in critically ill patients in the NICU. In addition, the gastrointestinal resorption is severely impaired in critically ill patients, which might have resulted in an erratic absorption of the drug. Serum levels of PER were tested in 30% of our patients and were within the therapeutic range after loading doses of 12 up to 32 mg, with observable dose dependency. Whether lower doses of PER result in sufficient plasma levels in the critically ill patients cannot be answered, as no serum levels were available in these patients.

Half of the patients (16/30, 53%) were treated with low doses, compared to the effective dose in animal models (median effective dose of 5.1 mg kg⁻¹, in combination with diazepam 1 mg kg⁻¹). When a high-dose approach was used with administration of PER up to 32 mg, SE was terminated in two patients (14%), which was not significantly higher than in the standard-dose group. A standardized testing of plasma levels is essential to properly evaluate treatment response to high doses of PER, and to identify the required loading dose to achieve effective plasma levels, especially in critically ill patients. As a recent approach in our hospital, a loading dose of PER 32 mg on the first day followed by PER 24 mg on the second day and thereafter reduction to a maintenance dose of 12 mg (in absence of enzyme-inducing AEDs like PHT) is used. In elderly patients, lower loading doses of 20-24 mg are most frequently used. Daily measurement of plasma levels has been performed since March 2017 for a more standardized assessment of off-label treatment with higher doses of PER in refractory and super-refractory SE. Regarding safety issues, no cardiorespiratory adverse events or laboratory changes were observed associated with off-label high-dose PER. Therefore, the administration of higher loading doses of PER proved to be safe and should be considered at an earlier stage of SE, with particular emphasis on the underlying pathophysiology.

The main limitations of our study are the retrospective study design and the critical assessment of drug response in patients with refractory SE, who always receive several drugs simultaneously or sequentially. Thus, a clear causal correlation between the administration of one drug and cessation of SE is difficult. Furthermore, little is known about the natural course of SE at this stage.

As excitation via glutamatergic N-methyl-D-aspartate and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors is probably one of the most important mechanisms of seizure perpetuation, these receptors are still promising targets for the treatment of refractory SE. Future prospective investigations with high-dose oral PER that follow a standardized treatment protocol including a larger number of patients are necessary to properly assess the full potential of PER in the treatment of refractory and super-refractory SE. The problem of an erratic absorption of the drug in critically ill patients can best be overcome with an intravenous formulation of PER.

DISCLOSURE OF CONFLICTS OF INTEREST
A.R. has received travel support from Eisai and acted as a paid consultant to Neuroconsult. E.T. has acted as a paid consultant to UCB, Eisai, Bial, Medtronics, EVER Neuro Pharma, Biogen Idec, and Sunovion; he or his institution has received research funding from GSK, Biogen Idec, Novartis, Red Bull, and UCB and speaker honoraria from GSK, Böhringer Ingelheim, Eisai, Bial, Cyberonics, Sanofi-Genzyme, the Austrian Science Fund, Jubiläumsfond der Österreichischen Nationalbank, and the EU. G.Ka. received travel support from UCB and Cyberonics. J.H. has received speaker honoraria from UCB and travel grants from UCB, Eisai, and Gerot Lancaster. H.F.N. has received speaker honoraria from Baxter Austria, Astellas Pharma, SCS-Angelini Pharmaceuticals, Fresenius Medical Care Austria, and Orion Pharma, compensation from UCB Pharma for clinical medication monitoring, and a travel grant from Fresenius Kabi Austria. M.L. reports grants from Medtronic and UCB Pharma, and personal fees from EVER Neuro Pharma and Eisai. The other authors have no conflicts of interest to report. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.
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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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