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Efficacy of perampanel in refractory nonconvulsive status epilepticus and simple partial status epilepticus

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ABSTRACT

We provide some evidence concerning the efficacy of perampanel (PER) in refractory status epilepticus (SE). We retroactively identified patients with SE treated in our department by searching for the term "status epilepticus" in the electronic archive of medical records. We present and analyze in this paper the subset of data of the patients treated with PER. We analyzed ten episodes of SE in nine patients. At the first administration, PER was given in a dosage of 6 mg to most of our patients (7 of 10). On average, PER was administered as the 6th antiepileptic drug (AED) (range: 2–10). Depending on the criterion for efficacy, PER appears effective for the termination of SE in 2 to 6 (of 10) episodes. Unfortunately, safety data for the administration of PER with loading doses needed for the treatment of SE are lacking. Because of this, PER should be used very carefully in refractory SE and only after first-line treatment options have failed.

1. Introduction

Status epilepticus (SE) is a common medical condition with an incidence of at least 20/100,000 annually in the Caucasian population [1]. In generalized convulsive status epilepticus (GCSE), guidelines agree that the treatment of refractory GCSE after the administration of a benzodiazepine and one other antiepileptic drug (AED), such as phenytoin or phenobarbital, requires anesthesia [2].

The recommendations for the treatment of nonconvulsive status epilepticus (NCSE) and simple partial motor status epilepticus or epilepsia partialis continua (EPC) are not that straightforward. Especially in EPC, common recommendations state that any drug effective in chronic epilepsy may be tried [3]. In NCSE, with the exception of subtle SE, it is recommended that by failure of the first-line therapy, further nonanesthetizing i.v. substances such as levetiracetam, phenobarbital, or valproic acid should be tried instead of anesthetics [4].

Studies in animals suggest that alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor-mediated glutamatergic transmission is strengthened during an established SE [5]. In late kainic acid-induced SE, the noncompetitive AMPA receptor antagonist GYKI 52466 was more effective than diazepam [6]. Perampanel was effective in the termination of diazepam-resistant SE in a lithium–pilocarpine rat model [7] and had synergistic effects with diazepam in this model [8].

These animal studies suggest that an AMPA-receptor antagonist should have a substantial effect in terminating late stages of SE. Therefore, perampanel (PER), a novel noncompetitive AMPA-receptor antagonist [9,10], should be effective in this condition.

In this paper, we present the experience with PER in the treatment of NCSE and EPC at the University Hospital of Rostock, which provides some evidence concerning the efficacy of PER in these conditions. In addition to presenting new data, we also address the conceptual issue of how to determine the efficacy of PER and other AEDs in this setting. This is particularly important in this case, as we observed in a previous database analysis of the treatment of status epilepticus at the University Hospital of Rostock over a 10-year time frame, that mostly a combination therapy of two to four drugs was established at the time of SE termination [11].

A review on topiramate (TPM) in SE [12] describes eight different criteria for possible or certain treatment effect of an AED, which were different from the criteria commonly used in randomized controlled prospective trials in SE (e.g., [13]). Gallentine et al. [14] consider a refractory SE responsive to levetiracetam (LEV) if seizure activity ceased within three days of initiation or dose increase of LEV. Albers et al. [15] considered a SE responsive to lacosamide (LCM) if EEG status resolved within 24 h after start of LCM-i.v. and no further AEDs were added to the treatment protocol during this time period. Hottinger et al. [16] rated the effect of TPM as successful if clinical improvement and electroencephalographical resolution of refractory SE occurred within 24 h after starting treatment with TPM and no further AEDs were required. The effect of TPM was rated as "probably successful", if

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improvement occurred within 72 h after starting treatment with TPM. In the database analysis mentioned above [11], we defined the last AED administered before SE cessation as the termination drug, regardless of the latency between its first administration and SE cessation.

These different approaches show that the scientific community has not yet found a global means to state when and if an AED is successful in ceasing a SE. Therefore, the aim of this study was not only to present our experiences with the use of PER in refractory SE but also to give an impression on how different criteria for the identification of an AED with a possible or certain treatment effect have an influence on the results of retrospective case series.

2. Methods

We present a data subset from a large retrospective study. Specifically, we evaluate every status epilepticus treatment at the neurological department of the University of Rostock from January 2010 to June 2013. This study was approved by the local ethics board at University of Rostock under the identifier A-2013-0099.

We identify the patients treated by searching the electronic medical records of our clinic for the term "status epilepticus". We then manually review the medical files of these patients to determine at which time a certain AED was administered, which AED was effective to terminate the epileptic condition, and the time of termination. We classify an antiepileptic drug as effective for the termination of SE using the four different criteria described below.

After collecting all the data, we compare and contrast the results of the different efficacy criteria. We chose the four criteria below, as we had found in a previous study [12] that these were the most commonly used criteria in other cases. Comparing the results of the different criteria allows us to study which criterion is a diagnostically conclusive method of determining the AED that actually leads to the cessation of the SE. At least, we will be able to give some advice on how to compare studies using different criteria in reviews concerning treatment effects in SE. As we evaluate every case with all four of these criteria, we show that even with a small number of cases, as in this paper, the criterion by which we decide the AED to be effective or not makes a big difference.

The four criteria by which we examine these cases are as follows:

1. the last AED administered before SE termination is defined as effective, regardless of the latency between its first administration and SE cessation;
2. the AED that was the last drug introduced into the antiepileptic therapy within 72 h before the cessation of the SE and without changes in the comedication;
3. the AED that was the last drug introduced into the antiepileptic therapy or increased in dose within 24 h before termination of the SE and without changes in the comedication;
4. the AED that was the last drug introduced into the antiepileptic therapy within 72 h before the cessation of the SE even allowing changes in the comedication.

The termination of SE is always defined as the end of convulsion in EPC and the return to baseline of consciousness or the resolution of previously documented electroencephalographic seizure activity in NCSE. Resolution of seizure activity was diagnosed when spikes, sharp waves, or rhythmic waveform showed a frequency below 1 Hz without significant evolution in field, morphology, and frequency [17]. We determine the origin of the SE using different diagnostics, such as the clinical status of the patient, CT, MRI, and, most importantly, EEG.

As comedication of the terminating drug, we listed all AEDs given during the 24 h before termination of SE. All subgroups of NCSE were classified according to the system of Shorvon [18]. The end of a generalized tonic–clonic seizure was assumed when convulsions stopped and stertorous breathing started. Episodes in which nonconvulsive seizure activity persisted were classified as NCSE in the postictal phase of tonic–clonic seizures according to the system of Shorvon [18]. Here, we present the subset of data concerning the patients treated with PER. The first episode of this series was published separately as a case report [19].

3. Results

Ten episodes of SE in nine patients (five female, four male) were treated with PER. Of these cases, there were two cases of EPC (remote symptomatic after stroke) and eight cases of NCSE. Four cases were with new-onset epilepsy. The age of the patients was 73.3 years on average, with a standard deviation of 9.7 years. As PER is not licensed for first-line treatment of SE in Germany, in the University Hospital of Rostock, it has only been given to patients with complicated cases of refractory NCSE or EPC, where first-line treatment has failed. Because of this, the patients in this case study have a higher rate of infirmity and seniority than those in other studies concerning the treatment of SE. For details of etiology and outcome, see Table 1. It has to be acknowledged that the patients in treatment episodes one and three were in a bad condition even prior to the SE. Since a return to baseline cannot be counted as a positive outcome in every case, patients in treatment episodes six and eight had the best outcome.

Perampanel was never used as the first AED (the median number of administration being six, with a range of two to ten) and more than 9 h after the onset of the clinical symptoms (median: 137.7 h, range: 9.25–427 h). In the first administration, PER was given in dosage of 6 mg in most of the cases (7 of 10). For details of PER administration, see Table 2.

Perampanel was the terminating drug in two cases according to criterion 1, in three cases according to criterion 2, in four cases according to criterion 3, and in six cases according to criterion 4. Treatment episodes five and nine were the only ones in which PER was not a termination drug according to any of our criteria.

Since most of our patients were in a state of impaired consciousness, minor neurotoxic adverse events cannot be ruled out, but there were no toxic effects on liver function, renal function, or blood cells. One patient died because of pneumonia. In this patient, PER was not effective, but NCSE was previously terminated with other AEDs. In all other patients, PER was still a part of the medication at the termination of the SE even when not considered as the termination drug to any of our criteria as in treatment episode nine. Taking all AEDs administered in the last 24 h before SE termination into account, a combination therapy of three to five compounds was found in all cases at the time of SE termination (median: four). For details of medication at cessation of SE, see Table 2.

4. Discussion

Depending on the different efficacy criteria, PER was the termination drug of NCSE or EPC in 2 to 6 of the 10 episodes in our group of patients. There is a bias in favor of PER, as we only included episodes in which PER was administered and because it is only such a small case study. Of course, the percentage in which PER is the terminating drug differs from one criterion to another. We believe that in this subdivision, criterion 3 is the criterion that holds the most substantiality of the four. Criterion 1 seems to be questionable because an AED, which has been administered several times for days or even weeks, may be identified as the termination drug after many ineffective administrations. Criterion 4 is questionable because an increase in the dosage of other AEDs may be more effective than the mere presence of an additional AED in the last three days before a termination of a SE. Therefore, we think the choice has to be made between criterion 2 and 3. According to these criteria, PER was effective in three or four episodes out of ten. Concerning a drug with pharmacokinetics as PER, further considerations should be taken into account. After oral administration, peak plasma concentrations of PER have been observed within 15 min to 2 h after application [10]. Perampanel distributes into the body tissue, and the remaining

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