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The efficacy of different kinds of intravenously applied antiepileptic drugs in the treatment of status epilepticus. How can it be determined?

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ABSTRACT

We explored the influence of four different efficacy criteria on the results of observational studies concerning the treatment of status epilepticus (SE) and its subtypes.
We compared and contrasted the results of four different efficacy criteria for the effectiveness of phenytoin, valproate, levetiracetam, and lacosamide. Criterion 1 = the last antiepileptic drug (AED) administered before SE termination. Criterion 2 = the last drug introduced into the antiepileptic therapy within 72 h before the cessation of SE and without changes in dosage or number of the co-medication. Criterion 3 = the last drug introduced into the antiepileptic therapy or increased in dose within 24 h before termination of the SE without changes in the co-medication. Criterion 4 = the last drug introduced into the antiepileptic therapy within 72 h before the cessation of SE even allowing changes in the co-medication. We used two-tailed χ^2-tests with the Yates adjustment for small samples to evaluate statistical differences between efficacy rates of different AEDs in the entire group and in subgroups of SE according to the second level of subdivisions in axis 1 and according to axis 2 of the new ILAE classification. A total of 145 treatment episodes in 124 patients (47 male, 77 female) were evaluated. There were 23 significant differences in efficacy according to the different criteria. Only criteria 1 and 3 led to significant results in our analysis. When incorporating theoretical considerations and the results of this study, criterion 3 seems to be the most appropriate measure for the evaluation of efficacy of an AED in the treatment of SE, because it seems to be more reasonable than criterion 1.

1. Introduction

It is generally accepted that status epilepticus (SE) is a serious neurological condition which requires immediate treatment to prevent irreversible neurological damage. Unfortunately, evidence from randomized controlled trials for the treatment of SE limited. The new guideline for the treatment of convulsive SE of the American Epilepsy Society (AES) is based on four class one trials, two class two trials, and 32 class three trials [1]. Therefore, guidelines for the management of SE have to rely additionally on expert opinions or observational analyses (for example, see the grading of recommendations of the Neurocritical Care Society Status Epilepticus Guideline Writing Committee [2]). In observational studies, an extensive diversity of approaches is used to determine the efficacy of a drug in terminating refractory status epilepticus. For example a review of topiramate (TPM) in SE [3] describes eight different criteria for a possible or certain treatment effect of an antiepileptic drug (AED). In another review on levetiracetam (LEV) as second-line treatment of SE [4], seven different criteria for a treatment effect of an AED were portrayed. The timeframe in which one AED was credited to have a treatment effect ranged from 3 min to 72 h.

In a meta-analysis [5] of published studies concerning the relative effectiveness of lacosamide (LCM), LEV, phenobarbital (PB), phenytoin (PHT), and valproate (VPA) in treatment of benzodiazepine-resistant convulsive SE, only about half of the papers cited indicated a specified timeframe in which they considered the seizure termination to be successful. This interval ranged from the completed administration of the infusion to 48 h after. Apart from preliminary data from our work [6,7], there are no data concerning the effect of different efficacy criteria resulting from observational studies on the use of certain AEDs for treatment of SE.

Another basic problem for the meta-analysis of observational studies may be that the treatment efficacy of certain AEDs can vary between the subtypes of SE. This problem could only be avoided if studies were limited to one form of SE. This will require multicenter studies to collect large enough samples of treatment episodes.

In a previous study concerning treatment episodes between January 1st 2000 and December 31st 2009 in our department [8], we found that clonazepam (CLN) was less effective in terminating nonconvulsive SE (NCSE) and epilepsia partialis continua (EPC) than generalized convulsive SE (GCSE). In this previous study, we used the classification system

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of NCSE-subgroups by Shorvon [9], which integrates semiologic and etiologic aspects in one axis. Due to the small number of patients in the various subgroups of NCSE, we only performed subgroup analyses concerning treatment effects between the two subgroups of GCSE and all other forms of SE. But in an analysis of clinical courses, limbic NCSE turned out to be more often refractory than nonlimbic NCSE [8]. Therefore the efficacy of AEDs may vary between the subgroups of NCSE as well. In 2015, the International League against Epilepsy (ILAE) launched a new classification-system of SE, which reflects semiologic and etiologic aspects on two different axes [10]. Future studies of SE should use this system to make their results comparable to other studies in the field. In the following study, we performed subgroup analyses according to the first and second axis of the new classification system of the efficacy of four AEDs with four efficacy criteria to explore the influence of these criteria and the subgroups of SE on the results of observational studies on SE.

2. Methods

We present data from a retrospective study, which covered all treatment episodes of SE at the neurological department of the hospital of Rostock University from January 2010 to June 2013. The study was approved by the local ethics board at Rostock University under the identifier A 2013-0099. We identified the patients treated in our department by searching for the term "status epilepticus" in the electronic archive of medical reports of our clinic. We then reviewed the medical files of these patients to determine the time each AED was administered and at which time an AED was effective to terminate the status episode. If the treatment had been started in another department or hospital, the treatment episode was only included if a thorough documentation of the therapy process was available. In the cases where the treatment had been started by the emergency service in the prehospital setting the data was usually sufficient to be included in the analysis.

We compared and contrasted the results of four different efficacy criteria for the effectiveness of PHT, VPA, LEV, and LCM. The criteria by which we analyze are as follows: Criterion 1 = the last AED administered before SE termination. Criterion 2 = the last drug introduced into the antiepileptic therapy within 72 h before the cessation of SE and without changes in dosage or number of the co-medication. Criterion 3 = the last drug introduced into the antiepileptic therapy or increased in dose within 24 h before termination of the SE without changes in the co-medication. Criterion 4 = the last drug introduced into the antiepileptic therapy within 72 h before the cessation of SE even allowing changes in the co-medication. Cessation of SE was defined as the end of convulsion in GCSE and 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 waveforms showed a frequency below 1 Hz without significant evolution in field, morphology, and frequency [11]. Subgroups of SE were classified accordant to axis 1 and axis 2 of the new ILAE system [10]. Each application of an AED was counted as new treatment attempt; e.g., when LEV was administered after two applications of lorazepam, this was classified as third treatment attempt. We used two-tailed χ^2-tests with the Yates adjustment for small samples (i.e., for less than 40 AED applications) to evaluate statistical differences between efficacy rates of different AEDs in the entire group and in subgroups of SE according to the second level of subdivisions in axis 1 and according to axis 2 of the new ILAE classification [10]. Only when an overall difference between the effects of the different AEDs was revealed in the χ^2-test did we perform pair-wise comparisons with the χ^2-test. Since this study was exploratory we did not perform a Bonferroni-Holmes procedure to correct for multiple statistical tests.

3. Results

One hundred and forty five episodes of SE in 124 patients (47 male, 77 female) could be evaluated. At the first treatment of an episode of SE in our department patients were on average 68.9 years old (SD = 18 years). Thirteen patients (1 male, 12 female, average age 80.8 years, SD 11.1 years) died during their hospitalization period (11.1% of patients, 9.6% of treatment episodes), mainly due to complications such as sepsis, pneumonia, renal failure or cardiac failure. These patients were significantly older than the ones who survived ($p < 0.001$). Additionally, in our group of patients the female gender seemed to be a risk factor for dying during SE treatment ($p = 0.02$). This might be due to the fact that in our cluster, women were significantly older than men at their first treatment episode (mean 73.6 SD 16.7 years vs. mean 61.1 SD 16.3 years, $p < 0.001$). The women who died were also significantly older than the women who survived (mean 80.8 SD 11.5 years vs. mean 72.5 SD 17.2 years, $p = 0.047$). On axis 1 of the new classification, the majority of treatment episodes in our sample were classified as NCSE without coma, on axis 2 the majority of treatment episodes of SE had a remote etiology. For details of the number of treatment episodes in different types of SE, see Table 1. Levetiracetam was administered significantly earlier than PHT ($p < 0.001$), LCM ($p < 0.001$), and VPA ($p < 0.001$). VPA was earlier administered than LCM ($p < 0.001$). For details of the first AED used and the dosages of the intravenously administered AEDs, see Table 2. From this table it can be estimated that LEV was mainly given in established SE whereas the other AEDs were mainly given in refractory or super-refractory SE. There was a huge range of efficacy rates according to the different criteria. The highest efficacy rates were 57.9% for LEV according to criterion 1 in SE episodes with acute etiology, 55.6% for LCM according to criterion 1 in focal motor SE, and 55.2% for LEV according to criterion 1 in NCSE without coma. But for each AED in at least one subgroup analysis with at least one criterion, the efficacy rate was zero! For details of the efficacy rates in the entire group and the subtypes, see Table 3. There were no significant differences in the proportion of use in the subgroups between the four AEDs ($p > 0.3$). There were 23 significant differences in the effectiveness of AEDs according to the different criteria. But only criteria 1 and 3 led to significant results in our analysis. When evaluating

Table 1
Types of status epilepticus according to Axis 1 and Axis 2 of the new ILAE classification.

Type of status epilepticus (SE) Axis 1	Number of episodes	Subtype of SE Axis 1	Number of episodes
Convulsive SE (A.1)	41	Focal onset evolving into bilateral convulsive SE (A.1.b)	29
		Unknown whether focal or generalized (A.1.c)	12
Focal motor (A.3)	20	Epilepsia partialis continua (A.3.b)	20
Nonconvulsive SE with coma (B.1)	8	Nonconvulsive SE with coma (B.1)	8
Nonconvulsive SE without coma (B.2)	76	Aphasic status (B.2.b.b)	13
		With impaired consciousness (B.2.b.c)	63
Type of status epilepticus (SE) Axis 2	Number of episodes		
Acute etiology	24		
Progressive etiology	12		
Remote etiology	106		
Unknown etiology	3		