TREATMENT OF STATUS EPILEPTICUS – A NARRATIVE REVIEW OF THE EVIDENCE SO FAR AND A PROPOSAL FOR THE DESIGN OF RETROSPECTIVE STUDIES

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ABSTRACT

Randomised controlled studies of the treatment of status epilepticus (SE) are difficult to perform due to ethical reasons. Therefore, the evidence for treatment guidelines is mainly based on observational studies, case series, case reports, and retrospective database analyses. The diversity of approaches used to determine the termination drug in a treatment episode of SE shows that the scientific community has not yet found a global means of defining when and if an antiepileptic drug is successful in terminating SE. More meta-analyses are needed in order to compare the treatment effects in the subtypes of non-convulsive SE because these are only small heterogeneous subdivisions in large database analyses. Furthermore, we propose that future case series, observational studies, or retrospective database analyses should follow certain standards to make them more comparable.

Keywords: Outcome criteria, subtypes of non-convulsive status epilepticus, status epilepticus (SE).

INTRODUCTION

Status epilepticus (SE) is a serious medical condition affecting at least 20 of every 100,000 Caucasian individuals per year.[1] The diagnosis of SE should be made when there are either continuous seizures lasting at least 5 minutes, or two or more discrete seizures between which incomplete recovery of consciousness occurs.[2] Randomised controlled trials (RCTs) of SE treatment are difficult to perform due to ethical reasons. Therefore, the evidence for treatment guidelines is mainly based on observational studies, case series, case reports, and retrospective database analyses. For example, in a study of levetiracetam (LEV) it was shown that retrospective studies report a higher efficacy rate than prospective studies, which indicates a possible publication bias.[3] It has been questioned whether there are truly sufficient reliable data to establish evidence-based guidelines for the treatment of SE.[4] In this narrative review we will present the evidence derived from prospective RCTs of SE treatment, with a focus on trials performed in adults. Furthermore, we will highlight some aspects of the evidence originating from reviews of safety studies, case series, case reports, observational studies, and retrospective database analyses. Included at the end of the review is a proposed procedure to improve the proficiency of the treatment of SE without prospective RCTs. It must be acknowledged that we focus on antiepileptic treatment with regard to the efficacy of the various antiepileptic drugs (AEDs).

THE EVIDENCE SO FAR

Prospective Randomised Controlled Trials

Prospective RCTs for the treatment of SE are rare: there have only been five prospective RCTs for the first-line treatment of SE. In the Veteran Affairs Status Epilepticus Study, 0.1 mg/kg lorazepam (LZP) was found to be superior to 18 mg/kg phenytoin (PHT) in terminating SE. Barring this superiority, no other statistically significant

differences were observed. This study also included treatment with 15 mg/kg phenobarbital (PB) and the combination of 0.15 mg/kg diazepam (DZP) with PHT.[5] In another study, 30 mg/kg valproate (VPA) was observed to be more effective than 18 mg/kg PHT in terminating generalised clonic status epilepticus (GCSE).[6] Two studies suggested a superiority of LZP (in doses of 2 mg and 4 mg) to DZP (in doses of 5 mg and 10 mg) as a first-line treatment for SE.[7,8] However, a statistical significance in the difference between the two drugs could not be shown. In addition, according to the World Health Organization's Collaboration Centre for Drug Statistics Methodology,[9] the authors compared 50% or 100% of a standard daily drug dose (DDD) of DZP with 80% or 160% of a DDD of LZP. The results may therefore be confounded by the low dose of DZP.

In another study it was proposed that LEV is as effective as LZP as a first-line treatment for terminating GCSE.[10] However, the sample size in this study was <80% of the calculated sample size for detecting a 20% difference, and so minor differences in efficacy may have been missed. The Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) showed that intramuscular midazolam is at least as safe and effective as intravenous LZP for prehospital seizure cessation in patients with convulsive SE.[11] There is only one prospective RCT concerning the second-line treatment of SE. In this study, VPA as a second-line treatment was found to be as effective as PHT.[12] For the treatment of refractory SE there is also only one randomised trial,[13] which is under-sampled. Nevertheless, this trial shows significantly longer mechanical ventilation time with the use of barbiturates compared with propofol.

Reviews of Case Series, Case Reports, and Retrospective Database Analyses

All other evidence concerning the treatment of SE is derived from non-randomised safety studies, case series, case reports, and retrospective database analyses. For example, efficacy rates for termination of SE calculated in narrative reviews were 55.9% for LEV,[14] 58% for lacosamide (LCM),[15] 47% for pregabalin,[16] and 37% for topiramate (TPM).[17] These reviews predominantly address the treatment of refractory SE. There may be a considerable publication bias in favour of these substances because in a large database analysis the success rate in terminating SE was between 30-55% regardless of the substances used.[18] When general anaesthesia cannot terminate SE the condition is termed super-refractory SE. The treatment of this issue is *terra incognita* from the point of view of evidence-based medicine.[19]

PROBLEMS FOR REVIEWS OR META-ANALYSES OF OBSERVATIONAL STUDIES, CASE SERIES, CASE REPORTS, AND RETROSPECTIVE DATABASE ANALYSES

Outcome Criteria

A review of TPM in SE describes eight different criteria for possible or certain treatment effect of an AED,[17] which were different from the criteria commonly used in prospective RCTs in SE.[5] In another review on LEV as second-line treatment of SE,[2] seven different criteria for a treatment effect of an AED were described. Some of these criteria are very similar to others mentioned in the review or to those mentioned in the review on TPM;[17] for an overview of these criteria see Table 1.[20-30] The time frame for the attribution of a treatment effect to the administration of a new AED ranges from 3 minutes to 72 hours. In a meta-analysis[31] of published studies concerning the relative effectiveness of LCM, LEV, PB, PHT, and VPA in the treatment of benzodiazepine-resistant convulsive SE, only about half of the articles cited a specified time frame in which they considered the seizure termination to be successful. The most commonly stated specification was the termination of seizures within 30 minutes of infusion (six articles, 22.2%). However, the time frames of other studies ranged from 3 minutes to 48 hours. One study even linked the time of the cessation of SE with the end of the infusion. These different approaches show that the scientific community has not yet found a global means of defining when and if an AED is successful in terminating SE. In this meta-analysis, the authors tried to control the effect of different criteria with statistical methods. Unfortunately, this cannot be done without knowing the extent of the effect.

In a case series concerning the treatment effect of perampanel (PER) in non-convulsive SE and simple partial SE,[32] four different outcome criteria were compared with each other. These criteria were: 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 <72 hours before the cessation of SE and without changes in the co-medication; 3) The AED that was the last drug introduced into the antiepileptic therapy or increased in dose <24 hours before the cessation of SE and without changes in the co-medication; 4) The AED that was the last drug introduced into the antiepileptic therapy <72 hours before the cessation of SE, even allowing changes in the co-medication. In this study, PER 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 (i.e. range of efficacy rates from 20-60%). A statistical definition of these differences in outcome seems to be difficult.

Different Entities of SE

Apart from generalised convulsive SE and simple partial SE, there is a large group of different types of non-convulsive SE with different responses to treatment. Shorvon[33] proposed 22 different types of non-convulsive SE, which, as shown in an extensive review, are partly associated with their own specific electroencephalographical patterns.[34] Unfortunately, in a retrospective database analysis these data could not be fully reproduced.[35] In the same database analysis[36] it was shown that the frequency of refractory courses differed between the types of SE. This was mainly due to the fact that all episodes of limbic SE were refractory, which stands in contrast to the episodes of generalised convulsive SE, non-limbic complex SE, and subtle SE.

Table 1: Criteria for a possible or certain treatment effect of an AED in the treatment of status epilepticus.

Reference	Criterion
20	• Successful: Clinical improvement and electroencephalographic resolution of refractory SE within 24 hours after starting with the new AED with no requirement for further AEDs. • Probably successful: Improvement occurring within 72 hours after starting treatment with the new AED, which may however also be due to other therapeutic measures or self-termination after longer treatment with no requirement for further AEDs.
21	• Successful: Increased alertness and responsiveness and electrographical improvement occurring within 96 hours following introduction of the new AED without modification of concomitant AEDs. • Possibly successful: Termination of SE associated with introduction or increase of the AED concomitantly with other AEDs.
22	• Full responder: Seizure activity terminated within 24 hours of initiation of the new AED. • Partial responder: Marked reduction or no seizure activity in response to increased doses of the new AED within 72 hours after first administration.
23	EEG status resolves within 24 hours after the start of the new AED and no further antiepileptic agents are added to the treatment protocol during this time period.
24	• In patients in burst suppression due to pharmacological coma, seizure response to the new AED was defined as the absence of electrographical seizure activity for 24 hours following the emergence from burst suppression. • Resolution of electrographical seizure activity within 4 hours of administration of the new AED.
25	Cessation of seizure activity within 3 days of initiation or dose increase of the new AED without addition or adjustment of other AEDs in the same time frame.
26	The last AED introduced before improvement in the EEG.
27	Clinical or electroencephalographical cessation of seizures within 24 hours after start of the new AED without need for other AEDs.
28	No need to introduce a further compound to control SE.
29	The absence of seizures within 24 hours after infusion of the new AED with no other AEDs administered during this time and no recurrence of SE during the hospital stay.
30	Cessation of the clinical manifestation of convulsive SE and electroencephalographically in non-convulsive and subtle SE within approximately 3 minutes.
10	Clinical seizure cessation within 30 minutes.

AED: antiepileptic drug; SE: status epilepticus; EEG: electroencephalogram.

Non-convulsive SE in the postictal phase of tonic—clonic seizures and cases of coma due to acute brain injury with epileptiform electroencephalogram changes were more often refractory than generalised convulsive SE. Since generalised convulsive SE has a more overt semiology than non-convulsive SE, treatment is initiated earlier than in other subtypes of SE.

The efficacy rates of some AEDs were also different in the various subtypes of SE. Anaesthesia and clonazepam both terminated generalised convulsive SE more effectively than non-convulsive SE and simple partial SE. LEV was the only AED that seemed to be more effective in terminating non-convulsive SE or simple partial SE than generalised convulsive SE. However, the discrepancy was not as significant due to the small number of patients treated with LEV. Because there were only small subgroups, no statistical comparison between the individual subtypes of non-convulsive SE was performed. It must be assumed that when the quota of refractory courses differs between the subtypes of non-convulsive SE then this will influence the efficacy rates of the AEDs used for treatment.

A PROPOSAL FOR THE DESIGN OF RETROSPECTIVE STUDIES

The implementation of RCTs is difficult due to ethical reasons. To broaden the evidence, especially for the treatment of non-convulsive SE, further database analyses are needed and outcome criteria should be standardised in order to better compare the studies of different research groups. We need more meta-analyses so that we can compare the treatment effects in the different subtypes of non-convulsive SE, which make up only small subgroups even in large database analyses. Therefore, we propose that future case series, observational studies, or retrospective database analyses should report their efficacy rates with reference to the subtypes of non-convulsive SE, even if there were no statistically significant differences in the reported sample of treatment episodes.

To make the studies more comparable, several outcome criteria should be used simultaneously. For first-line treatment, a treatment effect within 10 minutes seems to be favourable, and for second-line treatment a treatment effect within 30 minutes is probably reasonable because these time frames are used in guidelines for treatment of generalised convulsive SE. When second-line treatment in generalised convulsive SE does not work according to all guidelines, anaesthesia should be used. The situation in refractory non-convulsive SE is more complicated. We suggest that authors of future studies on this topic should at least use Criterion 3 of the study on PER as one of their outcome criteria (see above).[32] This criterion is very similar to the 24-hour criterion used in many studies cited in Table 1. This must be qualified by saying that for AEDs with a terminal half-life of <8 hours, the 24-hour criterion is appropriate only when a loading dose is used, otherwise the steady state of trough plasma levels will be reached later. It must be acknowledged that the time to treatment effect may not be the only relevant outcome criterion.

In one study, the return to baseline in the general condition after SE was taken as an outcome criterion.[37] Perhaps, in the future, outcome criteria like this should be taken into consideration as well. Another problem is that one AED may start to have an effect after another one has been introduced. Therefore, the last-introduced AED may be erroneously considered the effective one. This may particularly be the case with PER. After oral administration, peak plasma concentrations of PER have been observed within 15 minutes to 2 hours after application.[38] PER distributes into the body tissue, and the remaining plasma fraction has a terminal half-life of about 105 hours. Peak plasma concentrations, as well as trough plasma levels, increase for about 14 days if the initial daily dose is maintained. Because of these effects, if 6 mg PER is administered for the first time in a patient with 'normal' weight, there will probably only be a time frame of a few hours in which the plasma concentration is at a therapeutic level, but with repeated administrations the plasma concentration will increase considerably. Therefore, the effectiveness of PER to terminate SE should increase from day to day and it may have a considerable role in the termination of refractory SE even >72 hours after first administration.

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