Review

The relative effectiveness of five antiepileptic drugs in treatment of benzodiazepine-resistant convulsive status epilepticus: A meta-analysis of published studies

Zeid Yasiry [a,*], Simon D. Shorvon [b]

[a] Department of Medicine, University of Babylon/College of Medicine, Babil, Iraq
[b] Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, London, UK

A B S T R A C T

Purpose: Systematic evaluation of published evidence-base of the efficacy of five antiepileptic drugs – lacosamide, levetiracetam, valproate, phenytoin and phenobarbital – in convulsive benzodiazepine-resistant status epilepticus.
Methods: Data sources included electronic databases, personal communication, and back tracing of references in pertinent studies. These were prospective and retrospective human studies presenting original data for participants with convulsive benzodiazepine-resistant status epilepticus. Interventions were intravenous lacosamide, levetiracetam, phenobarbital, phenytoin and valproate. Outcome measured is clinically detectable cessation of seizure activity. Level-of-evidence was assessed according to Oxford Centre of Evidence-Based Medicine and The Cochrane Collaboration's Tool for Assessment of Risk. Twenty seven studies (798 cases of convulsive status epilepticus) were identified and 22 included in a meta-analysis. Random-effects analysis of dichotomous outcome of a single group estimate (proportion), with inverse variance weighting, was implemented. Several sources of clinical and methodological heterogeneity were identified.
Results: Efficacy of levetiracetam was 68.5% (95% CI: 56.2–78.7%), phenobarbital 73.6% (95% CI: 58.3–84.8%), phenytoin 50.2% (95% CI: 34.2–66.1%) and valproate 75.7% (95% CI: 63.7–84.8%). Lacosamide studies were excluded from the meta-analysis due to insufficient data.
Conclusion: Valproate, levetiracetam and phenobarbital can all be used as first line therapy in benzodiazepine-resistant status epilepticus. The evidence does not support the first-line use of phenytoin. There is not enough evidence to support the routine use of lacosamide. Randomized controlled trials are urgently needed.

© 2013 British Epilepsy Association. Published by Elsevier Ltd. All rights reserved.

1. Introduction

Status epilepticus (SE) is a neurological emergency with significant morbidity and mortality[1,2] and has to be treated in a timely manner before irreversible neuronal damage ensues.[3,4] Having a protocol for therapy is universally recommended, and standard protocols are widely accepted.[5,6] All of these recommend benzodiazepines as first line therapy[7–17] and there is now global consensus on this. In contrast, what action to take if benzodiazepines are ineffective is much less clear and there is perceived to be a lack of evidence to support the use of any particular agent currently employed in the protocols. Because of this paucity of evidence, this review was conducted with the aim of examining,

critically, the evidence relating to the efficacy of five anti-epileptic drugs in the treatment of benzodiazepine-resistant status epilepticus. These medications are lacosamide, levetiracetam, valproate, phenytoin and phenobarbital. The last two drugs have been extensively used for this indication for many years, based largely on the evidence derived from the Veterans Affair Trial[8]; although it is worth noting that these medications were sometimes given as a first-line treatment in that study. The other three antiepileptic drugs have been more recently introduced, and although widely prescribed in this situation, are not licensed specifically for use in status epilepticus.

2. Methods

2.1. Aims

To identify, via reproducible methodology, all the available literature related to the use of the five anti-epileptic drugs in

---

* Corresponding author at: Department of Internal Medicine, College of Medicine/University of Babylon, Babil, Iraq. Tel.: +964 (0)7707117766.
E-mail address: z.yasiry@ucl.ac.uk (Z. Yasiry).

benzodiazepine-resistant status epilepticus, to assess the heterogeneity and reliability of the data, to analyze the extracted data to quantify the relative efficacy of these drugs, and to provide recommendations for the use of the latter in patients with benzodiazepine-resistant status epilepticus.

2.2. Patients, methods and analysis

A pre-specified protocol was followed for the search, extraction, and analysis of data following the methodology of the "*Systematic Reviews: Centre of Review and Dissemination's guidance for undertaking reviews in health care*" published by the Centre of Review and Dissemination, University of York[18] and "*Cochrane Handbook of Systematic Reviews of Intervention*".[19] Patients reported in the published papers were included in the analysis if they fulfilled the eligibility criteria set out in Table 1. All patients with convulsive status epilepticus, of any type, and who had failed to respond to benzodiazepine therapy and were thus given one of the five study drugs as second-line therapy were included, regardless of age or other clinical variable.

Internet-based searches were implemented through the online databases MEDLINE and EMBASE, both accessed via Ovid (see supplementary material 1 for search protocol). The search results from the two databases were combined with the duplicates excluded. In addition, the references in the bibliographies of the relevant papers were individually searched and back-traced. In several instances, the authors of the identified studies were contacted via email or telephone, to answer specific queries relating to data analysis in their papers (notably to ascertain details of such aspects as the numbers of patients treated who were benzodiazepine-resistant and their outcome).

The papers were selected for the review by screening the search results by title and abstract for eligibility. The filtered studies would, then, be read as a whole, subjected to the inclusion criteria, stratified according to the intervention of interest, and scrutinized for their level of evidence and risk of bias. Then, they would go through data extraction, tabulation, pooling then meta-analysis, if eligible for the latter.

Papers were excluded where original data was not presented (for example reviews and expert opinions), which were published in non-English languages without abstract/accredited translation for the required data, where the drugs were used in more advanced stages of status epilepticus (where benzodiazepines, then anaesthetics and other antiepileptic drugs had been used before the medications of interest), and where data extraction/interpretation was not possible.

The papers were classified into levels according to the Oxford Centre of Evidence Based Medicine (CEBM).[20] In case of randomized trials and non-randomized prospective studies, assessment of the risk of bias was performed using *the Cochrane Collaboration's Tool for Assessment of Risk*.[21]

Data was extracted by filling out a proforma by one reviewer; the process was supervised by the other reviewer. Data were then analyzed using both STATA® 11 (by StataCorp LP, Texas, USA) and Comprehensive MetaAnalysis version 2 (CMA2®-by Biostat®, New Jersey, USA). The protocol is based on dichotomous outcome analysis of a single group estimate: inverse variance weighting is performed for each estimate, followed by random-effects analysis of the pooled estimates of all the studies describing an intervention, taking in consideration both the within-study and between-studies variances. The protocol and formulae for the random effect meta-analysis are given in the supplementary material 2. Single-patient case reports were not included in the meta-analysis due to lack of statistical dispersion. There was one case of epilepsia partialis continua found in the review, but as it was a single-patient report, it was not included in the meta-analysis.

The reasons for choosing random-effects model are varying sample sources, demographics, aetiology, and types of seizures, treatment with different doses, timing of administration, and definitions of outcome. All the aforementioned differences are substantial sources of heterogeneity that make fixed-effect meta-analysis unsuitable. The random-effects model was not chosen based on a statistical heterogeneity test.[22] However, heterogeneity was quantified via I^2, a statistic used to quantify how much of the variability in the results is due to real heterogeneity rather than a random sampling error.[23]

3. Results

3.1. Characteristics of publications analyzed

A total of 2754 papers were identified on MEDLINE/EMBASE (see supplementary material 1) from which 2652 papers were excluded due to non-relevance. From the remaining 102 (with an added 6 papers from reference tracing), only 27 papers were retrieved for data extraction. Some studies covered two or three drugs; therefore, the number of papers from summation of studies per drug was 32. The papers included consist of 1 randomized double-blinded trial, 5 open-label trials, 18 case series and 3 case reports. They described 798 episodes of convulsive status epilepticus.

The levels of evidence of the studies are as follows: level 4 (18 studies, 66%), level 4- (3 studies, 11%), level 2b (5 studies, 19%), and, level 1b (1 study, 4%) (see supplementary material 3). For prospective studies, assessment of the risk of bias was also performed, the results of which are illustrated in Table 2. It is worth noting that neither the prospective studies nor the single randomized controlled trial are registered at the NIH Clinical Trial Centre (http://clinicaltrials.gov/ct2/home).

Sources of heterogeneity were multiple; these include study design (retrospective, prospective, randomized and non-randomized, blinded and non-blinded), demographics (age, gender,

Table 1
Eligibility criteria.

Participants	Patients with status epilepticus who have been resistant to initial therapy with benzodiazepines were included. Only human studies and studies of convulsive (motor) status epilepticus were included. In some studies, simple and complex partial seizures were not subdivided, and it is thus possible that some non-convulsive cases were included; however where a study exclusively included non-convulsive status epilepticus, it was not considered. There was no restriction by age groups, co-morbidities or epilepsy background.
Interventions	Intravenous lacosamide, levetiracetam, valproate, phenytoin, and phenobarbital as second line therapy after failure of benzodiazepines. No dose or rate restrictions were specified.
Comparators	None
Outcomes	The variable extracted was cessation of seizure activity (other outcomes were also sought but are not reported here including, mortality, new neurological deficit, and tolerability). Cessation of seizure activity, or the drug's efficacy, was defined differently by different authors in the selected papers, and definition was, therefore, reported as a variable and acknowledged as one of the several sources of heterogeneity.
Study design	Original papers with any study design were included. There was no restriction on the number of patients in case series. All studies which provided data on outcome following treatment with one (or more) of the five drugs were included, whether these were controlled or uncontrolled and whether or not a comparator was included.