

What Is the Preferred First-Line Therapy for Status Epilepticus?

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SYSTEMATIC REVIEW SOURCE

This is a systematic review abstract, a regular feature of the *Annals'* Evidence-Based Emergency Medicine (EBEM) series. Each features an abstract of a systematic review from the Cochrane Database of Systematic Reviews and a commentary by an emergency physician knowledgeable in the subject area.

The source for this systematic review abstract is: Prasad K, Al-Roomi K, Krishnan PR, et al. Anticonvulsant therapy for status epilepticus. The Cochrane Database of Systematic Reviews 2006, Issue 1. Art No.: CD 003723. DOI: 10.1002/14651858.CD003723.

The *Annals'* EBEM editors assisted in the preparation of the abstract of this Cochrane systematic review, as well as selection of the Evidence-Based Medicine Teaching Points.

OBJECTIVE

The objective of this systematic review was to compare selected anticonvulsant therapies against each other or placebo for treatment of status epilepticus in terms of effectiveness and safety. Furthermore, the review attempted to identify reasons for disagreements in the literature about optimal anticonvulsant therapy, and to highlight areas for further research.

DATA SOURCES

The authors searched for randomized controlled trials from several electronic databases, including the Cochrane Epilepsy Group Specialized Register (July 2005), Cochrane Central Database of Controlled Trials (CENTRAL) (Issue 2, 2005), MEDLINE (1966 to August 2004), and EMBASE (1966 to January 2003).

STUDY SELECTION

Studies were selected if they were randomized controlled trials using random or quasirandom treatment allocation and included patients with several stages of status epilepticus: premonitory (period during which seizures became increasingly frequent or severe but did not meet the definition of status epilepticus), early (the first 30 minutes of seizure activity), established (either more than 30 minutes of continuous seizure activity or 2 or more seizures without recovery of full consciousness between the seizures), or refractory (seizure activity uncontrolled for 1 to 2 hours despite first-line

treatment). Selected studies compared anticonvulsant drugs against placebo or another anticonvulsant and examined the outcome of "treatment failure," defined primarily as the noncessation of seizure activity.

DATA EXTRACTION AND ANALYSIS

Two reviewers independently selected published trials for inclusion and methodologic quality; disagreements were adjudicated by a third reviewer. Data on the number of participants with a given outcome in each treatment arm were independently extracted and verified by 2 reviewers. The authors initially proposed to study risk of treatment failure as the primary outcome and to conduct separate analyses for each of several stages of status epilepticus, including premonitory, early, established, and refractory status epilepticus; however, this was not possible owing to limitations of the data, and these groups were combined for analysis. Heterogeneity among trials was examined with the χ^2 test, and where no heterogeneity was evident, trials were combined using a fixed-effects model to provide a summary estimate of effect.

MAIN RESULTS

Eleven studies with analyzable data containing 2,017 participants were included in the review. Five of the 11 trials studied patients with premonitory status, 1 each with established and refractory status, 2 with mixed status, and 2 with the stage poorly defined. Seven of these studies included only adult patients, 4 only children. Fourteen different therapeutic comparisons were made in these trials, but only 3 of these were replicated in multiple studies to permit meta-analysis.

All comparisons of the intravenously administered benzodiazepines diazepam and lorazepam against placebo significantly favored the intervention arms. The comparisons of lorazepam intravenously versus phenytoin intravenously, lorazepam intravenously versus diazepam intravenously, and an examination of diazepam intrarectal gel efficacy are of particular interest and will be presented in detail.

Lorazepam intravenously was superior to phenytoin intravenously in a single study with 198 participants, with lower risk for noncessation of seizures (relative risk [RR] 0.62; 95% confidence interval [CI] 0.45 to 0.86). According to 3 trials with 289 participants, lorazepam intravenously was more effective than diazepam intravenously for decreasing the risk of noncessation of seizures (RR 0.64; 95% CI 0.45 to 0.90) and

continuation of status epilepticus requiring a different drug or general anesthesia (RR 0.63; 95% CI 0.45 to 0.88); however, lorazepam did not significantly reduce the requirement for ventilatory support (RR 0.73; 95% CI 0.36 to 1.49) or the number of adverse effects (risk difference [RD] -0.03 ; 95% CI -0.10 to 0.03). Furthermore, there was no statistically significant difference in deaths between the groups according to data available from 2 of the studies with 203 patients (RD 0.02; 95% CI -0.04 to 0.08). Diazepam intrarectal gel was superior to placebo gel according to 2 studies with a total of 165 participants, demonstrating lower risk for noncessation of seizures (RR 0.43; 95% CI 0.30 to 0.62).

CONCLUSIONS

The authors conclude that lorazepam is superior to either diazepam or phenytoin for cessation of seizures, and compared to diazepam carries a lower risk of continuation of status epilepticus requiring the use of a different drug or general anesthesia. Lorazepam and diazepam are both better than placebo for the same outcomes, and diazepam intrarectal gel is useful in premonitory status.

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COMMENTARY: CLINICAL IMPLICATION

Status epilepticus is defined as a period of continuous motor seizure activity lasting 30 minutes or more or 2 or more consecutive seizures without a return to full consciousness between the seizures. Overall, seizure disorders are common in the emergency department (ED); however, status epilepticus is an infrequently encountered condition. Its importance lies in the fact that it is a dangerous disease, with high morbidity and mortality. First-line therapy for status epilepticus is usually a benzodiazepine, many of which are commonly available in EDs, including diazepam (Valium), lorazepam (Ativan), and midazolam (Versed). Benzodiazepine administration should be followed by phenytoin whose long-acting anticonvulsant properties prevent recurrence and thus play an integral role in the management of status epilepticus. Finally, in patients without a known seizure disorder, search for the causative insult (eg, bleeding, trauma, other medications, infections) is necessary.

Because of the rapidity with which severe injury or death can occur in status epilepticus, using optimal anticonvulsant therapy is essential to minimizing adverse outcomes such as cerebral injury, cardiac arrhythmias, aspiration, and rhabdomyolysis. Unfortunately, current emergency medicine textbooks and guidelines for treatment of status epilepticus either do not specify a preferred first-line agent^{1,2} or present limited

justification for their choice.³ This systematic review presents new evidence and highlights the need to update our resources with current evidence-based information.

This Cochrane review collected the best available evidence on the use of a variety of interventions for the treatment of status epilepticus. Overall, the review covers the topic broadly; however, it fails to identify sufficiently similar comparisons to draw useful conclusions to many questions. The meta-analysis evidence presented in this review suggests that lorazepam is more effective than diazepam for first-line treatment of status epilepticus, perhaps in part because of its more favorable pharmacokinetics, including a longer redistribution half-life than diazepam.⁴ The longer duration of clinical efficacy also facilitates the transition to antiepileptic medications such as phenytoin for long-term seizure control. Better control of status epilepticus results in not only improved patient outcomes but also considerable savings to the health care system, with less costly and invasive treatment requirements, such as airway control and general anesthesia. Given that lorazepam is only marginally more expensive than diazepam, lorazepam should be the preferred first-line agent for status epilepticus in the ED. Because diazepam intrarectal gel is also effective in controlling premonitory status epilepticus, with relative ease of use but high cost, it may be most useful in the out-of-hospital setting.

While the cessation of motor seizures is often used clinically to signify the termination of a status epilepticus episode, the absence of motor seizures does not preclude either nonconvulsive status epilepticus or subtle convulsive status epilepticus and concomitant ongoing cerebral injury. Thus, altered level of consciousness persisting after motor seizures have ceased should be treated with a high level of clinical suspicion in the ED and should be investigated further, ideally with emergency electroencephalogram.⁵

TAKE-HOME MESSAGE

Lorazepam provides better control over status epilepticus than does either diazepam or phenytoin. Both intravenous lorazepam and diazepam are effective in controlling status epilepticus; diazepam intrarectal gel also can be used in premonitory status. Standardization of seizure terminology and clinical research protocols is necessary to facilitate more detailed analyses of the therapeutic options for status epilepticus.

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EBEM TEACHING POINT

Broad versus narrow scope in systematic reviews. Systematic reviews may address questions that are either broad or narrow.⁶ Broad-based reviews might examine whether any of a variety of

therapeutic options are useful in achieving a certain outcome, as was done in this review examining the efficacy of various anticonvulsants in control of status epilepticus. In contrast, reviews with a narrow scope address a specific question, often directly examining the effect of a particular therapy on a well-defined outcome. Both approaches have advantages and disadvantages; whereas broad questions tend to be more easily generalizable to multiple settings and populations, they often prove more time consuming and expensive to answer. Furthermore, results may be difficult to synthesize and interpret, and validity may be compromised, particularly when the results of large numbers of heterogeneous studies are combined. Narrow questions may provide better-defined answers but tend not to be as generalizable. The choice of whether to use a narrow or broad-based approach in a systematic review should depend on the nature and complexity of the problem being addressed, the available evidence to synthesize, and the availability of resources to address it.

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2006 Pediatric Emergency Medicine Subspecialty Certification Examination

The American Board of Emergency Medicine (ABEM) and the American Board of Pediatrics (ABP) will administer the certifying examination in Pediatric Emergency Medicine on Thursday, November 16, 2006.

The eligibility criteria are available from both board offices or at www.abem.org and www.abp.org.

Physicians who are certified in Emergency Medicine by ABEM must submit an application to ABEM for the credentialing process. Physicians who are certified in General Pediatrics by ABP must submit an application to ABP for the credentialing process. Physicians who are certified by both boards may select the board through which they wish to apply. Upon successful completion of the examination, certification is awarded by the board through which the physician submitted the application.

Application materials will be available for ABEM diplomates on February 1, 2006, and will be accepted with postmark dates through May 1, 2006. ABP diplomates should contact ABP for application cycle information.

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