

Management of Status Epilepticus

JOSEPH I. SIRVEN, M.D., Mayo Clinic, Scottsdale, Arizona

ELIZABETH WATERHOUSE, M.D., Virginia Commonwealth University School of Medicine, Richmond, Virginia

Status epilepticus is an increasingly recognized public health problem in the United States. Status epilepticus is associated with a high mortality rate that is largely contingent on the duration of the condition before initial treatment, the etiology of the condition, and the age of the patient. Treatment is evolving as new medications become available. Three new preparations—fosphenytoin, rectal diazepam, and parenteral valproate—have implications for the management of status epilepticus. However, randomized controlled trials show that benzodiazepines (in particular, diazepam and lorazepam) should be the initial drug therapy in patients with status epilepticus. Despite the paucity of clinical trials comparing medication regimens for acute seizures, there is broad consensus that immediate diagnosis and treatment are necessary to reduce the morbidity and mortality of this condition. Moreover, investigators have reported that status epilepticus often is not considered in patients with altered consciousness in the intensive care setting. In patients with persistent alteration of consciousness for which there is no clear etiology, physicians should be more quickly prepared to obtain electroencephalography to identify status epilepticus. Physicians should rely on a standardized protocol for management of status epilepticus to improve care for this neurologic emergency. (Am Fam Physician 2003;68:469-76. Copyright© 2003 American Academy of Family Physicians.)

Status epilepticus is an under-recognized health problem associated with substantial morbidity and mortality. An estimated 152,000 cases occur per year in the United States, resulting in 42,000 deaths and an inpatient cost of \$3.8 to \$7 billion per year.¹⁻³ This review concentrates on the clinical management of status epilepticus (particularly convulsive status epilepticus), the theoretic and clinical considerations involved in choosing an antiepileptic drug to treat this emergency situation, and the consensus protocol devised by the Epilepsy Foundation of America (EFA) Working Group on Status Epilepticus.

Definition, Classification, and Epidemiology

DEFINITION

A decade ago, the EFA convened a working group to define status epilepticus.⁴ They described this condition as two or more sequential seizures without full recovery of consciousness between seizures, or more than 30 minutes of continuous seizure activity.⁴ This definition is generally accepted, although some investigators consider shorter durations of seizure activity to constitute status epilepticus.

Practically speaking, any person who exhibits persistent seizure activity or who does not regain consciousness for five minutes or more after a witnessed seizure should be considered to have status epilepticus.

CLASSIFICATION SCHEME

Although there is no consensus over a classification system for status epilepticus, classification is necessary for appropriate management of the condition because effective management depends on the type of status epilepticus. In general, the various systems characterize status epilepticus according to where the seizures arise—from a localized region of the cortex (partial onset) or from both hemispheres of the brain (generalized onset). The other major categorization hinges on the clinical observation of overt convulsions; thus, status epilepticus may be convulsive or nonconvulsive in nature.

Various approaches to classifying status epilepticus have been suggested.⁵⁻⁷ One version⁵ classified status epilepticus into generalized (tonic-clonic, myoclonic, absence, atonic, akinetic) and partial (simple or complex) status epilepticus. Another version⁶ divides the condition into generalized status epilepticus

See page 406 for definitions of strength-of-evidence levels.

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(overt or subtle) and nonconvulsive status epilepticus (simple partial, complex partial, absence). The third version⁷ takes a different approach, classifying status epilepticus by life stage (confined to the neonatal period, infancy and childhood, childhood and adulthood, adulthood only).

EPIDEMIOLOGY

Status epilepticus of partial onset accounts for the majority of episodes.^{1-4,8-12} One epidemiologic study¹ on status epilepticus found that 69 percent of episodes in adults and 64 percent of episodes in children were partial onset, followed by secondarily generalized status epilepticus in 43 percent of adults and 36 percent of children. The incidence of status epilepticus was bimodally distributed, occurring most frequently during the first year of life and

after the age of 60 years.^{1,2} Among adults, patients older than 60 had the highest risk of developing status epilepticus, with an incidence of 86 per 100,000 persons per year.¹⁻³ Among children 15 years or younger, infants younger than 12 months had the highest incidence and frequency of status epilepticus.¹ A variety of etiologies accounted for the condition. In adults, the major causes were low levels of antiepileptic drugs (34 percent) and cerebrovascular disease (22 percent), including acute or remote stroke and hemorrhage.¹⁻³

The rate of mortality from status epilepticus (defined as death within 30 days of status epilepticus) was 22 percent in the Richmond study.^{1,13} The mortality rate among children was only 3 percent, whereas the rate among adults was 26 percent.^{1,13,14} The elderly population had the highest rate of mortality at 38 percent.^{1,13,14} The primary determinants of mortality in persons with status epilepticus were duration of seizures, age at onset, and etiology.^{13,14} Patients with anoxia and stroke had a very high mortality rate that was independent of other variables.¹³⁻¹⁵ Patients with status epilepticus occurring in the setting of alcohol withdrawal or low levels of antiepileptic drugs had a relatively low mortality rate. In nonfatal cases, status epilepticus is associated with significant morbidity. Cognitive decline following an episode, as documented by neuropsychometric testing, is a well-established end result of prolonged secondarily generalized and partial status epilepticus.¹⁶

TABLE 1
Systemic Complications of Generalized Convulsive Status Epilepticus

Metabolic	Renal
Lactic acidosis	Acute renal failure from rhabdomyolysis*
Hypercapnia	Myoglobinuria*
Hypoglycemia	Cardiac/respiratory
Hyperkalemia	Hypoxia
Hyponatremia	Arrhythmia
CSF/serum leukocytosis	High output failure*
Autonomic	Pneumonia
Hyperpyrexia	
Failure of cerebral autoregulation*	
Vomiting	
Incontinence	

CSF = cerebrospinal fluid.

*—Rare complications of status epilepticus.

Information from references 7 and 17 through 19.

Systemic Pathophysiology

Generalized convulsive status epilepticus is associated with serious systemic physiologic changes resulting from the metabolic demands of repetitive seizures. Many of these systemic changes result from the profound autonomic changes that occur during status epilepticus, including tachycardia, arrhythmias, hypertension, pupillary dilation, and hyperthermia because of the massive catecholamine discharge associated with continuous generalized seizures. Systemic changes requiring medical intervention include hypoxia, hypercapnia, hypoglycemia, metabolic acidosis, and other electrolyte disturbances. *Table 1*^{7,17-19} summarizes the physiologic changes that occur during status epilepticus.

Management of Status Epilepticus

GENERAL MEASURES

The treatment of status epilepticus involves the use of potent intravenous medications that may have serious

adverse effects. Therefore, the first step in managing the condition is to ascertain that the patient has tonic-clonic status epilepticus, and that prolonged or repetitive seizures have occurred. A single generalized seizure with complete recovery does not require treatment. Once the diagnosis of status epilepticus is made, however, treatment should be initiated immediately. Necessary interventions include maintaining oxygenation and circulation, assessing the etiology and laboratory evaluations, obtaining intravenous access, and initiating drug therapy.

Physicians first should assess the patient's airway and oxygenation. If the airway is clear and intubation is not immediately required, blood pressure and pulse should be checked and oxygen administered. In patients with a history of seizures, an attempt should be made to determine whether medications have been taken recently. A screening neurologic examination should be performed to check for signs of a focal intracranial lesion.

Obtaining intravenous access is the next step, and blood should be sent to the laboratory for measurement of serum electrolyte, blood urea nitrogen, glucose, and antiepileptic drug levels, as well as a toxic drug screen and complete blood cell count. Isotonic saline infusion should be initiated. Because hypoglycemia may precipitate status epilepticus and is quickly reversible, 50 mL of 50 percent glucose should be given immediately if hypoglycemia is suspected. If the physician cannot check for hypoglycemia or there is any doubt, glucose should be administered empirically. Thiamine (100 mg) should be given along with the glucose, because glucose infusion increases the risk of Wernicke's encephalopathy in susceptible patients.

After administration of oxygen, blood gas levels should be determined to ensure adequate oxygenation. Initially, acidosis, hyperpyrexia, and hypertension need not be treated, because these are common findings in early status epilepticus and should resolve on their own with prompt and successful general treatment. If seizures persist after initial measures, medication should be administered. Imaging with computed tomography is recommended after stabilization of the airway and circulation. If imaging is negative, lumbar puncture is required to rule out infectious etiologies.

ROLE OF ELECTROENCEPHALOGRAPHY

Electroencephalography (EEG) is extremely useful, but underutilized, in the diagnosis and management of

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status epilepticus. Although overt convulsive status epilepticus is readily diagnosed, EEG can establish the diagnosis in less obvious circumstances. Researchers in one study²⁰ used EEG to diagnose status epilepticus in 37 percent of patients with altered consciousness whose diagnosis was unclear on the basis of clinical criteria. A surprising number of patients had no clinical signs of status epilepticus, and EEG was necessary to establish the diagnosis.

EEG also can help to confirm that an episode of status epilepticus has ended, particularly when questions arise about the possibility of recurrent episodes of more subtle seizures. In another study,²¹ investigators monitored patients for at least 24 hours after clinical signs of status epilepticus had ended. They found that nearly one half of their patients continued to demonstrate electrographic seizures that often had no clinical correlation. The investigators concluded that EEG monitoring after presumed control of status epilepticus is essential for optimal management.

Patients with status epilepticus who fail to recover rapidly and completely should be monitored with EEG for at least 24 hours after an episode to ensure that recurrent seizures are not missed. Monitoring also is advised if periodic discharges appear in the EEG of a patient with altered consciousness who has not had obvious seizures. Periodic discharges in these patients suggest the possibility of preceding status epilepticus, and careful monitoring may clarify the etiology of the discharges and allow the detection of recurrent status epilepticus.

Pharmacologic Management

Rapid treatment of status epilepticus is crucial to prevent neurologic and systemic pathology. The goal of treatment always should be immediate diagnosis and termination of seizures. For an anti-seizure drug to be effective in status epilepticus, the drug must be administered intravenously to provide quick access to the brain without the risk of serious systemic and neurologic adverse effects. Multiple drugs are available, each with advantages and disadvantages.

BENZODIAZEPINES

The benzodiazepines are some of the most effective drugs in the treatment of acute seizures and status epilepticus. The benzodiazepines most commonly used to treat status epilepticus are diazepam (Valium), lorazepam (Ativan), and midazolam (Versed). All three compounds work by enhancing the inhibition of γ -aminobutyric acid (GABA) by binding to the benzodiazepine-GABA and barbiturate-receptor complex.

Diazepam. Diazepam is one of the drugs of choice for first-line management of status epilepticus.^{18,22-24} [References 18 and 22 through 24—Evidence level A, randomized controlled trials (RCTs)] Although the drug enters the brain rapidly because of its high lipid solubility, after 15 to 20 minutes it redistributes to other areas of the body, reducing its clinical effect.^{24,25} Despite its fast distribution half-life, the elimination half-life is approximately 24 hours. Thus, sedative effects potentially could accumulate with repeated administration.

Diazepam in a typical intravenous dosage of 5 to 10 mg per minute terminates seizures of any type in about 75 percent of patients with status epilepticus.^{22,23,26} Adverse effects include respiratory suppression, hypotension, sedation, and local tissue irritation. Hypotension and respiratory suppression may be potentiated by the co-administra-

tion of other antiepileptic drugs, particularly barbiturates. Diazepam also may be given intramuscularly and rectally (Diastat).²⁷

Despite its pharmacokinetic and adverse effect limitations, diazepam remains an important tool in the management of status epilepticus because of its rapid and broad-spectrum effect.

Lorazepam. Lorazepam has emerged as the preferred benzodiazepine for acute management of status epilepticus.²⁴ [Evidence level A, RCT] Lorazepam differs from diazepam in two important respects. It is less lipid-soluble than diazepam, with a distribution half-life of two to three hours versus 15 minutes for diazepam. Therefore, it should have a longer duration of clinical effect.²⁴ Lorazepam also binds the GABAergic receptor more tightly than diazepam, resulting in a longer duration of action. The anticonvulsant effects of lorazepam last six to 12 hours, and the typical dose ranges from 4 to 8 mg. This agent also has a broad spectrum of efficacy, terminating seizures in 75 to 80 percent of cases.²⁶ Its adverse effects are identical to those of diazepam. Thus, lorazepam also is an effective choice for acute seizure management, with the added possibility of a longer duration of action than diazepam.

Midazolam. Although midazolam is rarely used as the first-choice benzodiazepine for treatment of status epilepticus in the United States, it is used commonly in Europe. A more complete review of this agent and its role in the treatment of status epilepticus is available elsewhere.^{28,29}

The Authors

JOSEPH I. SIRVEN, M.D., is director of electroencephalography and epilepsy at the Mayo Clinic in Scottsdale, Ariz., and assistant professor of neurology at Mayo Medical School, Arizona campus. Dr. Sirven received his medical degree from Louisiana State University, New Orleans, and completed a residency in neurology at the University of Minnesota Medical School—Minneapolis and a fellowship in electroencephalography and epilepsy at the University of Pennsylvania School of Medicine, Philadelphia. He served as the status epilepticus course director for the American Academy of Neurology from 1998 to 2001.

ELIZABETH WATERHOUSE, M.D., is associate professor of neurology at Virginia Commonwealth University School of Medicine, Richmond, where she is also coordinator of the clinical curriculum for third-year medical students and director of the neurology residency training program. Dr. Waterhouse received her medical degree from Harvard Medical School, Boston, where she completed a residency in neurology. She also completed a fellowship in electroencephalography and epilepsy at the University of Virginia School of Medicine, Health Sciences Center, Charlottesville.

Address correspondence to Joseph I. Sirven, M.D., Department of Neurology, Mayo Clinic, 13400 E. Shea Rd., Scottsdale, AZ 85262 (e-mail: Sirven.Joseph@mayo.edu). Reprints are not available from the authors.

PHENYTOIN

Phenytoin (Dilantin) is one of the most effective drugs for treating acute seizures and status epilepticus. In addition, it is effective in the management of chronic epilepsy, particularly in patients with partial and secondarily generalized seizures. The pharmacokinetic properties of phenytoin are reviewed elsewhere.^{23,25,30}

The main advantage of phenytoin is the lack of a sedating effect. However, a number of potentially serious adverse effects may occur. Arrhythmias and hypotension have been reported, particularly in patients older than 40 years. It is likely that these effects are associated with a more rapid rate of administration and the propylene glycol vehicle used as its diluent. In addition, local irritation, phlebitis, and dizziness may accompany intravenous administration.

FOSPHENYTOIN

Fosphenytoin (Cerebyx) received approval for treatment of status epilepticus from the U.S. Food and Drug Administration (FDA) in 1996. Fosphenytoin is a water-soluble pro-drug of phenytoin that completely converts to phenytoin following parenteral administration. Thus, the adverse events that are related to propylene glycol are avoided. Like phenytoin, fosphenytoin is useful in treating acute partial and generalized tonic-clonic seizures. Fosphenytoin is converted to phenytoin within eight to 15 minutes.³¹⁻³⁴ It is metabolized by the liver and has a half-life of 14 hours. Because 1.5 mg of fosphenytoin is equivalent to 1 mg of phenytoin, the dosage, concentration, and infusion rate of intravenous fosphenytoin are expressed as phenytoin equivalents (PE). The initial dose of fosphenytoin is 15 to 20 mg PE per kg, so it can be infused at a rate as high as 150 mg PE per minute, a rate of infusion that is three times faster than that of intravenous phenytoin. Intramuscular doses also can be given, but the drug does not reach a therapeutic level for 30 minutes.³⁵

Adverse effects that are unique to fosphenytoin include perineal paresthesias and pruritus; however, both are related to higher rates of administration.³⁰ Unlike phenytoin, fosphenytoin does not cause local irritation. Intravenous therapy has been associated with hypotension, so continuous cardiac and blood pressure monitoring are recommended. Although fosphenytoin represents an improvement over traditional phenytoin, it is expensive, and some hospital formulary committees are unwilling to pay the difference.¹⁸

PHENOBARBITAL

Phenobarbital typically is used after a benzodiazepine or phenytoin has failed to control status epilepticus. The normal loading dose is 15 to 20 mg per kg. Because high-dose phenobarbital is sedating, airway protection is an important consideration, and aspiration is a major concern. Intravenous phenobarbital also is associated with systemic hypotension. Although phenobarbital can be loaded fairly rapidly, a full therapeutic dose may take 30 minutes to infuse. It is diluted in 60 to 80 percent propylene glycol, which is associated with a number of complications, including renal failure, myocardial depression, and seizures.^{22,25} These limitations relegate phenobarbital to use in patients who have not responded to other agents.

Most authors agree that lorazepam or diazepam therapy should be initiated first in the treatment of status epilepticus, followed by phenytoin.

VALPROATE

The FDA approved valproate (Depacon) for use in 1997.³⁶ Parenteral valproate is used primarily for rapid loading and when oral therapy is impossible. It has a broad spectrum of efficacy and may be useful in patients with absence or myoclonic status epilepticus. Adverse effects include local irritation, gastrointestinal distress, and lethargy. This drug is not FDA-approved for the treatment of status epilepticus.

Choice of Antiepileptic Drug

Although there is no ideal drug for treatment of status epilepticus, a number of considerations influence the choice of antiepileptic drug for this condition. *Table 2* summarizes dosages, pharmacology, and adverse effects of medications used to manage status epilepticus and refractory status epilepticus. Comparative studies of treatments are few, but consensus has emerged concerning initial medications. Most authors agree that lorazepam or diazepam should be initiated, followed by phenytoin. The evidence for these choices is summarized below.

DIAZEPAM VS. LORAZEPAM

In one trial,²⁶ intravenous lorazepam was compared with diazepam as first-line treatment for status epilepticus. This randomized, double-blind trial, which included all types of status epilepticus, enrolled 78 patients who received 10 mg of diazepam or 4 mg of lorazepam by intravenous injection over two minutes. There were no significant differences in efficacy or latency of action between the drugs, but the number of patients was too small to determine true significance. Seizures were terminated in 58 percent of patients receiving diazepam compared with 78 percent of patients treated with lorazepam. Diazepam had a median latency of two minutes (range: immediate to 10 minutes) versus a median latency of three minutes with lorazepam (range: immediate to 15 minutes).²⁶

VETERANS AFFAIRS COOPERATIVE STUDY

The Veterans Affairs Status Epilepticus Cooperative Study Group²³ compared response rates for four different

TABLE 2
Antiepileptic Drugs Used in Status Epilepticus

<i>Drug</i>	<i>Loading dose</i>	<i>Maintenance dosage</i>	<i>Route of metabolism</i>	<i>Dialyzable (% protein binding)</i>	<i>Adverse effects</i>
Diazepam (Valium)	10 to 20 mg	None	Hepatic	>90	Respiratory depression, hypotension, sialorrhea
Lorazepam (Ativan)	4 mg	None	Hepatic	90	Same as diazepam
Phenytoin (Dilantin)	18 to 20 mg per kg at 50 mg per minute	5 mg per kg per day	Hepatic	70	Cardiac depression, hypotension
Fosphenytoin (Cerebyx)	18 to 20 mg per kg PE at 150 mg per minute	None	Hepatic	70	Cardiac depression, hypotension, paresthesias
Phenobarbital	20 mg per kg	1 to 3 mg per kg per day	Hepatic	50 to 60	Respiratory suppression
Pentobarbital	2 to 8 mg per kg	0.5 to 5 mg per kg per hour	Hepatic	59 to 63	Hypotension, respiratory suppression
Midazolam (Versed)	0.2 mg per kg	0.75 to 10 mg per kg per minute	Hepatic	96	Hypotension, respiratory suppression
Propofol (Diprivan)	2 mg per kg	5 to 10 mg per kg per hour initially, then 1 to 3 mg per kg per hour	Hepatic	97 to 98	Respiratory depression, hypotension, lipemia, acidosis

PE = phenytoin equivalents.

treatments in 384 patients with overt (presumably early) status epilepticus and 134 patients with subtle (presumably late) status epilepticus. The four regimens consisted of 0.15 mg per kg of diazepam followed by phenytoin (18 mg per kg), lorazepam (0.1 mg per kg), phenobarbital (15 mg per kg), or phenytoin alone (18 mg per kg). For overt status epilepticus, the highest response occurred in patients who received lorazepam (64.9 percent), followed by those who received phenobarbital (58.2 percent), diazepam with phenytoin (55.8 percent), and phenytoin monotherapy (43.6 percent).

Patients with subtle status epilepticus, which is often a late manifestation of status epilepticus, had significantly lower response rates to all treatments. Phenobarbital-treated patients had the highest response rate at 24.2 percent, followed by those receiving lorazepam (17.9 percent), diazepam plus phenytoin (8.3 percent), and phenytoin monotherapy (7.7 percent).²³ However, the

authors noted no statistically significant differences between treatments for overt and subtle status epilepticus.²³ There also were no differences between the treatments with respect to recurrence during the 12-hour study period, the incidence of adverse reactions, or the outcome at 30 days.

These data help to underscore the difference in response between early and late status epilepticus and the differing efficacies of medications, depending on the duration of the condition. Furthermore, the dramatic drop in response rate between early and late status epilepticus emphasizes the importance of early treatment. The authors conclude that lorazepam is the easiest medication to use among first-line agents in patients with status epilepticus.²⁰ [Evidence level A, RCT]

Recommendations of the Working Group

In 1993, the EFA's committee on the treatment of convulsive status epilepticus published guidelines and a treat-

ment protocol. The protocol was based on a literature review and input from expert reviewers and a professional advisory board.⁴ *Figure 1*^{4,18} outlines the protocol for the management of status epilepticus.

The committee made special mention of the treatment of status epilepticus in children. They noted that drug efficacy is similar in adults and children, but that children may tolerate more rapid intravenous administration than older patients. Although these guidelines are helpful, more stud-

ies are needed to determine whether this protocol is applicable to children and to address the role of newer drugs such as fosphenytoin, rectal diazepam, and parenteral valproate in the treatment of status epilepticus. If initial treatment with a benzodiazepine or fosphenytoin fails to control seizures, a neurologist should be contacted immediately.

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Protocol for Management of Status Epilepticus

At: zero minutes

Initiate general systemic support of the airway (insert nasal airway or intubate if needed)

- Check blood pressure.
- Begin nasal oxygen.
- Monitor ECG and respiration.
- Check temperature frequently.
- Obtain history.
- Perform neurologic examination.

Send sample serum for evaluation of electrolytes, blood urea nitrogen, glucose level, complete blood cell count, toxic drug screen, and anticonvulsant levels; check arterial blood gas values.

Start IV line containing isotonic saline at a low infusion rate.

Inject 50 mL of 50 percent glucose IV and 100 mg of thiamine IV or IM.

Call EEG laboratory to start recording as soon as feasible.

Administer lorazepam (Ativan) at 0.1 to 0.15 mg per kg IV (2 mg per minute); if seizures persist, administer fosphenytoin (Cerebix) at 18 mg per kg IV (150 mg per minute, with an additional 7 mg per kg if seizures continue).

At: 20 to 30 minutes, if seizures persist

Intubate, insert bladder catheter, start EEG recording, check temperature.

Administer phenobarbital in a loading dose of 20 mg per kg IV (100 mg per minute).

At: 40 to 60 minutes, if seizures persist

Begin pentobarbital infusion at 5 mg per kg IV initial dose, then IV push until seizures have stopped, using EEG monitoring; continue pentobarbital infusion at 1 mg per kg per hour; slow infusion rate every four to six hours to determine if seizures have stopped, with EEG guidance; monitor blood pressure and respiration carefully. Support blood pressure with pressors if needed.

or

Begin midazolam (Versed) at 0.2 mg per kg, then at a dosage of 0.75 to 10 mg per kg per minute, titrated to EEG monitoring.

or

Begin propofol (Diprivan) at 1 to 2 mg per kg loading dose, followed by 2 to 10 mg per kg per hour. Adjust maintenance dosage on the basis of EEG monitoring.

FIGURE 1. Suggested management of status epilepticus. (ECG = electrocardiography; IV = intravenous; IM = intramuscular; EEG = electroencephalography)

Adapted with permission from Treatment of convulsive status epilepticus. Recommendations of the Epilepsy Foundation of America's Working Group on Status Epilepticus. JAMA 1993;270:857, and Lowenstein DH, Alldredge BK. Status epilepticus. N Engl J Med 1998;338:972.

Status Epilepticus

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