critical care review

The Management of Status Epilepticus*

Paul E. Marik, MD, FCCP; and Joseph Varon, MD, FCCP

Status epilepticus is a major medical emergency associated with significant morbidity and mortality. Status epilepticus is best defined as a continuous, generalized, convulsive seizure lasting > 5 min, or two or more seizures during which the patient does not return to baseline consciousness. Lorazepam in a dose of 0.1 mg/kg is the drug of first choice for terminating status epilepticus. Patients who continue to have clinical or EEG evidence of seizure activity after treatment with lorazepam should be considered to have refractory status epileptics and should be treated with a continuous infusion of propofol or midazolam. This article reviews current information regarding the management of status epilepticus in adults.

(CHEST 2004; 126:582–591)

Key words: anticonvulsants; barbiturates; lorazepam; midazolam; phenytoin; propofol; refractory status epilepticus; status epilepticus

Abbreviations: CI = confidence interval; GABA = γ-aminobutyric acid; NMDA = N-methyl-D aspartate; VA = Veterans Affairs

S tatus epilepticus is a major medical emergency associated with significant morbidity and a mortality rate of up to 76% in elderly patients with refractory status epilepticus.[1] This clinical entity requires prompt management. The complications of status epilepticus include cardiac dysrrhythmias, derangements of metabolic and autonomic function, neurogenic pulmonary edema, hyperthermia, rhabdomyolysis, and pulmonary aspiration. Permanent neurologic damage occurs with prolonged uncontrolled convulsive activity. This article reviews the current information regarding the management of status epilepticus in adults.

Correspondence to: Paul Marik, MD, FCCP, Professor of Critical Care, Department of Critical Care Medicine, University of Pittsburgh, 640A Scaife Hall, 3550 Terrace St, Pittsburgh, PA, 15261; e-mail: maripe@ccm.upmc.edu

DEFINITION OF STATUS EPILEPTICUS

Status epilepticus is usually defined as continuous seizure activity lasting 30 min or as two or more discrete seizures between which consciousness is not fully regained.[2–4] Lowenstein et al[5] have proposed that status epilepticus be defined as a continuous, generalized, convulsive seizure lasting > 5 min, or two or more seizures during which the patient does not return to baseline consciousness. The rationale for this revised definition is based on the fact that a typical, generalized tonic-clonic seizure rarely lasts > 5 min, that spontaneous termination becomes less likely in seizures of > 5 min, and that the longer the seizure continues, the more difficult the seizure becomes to control with antiepileptic drugs, and the greater the degree of neuronal damage.[5–9] This definition is consistent with common clinical practice in which it would be unreasonable to wait 30 min before initiating antiepileptic drug therapy.

Refractory status epilepticus is usually defined as seizures lasting > 2 h, or seizures recurring at a rate of two or more episodes per hour without recovery to baseline between seizures, despite treatment with conventional antiepileptic drugs.[10] However, from a clinical perspective, it is preferable to consider refractory status epilepticus in any patient who has not responded to first-line therapy.[3,11]

CLASSIFICATION

Many types of epileptic seizures have been described, and, therefore, it follows that there are many types of status epilepticus. This has led to complex classifications of status epilepticus.[12] However, using electroclinical features, status epilepticus may be classified simply by the presence of motor convulsions (*convulsive status epilepticus*) or their absence (*nonconvulsive status epilepticus*). They may be further divided into status epilepticus that affects the whole brain (*generalized status epilepticus*) or only part of the brain (*partial status epilepticus*). This review will focus predominantly on generalized convulsive status epilepticus, which is the form most commonly observed in clinical practice.

EPIDEMIOLOGY

It has been estimated that up to150,000 cases of status epilepticus and 55,000 deaths from it occur annually in the United States.[13] Geography, sex, age, and race influence the epidemiology of status epilepticus. An incidence of between 6.2 and 18.3 per 100,000 population has been reported in the United States.[13–15] Regardless of geographic influences, status epilepticus appears to be more frequent among men, blacks, and the aged.[14,16–18] The incidence of status epilepticus in the elderly population is at least twice that of the general population.[19,20] Status epilepticus in the elderly is of great concern because of the existence of concurrent medical conditions that are more likely to complicate therapy and worsen the prognosis.[20,21]

ETIOLOGY

In many patients with a preexistent seizure disorder, no obvious precipitating factor can be determined. A fall in serum levels of antiepileptic drugs due to poor compliance with medications or to due to increased clearance associated with concurrent illness has been implicated in some patients.[22,23] Adult patients with a new diagnosis of epilepsy may first present while in status epilepticus.[20] Genetic factors likely play a role as twin studies[24] have demonstrated a greater concordance in monozygotic as apposed to dizygotic twins. Table 1 depicts the most common causes of status epilepticus seen in "first-world" populations.[8,9,16,18,25–32]

PATHOPHYSIOLOGY

It is likely that the ineffective recruitment of inhibitory neurons together with excessive neuronal

Table 1—*Common Causes of Status Epilepticus*

Antiepileptic drug noncompliance
Alcohol related
Cerebrovascular accidents
Drug toxicity (*ie*, cephalosporins, penicillins, ciprofloxacin, tacrolimus, cyclosporin, theophylline, and cocaine)
CNS infections (*eg*, meningitis and encephalitis)
CNS tumors (primary or secondary)
Metabolic disturbances (*eg*, electrolyte abnormalities, sepsis, and uremia)
Head trauma
Cerebral anoxia/hypoxia
Hypoglycemia or hyperglycemia

excitation play a role in the initiation and propagation of the electrical disturbance occurring in status epilepticus. γ-Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the CNS. It is released from GABAergic neurons and binds to several types of GABA receptors (*ie*, GABA-A, GABA-B, and GABA-C receptors). GABA receptors are macromolecular proteins that form a chloride ion channel complex and contain specific binding sites for GABA and a number of allosteric regulators, including barbiturates, benzodiazepines, and a number of anesthetic agents. GABA receptor-mediated inhibition may be responsible for the normal termination of a seizure. In addition, the activation of the N-methyl-D aspartate (NMDA) receptor by the excitatory neurotransmitter glutamate may be required for the propagation of seizure activity.[33,34] The activation of NMDA receptors results in increased levels of intracellular calcium, which may responsible for the nerve cell injury seen in patients in status epilepticus.[33–35] A growing body of basic science and clinical observation supports the concept that status epilepticus becomes more difficult to control as its duration increases.[7–9] It is been postulated that this may occur due to a mechanistic shift from inadequate GABAergic inhibitory receptor-mediated transmission to excessive NMDA excitatory receptor-mediated transmission.[36–41]

In humans and experimental animals, sustained seizures cause selective neuronal loss in vulnerable regions such as the hippocampus, cortex, and thalamus.[42,43] The degree of neuronal injury is closely related to the duration of seizures, underscoring the importance of the rapid control of status epilepticus.[43,44] Meldrum and Brierley,[45] and Nevander et al[46] have demonstrated that even without attendant hypoxia, acidosis, hyperthermia, or hypoglycemia, ongoing seizures in primates and rats can cause neuronal death. Wasterlain et al[47] reported neuronal loss in the hippocampus and other brain regions in patients with nonconvulsive status epilepticus who

did not have preexisting seizures or systemic abnormalities. Neuron-specific enolase, a marker for acute neurologic injury, has been demonstrated to be increased in patients with nonconvulsive status epilepticus who did not have preceding or coexistent cerebral injury.[48–51] Thom and coworkers[52] demonstrated evidence of acute neurol injury using heat shock protein-70 and c-Jun immunochemistry in patients who had sudden and unexpected death from epilepsy. Neuronal death is probably caused by the release of excitatory neurotransmitters. In an experimental model, Mikati and coauthors[53] have demonstrated that increased NMDA activation results in increased ceramide levels followed by programmed cell death.

Diagnosis

Status epilepticus may be divided into two stages.[54] The first stage is characterized by generalized convulsive tonic-clonic seizures that are associated with an increase in autonomic activity that results in hypertension, hyperglycemia, sweating, salivation, and hyperpyrexia. During this phase, cerebral blood flow is increased due to increased cerebral metabolic demands. After approximately 30 min of seizure activity, patients enter the second phase, which is characterized by the failure of cerebral autoregulation, decreased cerebral blood flow, an increase in intracranial pressure, and systemic hypotension. During this phase, electromechanical dissociation may occur in which, although electrical cerebral seizure activity continues, the clinical manifestations may be restricted to minor twitching.

The diagnosis of status epilepticus is straightforward in patients with witnessed generalized convulsive tonic-clonic seizures. However, status epilepticus may not be considered in patients who have progressed to the nonconvulsive phase of status epilepticus and present in coma. All comatose patients should therefore be carefully examined for evidence of minor twitching, which may involve the face, hands, or feet, or may present as nystagmoid jerking of the eyes. Towne and colleagues[28] evaluated 236 patients with coma and no overt seizure activity. Eight percent of patients in this study were found to have nonconvulsive status epilepticus, as determined by EEG monitoring. Therefore, it is essential that an urgent EEG be performed in patients with unexplained coma.

Treatment

Status epilepticus is a medical emergency that requires rapid and aggressive treatment to prevent neurologic damage and systemic complications. The longer status epilepticus remains untreated, the greater the neurologic damage. In addition, the longer an episode of status continues, the more refractory to treatment it becomes and the greater is the likelihood of chronic epilepsy. The management of status epilepticus involves the rapid termination of seizure activity, airway protection, the taking of measures to prevent aspiration, the management of potential precipitating causes, the treatment of complications, the prevention of recurrent seizures, and the treatment of any underlying conditions.

General Measures

As with any critically ill patient, the first step in the management of a patient with status epilepticus should be to ensure an adequate airway and to provide respiratory support. The patient should be positioned so that they cannot harm themselves during the seizure activity. Two large-gauge IV catheters should be inserted to allow fluid resuscitation and pharmacotherapy. Should peripheral venous access be difficult, the placement of a central venous catheter is recommended. Despite the periods of apnea and cyanosis that occur during the tonic or clonic phases of their seizure, most patients in status epilepticus breathe sufficiently well as long as the airway remains clear. An oral airway may be required once the seizure has terminated to prevent airway obstruction. Once the seizures are controlled, and if the patient is oxygenating and ventilating adequately, endotracheal intubation may not be required for airway protection, even if the patient remains comatose.[55] However, in this situation precautions should be taken to avoid aspiration, and a nasogastric tube should be placed to ensure that the stomach is empty. Endotracheal intubation will be required in patients who continue to experience seizures despite receiving first-line therapy. There are no available data as to the pharmacologic agents that are preferred for achieving endotracheal intubation. As these patients will be comatose and would already have received therapy with lorazepam, a hypnotic agent is usually not required. However, an anesthetic induction dose of propofol, midazolam, or etomidate may terminate the seizure activity and facilitate intubation.[56,57] Neuromuscular blockade will be required to facilitate intubation in patients who continue to have tonic-clonic seizure activity despite these pharmacologic interventions. Rocuronium (1 mg/kg), a short-acting, non-depolarizing muscle relaxant that is devoid of significant hemodynamic effects and does not increase intracranial pressure, is the preferred agent.[58,59] Succinylcholine should be avoided, if possible, as the patient may be

hyperkalemic as a consequence of experiencing rhabdomyolysis. Prolonged neuromuscular blockade should be avoided.

Hypoglycemia must be excluded rapidly, and corrective measures must be instituted if serum levels of glucose are low. If the prompt measurement of blood glucose levels is not possible, the patient should receive100 mg IV thiamine followed by a 50-mL bolus of 50% dextrose. BP, ECG, and temperature should be monitored. If the patient develops significant hyperthermia (ie, temperature > 40°C), then passive cooling is required.[11] Blood specimens should be obtained for the determination of serum chemistry levels. Continuous motor seizures may lead to muscle breakdown, with the release of myoglobin into the circulation. The maintenance of adequate hydration is necessary to prevent myoglobin-induced renal failure. Forced saline solution diuresis and urinary alkalinization should be considered in the presence of myoglobinuria or significantly elevated serum creatine kinase levels (ie, > 5,000 to 10,000 U/L).[4,11] Brain imaging with a CT scan and/or MRI as well as a lumbar puncture will be required in patients presenting with a previously undiagnosed seizure disorder once the seizure activity has been controlled. It is important to emphasize that the first priority is to control the seizures. Imaging studies should be performed only once the seizure activity has been controlled. Endotracheal intubation and neuromuscular paralysis for the sole purpose of imaging the patient may increase morbidity and is strongly discouraged.

Pharmacotherapy

Because only a small fraction of seizures go on to become status epilepticus, the probability that a given seizure will proceed to status is small at the start of the seizure and increases as the seizure duration increases. If a seizure lasts > 5 min, clinical experience suggests that the likelihood of spontaneous termination decreases. The goal of pharmacologic therapy is to achieve the rapid and safe termination of the seizure, and to prevent its recurrence without adverse effects on the cardiovascular and respiratory systems or altering the level of consciousness.[4] Diazepam, lorazepam, midazolam, phenytoin, fosphenytoin, and phenobarbital have all been used as first-line therapy for the termination of status epilepticus. These drugs have different pharmacodynamic and pharmacokinetic properties, which determine their rapidity of clinical effect, their efficacy in terminating status epilepticus, and their duration of action. The benzodiazepines bind to the benzodiazepine binding site on the GABA receptor complex,

increasing GABAergic transmission, while the barbiturates act directly on the GABA receptor. The antiseizure activity of phenytoin is complex, however, its major action appears to block the voltage-sensitive, use-dependent sodium channels.

The publication of the Veterans Affairs (VA) cooperative trial in 1998[9] and the San Francisco Emergency Medical Services study in 2001[25] allows for an evidence-based approach to the choice of the first-line agent to use in terminating status epilepticus. The VA cooperative study[9] randomized 384 patients with overt generalized status epilepticus into four treatment arms, as follows: lorazepam, 0.1 mg/kg; diazepam, 0.15 mg/kg, followed by 18 mg/kg phenytoin; phenytoin, 18 mg/kg; and phenobarbital, 15 mg/kg. Successful treatment required both clinical and EEG termination of seizures within 20 min of the start of therapy, and no seizure recurrence within 60 min from the start of therapy. Patients who did not respond to the first treatment received a second choice of treatment drug and, if necessary, a third choice. The latter choices were not randomized, because this would have resulted in some patients receiving two loading doses of phenytoin, but the treating physician remained blinded to the treatments being given. Status epilepticus was terminated in 64.9% of patients randomized to lorazepam, 58.2% of those randomized to phenobarbital, 55.8% of those randomized to diazepam and phenytoin, and 43.6% of those randomized to phenytoin (p = 0.002 for lorazepam vs phenytoin). There was no difference between the arms in recurrence rates.

The San Francisco Emergency Medical Services study[25] was a randomized, double-blind trial to evaluate IV benzodiazepine administration by paramedics for the treatment of out-of-hospital patients with status epilepticus.[25] In this study, 205 patients were randomized to IV diazepam (5 mg), lorazepam (2 mg), or placebo. An identical second injection was administered if needed. Status epilepticus had terminated at arrival in the emergency department in 59.1% of the patients treated with lorazepam, in 42.6% of the patients treated with diazepam, and in 21.1% of patients treated with placebo (lorazepam vs diazepam: odds ratio, 1.9; 95% confidence interval [CI], 0.9 to 4.3). The duration of the status epilepticus was shorter in the lorazepam group compared to the diazepam group (adjusted relative hazard, 0.65; 95% CI, 0.36 to 1.17). These data are supported by a double-blind study reported by Leppik et al[60] in 1983 in which 78 patients with status epilepticus were randomized to receive one or two doses of either lorazepam (4 mg) or diazepam (10 mg). Seizures were controlled in 89% of the episodes treated with lorazepam and in 76% of those treated with diazepam. Although the

dosages of lorazepam and diazepam differed in these three studies and phenytoin was added to diazepam in the VA study,[25] the summed data indicate that lorazepam is significantly more effective in terminating seizures than is diazepam (odds ratio, 1.74; 95% CI, 1.14 to 2.64; p = 0.01). Furthermore, the pharmacokinetic properties of lorazepam favor its use over that of diazepam. The anticonvulsant effect of a single dose of diazepam is very brief (20 min), whereas that of lorazepam is much longer (> 6 h), and the risk of respiratory depression may be greater with diazepam.[61] Although diazepam has a much longer elimination half-life, due to its high lipid solubility it is rapidly redistributed from the brain to the peripheral fat stores, accounting for its shorter antiseizure activity.

Based on these data, lorazepam in a dose of 0.1 mg/kg is recommended as first-line therapy for the control of status epilepticus. Although refrigeration is recommended for lorazepam, but not for diazepam, Gottwald and coworkers[62] have demonstrated that lorazepam retains 90% of its original concentration when stored without refrigeration in ambulances (in San Francisco) for 5 months. Based on this information, lorazepam should replace diazepam in hospital code carts and "orange bags," it should be stored in light-proof containers, and should be restocked every 4 to 6 months.[25,62] Many authorities recommend phenytoin, 20 mg/kg (or fosphenytoin), following the administration of lorazepam. While there are no data that demonstrate that phenytoin increases the response rate following the use of lorazepam, this agent may prevent recurrent seizures and is recommended in patients without a rapidly reversible process (*eg*, the effect of subtherapeutic antiepileptic drug concentrations).[3]

Continuous EEG monitoring is required in patients who do not recover consciousness once the convulsive seizure has aborted. In a study by DeLorenzo and colleagues,[63] after the cessation of convulsions, 48% of patients continued to have seizure activity and 14% of patients had persistent nonconvulsive status epilepticus.

Management of Refractory Status Epilepticus

In the VA cooperative study,[9] 55% of patients with generalized convulsive status epilepticus did not respond to first-line therapy. The aggregate response rate to a second first-line agent (*eg*, lorazepam, diazepam, phenytoin, or phenobarbital) was 7%, and to a third first-line agent it was 2.3%. Only 5% of patients with status epilepticus who did not respond to lorazepam and phenytoin therapy, responded to

phenobarbital administration. These data suggest that refractory status epilepticus is much more common than is generally appreciated and that phenobarbital should not be used as a second (or third-line) agent in patients who have failed to respond to lorazepam. Furthermore, the limited data available suggest that the administration of further doses of lorazepam will not be useful.[60]

A variety of agents has been recommended for the treatment of refractory status epilepticus, including midazolam, propofol, high-dose thiopentone or pentobarbital, IV valproate, topiramate, tiagabine, ketamine, isoflurane, and IV lidocaine. Treatment guidelines are difficult to formulate as refractory status epilepticus has not been studied in a prospective clinical trial. Currently, however, a continuous IV infusion of midazolam or propofol together with continuous EEG monitoring is the preferred mode of treatment.[8,64] Both agents have been reported[10,65–77] to be successful in the control of patients with refractory status epilepticus. It should, however, be pointed out that this recommendation is based on limited clinical data, with just > 100 cases of treatment with these agents having been reported.[64,67]

Claassen and colleagues[64] reported a "systematic review" that compared the outcome of patients with refractory status epilepticus who had been treated with pentobarbital, propofol, or midazolam. In this report, there were fewer treatment failures and breakthrough seizures with the use of pentobarbital than with the use of propofol or midazolam. As this study was a summation of 28 individual case series that did not control for the underlying medical condition, the cause of seizure, type of seizure, length of time prior to treatment, prior therapy, and end points of therapy, it is difficult to make any definitive conclusions regarding drug efficacy from this report.

The goal regarding the activity on the EEG remains a matter of debate. There is no prospectively collected evidence that a burst-suppression EEG pattern is required for, or is efficacious for, the termination of status epilepticus. Many patients can achieve complete seizure control with a background of continuous slow activity and do not incur the greater risks associated with higher doses of medication required to achieve a burst-suppression pattern.

Midazolam is a fast-acting, water-soluble benzodiazepine with a half-life of 4 to 6 h. The drug undergoes hepatic transformation into an active metabolite that is renally cleared. One of the major disadvantages of midazolam is tachyphylaxis. After 24 to 48 h, the dose of the drug often must be increased severalfold to maintain seizure control. Furthermore, the drug accumulates with prolonged infusion, which may result in a prolonged time to

awakening.[69,78] Midazolam is given as a loading dose of 0.2 mg/kg, followed by an infusion of 0.1 to 2.0 mg/kg/h titrated to produce seizure suppression by continuous EEG monitoring.

Propofol is an IV alkylphenol (2,6-diisopropylphenol), which has been used extensively for the induction and maintenance of anesthesia and for sedation in the ICU.[79] Propofol is a global CNS depressant. It directly activates the GABA receptor.[79,80] In addition, propofol inhibits the NMDA receptor, modulates calcium influx through slow calcium ion channels, and has antioxidant activity.[81–87] Experimental data have shown propofol to have strong anticonvulsant properties,[88–92] which have proved to be very effective in controlling refractory status epilepticus.[10,71–77,93] Propofol is highly lipophilic with a large volume of distribution. This property results in rapid uptake and elimination from the CNS, resulting in rapid onset of action and rapid recovery when discontinued. Recovery is rapid even with prolonged use. Propofol is metabolized by glucuronide and sulfate conjugation, and does not accumulate with long-term infusion. Dose reduction is not required in patients with hepatic or renal disease. Furthermore, the drug is easily titratable. A loading dose of 3 to 5 mg/kg is recommended followed by an infusion of 30 to 100 μg/kg/min titrated to EEG seizure suppression. After 12 h of seizure suppression, the dose is gradually titrated by 50% over the next 12 h and then titrated to 0% over the subsequent 12 h. If seizure activity should recur during the weaning period, a further loading dose of 1 to 3 mg/kg should be administered followed by infusion with the rate increased to obtain another 12-h seizure-free period.[71]

Propofol has been administered to > 40 million patients with a remarkable safety record. The most severe complication associated with propofol is the "propofol infusion syndrome," a very rare complication reported predominantly in pediatric patients and associated with high-dose propofol infusion.[94–96] The propofol infusion syndrome is characterized by severe metabolic acidosis, rhabdomyolysis, and cardiovascular collapse frequently leading to death.[94–96] Circumstantial data suggest that this disorder is due to interference with mitochondrial respiration.[97–100] It is possible that the full-blown propofol infusion syndrome occurs only in those individuals with a genetic susceptibility. However, the risk appears to be higher in children, in whom the drug is contraindicated. It is currently recommended that the dosage not exceed 100 μg/kg/min in adults.[94,101,102] Hyperlipidemia may result from the failure of free fatty acid metabolism and hence may be a useful early marker of the development of the syndrome. Consequently, triglyceride and creatine kinase levels (a marker of rhabdomyolysis) should be monitored in patients receiving prolonged high-dose infusions of propofol.

High-dose barbiturate therapy is associated with hemodynamic instability and immune paresis. Due to their side effects, therapy with barbiturates is reserved for those patients who do not respond to midazolam or propofol. Pentobarbital therapy, in a dose of 10 to 15 mg/kg/h followed by a dose of 0.5 to 1.0 mg/kg/h, is recommended. The pharmacologic approach to a patient in status epilepticus is outlined in Figure 1.

The Management of Nonconvulsive Status Epilepticus

Nonconvulsive status epilepticus constitutes approximately 20 to 25% of status epilepticus cases,[103,104] occurring in about 8% of all comatose patients without clinical signs of seizure activity,[28] and persisting in 14% of patients after generalized convulsive status epilepticus.[63] Some have suggested[104–107] that nonconvulsive status epilepticus is a benign condition that does not require aggressive therapy. However, the prognosis of nonconvulsive status epilepticus depends on the etiology and the level of consciousness. These are associated with significant morbidity in those patients with a depressed level of consciousness.[108–110] Furthermore, experimental and clinical data suggest that nonconvulsive status epilepticus may cause ongoing neuronal injury.[42,43,48–51] Shneker and Fountain[111] reviewed their experience with 100 cases of nonconvulsive status epilepticus. In this report, nonconvulsive status epilepticus was associated with a high mortality rate (18%) and a significant morbidity rate (39%), with the mortality rate correlating with the underlying etiology of nonconvulsive status epilepticus, the degree of impairment in mental status, and the development of acute complications. The mortality rate was 18% in those patients with cryptogenic nonconvulsive status epilepticus, attesting to the serious sequelae of ongoing seizures. Based on this information, we suggest that comatose patients with nonconvulsive status epilepticus and nonconvulsive status epilepticus following generalized convulsive status epilepticus be treated aggressively as outlined above for refractory convulsive status epilepticus.

Prevention of Seizure Recurrence Once Status Epilepticus Is Terminated

Once status epilepticus is controlled, attention turns to preventing its recurrence. The best regimen
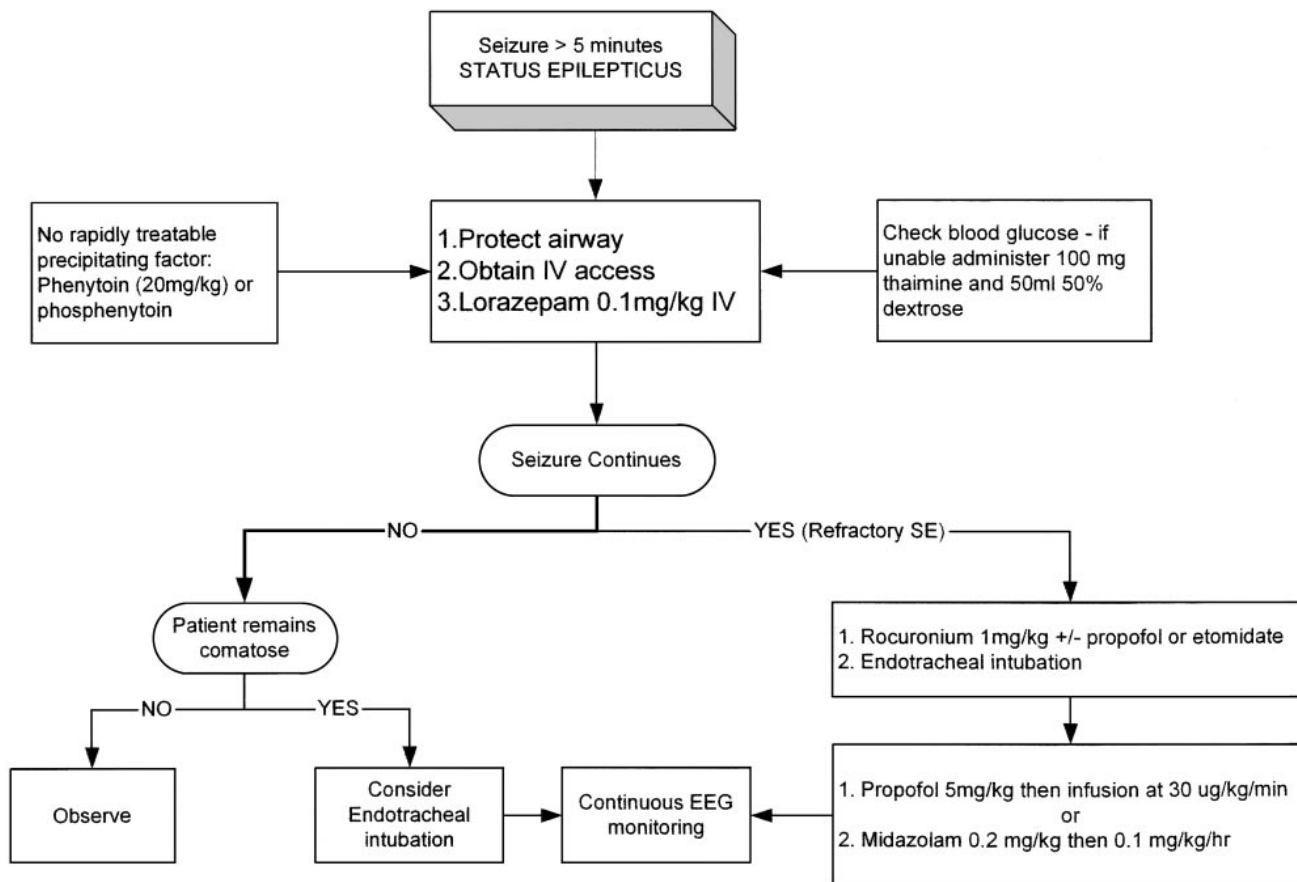
FIGURE 1. The pharmacologic approach to a patient in status epilepticus.

for an individual patient will depend on the cause of the seizure and any history of antiepileptic drug therapy. A patient who develops status epilepticus in the course of ethanol withdrawal may not need antiepileptic drug therapy once the withdrawal has run its course. In contrast, patients with new, ongoing epileptogenic stimuli (eg, encephalitis) may require high dosages of antiepileptic drugs to control their seizures.

PROGNOSIS

The prognosis of status epilepticus depends on several factors including the clinical presentation, the duration of seizures, the age of the patient, and, most importantly, the underlying disorder causing the seizures.[1] Refractory status epilepticus has a mortality rate of up to 76% in elderly patients.[1] In a population-based, long-term mortality study,[1] the 10-year cumulative mortality rate among 30-day survivors was 43%, with a standardized mortality ratio of 2.8. However, the mortality rate of those patients with idiopathic status epilepticus was not increased (standardized mortality ratio, 1.1).

CONCLUSIONS

Patients who have generalized seizures that continue for more than 5 min should be considered to have status epilepticus and should be treated with a single IV dose of lorazepam (0.1 mg/kg). Patients who continue to have clinical or EEG evidence of seizure activity after receiving treatment with lorazepam should be considered to have refractory status epilepticus and should treated with a continuous infusion of propofol or midazolam.

REFERENCES

1 Logroscino G, Hesdorffer DC, Cascino GD, et al. Long-term mortality after a first episode of status epilepticus. Neurology 2002; 58:537–541
2 Epilepsy Foundation of America. Treatment of convulsive status epilepticus: recommendations of the Epilepsy Foundation of America's Working Group on Status Epilepticus. JAMA 1993; 270:854–859
3 Lowenstein DH, Alldredge BK. Status epilepticus. N Engl J Med 1998; 338:970–976
4 Chapman MG, Smith M, Hirsch NP. Status epilepticus. Anaesthesia 2001; 56:648–659
5 Lowenstein DH, Bleck T, Macdonald RL. It's time to revise the definition of status epilepticus. Epilepsia 1999; 40:120–122

6 DeLorenzo RJ, Garnett LK, Towne AR, et al. Comparison of status epilepticus with prolonged seizure episodes lasting from 10 to 29 minutes. Epilepsia 1999; 40:164–169

7 Walton NY, Treiman DM. Response of status epilepticus induced by lithium and pilocarpine to treatment with diazepam. Exp Neurol 1988; 101:267–275

8 Mayer SA, Claassen J, Lokin J, et al. Refractory status epilepticus: frequency, risk factors, and impact on outcome. Arch Neurol 2002; 59:205–210

9 Treiman DM, Meyers PD, Walton NY. A comparison of four treatments for generalized convulsive status epilepticus: Veterans Affairs Status Epilepticus Cooperative Study Group. N Engl J Med 1998; 339:792–798

10 Prasad A, Worrall BB, Bertram EH, et al. Propofol and midazolam in the treatment of refractory status epilepticus. Epilepsia 2001; 42:380–386

11 Bleck TP. Management approaches to prolonged seizures and status epilepticus. Epilepsia 1999; 40(suppl):S59–S63

12 Browne TR, Holmes GL. Epilepsy. N Engl J Med 2001; 344:1145–1151

13 DeLorenzo RJ, Pellock JM, Towne AR, et al. Epidemiology of status epilepticus. J Clin Neurophysiol 1995; 12:316–325

14 Wu YW, Shek DW, Garcia PA, et al. Incidence and mortality of generalized convulsive status epilepticus in California. Neurology 2002; 58:1070–1076

15 Hesdorffer DC, Logroscino G, Cascino G, et al. Incidence of status epilepticus in Rochester, Minnesota, 1965–1984. Neurology 1998; 50:735–741

16 Knake S, Rosenow F, Vescovi M, et al. Incidence of status epilepticus in adults in Germany: a prospective, population-based study. Epilepsia 2001; 42:714–718

17 DeGiorgio CM, Altman K, Hamilton-Byrd E, et al. Lidocaine in refractory status epilepticus: confirmation of efficacy with continuous EEG monitoring. Epilepsia 1992; 33:913–916

18 Coeytaux A, Jallon P, Galobardes B, et al. Incidence of status epilepticus in French-speaking Switzerland: (EPISTAR). Neurology 2000; 55:693–697

19 Parviainen I, Uusaro A, Kalviainen R, et al. High-dose thiopental in the treatment of refractory status epilepticus in intensive care unit. Neurology 2002; 59:1249–1251

20 Hauser WA. Status epilepticus: epidemiologic considerations. Neurology 1990; 40:9–13

21 Ramsay RE, Pryor F. Epilepsy in the elderly. Neurology 2000; 55:S9–S14

22 Lowenstein DH, Alldredge BK, Allen F, et al. The prehospital treatment of status epilepticus (PHTSE) study: design and methodology. Control Clin Trials 2001; 22:290–309

23 Alldredge BK, Lowenstein DH. Status epilepticus: new concepts. Curr Opin Neurol 1999; 12:183–190

24 Corey LA, Pellock JM, Boggs JG, et al. Evidence for a genetic predisposition for status epilepticus. Neurology 1998; 50:558–560

25 Alldredge BK, Gelb AM, Isaacs SM, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. N Engl J Med 2001; 345:631–637

26 Dennis LJ, Claassen J, Hirsch LJ, et al. Nonconvulsive status epilepticus after subarachnoid hemorrhage. Neurosurgery 2002; 51:1136–1143

27 Krieger AC, Takeyasu M. Nonconvulsive status epilepticus in theophylline toxicity. J Toxicol Clin Toxicol 1999; 37:99–101

28 Towne AR, Waterhouse EJ, Boggs JG, et al. Prevalence of nonconvulsive status epilepticus in comatose patients. Neurology 2000; 54:340–345

29 Rumbach L, Sablot D, Berger E, et al. Status epilepticus in stroke: report on a hospital-based stroke cohort. Neurology 2000; 54:350–354

30 Dixit S, Kurle P, Buyan-Dent L, et al. Status epilepticus associated with cefepime. Neurology 2000; 54:2153–2155

31 Martinez-Rodriguez JE, Barriga FJ, Santamaria J, et al. Nonconvulsive status epilepticus associated with cephalosporins in patients with renal failure. Am J Med 2001; 111:115–119

32 Labovitz DL, Hauser WA, Sacco RL. Prevalence and predictors of early seizure and status epilepticus after first stroke. Neurology 2001; 57:200–206

33 Boggs JG, Painter JA, DeLorenzo RJ. Analysis of electrocardiographic changes in status epilepticus. Epilepsy Res 1993; 14:87–94

34 Rice AC, DeLorenzo RJ. NMDA receptor activation during status epilepticus is required for the development of epilepsy. Brain Res 1998; 782:240–247

35 Pal S, Sombati S, Limbrick DD Jr, et al. *In vitro* status epilepticus causes sustained elevation of intracellular calcium levels in hippocampal neurons. Brain Res 1999; 851:20–31

36 Bleck TP. Refractory status epilepticus in 2001. Arch Neurol 2002; 59:188–189

37 Kapur J, Stringer JL, Lothman EW. Evidence that repetitive seizures in the hippocampus cause a lasting reduction of GABAergic inhibition. J Neurophysiol 1989; 61:417–426

38 Kapur J, Lothman EW. Loss of inhibition precedes delayed spontaneous seizures in the hippocampus after tetanic electrical stimulation. J Neurophysiol 1989; 61:427–434

39 Kapur J, Macdonald RL. Rapid seizure-induced reduction of benzodiazepine and Zn2+ sensitivity of hippocampal dentate granule cell GABAA receptors. J Neurosci 1997; 17:7532–7540

40 Walton NY, Treiman DM. Motor and electroencephalographic response of refractory experimental status epilepticus in rats to treatment with MK-801, diazepam, or MK-801 plus diazepam. Brain Res 1991; 553:97–104

41 Borris DJ, Bertram EH, Kapur J. Ketamine controls prolonged status epilepticus. Epilepsy Res 2000; 42:117–122

42 During MJ, Spencer DD. Extracellular hippocampal glutamate and spontaneous seizure in the conscious human brain. Lancet 1993; 341:1607–1610

43 Lowenstein DH, Simon RP, Sharp FR. The pattern of 72-kDa heat shock protein-like immunoreactivity in the rat brain following flurothyl-induced status epilepticus. Brain Res 1990; 531:173–182

44 Tanaka K, Graham SH, Simon RP. The role of excitatory neurotransmitters in seizure-induced neuronal injury in rats. Brain Res 1996; 737:59–63

45 Meldrum BS, Brierley JB. Prolonged epileptic seizures in primates: ischemic cell change and its relation to ictal physiological events. Arch Neurol 1973; 28:10–17

46 Nevander G, Ingvar M, Auer R, et al. Status epilepticus in well-oxygenated rats causes neuronal necrosis. Ann Neurol 1985; 18:281–290

47 Wasterlain CG, Fujikawa DG, Penix L, et al. Pathophysiological mechanisms of brain damage from status epilepticus. Epilepsia 1993; 34(suppl):S37–S53

48 DeGiorgio CM, Gott PS, Rabinowicz AL, et al. Neuron-specific enolase, a marker of acute neuronal injury, is increased in complex partial status epilepticus. Epilepsia 1996; 37:606–609

49 Rabinowicz AL, Correale JD, Bracht KA, et al. Neuron-specific enolase is increased after nonconvulsive status epilepticus. Epilepsia 1995; 36:475–479

50 Rabinowicz AL, Correale JD, Couldwell WT, et al. CSF neuron-specific enolase after methohexital activation during

electrocorticography. Neurology 1994; 44:1167–1169

51 DeGeorgio CM, Correale JD, Ginsburg DL. Serum neuron specific enolase in status epilepticus [abstract]. Neurology 1994; 44(suppl):205

52 Thom M, Seetah S, Sisodiya S, et al. Sudden and unexpected death in epilepsy (SUDEP): evidence of acute neuronal injury using HSP-70 and c-Jun immunohistochemistry. Neuropathol Appl Neurobiol 2003; 29:132–143

53 Mikati MA, Abi-Habib RJ, El Sabban ME, et al. Hippocampal programmed cell death after status epilepticus: evidence for NMDA-receptor and ceramide-mediated mechanisms. Epilepsia 2003; 44:282–291

54 Lothman E. THe biochemical basis and pathophysiology of status epilepticus. Neurology 2003; 40(suppl):13–23

55 Coplin WM, Pierson DJ, Cooley KD, et al. Implications of extubation delay in brain-injured patients meeting standard weaning criteria. Am J Respir Crit Care Med 2000; 161: 1530–1536

56 Yeoman P, Hutchinson A, Byrne A, et al. Etomidate infusions for the control of refractory status epilepticus. Intensive Care Med 1989; 15:255–259

57 Wauquier A. Profile of etomidate: a hypnotic, anticonvulsant and brain protective compound. Anaesthesia 1983; 38(suppl):26–33

58 Marshall RJ, Muir AW, Sleigh T, et al. An overview of the pharmacology of rocuronium bromide in experimental animals. Eur J Anaesthesiol Suppl 1994; 9:9–15

59 Hudson ME, Rothfield KP, Tullock WC, et al. Haemodynamic effects of rocuronium bromide in adult cardiac surgical patients. Can J Anaesth 1998; 45:139–143

60 Leppik IE, Derivan AT, Homan RW, et al. Double-blind study of lorazepam and diazepam in status epilepticus. JAMA 1983; 249:1452–1454

61 Mitchell WG. Status epilepticus and acute repetitive seizures in children, adolescents, and young adults: etiology, outcome, and treatment. Epilepsia 1996; 37(suppl):S74–S80

62 Gottwald MD, Akers LC, Liu PK, et al. Prehospital stability of diazepam and lorazepam. Am J Emerg Med 1999; 17:333–337

63 DeLorenzo RJ, Waterhouse EJ, Towne AR, et al. Persistent nonconvulsive status epilepticus after the control of convulsive status epilepticus. Epilepsia 1998; 39:833–840

64 Claassen J, Hirsch LJ, Emerson RG, et al. Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. Epilepsia 2002; 43:146–153

65 Koul RL, Raj AG, Chacko A, et al. Continuous midazolam infusion as treatment of status epilepticus. Arch Dis Child 1997; 76:445–448

66 Igartua J, Silver P, Maytal J, et al. Midazolam coma for refractory status epilepticus in children. Crit Care Med 1999; 27:1982–1985

67 Ulvi H, Yoldas T, Mungen B, et al. Continuous infusion of midazolam in the treatment of refractory generalized convulsive status epilepticus. Neurol Sci 2002; 23:177–182

68 Singhi S, Murthy A, Singhi P, et al. Continuous midazolam versus diazepam infusion for refractory convulsive status epilepticus. J Child Neurol 2002; 17:106–110

69 Naritoku DK, Sinha S. Prolongation of midazolam half-life after sustained infusion for status epilepticus. Neurology 2000; 54:1366–1368

70 Claassen J, Hirsch LJ, Emerson RG, et al. Continuous EEG monitoring and midazolam infusion for refractory nonconvulsive status epilepticus. Neurology 2001; 57:1036–1042

71 Stecker MM, Kramer TH, Raps EC, et al. Treatment of refractory status epilepticus with propofol: clinical and pharmacokinetic findings. Epilepsia 1998; 39:18–26

72 Harrison AM, Lugo RA, Schunk JE. Treatment of convul-

sive status epilepticus with propofol: case report. Pediatr Emerg Care 1997; 13:420–422

73 Merigian KS, Browning RG, Leeper KV. Successful treatment of amoxapine-induced refractory status epilepticus with propofol. Acad Emerg Med 1995; 2:128–133

74 Tobias JD. The use of propofol to treat status epilepticus in a nine-month-old female patient. Pediatr Emerg Care 1998; 14:248–249

75 Pitt-Miller PL, Elcock BJ, Maharaj M. The management of status epilepticus with a continuous propofol infusion. Anesth Analg 1994; 78:1193–1194

76 Campostrini R, Bati MB, Giorgi C, et al. Propofol in the treatment of convulsive status epilepticus: a report of four cases. Riv Neurol 1991; 61:176–179

77 Mackenzie SJ, Kapadia F, Grant IS. Propofol infusion for control of status epilepticus. Anaesthesia 1990; 45:1043–1045

78 Hall RI, Sandham D, Cardinal P, et al. Propofol vs midazolam for ICU sedation: a Canadian multicenter randomized trial. Chest 2001; 119:1151–1159

79 Smith I, White PF, Nathanson M, et al. Propofol: an update on its clinical use. Anesthesiology 1994; 81:1005–1043

80 Hara M, Kai Y, Ikemoto Y. Propofol activates GABAA receptor-chloride ionophore complex in dissociated hippocampal pyramidal neurons of the rat. Anesthesiology 1993; 79:781–788

81 Orser BA, Bertlik M, Wang LY, et al. Inhibition by propofol (2,6 di-isopropylphenol) of the N-methyl-D-aspartate subtype of glutamate receptor in cultured hippocampal neurones. Br J Pharmacol 1995; 116:1761–1768

82 Hans P, Bonhomme V, Collette J, et al. Propofol protects cultured rat hippocampal neurons against N-methyl-D-aspartate receptor-mediated glutamate toxicity. J Neurosurg Anesthesiol 1994; 6:249–253

83 Zhou W, Fontenot J, Liu S, et al. Modulation of cardiac calcium channels by propofol. Anesthesiology 1997; 86:670–675

84 Olcese R, Usai C, Maestrone E, et al. The general anesthetic propofol inhibits transmembrane calcium current in chick sensory neurons. Anesth Analg 1994; 78:955–960

85 Green TR, Bennett SR, Nelson VM. Specificity and properties of propofol as an antioxidant free radical scavenger. Toxicol Appl Pharmacol 1994; 129:163–169

86 Tsuchiya M, Asada A, Maeda K, et al. Propofol versus midazolam regarding their antioxidant activities. Am J Respir Crit Care Med 2001; 163:26–31

87 Grasshoff C, Gillessen T. The effect of propofol on increased superoxide concentration in cultured rat cerebrocortical neurons after stimulation of N-methyl-d-aspartate receptors. Anesth Analg 2002; 95:920–922

88 Holtkamp M, Tong X, Walker MC. Propofol in subanesthetic doses terminates status epilepticus in a rodent model. Ann Neurol 2001; 49:260–263

89 Lee VC, Moscicki JC, DiFazio CA. Propofol sedation produces dose-dependent suppression of lidocaine-induced seizures in rats. Anesth Analg 1998; 86:652–657

90 Momota Y, Artru AA, Powers KM, et al. Posttreatment with propofol terminates lidocaine-induced epileptiform electroencephalogram activity in rabbits: effects on cerebrospinal fluid dynamics. Anesth Analg 1998; 87:900–906

91 Hasan Z, Hasan M, al Hader A, et al. A comparison of the anticonvulsant effects of propofol and thiopentone against pentylenetetrazol-induced convulsions in the rat. Clin Exp Pharmacol Physiol 1991; 18:691–695

92 Lowson S, Gent JP, Goodchild CS. Anticonvulsant properties of propofol and thiopentone: comparison using two tests in laboratory mice. Br J Anaesth 1990; 64:59–63

93 Hantson P, Van Brandt N, Verbeeck R, et al. Propofol for refractory status epilepticus. Intensive Care Med 1994; 20:611–612

94 Vasile B, Rasulo F, Candiani A, et al. The pathophysiology of propofol infusion syndrome: a simple name for a complex syndrome. Intensive Care Med 2003; 29:1417–1425

95 Parke TJ, Stevens JE, Rice AS, et al. Metabolic acidosis and fatal myocardial failure after propofol infusion in children: five case reports. BMJ 1992; 305:613–616

96 Kang TM. Propofol infusion syndrome in critically ill patients. Ann Pharmacother 2002; 36:1453–1456

97 Branca D, Roberti MS, Lorenzin P, et al. Influence of the anesthetic 2,6-diisopropylphenol on the oxidative phosphorylation of isolated rat liver mitochondria. Biochem Pharmacol 1991; 42:87–90

98 Branca D, Vincenti E, Scutari G. Influence of the anesthetic 2,6-diisopropylphenol (propofol) on isolated rat heart mitochondria. Comp Biochem Physiol C Pharmacol Toxicol Endocrinol 1995; 110:41–45

99 Rigoulet M, Devin A, Averet N, et al. Mechanisms of inhibition and uncoupling of respiration in isolated rat liver mitochondria by the general anesthetic 2,6-diisopropylphenol. Eur J Biochem 1996; 241:280–285

100 Schenkman KA, Yan S. Propofol impairment of mitochondrial respiration in isolated perfused guinea pig hearts determined by reflectance spectroscopy. Crit Care Med 2000; 28:172–177

101 McKeage K, Perry CM. Propofol: a review of its use in intensive care sedation of adults. CNS Drugs 2003; 17:235–272

102 Short TG, Young Y. Toxicity of intravenous anaesthetics. Best Pract Res Clin Anaesthesiol 2003; 17:77–89

103 Celesia G. Modern concepts of status epilepticus. JAMA 1976; 235:1571–1574

104 Dunne JW, Summers QA, Stewart-Wynne EG. Non-convulsive status epilepticus: a prospective study in an adult general hospital. Q J Med 1987; 62:117–126

105 Tomson T, Lindbom U, Nilsson BY. Nonconvulsive status epilepticus in adults: thirty-two consecutive patients from a general hospital population. Epilepsia 1992; 33:829–835

106 Cockerell OC, Walker MC, Sander JW, et al. Complex partial status epilepticus: a recurrent problem. J Neurol Neurosurg Psychiatry 1994; 57:835–837

107 Aminoff MJ. Do nonconvulsive seizures damage the brain? No. Arch Neurol 1998; 55:119–120

108 Kaplan PW. No, some types of nonconvulsive status epilepticus cause little permanent neurologic sequelae (or: "the cure may be worse than the disease"). Neurophysiol Clin 2000; 30:377–382

109 Kaplan PW. Assessing the outcomes in patients with nonconvulsive status epilepticus: nonconvulsive status epilepticus is underdiagnosed, potentially overtreated, and confounded by comorbidity. J Clin Neurophysiol 1999; 16:341–352

110 Kaplan PW. Prognosis in nonconvulsive status epilepticus. Epileptic Disord 2000; 2:185–193

111 Shneker BF, Fountain NB. Assessment of acute morbidity and mortality in nonconvulsive status epilepticus. Neurology 2003; 61:1066–1073