*Current Concepts*

## STATUS EPILEPTICUS

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A PATIENT in status epilepticus has continuous or rapidly repeating seizures. Although the danger of this pattern of seizure activity has been recognized since antiquity, our understanding of the pathophysiology of status epilepticus is incomplete. The frequency of cases in the United States is approximately 102,000 to 152,000 per year, and roughly 55,000 deaths are associated with status epilepticus annually.[1] Twelve to 30 percent of adult patients with a new diagnosis of epilepsy first present in status epilepticus.[2,3] This review focuses on generalized status epilepticus, which is the most common form of the disorder.[1,4] This is a life-threatening condition that always requires prompt management. Our review emphasizes issues relevant to adults and older children; status epilepticus in younger children has been reviewed in detail elsewhere.[5,6]

### DEFINITIONS

In 1981, the International League against Epilepsy defined status epilepticus as a seizure that "persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur."[7] The lack of a specific duration of the seizures has made this definition difficult to use. More recent publications have defined status epilepticus as seizures that persist for 20 to 30 minutes, which is an estimate of the duration necessary to cause injury to central nervous system neurons.[4,5,8] Practitioners recognize the need to begin therapy for status epilepticus well before 20 minutes have elapsed, so such a definition is also unsuitable as a guide for treatment. Since isolated tonic–clonic seizures in adults rarely last more than a few minutes, we advocate the use of an operational definition of status epilepticus: either continuous seizures lasting at least five minutes or two or more discrete seizures between which there is incomplete recovery of consciousness.[9,10] This definition differs from that of serial seizures, which are two or more seizures occurring over a relatively brief period (i.e., minutes to many hours), but with the patient regaining consciousness between the seizures.

### CLINICAL FEATURES OF GENERALIZED STATUS EPILEPTICUS

When first seen, patients with status epilepticus are unresponsive and usually have clinically obvious seizures, such as tonic, clonic, or tonic–clonic movements of the extremities. With time, however, the clinical manifestations often become subtle, and the diagnosis requires careful observation. Patients may have only small-amplitude twitching movements of the face, hands, or feet or nystagmoid jerking of the eyes.[11,12] Some patients have no observable, repetitive motor activity, and the detection of ongoing seizures requires electroencephalography.[12] Electrographic status epilepticus of this type may be more common in hospitalized, comatose patients than previously thought.[13] Patients who have electrographic status epilepticus with little or no motor activity (including patients paralyzed for airway management) are still at risk for central nervous system injury and require prompt treatment. Myoclonic status epilepticus, which is usually seen in patients after prolonged anoxia or other severe metabolic insults, consists of very brief, sudden movements of restricted parts of the body that may be triggered by external stimuli, such as mechanical ventilation.

### OUTCOMES AND CAUSES OF STATUS EPILEPTICUS

The overall mortality rate among adults with status epilepticus is approximately 20 percent, and patients who have a first episode of status epilepticus are at substantial risk for future episodes and the development of chronic epilepsy.[5] The outcome is usually worse in patients with status epilepticus of long duration and those who have severe physiologic disturbances. However, the predominant factor affecting outcome is cause. Status epilepticus has many causes, which vary depending on the patient population. It is useful to categorize the causes according to acute and chronic processes, because there are differences between the two in management, response to treatment, and outcome.[14-17]

Acute processes that cause status epilepticus include metabolic disturbances (e.g., electrolyte abnor-

malities, renal failure, and sepsis), central nervous system infection, stroke, head trauma, drug toxicity, and hypoxia. Seizures in this category are often difficult to control and are associated with a higher mortality, especially those occurring after hypoxia and in older patients.[16,17] Myoclonic status epilepticus after hypoxia carries an especially grave prognosis and is often not treated as aggressively as other forms of status epilepticus.[18]

Chronic processes that cause status epilepticus include preexisting epilepsy in which status epilepticus is due to breakthrough seizures or the discontinuation of antiepileptic drugs, seizures in the context of chronic ethanol abuse, and remote processes such as central nervous system tumors or strokes that lead to status epilepticus after a latent period that may span weeks to years. In general, patients with status epilepticus due to these chronic processes respond well to anticonvulsant treatment, and they recover from the acute episode of seizures.

## PATHOPHYSIOLOGY

The fundamental pathophysiology of status epilepticus involves a failure of mechanisms that normally abort an isolated seizure. This failure can arise from abnormally persistent, excessive excitation or ineffective recruitment of inhibition. The relative contributions of these factors are poorly understood. The temporal and spatial determinants of status epilepticus are also relatively unknown; experimental studies suggest there is induction of reverberating seizure activity between, for example, hippocampal and parahippocampal structures and that the seizures progress through a sequence of distinct electrographic changes.[19,20]

It is likely that numerous mechanisms are involved, depending on the underlying cause. Our best insights come from cases in which status epilepticus was caused by an exogenous toxin. The most notable example involved the ingestion in 1987 of mussels contaminated with domoic acid, an analogue of glutamate (the principal excitatory amino acid neurotransmitter in the brain).[21] Some patients had prolonged and profound status epilepticus.[22] This occurrence suggests that excessive activation of excitatory amino acid receptors can cause prolonged seizures and suggests that excitatory amino acids have a causative role in status epilepticus.[23] Status epilepticus can also be caused by penicillin and related compounds that antagonize the effects of γ-aminobutyric acid (GABA), the main inhibitory neurotransmitter of the brain.[19] Very recent studies suggest that the failure of inhibition may be due in some cases to a shift in the functional properties of the $GABA_A$ receptor that occurs as seizures become prolonged.[24]

Status epilepticus lasting approximately 30 to 45 minutes can cause cerebral injury, especially in limbic structures such as the hippocampus, and seizure activity itself is sufficient to damage the central nervous system.[25,26] This damage is partly a consequence of glutamate-mediated excitotoxicity and does not appear to be due primarily to an excessive metabolic demand imposed by repetitive neuronal firing. The superimposition of systemic stresses such as hyperthermia, hypoxia, or hypotension exacerbates the degree of neuronal injury in animal models of status epilepticus, a finding consistent with empirical observations in humans.[27,28]

## MANAGEMENT

The initial care of a patient with status epilepticus includes standard measures applicable to any acute medical emergency (Fig. 1). A few aspects of management deserve special mention. Proper assessment and control of the airway and of ventilation in a patient with ongoing convulsive seizures can be challenging. Arterial-blood gas monitoring is especially useful. Many patients have a profound metabolic acidosis (e.g., arterial pH <7.0) that corrects itself once seizures are controlled; treatment with sodium bicarbonate should be reserved for the most extreme circumstances.[14,29] However, arterial-blood gas values may also reveal respiratory acidosis or hypoxia that requires immediate treatment through airway management and supplemental oxygen.

Despite the periods of apnea and cyanosis that occur during the tonic or clonic phases of their seizures, most patients in status epilepticus breathe sufficiently as long as the airway remains clear. Nonetheless, patients should receive 100 percent oxygen by nasal cannula or a nonrebreathing mask, and airway patency should be maintained by an oral or nasopharyngeal device while the patient remains unresponsive. Nasal or orotracheal intubation or bag valve-mask ventilation should be undertaken if there is clinical or laboratory evidence of respiratory compromise. If neuromuscular blockade is needed to facilitate intubation, the use of a short-acting drug (e.g., 0.1 mg of vecuronium per kilogram of body weight) will help the physician promptly regain the ability to determine whether seizures are present clinically.

Hyperthermia occurs relatively frequently during status epilepticus (in 28 to 79 percent of patients), and in many cases it is primarily a manifestation of the seizures rather than evidence of an infection.[14,29] Given the damaging effects of fever in patients with central nervous system injury, hyperthermia should be treated promptly with passive cooling.

Electroencephalographic monitoring should be used for any patient who has received a relatively long acting paralytic agent, remains unconscious after the initial phase of antiepileptic-drug treatment, or requires prolonged therapy for refractory status epilepticus (discussed below). Electroencephalography continues to be underused in such patients. Relatively simple electroencephalographic monitoring devices
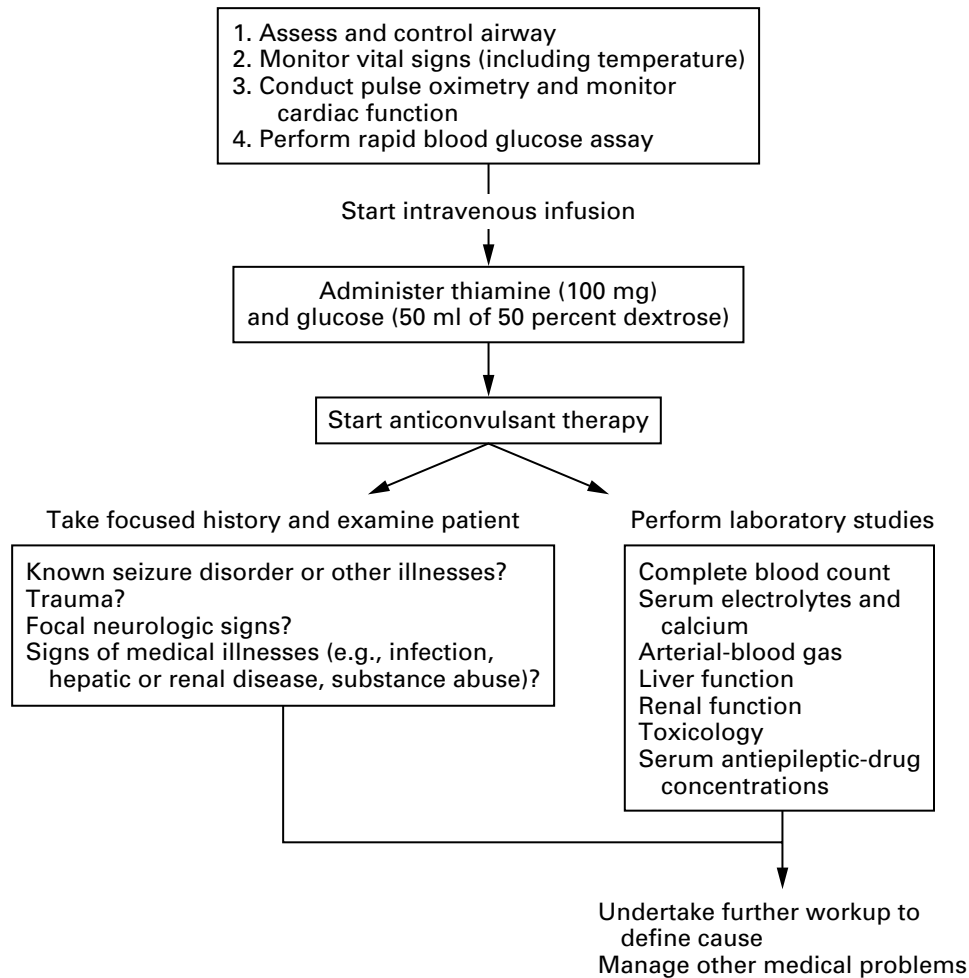
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┌─────────────────────────────────────────┐
│ 1. Assess and control airway             │
│ 2. Monitor vital signs (including temperature) │
│ 3. Conduct pulse oximetry and monitor    │
│      cardiac function                     │
│ 4. Perform rapid blood glucose assay      │
└─────────────────────────────────────────┘
             │
    Start intravenous infusion
             │
             ▼
┌─────────────────────────────────────────┐
│ Administer thiamine (100 mg)             │
│ and glucose (50 ml of 50 percent dextrose) │
└─────────────────────────────────────────┘
             │
             ▼
┌─────────────────────────────────┐
│ Start anticonvulsant therapy     │
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Take focused history and examine patient

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┌─────────────────────────────────────────┐
│ Known seizure disorder or other illnesses? │
│ Trauma?                                   │
│ Focal neurologic signs?                   │
│ Signs of medical illnesses (e.g., infection, │
│    hepatic or renal disease, substance abuse)? │
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Perform laboratory studies

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┌─────────────────────────────────────────┐
│ Complete blood count                      │
│ Serum electrolytes and                    │
│    calcium                                │
│ Arterial-blood gas                        │
│ Liver function                            │
│ Renal function                            │
│ Toxicology                                │
│ Serum antiepileptic-drug                  │
│    concentrations                         │
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Undertake further workup to
define cause
Manage other medical problems

**Figure 1.** Algorithm for the Initial Management of Status Epilepticus.

are now available and will probably become common in emergency departments and intensive care units.

## PRINCIPLES OF DRUG TREATMENT

The goal of treatment for status epilepticus is the prompt cessation of seizure activity. Ideally, a drug used in this setting would be easy to administer, have an immediate and long-lasting antiseizure effect, and be free of serious effects on cardiorespiratory function and the level of consciousness. Unfortunately, all current therapies fall short of this ideal. Benzodiazepines and barbiturates depress consciousness and respiratory drive in a dose-dependent manner, phenytoin and fosphenytoin cause infusion-rate–related hypotension and cardiac dysrhythmias, and limits on the rate of intravenous administration delay the maximal antiseizure effect of phenytoin, fosphenytoin, and phenobarbital.

Drug treatment for status epilepticus should be started without delay after the diagnosis has been established. This approach is supported by the correlation between the duration of status epilepticus and the extent of neurologic morbidity and by experimental and clinical observations that status epilepticus of longer duration is less responsive to drug therapy than that of shorter duration. For example, in a review of status epilepticus in San Francisco in the 1980s, we found that seizures were stopped by first-line therapy (usually diazepam followed by phenytoin) in 80 percent of patients when treatment was begun within 30 minutes of the onset of the seizures.[16] In contrast, the response rate was less than 40 percent when treatment was begun two hours or more after the onset of the seizures. In rats, status epilepticus becomes progressively less responsive to treatment with diazepam as electrographic seizures continue.[30]

Figure 2 is a suggested algorithm for the treatment of status epilepticus in adults and older children. The choice of drugs and the recommended sequence of administration are based on the rapid onset and extended duration of the effect of lorazepam and the presumed value of an additional long-acting
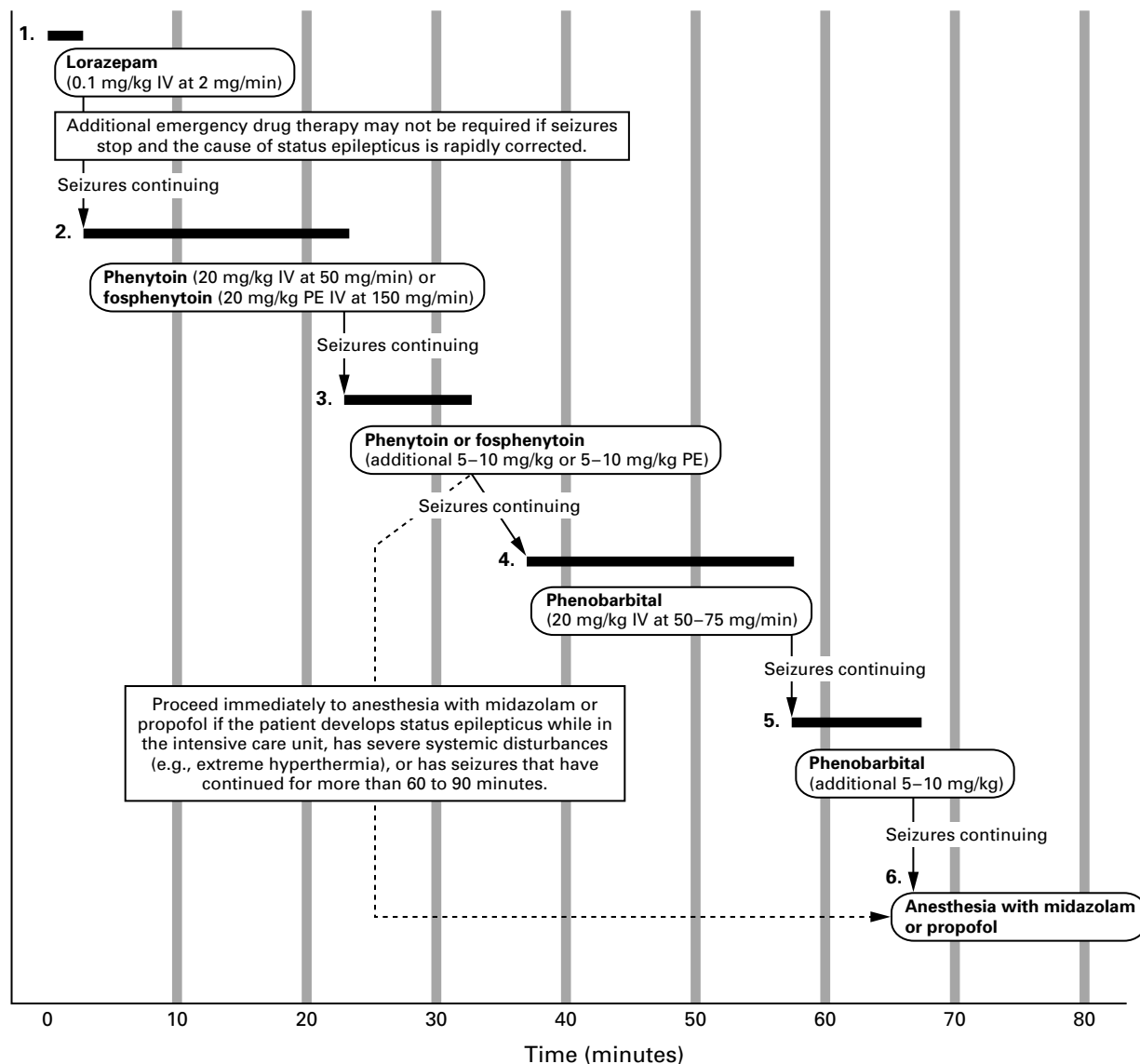
**1.**
Lorazepam
(0.1 mg/kg IV at 2 mg/min)

Additional emergency drug therapy may not be required if seizures stop and the cause of status epilepticus is rapidly corrected.

Seizures continuing

**2.**
Phenytoin (20 mg/kg IV at 50 mg/min) or fosphenytoin (20 mg/kg PE IV at 150 mg/min)

Seizures continuing

**3.**
Phenytoin or fosphenytoin (additional 5–10 mg/kg or 5–10 mg/kg PE)

Seizures continuing

**4.**
Phenobarbital
(20 mg/kg IV at 50–75 mg/min)

Proceed immediately to anesthesia with midazolam or propofol if the patient develops status epilepticus while in the intensive care unit, has severe systemic disturbances (e.g., extreme hyperthermia), or has seizures that have continued for more than 60 to 90 minutes.

Seizures continuing

**5.**
Phenobarbital
(additional 5–10 mg/kg)

Seizures continuing

**6.**
Anesthesia with midazolam or propofol

Time (minutes)
0  10  20  30  40  50  60  70  80

**Figure 2.** Antiepileptic-Drug Therapy for Status Epilepticus.
IV denotes intravenous, and PE phenytoin equivalents. The horizontal bars indicate the approximate duration of drug infusions.

drug, such as phenytoin or fosphenytoin. In a recent prospective, blinded clinical trial comparing lorazepam alone, phenytoin alone, diazepam with phenytoin, and phenobarbital alone for the treatment of generalized status epilepticus, the treatments were equally effective, except that lorazepam alone was superior to phenytoin alone when seizures were assessed 20 minutes after administration of the drug began.[31] Lorazepam followed by phenytoin (i.e., the medication sequence shown in Fig. 2) is currently the treatment preferred by many neurologists and epileptologists, but it was not studied in this trial. Nonetheless, the results of the study suggest that treatment with lorazepam alone may be sufficient and may obviate the need for intravenous phenytoin or fosphenytoin loading when status epilepticus is caused by a rapidly reversible process (e.g., the effects of subtherapeutic antiepileptic-drug concentrations or metabolic derangement).

## PHARMACOLOGIC THERAPY

### Benzodiazepines

Benzodiazepines (diazepam, lorazepam, midazolam, and clonazepam) are potent, fast-acting antiseizure drugs, and they (particularly diazepam and lorazepam) are therefore preferred as initial therapy.

Their primary pharmacologic actions are probably related to a benzodiazepine-receptor–mediated enhancement of GABAergic transmission. At higher concentrations, benzodiazepines also limit sustained repetitive neuronal firing in a manner similar to that of carbamazepine and phenytoin, and this effect may be relevant to their mechanism of action in status epilepticus.[32]

Lorazepam is less lipid-soluble than diazepam, and in animals, brain and cerebrospinal fluid concentrations of lorazepam rise at a slower rate than those of diazepam after intravenous injection.[33,34] However, a double-blind, randomized comparison of intravenous diazepam (10 to 20 mg) and lorazepam (4 to 8 mg) in patients with status epilepticus found both drugs to be equally fast-acting; the median time to the end of seizures was two minutes for diazepam and three minutes for lorazepam.[15] Both drugs were equally effective in controlling generalized convulsive, absence, and partial status epilepticus (response rates, 79 percent for diazepam and 89 percent for lorazepam). Despite their equivalence as initial therapies, lorazepam has a longer duration of antiseizure effect (12 to 24 hours) than diazepam (15 to 30 minutes), and it is this property that has made lorazepam preferable to diazepam for the treatment of status epilepticus.[4] Adverse effects of intravenous benzodiazepines include respiratory depression (in 3 to 10 percent of patients), hypotension (in <2 percent), and impaired consciousness (in 20 to 60 percent).[15,35,36]

### Phenytoin and Fosphenytoin

Phenytoin is useful for maintaining a prolonged antiseizure effect after rapid termination of seizures with a benzodiazepine, as an initial therapy for terminating status epilepticus, or when benzodiazepines fail. The recommended starting dose is 20 mg per kilogram administered intravenously at a maximal rate of 50 mg per minute. The common practice of giving a standard loading dose of 1000 mg of phenytoin (14.3 mg per kilogram for a patient weighing 70 kg) provides inadequate therapy for many adults.[37] As much as 30 mg per kilogram may be required to stop seizures in some patients.[37] This dose may be reduced in patients known to have a serum phenytoin concentration of more than 10 mg per liter at the onset of status epilepticus. However, therapy should not be delayed to measure serum drug concentrations.

Brain concentrations of phenytoin are nearly maximal at the end of an intravenous infusion.[38] Thus, it may take 20 to 25 minutes for phenytoin to attain its maximal effect when a typical loading dose is given to an adult.[39] When phenytoin is administered at the maximal recommended rate of 50 mg per minute, hypotension occurs in 28 to 50 percent of patients, and cardiac arrhythmias (bradycardia and ectopic beats) occur in 2 percent.[39,40] These adverse effects are more common in patients over 50 years old and those with preexisting cardiac disease. Cardiovascular complications of intravenous phenytoin, which are due to the phenytoin itself and to the propylene glycol diluent, can be mitigated by slowing or stopping the infusion.[40]

Fosphenytoin, a new water-soluble prodrug of phenytoin, is converted to phenytoin (half-life, 15 minutes) by nonspecific phosphatases. Doses of fosphenytoin are expressed as phenytoin equivalents, which are the amounts of phenytoin released from the prodrug in the presence of phosphatases. Fosphenytoin can be administered at phenytoin-equivalent rates of up to 150 mg per minute, since it is not formulated with propylene glycol. Therapeutic serum concentrations of phenytoin (≥1 mg per liter unbound) are attained within 10 minutes when fosphenytoin or phenytoin is administered at maximal infusion rates. Thus, fosphenytoin and phenytoin are likely to have a similar time to the onset of an effect in controlling status epilepticus.[41] No clinically significant differences between the hypotensive or adverse cardiac effects of phenytoin loading and those of fosphenytoin loading have been reported, although infusion-site reactions (phlebitis and soft-tissue damage) are less common with fosphenytoin.

### Phenobarbital

In a small, randomized study, phenobarbital was as effective as the combination of diazepam and phenytoin for the treatment of status epilepticus.[42] However, the depressant effects of phenobarbital on respiratory drive, level of consciousness, and blood pressure may complicate management, especially when phenobarbital is administered after a benzodiazepine.[43] For these reasons, phenobarbital (20 mg per kilogram at a rate of 50 to 75 mg per minute) is recommended only when benzodiazepines and phenytoin fail. Respiratory and blood-pressure support must be immediately available.

### Other Therapies

Intravenous valproic acid, recently marketed in the United States as an alternative to oral therapy, appears to stop some types of status epilepticus.[44] However, further experience is needed before this therapy can be recommended. Lidocaine, chlormethiazole (outside the United States), and paraldehyde (the availability of which is limited in the United States) have been used successfully to terminate status epilepticus.[45] Each has substantial toxicity, and they offer little or no advantage over the therapies previously discussed.

### Treatment of Refractory Status Epilepticus

Status epilepticus that does not respond to a benzodiazepine, phenytoin, or phenobarbital is considered refractory and requires more aggressive treatment.

Continuous intravenous infusions with anesthetic doses of midazolam, propofol, or barbiturates are the most useful treatments. A team approach to patient care, including the participation of an experienced neurologist and an intensivist, is often useful because of the need for higher-level neurologic and cardiovascular monitoring and ventilatory support.

The use of midazolam (0.2 mg per kilogram administered by slow intravenous bolus injection, followed by 0.75 to 10 μg per kilogram per minute) or propofol administered intravenously (1 to 2 mg per kilogram, followed by 2 to 10 mg per kilogram per hour) to induce anesthesia for the treatment of refractory status epilepticus (Table 1) has become very popular in recent years. Both drugs have the substantial advantage over barbiturates of rapid clearance, and midazolam has less pronounced hypotensive effects.[46-49] The infusion is typically maintained for 12 to 24 hours and is then withdrawn gradually while the patient is observed for clinical or electrographic evidence of seizure recurrence. If seizures continue, the therapy should be resumed for progressively longer periods, as needed. Midazolam may be associated with tachyphylaxis, leading to the need for exceedingly high doses. Seizures have been observed during the induction of anesthesia with propofol and emergence from it, but the importance of these proconvulsant effects in the management of status epilepticus is unknown.

Thiopental and pentobarbital are potent antiseizure drugs that have potential, though unproved, cerebral protective effects in the management of status epilepticus. In adequate doses these drugs will almost always control seizures, but severe hypotension requiring pressor therapy limits their safety.[5,50] We therefore prefer to reserve anesthesia with barbiturates for patients in whom midazolam or propofol fails. Thiopental has pharmacokinetic disadvantages, including saturable metabolism, an active metabolite (pentobarbital), and the fact that it accumulates in lipoid tissues during prolonged infusions, with resultant delays in postinfusion recovery.[5] Pentobarbital (10 to 15 mg per kilogram administered intravenously over a period of one hour, followed by a dose of 0.5 to 1 mg per kilogram per hour) is highly effective, but cardiovascular toxicity is occasionally life-threatening and postinfusion weakness may delay weaning from ventilatory support.[37,47]

## OUT-OF-HOSPITAL TREATMENT

Status epilepticus frequently occurs outside the hospital in situations in which treatment with intravenous medications is not feasible or in which there are inadequate resources to manage the potential complications of intravenous therapy. Rectal and intramuscular routes of drug administration may be useful in these settings. Intramuscular midazolam is rapidly absorbed (mean time to peak serum concen-

**TABLE 1.** PROTOCOL FOR THE TREATMENT OF REFRACTORY STATUS EPILEPTICUS WITH EITHER MIDAZOLAM OR PROPOFOL.

1. Intubate and ventilate patient; admit to intensive care unit.

2. Place electroencephalographic monitor.

3. Place arterial catheter and central catheters if indicated.

4. Administer either midazolam at a loading dose of 0.2 mg per kilogram (slow intravenous bolus), then at a dose of 0.75 to 10 μg per kilogram per minute; or propofol at a dose of 1 to 2 mg per kilogram intravenously, followed by a dose of 2 to 10 mg per kilogram per hour. Adjust maintenance dose on the basis of electroencephalographic-monitoring results. Continue electroencephalographic monitoring throughout therapy — i.e., check hourly once patient achieves a stable response to the selected drug. Primary end point for therapy is suppression of electroencephalographic spikes. If blood pressure is adequate, secondary end point is burst-suppression pattern with short intervals between bursts (i.e., <1 second).

5. Continue maintenance doses of phenytoin and phenobarbital; track concentrations to determine optimal doses.

6. Use intravenous fluids and low-dose dopamine to treat hypotension. If necessary, add low-dose dobutamine. Decrease dosage of midazolam or propofol if there are any signs of cardiovascular compromise.

7. Taper infusion at 12 hours to observe for further seizure activity. If seizures recur, reinstate infusion in intervals of at least 12 hours.

tration, 25 minutes), and limited experience in both children and adults suggests that serial seizures and status epilepticus are usually terminated within 10 minutes of administration.[51-53] The usual dosage is 0.15 to 0.3 mg per kilogram. Rectal administration of a parenteral solution of 0.5 mg of diazepam per kilogram (maximal dose, 20 mg) is approximately 80 percent effective in controlling prolonged seizures in children, usually within 15 minutes.[54] A gel formulation of diazepam in a prefilled syringe for rectal administration (Diastat, Athena Neurosciences, South San Francisco, Calif.) has recently become available in the United States for the treatment of seizure clusters in children and adults. Rectal administration of diazepam gel may be useful for out-of-hospital management of status epilepticus. However, the onset of the antiseizure effect of the gel formulation requires further study.[55]

In many emergency-medical-service systems, intravenous benzodiazepine therapy is administered by paramedics to patients with status epilepticus, with the presumption that initiating therapy before patients arrive at the emergency department will improve outcomes. Retrospective studies in adults and children suggest that prehospital therapy shortens the duration of status epilepticus and simplifies subsequent management in the emergency department.[56,57] Nonetheless, this approach has not been studied prospectively, and the relative risks and benefits remain unknown.

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