

TREATMENT OF STATUS EPILEPTICUS

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Status epilepticus (SE) is a medical emergency that may result in significant morbidity and mortality if not addressed in a timely and effective manner. Because a single seizure and SE are viewed as two extremes in a spectrum of seizure frequencies,⁵⁷ it is important to determine when a prolonged seizure or repetitive seizures may cause harm and should be considered SE. Medical therapy has been the mainstay for treating SE, but other treatments with reported success include surgical resection,³⁶ multiple subpial transection,⁷¹ electroconvulsive therapy,³⁵ caudate stimulation,³¹ and acupuncture.⁴⁷ In reviewing treatment options available for SE, the physician needs to consider not only the definition of SE, specifically duration, but also the type of status, and the milieu in which treatment is provided.

The approval of eight new antiepileptic medications in the United States over the last decade has resulted in significant changes in the approaches and options available when treating patients with epilepsy. Unfortunately, many of these agents are limited to chronic oral administration, and the development of newer parenteral agents for the acute treatment of seizures in emergency settings (i.e., status epilepticus) has not occurred. Understanding the need for rapid intervention, modifications to existing agents have been made enabling their potential use in SE. These include intravenous valproic acid and the prodrug fosphenytoin. Diazepam solution has been administered rectally in the past, and now a rectal gel delivery system (Diastat) is available. Use of the anesthetic agents, propofol

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and midazolam, has received more attention and allowed other options for treating refractory status epilepticus barbiturates.

Many protocols for the treatment of SE have been postulated in the past and require frequent review. The approach to the patient in generalized convulsive SE is being modified by changing concepts regarding the definition of SE, and studies justifying more aggressive treatment, with earlier intervention outside the emergency room. The authors will focus on agents available for the treatment of generalized convulsive SE in the adult population, with some caution concerning the care of children.

DEFINITION

Status epilepticus was defined in the first International Classification of Epileptic Seizures¹⁶ as a condition in which "a seizure persists for a sufficient length of time or is repeated frequently enough to produce a fixed and enduring epileptic condition." Slight modifications, in 1981, by the International League Against Epilepsy¹⁷ still left practical uncertainty in the definition of SE, specifically concerning duration of seizure activity. Recommendations of the Epilepsy Foundation of America's Working Group on Status Epilepticus, in 1993, defined SE as more than 30 minutes of: a, continuous seizure activity, or b, two or more sequential seizures without full recovery of consciousness.¹²⁴ The concept of potential neuronal injury related solely to the duration of SE is based in part on animal studies. Despite optimal circumstances during SE, with animals paralyzed and ventilated, neuronal damage may occur after 30 minutes in the substantia nigra pars reticularis, and after 45–60 minutes in the third and fourth layers of the cerebral cortex and the CA-1 and CA-4 sublayers of the hippocampus.^{70, 73, 96}

Bleck⁶ defined SE as a state in which seizures last, or are frequently repeated without clinical recovery, for a period exceeding 20 minutes. This was based on pathophysiologic data regarding changes in tissue oxygenation presented at an international workshop on the management of SE in 1980. Recent studies, including the VA Cooperative Trial on Treatment of Generalized Convulsive Status Epilepticus¹¹² and the Pre-Hospital Treatment of Status Epilepticus (PHTSE) study,⁶³ used seizure duration of 10 and 5 minutes respectively as inclusion criterion for SE.

Lowenstein, Bleck, and Macdonald⁶³ proposed an operational definition for generalized convulsive SE in adults and older children (>5 years old) to incorporate the practical considerations of patient management. Generalized, convulsive status epilepticus in adults and older children (>5 years old) refers to ≥ 5 minutes of (a) continuous seizures or (b) two or more discrete seizures between which there is incomplete recovery of consciousness. This determination was based in part on a study completed by Theodore et al¹⁰¹ that analyzed 120 generalized tonic-clonic seizures recorded during inpatient monitoring and reported a mean seizure duration of 62 seconds. Because no seizures lasted more than 2 minutes, more prolonged seizures encourage the development of SE and the need for intravenous (IV) therapy. This determination excludes children less than 5 years old because relatively little is known about typical "single" seizures

in this age group. Initial febrile seizures⁵ and acute symptomatic seizures⁶⁶ in children can be prolonged but do not result in the same morbidity seen in adults with prolonged seizures. Further work, specifically in the pediatric population, is needed before an operational definition can be formulated and treatment strategies devised.

CLASSIFICATION OF STATUS EPILEPTICUS

Gastaut³³ has suggested that there are as many types of SE as there are seizures, and there are other SE syndromes described in the literature.^{94, 113} Classification of SE is similar to the classification of single seizures in that they are both based on clinical and electroencephalogram (EEG) findings; however, the emergent nature of patient presentation makes this difficult. In an attempt to simplify the classification for emergency treatment situations, SE has been divided into generalized convulsive SE, nonconvulsive SE (complex-partial SE and absence SE), and simple-partial SE.^{13, 105}

Recurrent convulsions without complete recovery between seizures is overt generalized convulsive SE and easily recognized. On the other hand, there are patients who present in a comatose state with subtle convulsive features (rhythmic muscle twitches or tonic eye deviation) who require an EEG to demonstrate ongoing epileptiform ictal patterns. This has been classified as symptomatic-myoclonic SE⁷⁵ or nonconvulsive SE, but Treiman¹¹¹ argues this should be called subtle generalized convulsive SE. Treiman describes generalized convulsive SE as a dynamic process that if inadequately treated can progress from overt generalized convulsive SE, to subtle generalized convulsive SE, and then to electrical generalized convulsive SE. Clinical changes, from discrete seizures to subtle movements to a profound SE-induced encephalopathy in which no motor activity can be processed, may occur.¹¹⁰ The EEG also goes through a predictable sequence of changes from repetitive discrete seizures to periodic epileptiform discharges.¹⁰⁷ Treiman¹¹¹ suggested that recognition of these ictal EEG patterns, even in a patient with subtle or completely absent motor evidence of ongoing SE, should lead to the diagnosis of generalized convulsive SE and the initiation of aggressive therapy.

The classification of subtle generalized convulsive SE continues to receive significant debate. Gastaut³³ described "so-called myoclonic status epilepticus during acute or subacute brain disorders in nonepileptics." This SE involves myoclonic features, generally occurring in adults, and they are always secondary to acute or subacute encephalopathy whose origin is metabolic (especially anoxia), toxic, viral, or degenerative. It is Gastaut's opinion that this type of myoclonic syndrome should not be regarded as SE in the strict sense of the term but as the late myoclonic phase of the underlying condition. The outcome is always very severe, if not fatal.

Not all physicians are convinced of this theory, and they argue that this type of presentation should not be classified as a form of SE or receive aggressive treatment. Are these patients exhibiting both clinical and electrographic symptoms that remain after an acute diffuse cerebral injury

(i.e., anoxia) with no relationship to SE? Or, are these findings end-stage remnants of an untreated, rapidly evolving, epileptic process (SE)? Can a controlled prospective study be completed showing that aggressive treatment in this population makes a difference? These are important questions that may be difficult to answer. Patients with a history of acute clinical seizure activity or with an EEG pattern showing evolving features should be treated aggressively. The comatose patient with severe hypoxic encephalopathy, no reported seizure activity, and a nonreactive EEG pattern will often receive treatment with benzodiazepines, phenytoin, or phenobarbital, but not more aggressive treatment.

MORBIDITY AND MORTALITY

The overall incidence of SE is approximately 100,000 to 150,000 people annually and accounts for about 7% of all epilepsy cases.^{24, 43, 62} The mortality of generalized convulsive SE has been estimated to be about 20% (range 3%–35%)^{43, 124} with age and etiologic factors having prognostic significance. It occurs most frequently in the very young and elderly.^{24, 43} Typically, outcome is worse when SE is of longer duration (>1 hour),^{23, 103} occurs in the elderly, or has an etiology of anoxia. Patients with an acute central nervous system injury, (i.e., head injury, rapidly growing brain tumor, anoxic encephalopathy, stroke, central nervous system infection, and toxicity) are usually more difficult to control.⁵⁷

Chronic processes may also lead to status epilepticus, but patients with SE and these etiologies tend to respond better to antiepileptic therapy, and the patient is much more likely to return to baseline functioning. Chronic processes may include patients with preexisting epilepsy (acute exacerbation and antiepileptic drug reduction), alcohol withdrawal, and remote focal epileptogenic lesions (tumor, stroke, and posttraumatic injury). As with most conditions, children show more resilience and have a lower mortality rate.³⁹

PREHOSPITAL TREATMENT

The major variable of SE that can be altered with rapid and effective treatment is its duration. Historically, the start of effective treatment has occurred in the emergency department (ED), but often this is too late. In the VA randomized study, Treiman et al¹¹² reported the median duration of SE prior to initiation of treatment was 2.8 hours for 384 patients with overt generalized convulsive SE and 5.8 hours for 134 patients with subtle SE. Jordan⁴⁸ completed a retrospective review of 30 patients with SE who presented to the ED. Treatment access time was determined from the onset of SE to arrival of the emergency medical team (EMT) (treatment access time 1), transit time from the arrival of EMT to delivery in the ED (treatment access time 2), and arrival in the ED to initiation of treatment according to the hospital's SE protocol (treatment access time 3). The average duration of treatment access time 1 was 30 minutes (range 15–140 minutes), treatment

access time 2 was 20 minutes (range 10–40 minutes), and treatment access time 3 was 35 minutes (range 15–83 minutes). The cumulative delay in this group of patients, from the onset of SE outside the hospital to the initiation of a treatment protocol, averaged 85 minutes (maximum 6.5 hours).

In an attempt to provide earlier intervention in SE, paramedics have become involved in the delivery of first-line antiepileptic drug treatment, in addition to stabilizing the patient. Because benzodiazepines stop seizures most rapidly regardless of the etiology,⁷⁹ they are considered first-line treatment for SE before arrival in the hospital and in the emergency room.

TREATMENT

Benzodiazepines

Benzodiazepines, as antiepileptic drugs, include diazepam, clorazepate, oxazepam, lorazepam, clonazepam, nitrazepam, and clobazam.⁴⁴ Probable pharmacologic actions include benzodiazepine-receptor-mediated enhancement of gamma-aminobutyric acid mediated transmission and, at higher doses, limited, sustained repetitive neuronal firing.⁶⁷ The role of benzodiazepines in acute seizures has been addressed in multiple publications.^{106, 108} The author will focus on the agents available in the United States (diazepam, lorazepam, and midazolam) that have been used outside the hospital setting. Oral diazepam and lorazepam, and sublingual lorazepam, have been successfully used to treat acute episodes, but treatment is delayed by slow absorption. Placement of medication in the oral cavity during a generalized convulsive SE is also not recommended.⁸⁴ Intravenous administration is the preferable route of delivery but may be limited by an inability to obtain intravenous or intraosseous access. Rectal, intramuscular, and intranasal routes are alternatives in some circumstances.

Diazepam

Diazepam is available in tablet, intravenous, and rectal gel forms. Naquet et al⁷² and Gastaut et al³² were the first to document the use of intravenous diazepam in the treatment of SE. The efficacy of intravenous diazepam is known from experience in the ED but use in the prehospital setting is less documented. Earlier studies of prehospital treatment of children with SE led to some recommendations against the use of intravenous diazepam because of a high risk of intubation-related complications.⁸⁰ The use of parenteral diazepam solution administered rectally to children first occurred in 1975.¹ Subsequent work by Knudsen⁵¹ showed that rectal diazepam was effective in aborting seizures and preventing febrile seizures. It stopped seizures in 96% of patients if given within 15 minutes of seizure onset but in only 57% of patients if given later. Rectal diazepam is the most commonly used medication given before admission to the hospital. The rectal route of administration is not, however, always acceptable or convenient. Many teachers, parents, and caregivers are reluctant to administer rectal medication for fear of sexual abuse allegations.⁹⁰

Because of issues of overall efficacy and potential complications of prehospital treatment, studies were undertaken to compare intravenous and rectal diazepam preparations for early SE. An initial study completed by Dieckmann²⁷ compared the effectiveness and safety of rectal and intravenous diazepam in 36 children in status epilepticus. Rectal and intravenous diazepam were initially effective in terminating status epilepticus in 81% and 100% of children, respectively; however, seizures recurred in only 30.8% of the children treated with rectal diazepam, as opposed to 60% treated with intravenous diazepam. Two patients treated with intravenous diazepam required intubation prior to arrival in the ED because of respiratory depression, while none in the rectal diazepam group required prehospital intubation. This study did not include a comparison group of children who did not receive prehospital therapy for SE.

Using a retrospective case-control study design, Alldredge et al² compared the clinical course of children with SE who received prehospital diazepam therapy (either by rectal or intravenous administration) with a group of children who received only standard ED antiepileptic drug therapy. Prehospital diazepam therapy was associated with SE of shorter duration (32 minutes versus 60 minutes) and a reduced likelihood of recurrent seizures in the ED (58% versus 85%). There were no significant differences between rectal and intravenous diazepam therapy with regard to SE duration, intubation, or recurrent seizures in the ED.

The benefits unique to rectal diazepam compared with oral or intravenous preparations include desirable pharmacokinetics, improved safety, and ease of administration.⁷⁹ Various preparations have been available throughout the world, and most clinicians have used an intravenous solution drawn into a syringe and given either directly or through a rectal tube. Because of the inconvenience of having to accurately measure the preparation prior to administration, a diazepam rectal gel (Diastat) was formulated, which is now available in 5, 10, 15, and 20 mg preparations.

Lorazepam

Lorazepam is considered the drug of choice in the emergency room but has had limited use by paramedics in the field. Lorazepam has been compared with diazepam in multiple clinical trials and is considered by many as the drug of choice for SE.^{108, 117} Leppik et al⁵⁶ compared lorazepam and diazepam in a double-blind study for treatment of SE. With the initial injection of lorazepam 4 mg intravenous or diazepam 10 mg intravenous, status epilepticus was stopped in 78% and 58% of patients, respectively. After a second injection, these numbers improved to 84% and 76%, respectively. Although diazepam enters the brain rapidly and somewhat faster than lorazepam, this does not significantly alter the speed of clinical effect. Because of rapid and extensive redistribution of diazepam to peripheral fat stores, the duration of clinical effectiveness with diazepam is only 20 to 30 minutes. Lorazepam has a different volume of distribution of the free drug; therefore, its clinical effectiveness can last for several hours. A

previous study completed by Levy and Krall⁵⁸ suggested that the use of lorazepam for SE might be safer, in that only one out of 53 patients experienced respiratory depression with intravenous lorazepam as compared with eight of 33 treated with intravenous diazepam. The frequency of endotracheal intubation during SE in children who received lorazepam was significantly lower (27%) compared with those who received diazepam (73%), when either agent was given alone or combined with phenytoin.¹⁵ Also, when given intravenously for SE, lorazepam causes fewer side effects than diazepam.²⁸

Only one formal clinical study comparing intravenous lorazepam (2 mg) and diazepam (5 mg) in a prehospital setting has been undertaken. Lowenstein et al⁶⁴ designed a prospective, randomized, double-blind placebo-controlled trial administered by paramedics in the San Francisco area. This trial included adults with prolonged (> 5 minutes) or repetitive generalized convulsive seizures. The primary outcome measure was cessation of SE by the time of ED arrival, and the secondary outcome measure was prehospital complications. Of 205 patients enrolled, 39 of 66 (55%) responded to lorazepam therapy, 29 of 68 (43%) responded to diazepam therapy, and 15 of 71 (21%) responded to placebo therapy. The physicians' conclusion was that paramedics can administer benzodiazepines in a safe and effective manner out-of-hospital in adults, and intravenous lorazepam was superior to diazepam; a potential limitation is the need for refrigeration, which may limit its use outside the hospital.⁴⁰

Rectal lorazepam has not been studied as extensively as rectal diazepam. Most of the studies have been performed with children in part because of the uncomfortable (physical and social) route of delivery in adults. Rectal lorazepam has a slower onset of action compared with diazepam.³⁷ In the pediatric study comparing rectal and intravenous delivery of diazepam and lorazepam, there were minimal differences in the mean time to seizure cessation for both drugs with both types of administration. Those receiving diazepam, however, were much more likely to require additional drugs for seizure control.³

Lorazepam is also used by the sublingual route for rapid effect, because any form of therapy through the buccal cavity bypasses the liver and avoids first-pass elimination. Yager and Seshia¹²⁶ reported absorption of sublingual lorazepam within 20 seconds and subsequent control of serial seizures in 8 of 10 children within 15 minutes. A concentrated oral solution of lorazepam has been described by Schroeder et al⁸⁸ for the management of hospitalized pediatric patients with epilepsy.

Midazolam

Midazolam is an imidazobenzodiazepine drug, which stands out in comparison with the other benzodiazepines because it is water-soluble and can be administered intramuscularly (IM). When injected, the benzodiazepine ring closes at physiologic pH and the substance becomes lipid-soluble allowing rapid cerebral penetration.⁹⁵ Both diazepam and

lorazepam may be administered IM but this is not recommended treatment because of slower, more erratic absorption and increased local discomfort. Since its introduction as an agent with antiepileptic effects, midazolam has been used in the prehospital setting for status epilepticus via intravenous, intramuscular, intranasal, rectal, and buccal routes.

Intramuscular midazolam is very effective in stopping seizure activity within 5 to 10 minutes¹⁰⁴ with no significant adverse effects. A prospective, randomized study, including 24 children requiring acute treatment for seizures upon arrival in the ED, compared the effectiveness of intramuscular midazolam and intravenous diazepam. There was approximately a 4-minute difference in both the times for drug administration and seizure cessation in favor of IM midazolam.¹⁴ There have been no prehospital studies completed using IM midazolam and experience is limited to case reports.⁵⁵ Intravenous access in the prehospital setting can be difficult in certain patients who are seizing, especially children, the elderly, or obese patients. Intramuscular midazolam treatment may be an easier, safer, more predictable and effective treatment option than either diazepam or lorazepam treatment by the rectal or IM routes.¹⁰⁴

Scott et al⁸⁹ were the first physicians to show that buccal/sublingual midazolam could be rapidly absorbed, with a cerebral effect seen on EEG in ten normal subjects, within 5 to 10 minutes. The physicians subsequently performed a study in a residential center with children and young people with severe epilepsy who had continuous seizures of more than 5 minutes. The patients either received sublingual/buccal midazolam (10 mg) or rectal diazepam (10 mg). For administration, midazolam (2 mL; 10 mg) was drawn into a 2-mL syringe, the student's lips were parted, and the drug was squirted around the buccal mucosa. Midazolam stopped 30 of 40 (75%) seizures in 14 students, whereas diazepam stopped 23 of 39 (59%) seizures in 14 patients. Buccal midazolam appeared to have some distinct advantages over rectal diazepam, but Holmes⁴⁵ suggested some caution be used in extrapolating these results for the standard treatment of SE.

Nasal administration of midazolam has been used as a sedative¹⁸ and preinduction agent¹²² by anesthesiologists in the past. O'Regan et al⁷⁶ subsequently demonstrated decreases in interictal epileptiform activity with intranasal midazolam administration. Two cases of SE terminated with the administration of intranasal midazolam, while IV access was being attempted were subsequently documented.⁵⁰ Lahat et al⁵⁴ completed a 3-month study in which all children who presented to the pediatric ED with generalized motor seizures of at least 10 minutes received midazolam solution (5 mg/mL) at a dose of 0.2 mg/kg dropped into both nostrils. Twenty children participated in the study and seizure control was achieved in all but one case in which IV diazepam was also ineffective. The mean time until seizure control was 3.5 minutes despite a mean seizure duration of 17 minutes prior to drug administration. In a commentary by Wallace,¹¹⁹ the author noted that children who have seizures when febrile, frequently have an upper respiratory tract infection. Nasal secretions can dilute the midazolam solution and make it more difficult for this agent to have contact with the absorbing surface. Further studies of intranasal midazolam

in the treatment of SE are needed, especially in children with respiratory infections.

Propofol

Propofol (2,6-diisopropylphenol) is a rapidly acting, highly lipid-soluble anesthetic used in the induction of general anesthesia. Propofol has a short duration of action, barbiturate- and benzodiazepine-like effects on the GABA-A receptor, and can suppress central nervous system metabolic activity.¹¹ The initial case report of inpatient treatment of SE with propofol infusion was in 1988,¹²³ and the first study of prehospital use of propofol was from Helsinki in 1995.⁵³ A prehospital treatment protocol for convulsive SE using IV diazepam (≤ 20 mg) already existed; this was followed by general anesthesia induced with thiopental sodium or propofol. Eight consecutive adult patients with SE were treated by a physician-manned mobile intensive care unit in 1994. The physicians administered propofol boluses of 30 mg every 30 seconds in patients who continued to seize despite adequate doses of IV diazepam. All patients required intubation and mechanical ventilation because of hypoxia or inefficient ventilation. All patients stopped convulsing with propofol administration. Only one patient required intensive care unit admission.

An approach to the initial treatment of SE in the prehospital setting is shown in Figure 1. Midazolam has significant potential but has limited practical experience in the community. More aggressive options, including propofol, will have to be reserved for communities in which emergency medical services are equipped to provide cardio pneumatic support and direct physician input. Unfortunately, in many communities, more basic concerns such as delayed response time and limited funding need to be addressed before these changes can be considered.

EMERGENCY DEPARTMENT INPATIENT TREATMENT

VA Status Epilepticus Cooperative Study Group

The main objective in the treatment of SE is to abort seizures and treat the condition.⁴⁰ How physicians approach the neurologic emergency of SE (Table 1) has not changed dramatically, but the initial evaluation continues to be paramount in determining appropriate intervention. Decisions made concerning drug selection (first-line therapy) have been based on past experience. Phenobarbital, phenytoin, diazepam plus phenytoin, and lorazepam were all advocated for the initial treatment of generalized convulsive SE. There were few controlled studies using these agents for direct comparison. A five-year randomized, double-blind, multicenter trial comparing these four intravenous regimens was undertaken by the VA Status Epilepticus Cooperative Study Group and the results were published in 1998.¹¹²

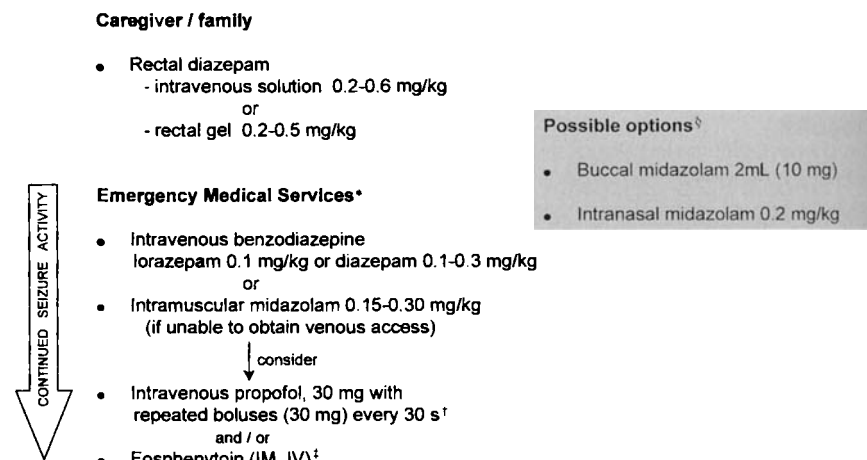


Figure 1. Prehospital treatment of status epilepticus. *Emergency medical service options may be limited by availability of the medications and the need for Advanced Cardiac Life Support (ACLS) certification. [†]Previous reported experience with prehospital propofol administration includes physician supervision. [‡]Option to be considered, no reported prehospital experience. [§]No prehospital trials or experience reported in the United States. IM—intramuscular; IV—intravenous. Data from Kuisma M, Roine RO: Propofol in prehospital treatment of convulsive status epilepticus. *Epilepsia* 36:1241–1243, 1995; Runge JW, Allen FH: Emergency treatment of status epilepticus. *Neurology* 46(suppl 1):S20–S23, 1996; and Scott RC, Besag FM, Neville BG: Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence: A randomized trial. *Lancet* 353:623–626, 1999.

The study demonstrated that all of the four treatment arms (lorazepam 0.1 mg/kg; diazepam 0.15 mg/kg, followed by phenytoin 18 mg/kg; phenytoin 18 mg/kg; and phenobarbital 15 mg/kg) studied were efficacious in treating overt SE. Treatment was considered successful when all motor and electrographic seizure activity ceased within 20 minutes after the beginning of the drug infusion and there was no return of seizure activity during the next 40 minutes. Success rates in overt generalized convulsive SE were highest with lorazepam (64.9%), followed by phenobarbital (58.2%), diazepam and phenytoin (55.8%), and phenytoin (43.6%). In a pairwise comparison, the only significant difference was the effectiveness of lorazepam when compared with phenytoin. In the group with a diagnosis of subtle generalized convulsive SE, no significant differences among the treatments were detected. The 20-minute time interval requirement for seizure cessation was thought by some physicians to be a disadvantage with phenytoin because of the mandatory slow infusion rate. The length of infusion was 33.0 ± 20.1 minutes for phenytoin, significantly longer than the 4.7 ± 7.2 minutes for lorazepam.

Important differences in the response to therapy and outcome were also noted between the overt and subtle generalized convulsive SE groups. The median duration of status epilepticus in the overt generalized convulsive SE group at the time of enrollment was 2.8 hours and in the

Table 1. EMERGENCY DEPARTMENT/INPATIENT MANAGEMENT OF STATUS EPILEPTICUS**Stabilization/Diagnosis****ABCs (Airway, Breathing, Circulation) of life support**

- Assess and control airway, consider intubation (C-spine precautions)
- Pulse oximetry (consider ABC's), low-flow oxygen (nasal cannula or a nonrebreathing mask)
- Nasal or orotracheal intubation or bag valve-mask if respiratory compromise; if neuromuscular blockade is needed, use a short-acting drug (e.g., 0.1 mg/kg vecuronium)
- Monitor vital signs (including temperature), if elevated provide passive cooling, antipyretics

Briefly observe patient to confirm diagnosis (continued seizure activity or one additional seizure)

- Obtain available history
- Perform neurologic and physical examination

Identify and correct metabolic abnormalities

- Blood tests for antiepileptic drug levels, glucose, calcium, magnesium, electrolytes, complete blood count with differential, renal function (blood urea nitrogen, creatinine), hepatic enzymes, toxicology screen

Start an intravenous line with normal saline (intraosseous line in young child if IV access not obtained)**Initial treatment****If hypoglycemia confirmed or if blood glucose determination unavailable**

- Adults—100 mg thiamine, 50 mL of 50% glucose
- Pediatric—2 mL/kg or 25% glucose; pyridoxine 100–200 mg IV push (< 18 months old)

Initiate antiepileptic drug therapy (see Fig. 2)**Additional studies****CT scan of the brain—if intracranial hypertension, cerebral mass lesion, or obstruction of CSF is suspected; CT scan should be performed before lumbar puncture****LP—if central nervous system infection is a major consideration; should be deferred until seizures are stopped and patient is hemodynamically stable; prompt antibiotic or antiviral therapy should be instituted before LP**

CSF = cerebrospinal fluid; CT = computer tomography; LP = lumbar puncture; IV = intravenous.

subtle generalized convulsive SE group, 5.8 hours. The first drug treatment was successful in only 14.9% of patients with subtle generalized convulsive SE compared with 55.5% of patients in the overt generalized convulsive SE group. The morbidity rate for those with subtle generalized convulsive SE (64.7%) was much worse than that for the overt generalized convulsive SE group (27%). This data proved that mortality is largely attributable to the underlying cause and the duration of the episode. The final recommendation from the study suggested lorazepam as the initial intravenous treatment for generalized convulsive SE because of its ease of use.

In a subsequent analysis, Treiman¹¹⁴ reported that the second and third arms of drug treatment were only successful in aborting status epilepticus in 9.3% of overt generalized convulsive SE and 7.5% in subtle generalized convulsive SE. In patients who continued to seize, IV general anesthesia produced an additional 23.2% (overt generalized convulsive SE) and 27.6% (subtle generalized convulsive SE) response rate. In light of these findings, Treiman suggested that generalized convulsive SE treatment protocols

should be revised to call for the rapid addition of IV general anesthesia, because little is gained by adding standard second-line drugs. Previously, Lowenstein and Alldredge⁶⁰ had suggested, under certain conditions, proceeding directly to IV general anesthesia with midazolam or propofol if second-line treatment with phenytoin or fosphenytoin had failed, as opposed to third-line treatment with phenobarbital. This treatment was suggested for patients who developed SE in the Intensive Care Unit, had severe systemic disturbances (e.g., extreme hyperthermia), or seizures that had continued for more than 90 minutes.

Treatment Plan

Initial Assessment and Stabilization

Emergency evaluation of the patient with SE or presumed SE is well documented in the literature and will not be further addressed here. Table 1 provides an overview of the initial assessment, testing, and treatment in the emergency room. Although EEG is not always available upon arrival in the emergency room, attempts should be made to obtain EEG monitoring as soon as possible if the patient does not clearly respond to initial treatment. An EEG may be the only way to accurately diagnose subtle generalized convulsive SE, complex-partial SE, or absence SE.^{109, 110} In a review of 26 patients admitted to the Intensive Care Unit, Walker et al¹¹⁸ identified six patients who were inaccurately diagnosed with SE and actually were in pseudoepilepsy. In the VA Cooperative Study, 20% of patients in whom convulsive activity was stopped with drug treatment had persisting ictal discharges on the EEG.²⁰ EEG monitoring is essential for both accurate diagnosis of SE and detection of subclinical seizure activity after control of convulsive seizures.²⁵

Lorazepam

The current recommendation for first-line treatment of generalized convulsive SE is lorazepam 0.1 mg/kg (Fig. 2). If seizures continue, additional increments of lorazepam are unlikely to be successful.⁵⁶ If no response is seen within 5 to 7 minutes a second drug should be administered.⁸ Based on the results of the VA study, a second conventional agent (phenytoin or phenobarbital) will only be successful in terminating status epilepticus in an additional 3% to 7%. Because the VA study included patients with a long duration of status epilepticus (2.8–5.8 hours) who tend to be more refractory, it may not accurately reflect the ability of a second-line agent to abort status epilepticus in all situations; however, Treiman proposed directly proceeding to an agent usually reserved for the treatment of refractory SE after failure of a first-line agent.¹¹⁴

Phenytoin/Fosphenytoin

Presently, intravenous fosphenytoin or phenytoin loading (20 mg/kg) is considered the appropriate next step in SE treatment. Fosphenytoin

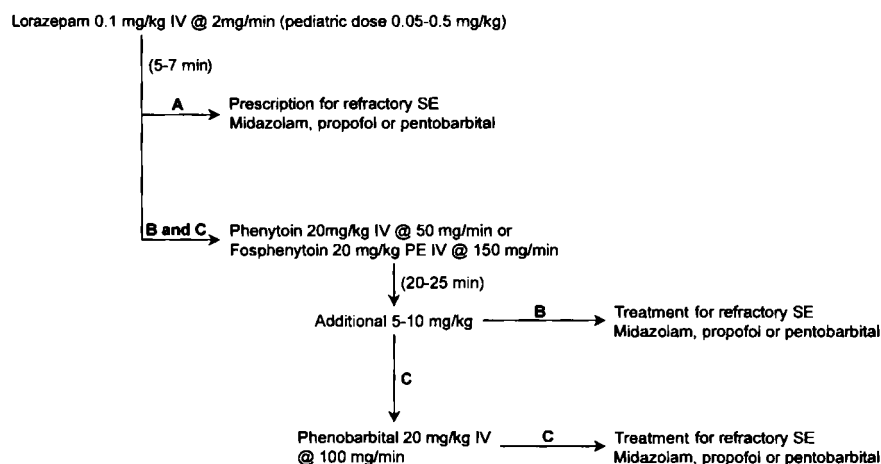


Figure 2. Treatment pathways (A, B, C) for generalized convulsive SE. **A**, Approach in patients with SE duration more than 60 minutes; supported by lack of efficacy demonstrated with second-line agents in the VA study. **B**, Modified approach from previously accepted protocols, bypasses additional time required for phenobarbital administration. **C**, Previous recommendation of the Epilepsy Foundation of America's Working Group on Status Epilepticus.¹²⁴ Treatment approach may have to be modified based on prehospital intervention and administration of medications. SE—status epilepticus; IV—intravenous. *Data from Treiman: VA Status Epilepticus Cooperative Study Group: Treatment of status epilepticus if first drug fails [abstract]. Epilepsia 40(suppl 7):243, 1999 and Working Group on Status Epilepticus: Treatment of convulsive status epilepticus. Lancet 1:480-481, 1998.*

is a phosphate ester prodrug of phenytoin that is highly water-soluble and buffered to a pH of 8.6 to 9.0. On reaching the vascular compartment fosphenytoin is rapidly converted to phenytoin by organ and blood phosphatases.¹²¹ This produces a faster administration (150 mg phenytoin equivalents/min) and attainment of a free phenytoin level of approximately 2 mg/mL. This was accomplished in 10 minutes less than with phenytoin. In a meta-analysis, Kugler et al⁵² suggested that fosphenytoin and phenytoin are likely to have a similar time to the onset of effect in controlling SE. The benefits of fosphenytoin with a slightly faster administration rate and less adverse effects (hypotension, phlebitis, and soft-tissue injury from extravasation), compared with phenytoin, remain controversial in light of the significant difference in cost.³⁸ Runge⁸⁵ postulated that because fosphenytoin is easy to administer and has a low potential for toxicity, it may be suitable for administration in an ambulance. No experience in this setting has been reported.

Phenobarbital

In accepted protocols of SE, if the patient continues to be in status epilepticus despite phenytoin administration (25–30 mg/kg), phenobarbital loading (20 mg/kg) is attempted. With the limited yield from a third agent and the added adverse effect of prolonging SE, there is a tendency to

skip this step and proceed directly to the agents usually reserved for refractory status epilepticus (pentobarbital, midazolam, and propofol). A number of authors have suggested this option in previous publications.^{7, 86, 87} Administration of phenobarbital, at doses necessary in the treatment of SE, uniformly causes some degree of respiratory depression and central nervous system alteration in patients who are not taking barbiturates. In combination with benzodiazepines, hypotension and respiratory depression are significant concerns.

Other Therapies

Intravenous valproic acid is available following the demonstration of its safety and tolerability in two United States studies.^{26, 82} Two European studies were completed using intravenous valproate for SE.^{34, 81} Positive results were seen in both studies, although a relatively high loading dose was required and rapid administration was key to aborting the seizures within an acceptable time frame. The approved method for administering valproic acid intravenously requires one-quarter of the total daily dose to be delivered over 1 hour every 6 hours.⁸³ In an open-label study to determine IV valproate loading, Venkataraman and Wheless¹¹⁶ suggested that an infusion of 6 mg/kg/min in a 1:1 dilution with 5% dextrose could be administered safely and rapidly without serious adverse events. More recently, in a study completed by Ramsay et al,⁸³ a rapid infusion of a 15 mg/kg loading dose administered at 3 mg/kg/min was recommended. The role of IV valproate in the treatment of generalized convulsive SE remains unclear. Valproate has also been given rectally in the past for both acute seizures and SE with success.^{98, 115} This treatment has had a limited role in the pre-hospital setting.

The decision of which path to follow in the treatment of SE (Fig. 3) will be effected by prehospital treatment, available agents at the site of treatment, duration of status epilepticus, cardiopneumatic and vascular stability, the ability to provide multidisciplinary intensive care support, and physician experience. When finalizing a protocol for treatment of SE at an institution, an objective analysis of the systems structure and capabilities need to be realistically reviewed before determining how aggressive the intervention.

REFRACTORY STATUS EPILEPTICUS

The definition of refractory SE varies in the literature¹⁰⁰ and is based on failure of appropriate medical treatment and the duration of SE. Definitions of refractory SE have included a seizure that is unresponsive to an adequate dose of a first-line parenteral anticonvulsant²¹ and seizures that continue for 60 to 90 minutes after the initiation of therapy.⁹³ Patients are considered in refractory SE when they have not responded to sequential treatment with a benzodiazepine, phenytoin, and phenobarbital.^{46, 61} Aggressive intervention with high-dose barbiturates (e.g., pentobarbital,

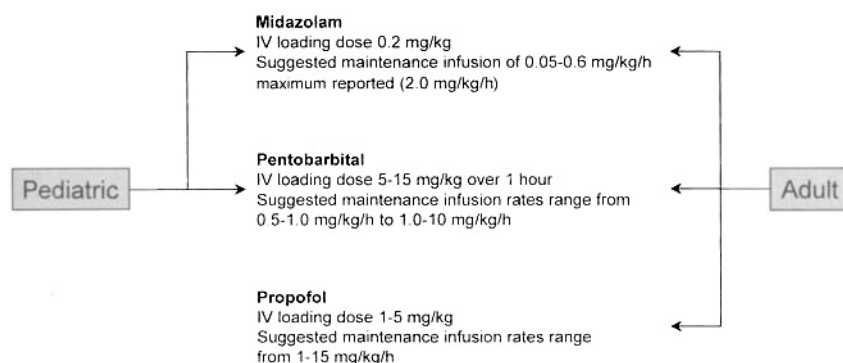


Figure 3. Medical treatment of refractory GCSE. Other options for treatment of refractory status epilepticus. Based on anecdotal reports in the literature; no formal trials have been completed. If a patient fails the initial treatment choice, one of the other recommended agents should be attempted.

thiopental, phenobarbital), high-dose benzodiazepines (e.g., midazolam, lorazepam), or an anesthetic agent (e.g., propofol) is indicated and requires intensive care support and EEG monitoring.

Pentobarbital

Pentobarbital is a potent antiseizure drug with the most experience for short-acting barbiturates and is a standard choice for refractory SE. Recommended loading doses range from 5 to 12 mg/kg IV⁸ to 10 to 15 mg/kg IV over 1 hour,⁶⁰ followed by maintenance infusion rates ranging from 0.5–1 mg/kg/hr to 1–10 mg/kg/hr. These doses usually result in a burst suppression pattern on EEG. When the patient has been seizure free for 12 hours, a reduction of the dose by 50% is attempted. The major adverse effect with pentobarbital infusions is severe hypotension requiring pressor therapy.¹²⁵ Other concerns with pentobarbital include potentially life-threatening cardiovascular toxicity and post-infusion weakness, which can delay weaning from a ventilator.^{8,77}

Thiopental is used as a first-line treatment in refractory SE in some countries,⁸⁷ in part owing to a lack of pentobarbital. It is the most rapidly acting barbiturate, with saturable metabolism and an active metabolite (pentobarbital). Its accumulation in lipid tissues may result in prolonged postinfusion recovery.⁹³

Midazolam

Midazolam is the benzodiazepine of choice for continuous infusion in refractory SE in children and adults. It is more than 90% bioavailable after IV and IM administration with onset of action within 3 minutes and

5 minutes, respectively. A loading dose of 0.2 mg/kg is followed by a continuous infusion usually ranging from 0.05 to 0.6 mg/kg/hr, but higher doses (2.0 mg/kg/hr) maintain seizure suppression.⁸ The drug is rapidly redistributed in lipid stores and has a short half-life that leaves a risk of seizure recurrence similar to diazepam.^{14,29} Tachyphylaxis occurs in some patients within 24 to 48 hours,⁸ and the dose may need to be increased severalfold to maintain seizure control. Prolonged infusions may result in patients not waking for days. This may be in part because of a longer elimination half-life and increased volume of distribution in the critically ill, but also owing to accumulation of the 1-hydroxy-midazolam metabolite.⁹¹ Analysis of midazolam clearance in two patients on prolonged infusions suggests use-dependent pharmacokinetics and that the drug does not remain a "short-acting" drug after sustained IV use.⁹⁷ Flumazenil, a benzodiazepine antagonist, may reverse the effects of midazolam, but also may result in seizures.⁹

Propofol

Propofol is a nonbarbiturate anesthetic agent with hypnotic, antiemetic, antipruritic, antioxidant, and anticonvulsant activity.¹² Studies suggest that propofol acts at a location other than the benzodiazepine binding site, and modifies the chloride channel in a way that is different from, and possibly synergistic with, benzodiazepines and barbiturates.⁶⁹ Propofol's anticonvulsant activity was first demonstrated by significant dose-related reduction in seizure duration during electroconvulsive therapy.⁴ Several case reports and two small studies were completed showing efficacy in the management of refractory SE.¹¹ Propofol is usually administered as an intravenous loading of 1 to 3 mg/kg, although 3 to 5 mg/kg⁸ have also been recommended. This is followed by an infusion ranging from 1 to 15 mg/kg/hr.⁹⁹ This dose is titrated to seizure control and maintained for 12 hours before an attempt at a taper. The rate of taper has been recommended to be 5% reduction of the maintenance infusion per hour. Propofol is more likely to provide rapid seizure control and less likely to cause tachyphylaxis at a lower cost when compared with midazolam. With administration of propofol, the high lipid content should be taken into account when determining fat and caloric intake. The initial production of propofol did not contain preservatives and the lipid emulsion served as a culture medium for bacteria, raising concerns about infections. EDTA acid has been added as a preservative, but an aseptic technique still should be adhered to.¹⁰²

Stecker et al⁹⁹ completed a study comparing propofol with high-dose barbiturates in the treatment of refractory SE. Seizure control was obtained in five of eight treatments with propofol and in nine of eleven with high-dose barbiturates. The difference in efficacy between the two protocols did not reach statistical significance, but the time to seizure control in patients who responded to therapy did (2.6 [$\pm$ 0.75] minutes with propofol, and 123 [$\pm$ 33] minutes with barbiturates). The high mortality^{11/16} was expected

because all patients presented in subtle generalized convulsive SE of prolonged duration (4.5–36 hr [median 17 hr]), and most had coexisting severe systemic illnesses with multiorgan failure.

Previous studies suggest that propofol is not safe for the pediatric population. Metabolic acidosis, myocardial failure, rhabdomyolysis, pulmonary hypotension, and hypoxia have been reported after propofol infusions for SE.^{42, 78}

There is controversy concerning the proconvulsant effects of propofol^{22, 65} and its likelihood to cause seizures. Neuroexcitatory events including opisthotonos, muscle rigidity, choreoathetoid movements, myoclonus, and seizures have been reported.¹² Some of these abnormal movements (e.g., dystonia, choreiform movements) appear to have subcortical origin.¹⁰

OTHER FORMS OF STATUS EPILEPTICUS

Other forms of SE have received much less attention in the literature because of their relatively rapid response to appropriate therapy and lack of proven increased morbidity and mortality with SE of long duration. The aggressive treatment of complex partial SE has been argued.⁴⁹ It has been difficult to determine whether morbidity in complex partial SE is secondary to continued seizure activity or a direct consequence of the acute neurologic disorder. Treatment is usually approached in a similar manner to generalized convulsive SE but with less emphasis on speed and aggressive intervention (treatment requiring intubation). Absence SE, atypical SE, and forms of primarily generalized SE should benefit from the availability of intravenous valproate. Treatment recommendations for other types of status epilepticus have been covered¹²⁰ and are available in recent editions of comprehensive epilepsy textbooks.

FUTURE DIRECTIONS

The processes involved in the transition from a single seizure to SE were reviewed in a classic paper by Lothman.⁵⁹ Tremendous progress into understanding the pathogenesis that occurs in SE has been made.^{19, 68} Development of agents directed towards altered excitatory amino acid receptors (NMDA) and ion channels (Ca^{2+}) are examples of potential treatment options in the future.

Fountain³⁰ suggested that a rational approach to treating SE is a GABA agonist, such as lorazepam, to stop generalized convulsive SE, and a NMDA antagonist to prevent neuronal injury. With existing agents, some neuroprotective effects have been demonstrated with topiramate and tiagabine in experimental status epilepticus.^{41, 74} Whether these drugs will serve any role in the treatment of SE remains to be seen. No intravenous forms of these drugs yet exist.

SUMMARY

Status epilepticus is a neurologic emergency that needs to be treated rapidly and effectively. Great treatment strides in the last decade have included: (1) completion of the first randomized double-blind multicenter study aimed at comparison of treatment options in SE; (2) development of strategies to provide prehospital treatment early in the course of status epilepticus when the condition is most responsive; (3) promotion of more aggressive treatment of SE, starting with redefining the duration of seizure activity that is considered SE; (4) further experience with agents used in refractory status epilepticus (midazolam and propofol); and, (5) research that has provided further insights into pathophysiologic processes occurring during SE, and potential strategies to prevent downstream cell death.

Despite these advances, the following shortcomings need to be addressed: (1) correction of errors in the approach and diagnosis of status epilepticus; (2) increased availability of EEG monitoring for patients suspected or being treated for SE; (3) more controlled studies with available agents in the prehospital setting, emergency department, and intensive care unit; (4) further investigation of refractory SE and comparison of agents being used to treat this entity; and, (5) continued development of the multidisciplinary approach to treatment of SE.

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