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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 Seizures[16] 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 Epilepsy[17] 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]

Bleck[6] 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 Epilepticus[112] 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 Macdonald[63] 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 al[101] 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 seizures[5] and acute symptomatic seizures[66] 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

Gastaut[33] has suggested that there are as many types of SE as there are seizures, and there one 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 SE[75] or nonconvulsive SE, but Treiman[111] 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] Treiman[111] 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. Gastaut[33] 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 anually 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 al[112] 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. Jordan[48] 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 al[72] and Gastaut et al[32] 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 Knudsen[51] 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]

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