Status epilepticus (SE): the role of benzodiazepines

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STATUS EPILEPTICUS (SE), "a condition characterized by an epileptic seizure which is so frequently repeated or so prolonged as to create a fixed and lasting condition"[1] is a medical emergency; prompt and appropriate treatment is essential to prevent brain damage and possible death. Recent advances in the treatment of SE have improved the prognosis for this condition.[2–4]

CLINICAL FEATURES

Any type of epileptic seizure can develop into SE. The syndrome most commonly associated with the name SE is tonic-clonic ("convulsive") status epilepticus—which is also the most common form of SE; an estimated 50,000 to 60,000 persons in the United States will have at least one episode of convulsive SE in a given year.[5] Nonconvulsive SE is less common and its seizures may be generalized ("absence" status) or partial.

In convulsive SE, the person suffers from repeated generalized tonic-clonic (GTC) seizures without recovering consciousness and remains in the postictal state between seizures. The GTC seizures usually last for 2 to 3 minutes; during these, the patient convulses violently. Because of the tonic axial muscle contractures, respiration is halted. During the clonic phase, small amounts of air may be exchanged. the patient often appears cyanotic, both because of desaturation of the hemoglobin and increased intrathoracic pressure impeding venous return. Immediately after the GTC seizure, there is increased respiratory drive and the patient has deep rapid respiration. The patient remains unconscious, however. If the SE is not caused by an acute central nervous system (CNS) insult, the level of consciousness may increase prior to the next seizure; but if there is no improvement in consciousness, a new CNS insult should be suspected. In adults, GTC seizures are followed by 20 to 30 minutes of a postictal state which is then followed by another seizure. In children, GTC seizures may be continuous.

Systemic effects of repeated GTC seizures include cardiovascular, respiratory, and renal failure. The cardiovascular system is particularly stressed because of the excessive demands placed upon it by the repeated tonic contractions of the skeletal muscle system. Tachycardia is inevitable; bradycardia may occur from vagal tone modulated by CNS activity; and cardiac arrhythmias may occur from hyperkalemia. Drugs used to treat SE may contribute further to these problems; barbiturates may depress the myocardium and phenytoin (PHT) and its solvent, propylene glycol, may cause arrhythmias and hypotension. A single GTC seizure is usually followed by great respiratory effort stimulated by hypercarbia; but following a series of seizures, respiratory failure may occur. Respiratory drive may also be depressed by the disorder precipitating SE and by the barbiturates and benzodiazepines used to treat the patient. Altered lymph flow may induce pulmonary edema.[6] Rhabdomyolysis leads to myoglobinuria and may cause renal failure. The metabolic-biochemical complications of GTC seizures include respiratory and metabolic acidosis, anoxemia, hyperazotemia, hyperkalemia, hypoglycemia, and hyponatremia. Massive activation of both sympathetic and parasympathetic systems leads to severe autonomic nervous system

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TABLE 1
STATIC OR ACUTE CNS PATHOLOGY AS CAUSES OF STATUS EPILEPTICUS*

Group I — Static
Exacerbation of seizures in persons with epilepsy
Alcohol or drug abuse
Withdrawal from drugs
Miscellaneous or undetermined (no acute CNS lesion or metabolic cause identified)
Group II — Acute
Anoxic encephalopathy
Acute vascular event (stroke, intracerebral hemorrhage)
CNS neoplasm
Acute trauma
Metabolic encephalopathy
Meningitis

* Modified from Cranford et al[1]

TABLE 2
TIME FRAME FOR TREATMENT OF STATUS EPILEPTICUS

0–9 min:	Assess cardiorespiratory function, obtain history and perform neurological and physical examination. Blood for antiepileptic drug levels, glucose, BUN, electrolytes, metabolic screen and drug screen. Insert oral airway and administer oxygen if needed. Start intravenous infusion with saline solution. Administer 25 grams of glucose and B vitamins.
10–30 min:	Begin infusion of phenytoin (PHT), 20 mg/kg at a rate no faster than 50 mg/min. This may take 20–40 min. Monitor EKG and blood pressure. Lorazepam (4 to 8 mg) or diazepam (10 to 20 mg) may be given if convulsions occur while PHT is being infused.
31–60 min:	If seizures persist, give phenobarbital, 10 mg/kg at 100 mg/min intravenously.
At 1 hour:	If seizures persist, barbiturate coma or general anesthesia—using agents with which the facility is familiar—should be employed.

disturbances including hyperpyrexia, excessive sweating, and salivary and tracheobronchial hypersecretion. Endocrine abnormalities—including marked elevations in plasma prolactin, glucagon, growth hormone, and ACTH—have been reported.[7] Cerebrospinal fluid pleocytosis attributable to SE has also been observed.[8]

Nonconvulsive generalized SE consists of frequent or continuous absence seizures and is characterized clinically by clouding of consciousness. The electroencephalogram (EEG) usually shows typical 3 Hz generalized spike and wave discharges. Although absence status is most common in children and adolescents, it has occasionally been reported in adults.[9] Complex partial SE may present with clinical behavior ranging from a "twilight" state, with partial responsiveness and semipurposeful automatisms, to total unresponsiveness, speech arrest and stereotypical automatisms.[10] Aphasic SE, characterized by episodes of inability to speak lasting from a few hours to several days, must be considered in patients presenting with dysphasia or aphasia with no other findings of cerebrovascular disease. Fortunately, the EEG is usually diagnostic for these conditions; treatment with a benzodiazepam (during the EEG) often results in a rapid normalization of the EEG and clearing of the sensorium.[11] The differential diagnosis of an acute confusional state should always include absence ("petit mal") SE and complex partial SE.

Not all persons appearing to have convulsions are having epileptic seizures. The syndrome of nonepileptic SE, in which a person has serial nonepileptic convulsions ("pseudoseizures"), must be considered whenever there is an unusual presentation for the seizure type or if response to antiepileptic drugs (AEDs) does not follow the expected pattern.[12] Occasionally, a person with intermittent decorticate or decerebrate posturing may be mistakenly diagnosed as having SE.

The reported causes of convulsive SE vary and reflect the population serviced by the hospitals. Two broad groups of patients can be identified (*Table 1*): those with no new structural CNS lesion (Group I) and those with an acute CNS injury (Group II). Group I includes patients with a history of epilepsy who have an acute exacerbation of seizures.[2,13–15] Withdrawal from AEDs is the cause of exacerbation of seizures in the majority of these patients and may be documented by measuring AED serum levels. In some settings, drug abuse involving phencyclidine (PCP, "angel dust") or other street drugs may be a frequent occurrence. Unusual causes for seizure exacerbation include baclofen withdrawal[16] or secondary hyperparathyroidism.[17] Group II patients consists of individuals with an acute neurological insult such as head injury, rapidly growing brain tumor, anoxic encephalopathy, meningitis, encephalitis, or other acute CNS process.

Mortality and morbidity

Mortality rates for convulsive SE were as high as 50% prior to 1960.[18] More recent figures for acute mortality are in the range of 8% to 12%. Currently, with appropriate therapy, death is related to the etiology of the SE, with Group II patients having much higher mortality than those of Group I.[2,19]

Central nervous system morbidity may be caused by the systemic effects of the seizures, as already described, or by prolonged electrical discharges. Prolonged electrical activity within the CNS can, by itself, cause irreversible neuronal damage. Meldrum and co-workers have shown that neuronal damage results even when

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TABLE 3
ADVERSE EVENT DATA FROM 81 EPISODES OF STATUS EPILEPTICUS IN 78 PATIENTS FROM A DOUBLE-BLIND STUDY OF DIAZEPAM VS LORAZEPAM[24]

Percent of patients with adverse events	Patient age (yrs)	Dose (mg)	Adverse event	Severity	Associated diagnoses
Diazepam					
12 (5/41)	55	15	Respiratory arrest	+++	0
	96	10	Respiratory arrest	+	0
	32	10	Sedation	++	0
	64	10	Respiratory depression	++	0
	50	10	Respiratory depression	+	0
Lorazepam					
12 (5/40)	54	4	Respiratory depression	+++	1
	69	4	Respiratory depression	++	2
	57	4	Respiratory arrest	+++	3
	86	4	Respiratory arrest	++	4
	71	4	Hypotension	++	0

+ = Mild
++ = Moderate
+++ = Severe
0 = None
1 = Diabetes mellitus, sepsis
2 = Alcoholism
3 = Active gastrointestinal bleeding
4 = Renal failure, pneumonia, cardiac disease

animals are paralyzed and ventilated in order to prevent the metabolic consequences of muscle activity, if the abnormal electrical activity is not suppressed.[20] There appears to be a 30 to 60 minute period during which these changes are still reversible; but after 60 minutes, neuronal death is evident.[21] Since the developing brain is particularly vulnerable to seizure activity, permanent damage can occur in the neonatal brain under conditions that do not affect a mature brain.[22] Prolonged or permanent deficits of memory after complex partial SE[10] and widespread neuronal necrosis following epilepsia partialis continua[23] have been observed.

TREATMENT

Time is of the essence in the treatment of SE because the morbidity and mortality are related to duration of seizure activity.[4] Every facility should therefore have a predetermined protocol that also includes a time frame. It is easy to be distracted by other needs and too often attention is directed from a patient with SE after the seizures seem to have been stopped. As can be seen from *Table 2*, the first few minutes should be spent assessing the patient's condition. The individual should be examined for clues that might indicate an etiology for this particular episode of SE. The Med Alert bracelets worn by many persons with epilepsy may provide helpful information. Evidence of a recent head injury may suggest the presence of an intracerebral hematoma. Historical details surrounding the onset of SE should be obtained. Such information can often be provided by paramedical personnel or by friends or relatives accompanying the individual. Diagnostic laboratory testing should be done to rule out metabolic causes of seizures; SE from hypoglycemia, hypernatremia, and other metabolic conditions do not respond to antiepileptic medications. Drug therapy should begin as soon as it becomes clear that the patient does meet the criteria of treatment.

Ideally, the drug chosen for the treatment of SE should enter the brain rapidly, have an immediate onset of anticonvulsant activity, should not depress consciousness or respiratory function, should have a long half-life so that the therapeutic concentrations are maintained for hours, and should effectively block both the somatic manifestations of seizures as well as the neuronal discharges.

Diazepam

Diazepam became popular in the mid-1960s following a few case reports about its success in treating SE. Its profile of activity is a function of the drug's physiochemical properties. Since approximately 20% of cardiac output goes to the brain, as much as 20% of an intravenous dose of diazepam enters the CNS after injection, accounting for the rapid onset of anticonvulsant activity of this drug. However, the binding of diazepam to the benzodiazepam receptor site is relatively weak. Furthermore, diazepam is also quite lipid soluble and, with recirculation, relatively high initial brain concentrations decrease quickly as diazepam is redistributed to the much greater bulk of fatty tissue. Thus, the duration of diazepam's effectiveness in the brain is less than 30 minutes. Its short cerebral half-life has been clearly shown in the cat, by simultaneous measurement of EEG recordings and of blood and brain concentrations of diazepam.[24] A similar time course

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has been observed in the treatment of clinical SE, when a significant number of patients receiving diazepam alone had recurrence of seizure.[2] In view of these findings, it is no longer sufficient simply to administer a dose of diazepam, return to other pressing duties, and plan for additional treatment only if further seizures occur. Instead, diazepam should be used in conjunction with, or be followed by, loading with a medication with a longer time course of action in the central nervous system.

Lorazepam

Lorazepam has recently been advocated for the treatment of SE because of its longer CNS action. Lorazepam has higher affinity binding to the benzodiazepam receptor sites, compared to diazepam, and—theoretically—a longer effective life at the receptor site. It also appears to be more potent: 4 mg of lorazepam appear to have the same effectiveness as 10 mg of diazepam. In the first large double-blind random study of benzodiazepines in SE (N = 78), a single 4-mg dose of lorazepam was compared with a 10-mg dose of diazepam and found to be equivalent in terms of effectiveness and number of side effects.[25] Overall, one or two consecutive doses of diazepam (10 mg) or lorazepam (4 mg) were effective in 76% and 89% of 81 episodes, respectively. Depression of respiration in some patients was observed with both medications (*Table 3*). However, persons experiencing adverse effects with lorazepam had concurrent medical illnesses whereas those with diazepam did not.

Because this study[25] was double-blind and many of the subjects would receive diazepam, the protocol's safety component required that all patients be given an 18 mg/kg phenytoin load 0.5 hour after the infusion of the study drug, regardless of whether seizures had occurred. Therefore, the question of differences in the duration of action of the two study drugs could not be answered by this trial. A study comparing phenytoin with lorazepam is in progress, and its results should permit assessment of the future role of lorazepam in SE.[26]

At this time, lorazepam has been approved for use in SE in Canada; approval for use in SE in the United States is pending. Clonazepam has been used successfully in Europe for the treatment of SE, but a parenteral form is not available in the United States.[27]

The role of benzodiazepines in SE is limited by their depression of consciousness and of respiration. These adverse effects may be critical during assessment of the level of consciousness following a series of seizures. Return of consciousness after a GTC seizure is typical of a Group I patient, while no change or deepening of stupor or coma after a seizure may alert the physician that this is a Group II patient. In addition, since benzodiazepines depress respiratory drive, postictal monitoring of respiration is more crucial after using this class of drugs; the physician should therefore be ready to intubate if necessary.

Phenytoin

The main advantages of phenytoin (PHT) are its effectiveness in controlling convulsions, its relative long half-life and its lack of significant CNS depression. Its disadvantages include cardiovascular toxicity when given too rapidly, the time required for administering the full loading dose, and its relative ineffectiveness in suppressing focal epileptic activity. Phenytoin is effective in suppressing experimental seizures as soon as adequate brain concentrations are attained which, in rats, is within a few minutes[28]; in humans, the drug penetrates the brain rapidly.

The currently available preparation of phenytoin contains propylene glycol and ethanol, and it may be diluted to 5 mg/ml or less in normal saline solution to permit steady administration by infusion equipment.[29] Injection of a bolus of undiluted PHT by hand can be dangerous.[30] Both blood pressure and electrocardiographic (EKG) tracings should be monitored during PHT infusion. In some situations—eg, tricyclic antidepressant overdose, in which hypotension can become a cardinal feature of SE—the use of PHT needs to be monitored especially closely. In the intensive care unit, the administration of PHT to a critically ill patient may be associated with more hypotension and/or cardiac abnormalities, and the addition of barbiturates can depress myocardial contractility and decrease blood pressure even further. If the seizures do not respond to PHT infusion, there is a very high probability that a significant acute CNS insult has occurred and that the person belongs to Group II.

The volume of distribution of PHT in adults is approximately 0.75 liters/kg.[19] This means that a loading dose of 20 mg/kg will result in blood concentrations of approximately 26 ug/ml at the end of infusion (assuming the level was zero prior to the load). The half-life of PHT after doses of 18 to 20 mg/kg is in excess of 36 hours. Thus, after one load of PHT, blood levels will remain high for many hours. Brain concentrations of PHT in humans parallel blood concentrations.[31] If seizures continue after a loading dose of PHT, other agents should be used because the

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administration of more PHT will result in toxic levels and in the theoretical possibility of precipitating more seizures.

The kinetics of intravenous phenytoin may be different in children.[32] A new preparation of a pro-drug appears to overcome many of the disadvantages of the present preparation of PHT.[33]

Phenobarbital

Phenobarbital (PB) has the advantage of a very long half-life and effectiveness in both generalized and partial seizures; it can also be administered more rapidly than PHT. The disadvantages of PB are depression of consciousness and of respiration; the respiratory depression may be more profound in a patient initially treated with diazepam. The volume of distribution of PB is approximately 1, meaning that 1 mg/kg should result in a serum concentration of approximately 1 μg/ml. A loading dose of 10 mg/kg of PB is often used and can be followed by an additional dose of 10 mg/kg if needed.

Pentobarbital coma

Pentobarbital coma has been successfully utilized in SE refractory to diazepam, PHT, or other drugs.[34–36] Its use needs to be carefully monitored by EEG recording. Doses should be tailored to maintain a burst suppression pattern on the EEG. Treatment with pentobarbital coma may be required for many days or even weeks.

Treatment of SE in infants and children

Diagnosis in the neonate may be difficult because the seizures are subtle, with symptoms including sucking, random eye movements, stretching, yawning, bicycling, and apnea. Seizures in neonates are unlike the events seen in older persons because of the lack of myelin and dendritic connections. Nevertheless, these seizures are often associated with serious CNS disturbances. A standard loading dose of 20 to 25 mg/kg of phenobarbital has been found to be effective and necessary to attain effective concentrations. This may be followed by a dose of PHT, 18 mg/kg. Benzodiazepines are also used by some pediatricians in addition to these drugs. Paraldehyde is very useful in some instances; however, because of liability issues, its availability is becoming limited in the USA and may become unavailable in the future. Treatment of SE in children can be accomplished by using many of the drugs found useful in treating adults.[37]

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