Current Treatment of Status Epilepticus

Harold H. Morris III, MD
Galveston, Texas

Generalized tonic-clonic status epilepticus is a relatively common neurologic emergency. The differential diagnosis of this condition includes decerebrate spasms and hysterical seizures. Initial therapy includes establishing an airway and securing an intravenous line. Blood should be obtained for chemistries and anticonvulsant levels. Administration of anticonvulsants should *not* be delayed until laboratory results are obtained. Intravenous diazepam will usually stop continuous tonic-clonic seizure activity, but because of a rapid redistribution phase, it necessitates administration of a longer acting anticonvulsant such as phenytoin or phenobarbital. Intravenous phenytoin should be administered slowly at a dose of 15 mg/kg while carefully monitoring vital signs. Intravenous phenobarbital produces sedation and may cause respiratory depression. Occasionally, other anticonvulsants such as paraldehyde, lidocaine, and general anesthesia will be needed to break status epilepticus. Careful follow-up of the patient and monitoring of the anticonvulsant levels may prevent future bouts of status epilepticus.

Status epilepticus is one of the most common neurologic emergencies faced by the nonneurologist. Prompt treatment of the condition significantly lowers mortality and morbidity. While no new anticonvulsants are available for treatment of this condition, clinical application of current pharmacologic knowledge can result in more effective care of patients with this life threatening condition.

This paper will discuss only generalized tonic-clonic seizures. Complex partial status (psychomotor status), simple partial status (focal motor or sensory status), and absence status (petit mal status) are less of a threat to life and are treated less vigorously.

Diagnostic Considerations

Status epilepticus may be defined as a single, generalized convulsion that lasts longer than 30 minutes or recurrent tonic-clonic convulsions occurring so frequently that the patient remains obtunded between seizures.

Not uncommonly, two conditions may be con-

From the Department of Neurology, University of Texas Medical Branch, Galveston, Texas. Requests for reprints should be addressed to Dr. Harold H. Morris III, Department of Neurology, University of Texas Medical Branch, Galveston, TX 77550.

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fused with status epilepticus, and inappropriate treatment may result. Decerebrate spasms are associated with lesions that directly or indirectly affect the midbrain (eg, during transtentorial herniation). These movements consist of unilateral or bilateral tonic extension with pronation of the upper and lower extremities. Frequently a variable degree of opisthotonos is also present. The movements last several seconds and may be precipitated by external stimuli such as pain or touch. These spasms occur in a patient who is unconscious, usually has pupillary abnormalities and abnormal reflex eye movements, and exhibits central nervous system abnormalities of respiration. Treatment should be directed at the cause of these spasms rather than at the spasms themselves.

Recurrent hysterical "seizures" are commonly confused with status epilepticus. Clues to the functional nature of these "spells" include directed behavior such as kicking, biting, or striking at others, pelvic thrusting movements, lack of pupillary changes or extensor plantar reflexes during a seizure, absence of a postictal state, and admission by the patient that he or she can hear and understand but cannot respond during the "spell." These episodes frequently can be rapidly terminated by the physician's placing his or her hand over the patient's nose and mouth and briefly occluding the airway. A functional patient's response is to attempt to remove the hand or stop the episode; a patient who is having a genuine seizure will not react in a defensive manner. An electroencephalogram usually is normal during the episode.[1]

It is helpful to group patients with status epilepticus into two large categories: (1) those who have a history of epilepsy and (2) those in whom the onset of seizures is secondary to a relatively acute central nervous system insult. By far the most common cause of status epilepticus in the first group of patients is the discontinuation or erratic administration of an anticonvulsant. Treatment of the seizures in these individuals is usually uneventful, and in general the prognosis is good for a satisfactory outcome. Patients in the second group, however, may have seizures that are resistant to control by anticonvulsants. To a large extent the prognosis in this second category depends on the nature and possibility of correction of the underlying acute process that precipitated the seizures. The most common causes of symptomatic status epilepticus are metabolic derangements, (especially renal failure, hyponatremia, and hyperosmolar coma), intracranial infections, some acute forms of cerebrovascular disease, and brain tumors (especially frontal lobe).[2,3]

Current Treatment

Treatment of status epilepticus (Figure 1) should begin by establishing an airway. Most patients ultimately need to be intubated both to avoid aspiration of gastric contents and to provide ventilatory assistance. Frequently nasotrachial intubation is the easiest route to a clear airway. With a secure airway the patient can receive large doses of anticonvulsants, many of which depress respirations.

Blood should be drawn to determine laboratory values for the following: complete blood count, electrolytes, glucose, urea nitrogen, anticonvulsant levels, liver function studies, and serum calcium. Other hematologic studies may be appropriate depending upon the clinical circumstances.

A secure intravenous line should be established, and a bolus of 50 percent glucose administered after blood has been drawn. If the patient may be an alcohol abuser, also give 50 mg of thiamine hydrochloride intravenously. Administration of anticonvulsants should *not* be delayed until the results of the blood and other tests are known. A list of anticonvulsant drugs useful in the treatment of status epilepticus is given in Table 1.

An examination of the cerebral spinal fluid should be made if meningitis is suspected, but a lumbar puncture should *not* be done if there is a suspicion of a cerebral tumor, abscess, or other mass lesion. A computed tomographic (CT) scan with contrast is usually indicated when the cause of the patient's seizures is unknown.

When the patient has continuous tonic-clonic activity, intravenous diazepam (Valium) should be given to stop the seizures. The dose is 5 to 10 mg for adults and 0.1 to 0.2 mg/kg for children. The drug should be administered over a period of one to three minutes. Intramuscular diazepam should not be used because it is absorbed too slowly and too erratically to produce therapeutic anticonvul-

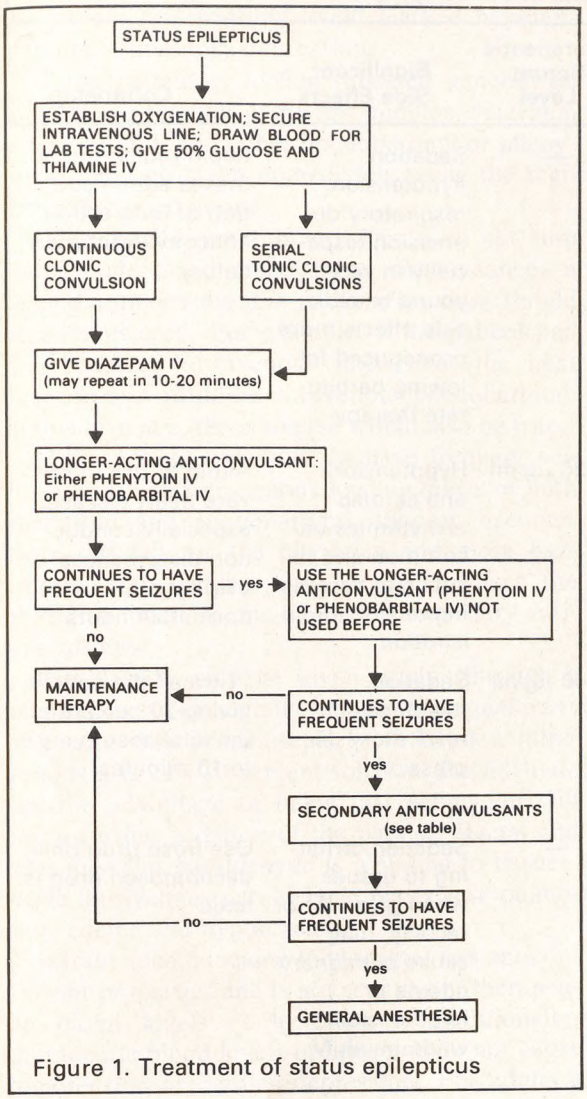

Figure 1. Treatment of status epilepticus

sant levels. Because of a rapid redistribution phase, the serum diazepam level rapidly falls and may be subtherapeutic within 15 to 30 minutes of administration. This pharmacologic property requires immediate administration of a second, longer acting anticonvulsant for long-term protection.[4] Diazepam rapidly penetrates into brain and exerts its anticonvulsant effect within several seconds to a minute or so.[5] If needed, a second intravenous injection of diazepam may be given 15 to 30 minutes after the first. Hypotension and depression of respirations are the most significant side effects of intravenous diazepam. These complications are more likely to occur in the very young or in elderly individuals, especially if these patients have previously received barbiturates.

In patients previously taking phenytoin (Dilantin) or who will be placed on maintenance phenytoin following cessation of the status epilepticus, phenytoin is a logical choice for the longer acting anticonvulsant.[2] The drug may be given as a slow intravenous infusion to a loading dose of 15 mg/kg for adults and children. The same dose is recommended even if the patient is known to be receiving phenytoin and the serum level is unknown. Transient toxic symptoms of nystagmus and chorea may appear, but these are not dangerous. An additional dose of 5 mg/kg of phenytoin should be given 12 hours after the first. When given intravenously, the drug should not be diluted and should be given no faster than 50 mg/min to adults; it should be given proportionately slower for children. Phenytoin penetrates brain rapidly and is virtually in equilibrium by the time the infusion is complete. Significant complications of intravenous phenytoin are hypotension and cardiac arrhythmias. These problems are uncommon when the agent is given slowly and they usually respond promptly to decreasing the rate of infusion. Constant monitoring of blood pressure and heart rhythm are required during drug administration. Monitoring the electrocardiogram during the infusion is ideal but not always practical. A relative contraindication to intravenous phenytoin is the presence of severe heart disease, especially when there are significant disturbances of cardiac conduction. Phenytoin should not be used intramuscularly to treat status epilepticus, as it is absorbed extremely slowly.

In patients who will probably be placed on maintenance phenobarbital following the acute episode of seizures (many children and adults allergic to phenytoin), it is reasonable to use this agent as the long acting anticonvulsant. The loading dose of phenobarbital is 5 to 10 mg/kg for adults, 10 to 15 mg/kg for children, and 15 to 20 mg/kg for neonates. To assure rapid absorption, intravenous phenobarbital is best administered slowly. Giving 20 percent of the total dose every 5 to 10 minutes will allow the physician to "titrate"

Table 1. Anticonvulsants Useful in Status Epilepticus

Drug	Adult	Pediatric	Therapeutic Serum Level	Significant Side Effects	Comments
Diazepam (Valium)—do not dilute solution	5-10 mg IV over 1-2 minutes; may repeat in 15-30 minutes	0.3 mg/kg IV over 2-5 minutes; may repeat in 15-30 minutes	—	Sedation, hypotension, respiratory depression (especially in very young or old); side effects more pronounced following barbiturate therapy	Rapid redistribution makes administration of long acting anticonvulsant mandatory
Phenytoin (Dilantin)—do not dilute solution	15 mg/kg IV and 5 mg/kg IV after 12 hours; administer no faster than 50 mg/min	15 mg/kg IV and 5 mg/kg IV after 12 hours; administer over approximately 20 minutes	10-20 μg/ml	Hypotension and cardiac arrhythmias uncommon and respond to decreasing rate of administration	Avoid IV use in severe heart disease, especially conduction disturbances; begin maintenance dose at 24 hours
Phenobarbital	5-10 mg/kg IV	Over 1 month, 10-15 mg/kg IV; neonates, 15-20 mg/kg IV	20-40 μg/ml	Sedation, hypotension, respiratory depression	"Titrate" the patient, giving 20 percent of the total dose every 5 to 10 minutes
Paraldehyde	4-8 ml	0.20 ml/kg	—	Sedation, irritating to tissues when given IM or rectally, may cause pulmonary edema or hypotension when given IV	Use fresh drug only; decomposed drug is toxic
	Deep IM injection with no more than 4 ml at single site, or as a retention enema mixed with an equal volume of mineral oil, or as a 10 percent IV solution (eg, 1 ml paraldehyde in 10 ml 5% dextrose in water) given very slowly. May repeat dose in 2-6 hours				
Lidocaine (Xylocaine)	100 mg IV with additional 50 mg in 20 minutes; begin constant infusion at 2 mg/minutes at time of first bolus	1.5 mg/kg IV initially, followed by .75 mg/kg in 20 minutes; constant infusion at 30/μg/kg/min; begin at time of first bolus	2-5 μg/ml	Early toxic symptoms are confusion and tremors; more severe toxic effects include seizures, hypotension, ventricular fibrillation	Not approved as an anticonvulsant; reduce dose in liver disease and severe congestive heart failure
Valproic acid (Depakene)	Initiate at 5-10 mg/kg in divided doses and increase to 15-30 mg/kg as tolerated; mix syrup with 30 ml water and give as retention enema or through nasogastric tube		50-100 μg/ml	Hepatotoxic on rare occasion, but this has been reported only with chronic administration	Degree of efficiency unknown in status epilepticus

the patient and possibly avoid marked hypotension and respiratory depression.

If the patient is having repeated generalized tonic-clonic seizures every few minutes, diazepam is less helpful, and either phenobarbital or phenytoin should be given immediately using the regimens discussed above.

Occasionally one anticonvulsant will not stop status epilepticus; under these circumstances a second anticonvulsant *in full loading dose* should be administered. For example, if the patient had first received intravenous phenytoin, the next agent to use would be intravenous phenobarbital. In this instance, the converse would also be true.

If the patient continues to have frequent seizures after full intravenous loading doses of both phenytoin and phenobarbital, therapy becomes more difficult for the physician and more hazardous to the patient. In this circumstance the physician must use one of several secondary anticonvulsants.

Paraldehyde may be given orally (through a nasogastric tube), rectally (mixed with equal parts of mineral oil), intramuscularly, or by slow intravenous drip of a 10 percent solution. Paraldehyde has the advantage of being fast acting but will cause further sedation of the patient. Rectal and intramuscular paraldehyde is irritating to tissues, while intravenous paraldehyde may cause pulmonary edema and hypotension.

Intravenous lidocaine (Xylocaine) has anticonvulsant properties and is not sedating at therapeutic blood levels (2 to 5μg/ml). Additionally, therapeutic blood levels of lidocaine do not cause hypotension or cardiac depression. For adults a bolus of 100 mg given intravenously is recommended, followed by a second 50-mg bolus after 20 minutes. A continuous infusion of 2 to 3 mg/minute is started at the time the first bolus is given. Because lidocaine is metabolized by the liver, the rate of administration should be lower in patients with liver disease or congestive heart failure. At mildly toxic levels lidocaine causes confusion; at higher levels it may cause convulsions. Lidocaine is not approved for use as an anticonvulsant in the United States.[6]

Oral or rectal valproic acid (Depakene) has also been used with some success in treating status epilepticus, but its degree of effectiveness in this clinical situation is unknown.[7]

If all else fails, general anesthesia may be used to stop status epilepticus. With current anticonvulsants and pharmacologic principals, however, this is rarely needed.

Comment

Some of the more common medical complications following status epilepticus include aspiration pneumonia, postictal pulmonary edema, transient (usually self-limiting) lactic acidosis, myoglobinuria with renal failure, and fractures of thoracic vertebrae. These entities can be dealt with on an individual basis.

Following discharge from the hospital, the importance of taking medications on a regular basis and the hazards of noncompliance should be explained to the patient. Monitoring of serum anticonvulsant levels during and following hospitalization is indispensible in detecting toxicity, noncompliance, and inadequate doses, thereby preventing future bouts of status epilepticus.

References

1. Riley TL, Brannon WL: Recognition of pseudoseizures. J Fam Pract 10:213, 1980

2. Cranford RE, Leppik IE, Patrick B, et al: Intravenous phenytoin in acute treatment of seizures. Neurology 29:1474, 1979

3. Celesia GG: Modern concepts of status epilepticus. JAMA 235:1571, 1976

4. Brown TR: Drug therapy of status epilepticus. Am J Hosp Pharm 35:915, 1978

5. Ramsay RE, Hammond EJ, Perchalski RJ, et al: Brain uptake of phenytoin, phenobarbital, and diazepam. Arch Neurol 36:535, 1979

6. Morris HH: Lidocaine: A neglected anticonvulsant? South Med J 72:1564, 1979

7. Thorpy MJ: Rectal valproate syrup and status epilepticus. Neurology 30:1113, 1980