



Treatment of status epilepticus

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OVER the past 250 years, many accounts of status epilepticus have been published, but its true frequency is difficult to judge. Status epilepticus has been recognized as a clinical entity since 1824 when Calmeil¹ first described patients who had repeated or prolonged uninterrupted epileptic seizures. It has been estimated that about 5% of all epileptic patients at some time in their lives experience an episode of status. Each year about 8,000 persons in the United States are hospitalized because of convulsive status epilepticus. Reports of epilepsy presenting as status epilepticus vary from 12% to 77% of the published reports.

Status epilepticus is defined as "a condition characterized by an epileptic seizure which is so frequently repeated or so prolonged as to create a fixed and lasting condition."² For practical purposes, duration of the seizure has been defined as 30 minutes. There are essentially as many types of status epilepticus as there are types of epileptic seizures. Status may be classified by etiology—symptomatic *v* idiopathic—and by seizure type—generalized *v* focal. Generalized seizures have been further classified as convulsive or nonconvulsive.

In considering the pathogenesis of status epilepticus, it is important to distinguish between underlying cause and precipitating factors. In nearly all reported series, the majority of cases have an underlying demonstrable cause of their epilepsy and have symptomatic rather than idiopathic epilepsy. Underlying factors vary with the patient's age. The precipitating factor in many cases is also the underlying cause. A change or withdrawal of anticonvulsants is a common precipitating cause of status. An association between withdrawal of anticonvulsants and status epilepticus was first sug-

gested by Hunter,³ who appreciated that the frequency of status epilepticus had increased since the introduction of bromides in 1861. Aminoff and Simon⁴ in 1980 reported that 28% of all episodes of status epilepticus were thought to be related to a change of anticonvulsants.

The true incidence of neurologic and mental sequelae of status epilepticus is not known but is assumed to be significant. Studies in animals with prolonged generalized status have demonstrated significant changes in brain metabolism and circulation with corresponding neuropathologic alterations.⁵ Clinically, it is difficult to determine if the sequelae are secondary to the underlying condition causing status or to status itself. Neurologic morbidity is assumed to be higher in children than in adults. Aicardi⁶ reported a 42% incidence of neurologic deficits, most commonly hemiplegia and mental retardation. The mortality rate from status epilepticus has declined considerably over the past 60 years but remains significant. The incidence of death varies from 3% to 20%. Approximately 50% of deaths are caused by the consequences of status and 50% from its etiology.

Treatment of status remains a medical emergency and a persistently difficult problem. Management is divided into three phases: 1) stabilization of the patient, 2) termination of the seizure, and 3) diagnostic evaluation. For practical purposes, the three phases should be pursued almost simultaneously.

GENERAL MEASURES

The first concern for a child who presents in the midst of a convulsion should not be administration of an anticonvulsant. That first and foremost concern should be the child's vital signs in the priority of (1)

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airway patency and ventilation, (2) an intact cardiovascular system—i.e., pulse rate and blood pressure, and (3) temperature elevation and/or signs and symptoms of infection or of a metabolic or toxic process. It is absolutely essential to secure a patent airway. This can often be accomplished by positioning the child on one side to allow for drainage of secretions, and gentle extension of the head and elevation of the jaw. Suctioning should be used only sparingly to remove excess secretions. Oxygen may be administered by nasal cannula. If it can be easily placed, a soft plastic oral or nasal airway should be inserted and taped securely. Wooden tongue blades and other hard objects should not be used because they may cause injuries to the mouth and teeth. The patient needs to be protected from personal injury.

If vital signs are stable, the next priority is to check the blood glucose by finger stick at the bedside. Blood should be drawn to search for a metabolic cause of the seizures and, if an anticonvulsant has been previously prescribed, to measure its serum levels. Initial blood tests should include glucose, electrolytes, BUN, CBC, liver function tests, and toxicology screen. If the patient has a fever, blood cultures should be obtained and lumbar puncture considered. Simultaneously, a stable intravenous (IV) line should be established; however, if a vein is not readily available, this may not be absolutely necessary. Initial anticonvulsant therapy may be administered rectally.

It is then important to assess the patient's overall condition, perform a general and neurologic examination, and obtain the history surrounding onset of the status epilepticus. Subsequent evaluation and treatment are often determined by prior history, as in the case of a patient who is a known epileptic with a previously established seizure disorder. In some cases, status epilepticus may be a presenting manifestation of a neurologic event.

DRUG TREATMENT

It is generally accepted that the longer a seizure continues, the more difficult it is to stop it, and the greater the possibility of permanent brain damage. Once it has been established, therefore, that the patient is having a "sustained" seizure, then drug therapy should be initiated. One should be certain, however, that the patient's seizure has not ceased and that he is not merely postictal; all too often patients

who are postictal receive unnecessary anticonvulsant treatment, which may add to their sedation.

Various clinicians and medical centers have recommended a number of treatment protocols that have proven successful,⁷⁻¹² but there is no standard treatment because there is no "ideal anticonvulsant": one easily administered, with a broad spectrum of effectiveness, a rapid onset and prolonged duration of action, and freedom from serious side effects. As new drugs become available and old standby agents disappear, the basic truisms in the drug treatment of status epilepticus constantly change.

The anticonvulsant treatment of status epilepticus should include selection of a drug for immediate termination of the seizure and a second drug for maintenance of suppression of the seizures. Although various investigators have emphasized the classification of seizures in determining the treatment of status epilepticus, the immediate treatment is essentially similar regardless of the seizure type. The anticonvulsant chosen for maintenance treatment, however, does often vary, depending upon the type of epilepsy; and the history may be of particular significance in deciding the drug chosen for maintenance treatment. One of the most common causes of status epilepticus is withdrawal of anticonvulsants. In such a situation, it is probably prudent to try to re-establish a therapeutic blood level of the anticonvulsant withdrawn. Recent investigations and new studies of drug distribution to the brain have led to some definite first choices in treatment. First-choice agents include the benzodiazepines, phenytoin, and phenobarbital.

BENZODIAZEPINES

Since the mid 1960s, *diazepam* has been considered the drug of choice to initiate therapy of status epilepticus. Its advantage is its rapid onset of action due to a quick distribution to the brain. An off-setting disadvantage is its short central nervous system (CNS) half-life that limits its clinical effectiveness to less than one half hour. Other concerns are its tendency to depress respiration and consciousness and its tendency to change clonic status into treatment-resistant tonic status in patients with slow spike and wave electroencephalograms (EEGs).¹³ The recommended dosage of diazepam in children less than 5 years of age is 0.2 to 0.5, which may be administered every two to five minutes up to a maximal dosage of 5 mg. In children 5 years of age or older, the recommended dosage is 1 mg

every two to five minutes up to a maximum of 10 mg. Recent studies of rectally administered diazepam, using dosages similar to the IV dosage, have shown that rectal administration yields nearly as rapid an onset as IV administration, with similar blood levels, equal effectiveness, and less respiratory depression.¹⁴

Lorazepam is a relatively new anticonvulsant, but studies in both children and adults have shown it to have similar latency of onset and to be at least as effective as and similar in toxicity to diazepam.¹⁵⁻¹⁹ The primary clinical advantage of lorazepam is its relatively long half-life, which is at least three to four times that of diazepam. Some studies report less respiratory depression with lorazepam than with diazepam after previous administration of other anticonvulsants. Lorazepam has been found effective in at least 75% of all types of status and 90% of cases of generalized convulsive status. The long half-life makes it somewhat less urgent to begin administration of a maintenance anticonvulsant. This allows the option of attaining therapeutic levels of alternate anticonvulsants such as carbamazepine and sodium valproate, either of which can be administered by oral, nasogastric tube, or rectal route. The adult dosage of lorazepam has varied between 2 and 10 mg, most often 4 mg. In children the dosage is between 0.05 and 0.4 mg/kg, with the higher dosage being recommended in the younger child.

PHENYTOIN

The main advantage of phenytoin is its effectiveness in controlling convulsions,²⁰ its relatively long half-life, and its lack of CNS depression. Disadvantages are its cardiotoxicity if given too rapidly and the time required for giving a full IV loading dose. In children, it is less desirable as a maintenance drug because of its poor absorption in infants, its possible cosmetic effects, and its effects on learning and behavior.

The IV loading dose for phenytoin is between 18 and 20 mg/kg. This dosage, both for adults and children, will result in a therapeutic level that may vary between 18 and 22 mg/100 mL. At this loading dose, the elimination half-life is nearly 36 hours. The IV rate of administration should not exceed 50 mg/minute; in an adult, administration of a full loading dose will require nearly 20 minutes. Heart rate by electrocardiogram and blood pressure should be monitored; cardiac arrhythmias and hypotension may occur with too rapid an infusion. To avoid precipitation, phenytoin should be administered in a glucose-free solution. Chemical phle-

bitis commonly occurs if it is administered through a superficial vein. Intramuscular phenytoin is very slowly absorbed and should never be used. The phenytoin preparation available in the United States contains propylene glycol, which may be cardiotoxic. A diluted phenytoin solution is available in Europe and may be safely administered more rapidly.²¹

PHENOBARBITAL

Surprisingly, little has actually been published about the usefulness of phenobarbital in the treatment of status epilepticus despite the high frequency of its administration.²² Advantages of phenobarbital are that it has a long half-life and can be administered fairly rapidly without acute toxicity. A disadvantage is the CNS and respiratory depression that may be associated with its use. It is well absorbed in infants and may be used as a maintenance drug, but a hyperactivity behavioral response may occur in up to 25% of children. The loading dosage is 15 to 20 mg/kg. In neonates this is administered as a single dose, but in adolescents and adults, it is often divided into two doses of 10 mg/kg. Phenobarbital may be administered at a rate of 60 mg/minute. It may be administered with all standard IV solutions without concern for precipitation. The effective blood level in status epilepticus may be less than the commonly recommended blood level of 15 to 40 mg/100mL. It is commonly stated that there is a delay of up to 20 minutes to the onset of action with an IV loading dose of phenobarbital. However, a recent study²³ reported the median time of onset to be 5.5 minutes, which is less than that of the combined treatment with diazepam-phenytoin. In this study, phenobarbital was found to be equal to treatment with diazepam-phenytoin and its side effects were similar.

OTHER DRUGS

Paraldehyde has been used as an alternate anticonvulsant for treatment of status epilepticus, but an intravenous form is no longer available.

Valproic acid has occasionally been used in the treatment of status.²⁴⁻²⁸ A parenteral form is not available; oral administration can be hazardous and is often limited by paralytic ileus. Valproic acid may be given rectally,²⁵⁻²⁸ but a disadvantage is its slow absorption. If the initial seizures are controlled by a drug with a relatively long half-life such as lorazepam, then

valproate is a reasonable alternate anticonvulsant. Peak serum concentrations occur in two to four hours after rectal administration. The commercially available sodium valproate (Depakene, 250 mg/5 mL) may be diluted 1:1 with water and given as a rectal enema. A dosage of 20 mg/kg will achieve a blood level of 40 to 50 mg%.²⁵

Carbamazepine also is not available in a parenteral form, but the commercially available suspension preparation can be administered rectally to achieve therapeutic blood levels. Considerations are similar to those mentioned for sodium valproate.²⁹

Lidocaine has been recommended in adults, but has seldom been prescribed for children. A dosage of 50 to 100 mg given IV push, followed by a 1 to 2 mg/minute infusion has been used. Because of the propensity of high dosages to cause seizures and the variable brain distribution of lidocaine, its use is not generally recommended.⁷

Other drugs (including chlormethiazole,^{30,31} alpha-sarone,³² clobazam,³³ and midazolam³⁴) are cited in the literature but in general are not currently recommended.

REFRACTORY STATUS EPILEPTICUS

The term refractory status epilepticus refers to sustained seizures that fail to respond to appropriate "first-line" drug therapy and persist for longer than 60 minutes. This becomes a critical situation, as experimental studies in animals have shown that permanent neuronal damage develops after 60 minutes of convulsive status, even in circumstances of proper ventilation and correction of systemic metabolic parameters. If convulsive status epilepticus has not been controlled within 30 minutes, it is reasonable to begin to make arrangements for more aggressive therapy with either general anesthesia or barbiturate coma. During the initial 30 minutes, the first- and second-choice anticonvulsants should have been administered; during the second 30 minutes, the third agent may be infused. In the meantime, a more detailed history should be obtained; and a detailed neurologic examination should be performed. The initial tests to search for a metabolic disorder should be available. Prior to initiating general anesthetic or barbiturate coma, it is preferable to obtain a computed tomography scan and perform a lumbar puncture to search for a structural lesion or CNS infection.

General anesthesia has definite limitations but may

be effective in the treatment of status epilepticus. It requires constant staffing by an anesthesiologist, and there are significant logistic concerns to administering an anesthetic agent outside an operating room. Only a few studies compare the various general anesthetic agents.³⁵⁻³⁷ Halothane is commonly recommended, but reports indicate that even a high concentration may fail to suppress seizure activity while causing hemodynamic alterations. Enflurane, an isomer of isoflurane, has been reported to cause as well as suppress seizures. Nitrous oxide at standard anesthetic concentrations is reported to have minimal effects on suppression of seizure activity. The most effective of the general anesthetics in producing an isoelectric EEG without causing hemodynamic complications has been isoflurane.

BARBITURATE COMA

Short-acting barbiturates are a recognized effective treatment of convulsive status epilepticus that is refractory to conventional antiepileptic therapy.³⁸⁻⁴³ Such barbiturates allow treatment of the patient in the setting of an intensive care unit. Advantages of the short-acting barbiturates are that they have rapid onset of action and a relatively short half-life, and the consequences of treatment can be closely monitored: clinical seizures, EEG electrical activity, and the patient's vital signs. Short-acting barbiturates may have additional benefit in suppressing cerebral oxidative metabolism and a protective value in cerebral hypoxia. Different treatment protocols have been used, including the use of either pentobarbital or thiopental, the use of hypothermia, and the depth of drug-induced coma that is maintained, either burst suppression or continuous isoelectric EEG tracing. The recommended duration of coma treatment has not been established, but most studies have used 48 to 72 hours. Barbiturate coma requires an intensive care setting with neuromuscular blockade, controlled mechanical ventilation, and monitoring of blood volume and cardiac function.

CONCLUSION

The academic definition of status epilepticus gives physicians a common reference point to facilitate the evaluation of epileptic patients; it clearly identifies a critical seizure syndrome. The definition is not so precise or so clearly delineated, however, as is often assumed. The terms "frequently repeated," "pro-

longed," and "fixed and lasting" elude precise definition. Does the patient with hypsarrhythmia or continuous slow spike and wave EEG have status epilepticus? What are the consequences of frequent focal epileptic activity? Does a child who has five or six generalized seizures within 24 hours have status epilepticus? Is there potential for permanent neurologic sequelae in this situation, and should the patient be aggressively treated as being in status epilepticus?

Because recurrent and prolonged seizures may pose significant risk to the patient, a treatment plan, including reasonable options, should be initiated when a patient has an acute exacerbation of seizures. The plan

should be prepared for the possibility of refractory status epilepticus and geared to stopping seizures in less than an hour. Establishing such a protocol in advance and making sure that the physician and assisting medical personnel are comfortable with it will enhance the ease and success of its implementation pending clinical response.

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REFERENCES

- Calmeil L. De l'épilepsie. Thesis, University of Paris, 1824.
- Gastaut H. Dictionary of Epilepsies. Part I: Definitions. Geneva, World Health Organization, 1973.
- Hunter RA. Status epilepticus. History, incidence and problems. *Epilepsia* 1959; 1:162-188.
- Aminoff MJ, Simon RP. Status epilepticus. Causes, clinical features and consequences in 98 patients. *Am J Med* 1980; 69:657-666.
- Meldrum BS, Brierley JB. Prolonged epileptic seizures in primates. Ischemic cell change and its relation to ictal physiologic events. *Arch Neurol* 1973; 28:10-17.
- Aicardi J. Status epilepticus in infants and children: consequence and prognosis. *Int Pediatr* 1987; 2:189-195.
- Brown TR. Therapy of status epilepticus. *Compr Ther* 1982; 5:28-36.
- Delgado-Escueto AV, Wasterlain C, Treiman DM, Porter RJ. Management of status epilepticus. *N Engl J Med* 1982; 306:1337-1340.
- Duffy FH, Lombroso CT. Treatment of status epilepticus. *Clin Neuropharmacol* 1978; 3:41-56.
- Lederman RJ. Status epilepticus. *Clev Clin Q* 1984; 51:261-266.
- Rothner AD, Erenberg G. Status epilepticus. *Pediatr Clin North Am* 1980; 27:593-602.
- Leppik IE. Status epilepticus. *Clin Ther* 1985; 7:272-278.
- Bleck TB. Therapy for status epilepticus. *Clin Neuropharmacol* 1983; 6:255-269.
- Milligan N, Dhillon S, Richens A, Oxley J. Rectal diazepam in the treatment of absence status: a pharmacodynamic study. *J Neurol Neurosurg Psychiatry* 1981; 44:914-917.
- Crawford TO, Mitchell WG, Snodgrass SR. Lorazepam in childhood status epilepticus and serial seizures: effectiveness and tachyphylaxis. *Neurology* 1987; 37:190-195.
- Homan RW, Walker JE. Clinical studies of lorazepam in status epilepticus. *Adv Neurol* 1983; 34:493-498.
- Lacey OJ, Singer WD, Horowitz SJ, Gilmore H. Lorazepam therapy of status epilepticus in children and adolescents. *J Pediatr* 1986; 108:771-774.
- Leppik IE, DeRivan AT, Homan RW, et al. Double-blind study of lorazepam and diazepam in status epilepticus. *JAMA* 1983; 249:1452-1454.
- Sorel L, Mechler L, Harmant J. Comparative trial of intravenous lorazepam and clonazepam in status epilepticus. *Clin Ther* 1981; 4:326-336.
- Wilder BJ. Efficacy of phenytoin in treatment of status epilepticus. *Adv Neurol* 1983; 34:441-446.
- von Albert HH. A new phenytoin infusion concentrate for status epilepticus. *Adv Neurol* 1983; 34:453-456.
- Goldberg MA, McIntyre HB. Barbiturates in treatment of status epilepticus. *Adv Neurol* 1983; 34:499-503.
- Shaner DM, McCurdy SA, Herring MO, Gabor AJ. Treatment of status epilepticus: a prospective comparison of diazepam and phenytoin versus phenobarbital and optional phenytoin. *Neurology* 1988; 38:202-207.
- Steinberg A, Shalev RS, Amir N. Valproic acid in neonatal status convulsions. *Brain Dev* 1986; 8:278-280.
- Snead OC, Miles MV. Treatment of status epilepticus in children with rectal sodium valproate. *J Pediatr* 1985; 106:323-325.
- Vajda FJ, Mihaly GW, Miles JL, et al. Rectal administration of sodium valproate in status epilepticus. *Neurology (Minneapolis)* 1988; 28:897-899.
- Vajda FJE. Valproic acid in the treatment of status epilepticus. *Adv Neurol* 1983; 34:519-529.
- Viani F, Jussi MI, Germano M, et al. Rectal administration of sodium valproate for neonatal and infantile status epilepticus. *Dev Med Child Neurol* 1984; 29:678-679.
- Graves NM, Kriel RL. Rectal administration of antiepileptic drugs in children. *Pediatr Neurol* 1987; 3:321-326.
- Harvey PKP, Higenbottam TW, Loh L. Chlormethiazole in treatment of status epilepticus. *Br Med J* 1975; 2:603-605.
- Lingam S, Bertwistle H. Problems with intravenous chlormethiazole (Hemenevrin) in status epilepticus. *Br Med J* 1980; 1:155-156.
- Jianjia C. Status epilepticus treated by alpha-asarone, report of 18 cases. *J Trad Chin Med* 1984; 4:217-218.
- Tinuper P, Aguglia U, Gastaut H. Use of clobazam in certain forms of status epilepticus and in startle-induced epileptic seizures. *Epilepsia* 1986; 27:518-526.
- Kaneko S, Kurahashi K, Fujita S, et al. Potentiation of GABA by midazolam and its therapeutic effect against status epilepticus. *Folia Psychiatr Neurol Jpn* 1983; 37:307-309.
- Kojke WA, Snider MT, Yoby RSR, Romer JC. Prolonged low flow isoflurane anesthesia for status epilepticus. *Anesthesiology* 1988; 62:653-656.
- Opitz A, Marschall M, Degen R, Koch D. General anesthesia in patients with epilepsy and status epilepticus. *Adv Neurol* 1983; 34:531-535.
- Ropper AH, Kofke A, Bromfield ER, Kennedy SK. Comparison of isoflurane, halothane and nitrous oxide in status epilepticus. *Ann Neurol* 1986; 19:98-99.
- Amit R, Goitein KJ, Mathot I, Yatziv S. Prolonged electro-cerebral silent barbiturate coma in intractable seizure disorders. *Epilepsia* 1988; 29:63-66.
- Gortein KJ, Mussaffi H, Melamed E. Treatment of status epilepticus with thiopentone sodium anesthesia in a child. *Eur J Pediatr* 1983;

- 140:133–135.
40. Rashkin MC, Youngs C, Penovich P. Pentobarbital treatment of refractory status epilepticus. *Neurology* 1987; 37:500–507.
41. Young RSK, Ropper AH, Hawkes D, et al. Pentobarbital in refractory status epilepticus. *Pediatr Pharmacol* 1983; 3:63–67.
42. Orlowski JP, Erenberg G, Leuders H, Cruse RP. Hypothermia and barbiturate coma for refractory status epilepticus. *Crit Care Med* 1984; 12:367–372.
43. Burton K, Holland JT. Convulsive status epilepsy: Is there a role for thiopentone-induced narcosis. *Clin Exp Neurol* 1984; 20:47–56.