Status epilepticus[1]

Richard J. Lederman, M.D., Ph.D.

Status epilepticus (SE), defined as clinical or electrical seizures continuing for at least 30 minutes, occurs in a minority of patients with epilepsy and is more common in symptomatic than in idiopathic forms. In adults, brain tumor, trauma, and stroke account for a substantial proportion of cases, whereas in children, various infectious processes, toxic or metabolic disorders, and chronic encephalopathies may be found. SE is often precipitated by sudden withdrawal of anticonvulsant drugs or intercurrent infection. Prolonged seizures lead to a series of metabolic derangements which may subsequently cause neuronal damage. Therapy aimed at preventing this sequence of events includes general measures, such as ensuring sufficient oxygenation, maintaining adequate blood pressure, and preventing hyperthermia or hypoglycemia. Specific anticonvulsant drug therapy is reviewed, including recommended doses, mode and rate of administration, and potential hazards.

Index terms: Anticonvulsants • Epilepsy • Status epilepticus

Cleve Clin Q 51:261–266, Summer 1984

The term "status epilepticus" (SE) was first used by Calmeil in 1824 to describe a succession of uninterrupted epileptic attacks, a condition clearly perceived to be life-threatening.[1] Although epilepsy has been known for more than 4,000 years, SE has been recognized for only a few hundred years and seems to have become a disorder of major clinical importance only since the introduction of bromide therapy in 1861.[2] The implications of this association were emphasized by Hunter.[3]

Definition and incidence

The generally accepted definition of SE is that of a

[1] Department of Neurology, The Cleveland Clinic Foundation, Submitted and accepted for publication Oct 1983.

0009-8787/84/02/0261/06/$2.50/0

seizure which "persists for a sufficient length of time or is repeated frequently enough to produce a fixed and enduring epileptic condition."[4] In practical terms, SE is said to exist when clinical or electrical seizures continue for at least 30 minutes, usually (although not invariably) associated with unconsciousness which persists for the duration of the seizures. Two major types are recognized: convulsive and non-convulsive. Convulsive SE may be generalized from the outset, or secondarily after focal onset; this is the most common type and also the most ominous. Motor activity is usually bilateral, and in adults, generally includes both tonic and clonic phases. Pure tonic SE is common in children or adolescents, while pure clonic SE is seen only in infants and young children. SE may rarely be myoclonic, and persistently focal (e.g., unilateral) SE may also be seen. Non-convulsive forms include partial SE (both simple and complex types) and so-called absence or petit mal seizures. Neonatal SE most often consists of either irregular and frequently subtle motor phenomena or else recurring tonic contractions.

The true frequency of SE is difficult to judge from the literature. Hunter[3] identified it in 1.3% of all admissions to the National Hospital at Queen Square. Oxbury and Whitty[5] found 166 cases of SE among the 2,500 patients with epilepsy admitted to the United Oxford Hospitals (6.6%). Janz[6] reported encountering at least one episode of SE in 95 of 2,588 patients (3.7%) with epilepsy, and Celesia[7] identified it in 60 out of 2,290 cases (2.6%). SE is much more common in patients whose epilepsy has a demonstrable cause. Janz[6] wrote that SE occurred in 9% of those with "symptomatic" epilepsy and 1.6% of those with the idiopathic type. In nearly all reported series, patients with symptomatic or secondary epilepsy represent a disproportionate fraction of the total number. Rowan and Scott[8] reported SE as the initial manifestation of epilepsy in only 5 of their 42 patients (12%), while Hauser[9] identified 132 of 1,047 epileptic patients (12.6%) in whom SE was the presenting event. On the other hand, in 28% of the patients in Oxbury and Whitty's series[5] and 56% of Roger and associates' series,[10] SE was the initial ictal event. In children, this sequence of events appears to be even more common, including 77% of Aicardie and Chevrie's patients.[11] SE is only occasionally the initial ictal event in idiopathic epilepsy in all adult series, and if febrile status is considered within the symptomatic group, in children as well.

Pathogenesis

In discussing the pathogenesis of SE, it is important to distinguish between the underlying causes and the precipitating factors. Statistics from seven reported series are collated in *Table 1*, though they should be compared with caution because of differences in patient populations and presentation of data. Brain tumors, craniocerebral trauma, and cerebrovascular disease represent clearly identifiable causes in a substantial group of adults, whereas acute infections, toxic or metabolic disorders, and a variety of chronic encephalopathies of congenital or perinatal origin comprise a large percentage of infants and children with SE. With respect to the possibility of drug treatment as a precipitating factor in SE, Hunter[3] found that 23% of episodes of SE in his patients could be attributed to a change in medication and 30% to intercurrent infection and

Table 1. Causes of status epilepticus

Cause	Oxbury and Whitty[5] [n = 86]	Janz[6] [n = 95]	*Roger et al[10] [n = 56]	†Rowan and Scott[8] [n = 42]	‡Celesia[7] [n = 60]	§Aicardie and Chevire[11] [n = 239]	*Hauser[9] [n = 132]
Tumor	19 (22%)	24 (25%)	11 (20%)	2 (5%)	3 (5%)	—	4 (3%)
Trauma	4 (5%)	23 (24%)	22 (39%)	5 (12%)	7 (12%)	2 (1%)	23 (17%)
Degenerative	—	—	—	1 (2%)	3 (5%)	10 (4%)	—
Cerebrovascular	13 (15%)	4 (4%)	7 (12%)	3 (7%)	9 (15%)	—	17 (13%)
Infection	9 (10%)	3 (3%)	—	4 (9%)	1 (2%)	29 (12%)	19 (15%)
Congenital/infantile	4 (5%)	3 (3%)	—	7 (16%)	4 (7%)	40 (17%)	—
Miscellaneous	5 (6%)	6 (6%)	9 (17%)	12 (28%)	10 (17%)	32 (13%)	27 (20%)
Idiopathic or unknown	32 (37%)	32 (34%)	7 (12%)	9 (21%)	23 (38%)	126 (53%) (67 febrile)	42 (32%)

* Patients with SE as the initial event
† Eleven patients were ≤10 yrs old
‡ Includes some children
§ All under 15 yrs

suggested that SE is precipitated by acute infection only in patients on anticonvulsants. Janz[6] ascribed 14/110 episodes of SE to drug withdrawal and 23/110 to infection. Similarly, Rowan and Scott[8] considered 13 out of 50 episodes in their series to be drug-related and 9 out of 50 to be precipitated by acute systemic infection. In Aminoff and Simon's series,[12] 28% of all episodes of SE and 53% of those in patients with a history of seizures were thought to be related to a change in anticonvulsant drug regimen. Only 4 out of 98 patients in their series had intracranial infection.

Before turning to the management of SE, we should consider the pathophysiology of sustained epilepsy and its effect on the brain. Analysis of the metabolic and circulatory changes occurring during seizures in humans has been hampered by both technical and ethical considerations. Studies such as those by Posner et al[13] have demonstrated that cerebral metabolism increases markedly during seizure activity, and with it, the need for substrates and oxygen. Their data suggest that if the supply of oxygen and glucose to the brain could be maintained during a seizure and the metabolic effects of muscle hyperactivity mitigated, neuronal damage might be prevented. However, this has not proved to be true in all cases, since even a prolonged focal discharge may induce localized neuronal changes[14] or clinical sequelae.[15] Newer techniques such as positron emission tomography or magnetic resonance scanning may provide additional information.

Similar results have been obtained using animal models such as that developed by Meldrum and Horton.[16] When prolonged seizures were induced in adolescent baboons or rats using the gamma-aminobutyric acid (GABA) inhibitor bicuculline or other toxins, a predictable sequence of events occurred during sustained epilepsy. Changes seen during the first 20 minutes included arterial hypertension, marked increases in cerebral blood flow, substantial increases in cerebral metabolic rate, diminished cerebral arteriovenous PO_2 and PCO_2, lactic acidemia with systemic acidosis, and hyperglycemia after a brief and usually mild initial drop in blood glucose. The late phase, seen after 25 minutes of continuous seizure activity, was characterized by hypoglycemia, hyperthermia, mild arterial hypotension, mild hypoxemia, hyperkalemia, and normalization of arterial pH. Cerebral hypermetabolism was maintained, though at a slightly lower level; cardiovascular collapse tended to occur during this phase, if at all. Neuronal damage also seemed to be produced during this later phase,[17] suggesting that the factors involved in its pathogenesis (singly or in combination) were hyperpyrexia, arterial hypotension, hypoxia, and hypoglycemia. It has been proposed[18] that this neuronal damage may depend upon the intracellular oxidative mechanisms which accompany intense electrical activity, perhaps resulting in free radical accumulation, and that this series of events may be triggered by excess intracellular calcium.

Neuropathological changes in these animal models bear a striking resemblance to those which for many years have been known to occur in humans with long-standing and often poorly controlled epilepsy or in those who died following SE. Gross changes are often meager, revealing only mild brain swelling and some vascular congestion. Microscopic abnormalities usually occur primarily in the middle neuronal layers of the neocortex, the hippocampus (particularly the pyramidal cells of Sommer's sector), and the Purkinje cell layer of the cerebellum. Changes are representative of severe hypoxic and ischemic damage, including neuronal atrophy with cytoplasmic eosinophilia. The nuclei are usually hyperchromatic and shrunken, and astrocytic and microglial proliferation is observed.[19]

Therapy

The studies described above help to provide a rational basis for the design of a therapeutic approach to SE, with the goal of preventing the pathological changes characteristic of hypoxia and ischemia as well as the attendant clinical sequelae. Diagnosis and therapy must proceed simultaneously and without delay. If there is a single point of agreement throughout the literature, it is that the prognosis of SE depends largely on the time between onset of continuous seizure activity and initiation of therapy. Persistence of convulsive (or perhaps non-convulsive) SE for more than 60 minutes is generally considered to result in irreversible neuronal damage. Although it is the deleterious effects of prolonged convulsions that have been demonstrated most clearly, all forms of SE should be controlled as quickly as possible.

The circumstances of presentation obviously influence management, both in a diagnostic sense and to a lesser extent in therapy. Nevertheless, certain guidelines can be offered. Therapeutic intervention can be divided into general and

specific anticonvulsant measures, as outlined in *Table 2*. Initial treatment must be aimed at providing satisfactory ventilation, maintaining adequate cardiac output and cerebral perfusion, and preventing further injury as the direct result of the violent motor activity. Excessive elevations of body temperature must be prevented as well. Patients in SE will generally require tracheal intubation; at times, usually as an initial measure, an oral airway may suffice. Oxygen is administered by nasal cannula or mask if the patient is not intubated. Systemic blood pressure must be maintained; pressors are rarely required, but intravenous fluids are often critical, especially in children. A sturdy intravenous line should be inserted immediately, while at the same time taking blood for chemical screening and testing an arterial sample for pH and PO_2. I generally take several extra tubes of blood for toxic screening and measurement of anticonvulsant drug levels, at least in older children and adults. This additional blood loss is unlikely to be detrimental, and the availability of frozen serum may save much grief and self-recrimination when a more leisurely inquiry is possible. As soon as blood has been withdrawn, a bolus of 50 mL of 50% glucose (or 2 mL/kg in a child) is rapidly infused, followed by maintenance fluids. Since accurate assessment of fluid balance is critical in SE, a bladder catheter is generally required. Hyperthermia must be treated aggressively and immediately.

Specific therapy consists primarily of anticonvulsant drugs, although diagnostic studies may reveal causative factors such as magnesium, calcium, hypertonic saline, or bicarbonate which call for specific measures. Such drugs must be given with the goal of immediately achieving and then maintaining a seizure-free state. They are administered intravenously in almost all cases, as the urgency of the situation and the uncertainty of absorption by other routes override any increase in risk if, of course, the physician administering the therapy is thoroughly familiar with the drugs used.

Of the three types of drugs usually selected for initial therapy, I generally favor benzodiazepines, either a 5–10-mg bolus of diazepam (0.3 mg/kg in infants and children) or lorazepam (2–4 mg; 0.05–0.2 mg/kg); while larger amounts may occasionally be required, most patients respond to less than 40 mg of diazepam or 15–20 mg of lorazepam. These drugs take effect quickly—often within one or two minutes—but this effect may also be short-lived, particularly with diazepam; therefore maintenance therapy with another drug, generally phenytoin, should be insti-

Table 2. Therapy in status epilepticus

General Measures

1. Provide adequate ventilation and O_2 (oral airway or nasotracheal tube)
2. Maintain cardiac output
3. Prevent physical injury
4. Treat hyperthermia
5. Administer intravenous fluids
6. Give a bolus of 50% glucose (50 ml in adults, 2 ml/kg in children)
7. Place a bladder catheter

Specific Anticonvulsant Therapy

Drug	Dosage (IV) (A = adults C = children)	Precautions	Toxic/Side effects	Remarks
Diazepam				
Bolus	A 5–10 mg up to 40 mg C 0.3 mg/kg	Direct IV, 5 mg/min	Respiratory depression, hypotension	Long-term treatment must be initiated simultaneously
Infusion	8 mg/hr			
Lorazepam	A 2–15 mg C 0.05–0.2 mg/kg	Direct IV, 2 mg/min	Mild respiratory depression	Limited experience in children
Phenytoin	A 800–1,200 mg C 15–18 mg/kg	Direct IV, 50 mg/min	Cardiac dysrhythmia, hypotension	Useful acutely and for maintenance
Phenobarbital	A 200–400 mg C 5–10 mg/kg	Given over 10–15 min	Respiratory depression, sedation	Preferred in neonates
Paraldehyde	A 1–3 ml C 0.1–0.15 mg/kg	Given over 10–30 min	Pulmonary hemorrhage, chronic congestive heart failure, hepatic/renal toxicity	Infusion of 4% solution in saline
Lidocaine				
Bolus	2–3 mg/kg	50 mg/min maximum	Seizures in high doses	Added to 5% d/w for infusion
Infusion	3–10 mg/kg/hr			

tuted more or less simultaneously with diazepam. A constant intravenous infusion of diazepam has also been advocated if initial bolus treatment fails.[20] I dilute diazepam in 5% dextrose and water (100 mg/500 mL) and administer it at a rate of 8 mg/hr. Major side effects of the benzodiazepines include respiratory (and occasionally cardiac) depression or arrest and hypotension, especially in infants and elderly patients, and prior barbiturate treatment may markedly increase the risk of respiratory arrest.

The second drug being considered here is phenytoin, which is recommended by some for acute as well as more long-lasting control of seizures. I recommend a dose of 15–18 mg/kg (800–1,200 mg for most adults) and a rate of no more than 50 mg/min. At this dosage, therapeutic blood levels are achieved within five minutes, and seizure activity usually diminishes or ceases altogether before the infusion is even completed. In addition, phenytoin affords less sedation and is effective longer than diazepam. Although it can cause cardiac arrest or hypotension, this is rarely a serious problem if the above recommended rate of administration is followed. Maintenance doses of 5 mg/kg per day are continued once control is achieved.

The third drug commonly used for SE is phenobarbital. I favor 5–10 mg/kg (generally 200–400 mg for adults) over a 10–15-minute period. Although the half-life of phenobarbital is long, high brain and plasma levels are reached within several minutes and seizures are generally controlled during the initial infusion. A repeat dose may be given if necessary within 20–30 minutes; however, the full initial dosage of 15 mg/kg is generally given within the first four to 12 hours. Phenobarbital seems to be the initial treatment of choice in neonatal SE, with loading doses of 20 mg/kg required.[21,22] In most patients, maintenance doses (5 mg/kg per day) are begun after 12 to 24 hours. Sedation and some respiratory suppression are virtually certain, and routine endotracheal intubation is recommended.

If seizures persist despite the above drugs, there are a number of secondary anticonvulsants which can be used, including paraldehyde and lidocaine, before resorting to general anesthesia. Paraldehyde can be given in a dose of 1–3 mL as a 4% solution in normal saline over a period of 10 to 30 minutes; a less satisfactory alternative is 3–5 mL by deep intramuscular injection or per rectum diluted 2:1 in cottonseed oil. Although I have given as much as 40 mL of intravenous paraldehyde safely over a 24-hour period, such a dose is potentially dangerous and not generally recommended. Toxic side effects include pulmonary hemorrhage or edema, cardiac failure, hepatitis, and nephrosis, and maintenance therapy with another drug should be instituted as soon as control is obtained. Paraldehyde may be the treatment of choice in SE associated with alcohol withdrawal.[23] Intravenous infusions of lidocaine in doses of 3–10 mg/kg per hour may sometimes be highly effective in establishing control of SE.[23] It is generally added to 5% dextrose and water for infusion; additional boluses of 50–100 mg may be given intravenously. I have given up to 4,000 mg over 24 hours with impunity, but it must be recognized that seizures or even cardiopulmonary arrest can be precipitated by high doses. Maintenance therapy with a standard anticonvulsant is required once seizures are controlled. Other drugs which have been reported to be useful in isolated situations include valproic acid (given via a nasogastric tube or per rectum),[24] alfaxalone,[25] and chlormethiazole.[23,26]

When the drug regimens outlined above fail, general anesthesia may be required to minimize the metabolic sequelae of prolonged seizure activity or suppress the process permanently. Unfortunately, few clear and reliable guidelines regarding depth or duration of anesthesia are available, and there are few data regarding the advantages of inhalation versus intravenous agents. Opitz et al[27] have suggested that halothane or enflurane are the preferred inhalation agents in epileptic patients, while Goldberg and McIntyre[28] have proposed a protocol for use of intravenous pentobarbital.

Despite the number of potent and relatively safe drugs available today, SE remains a serious and life-threatening condition. A major factor in prognosis is delay in instituting effective anticonvulsant therapy. Overall, some 30%–50% of adults will die within six months of the first episode, either as a direct result of SE (or its treatment) or the underlying disease process. Since death among symptomatic patients is much more common, underlying illness is probably the second most important factor in prognosis next to delay in treatment. In Celesia's series,[7] for example, there were no deaths among the 15 patients with primary epilepsy and only 1 among the 8 with idiopathic epilepsy; in contrast, 15 of the 37 symptomatic patients (40%) died, 4 as a direct result of SE and 11 from the underlying disease. Aminoff and Simon[12] noted that 16 of

their 92 patients with SE died, death being due to the primary pathological process in 14 cases. Among children, similar dismal results have been reported. In Aicardie and Chevrie's series,[11] 27 of 239 patients (11%) died and 88 (37%) had a significant residual neurological deficit, although some of these problems had been present before SE. Morbidity is also high among adults. Thus at present there are neither satisfactory answers to the nature of the electrochemical events in SE nor an ideal treatment. Only time will tell whether new drugs and improved understanding of the pathophysiology and treatment of SE will alter the currently unsatisfactory statistics.

References

1. Calmeil LF. De l'epilepsie, etudiée sous le rapport de son siège et de son influence sur la production l'aliénation mentale. Thèse de Paris, 1824.
2. Reynolds JR. Epilepsy. Its Symptoms, Treatment and Relation to Other Chronic Convulsive Disorders. London, Churchill, 1861.
3. Hunter RA. Status epilepticus; history, incidence and problems. Epilepsia 1959; **1**:162–188.
4. Gastaut H. Clinical and electroencephalographical classification of epileptic seizures. Epilepsia 1969; **10**:(Suppl):S2–S13.
5. Oxbury JM, Whitty CWM. Causes and consequences of status epilepticus in adults. A study of 86 cases. Brain 1971; **94**:733–744.
6. Janz D. Conditions and causes of status epilepticus. Epilepsia 1961; **2**:170–177.
7. Celesia GG. Modern concepts of status epilepticus. JAMA 1976; **235**:1571–1574.
8. Rowan AJ, Scott DF. Major status epilepticus. A series of 42 patients. Acta Neurol Scand 1970; **46**:573–584.
9. Hauser WA. Status epilepticus: frequency, etiology, and neurological sequelae. [In] Delgado-Escueta AV, Wasterlain CG, Treiman DM, Porter RJ, eds. Status Epilepticus. New York, Raven Press, 1983, pp 3–14.
10. Roger J, Lob H, Tassinari CA. Status epilepticus. [In] Vinken RJ, Bruyn GW, eds. Handbook of Clinical Neurology, Vol. 15. Amsterdam, North-Holland, 1974, pp 145–188.
11. Aicardie J, Chevrie JJ. Convulsive status epilepticus in infants and children. A study of 239 cases. Epilepsia 1970; **11**:187–197.
12. Aminoff MJ, Simon RP. Status epilepticus. Causes, clinical features and consequences in 98 patients. Am J Med 1980; **69**:657–666.
13. Posner JB, Plum F, Van Poznak A. Cerebral metabolism during electrically induced seizures in man. Arch Neurol 1969; **20**:388–395.
14. Meldrum BS, Horton RW, Brierley JB. Epileptic brain damage in adolescent baboons following seizures induced by allylglycine. Brain 1974; **97**:417–418.
15. Engel J Jr, Ludwig BI, Fetell M. Prolonged partial complex status epilepticus: EEG and behavioral observations. Neurology 1978; **28**:863–869.
16. Meldrum BS, Horton RW. Physiology of status epilepticus in primates. Arch Neurol 1973; **28**:1–9.
17. Meldrum BS, Brierley JB. Prolonged epileptic seizures in primates. Ischemic cell change and its relation to ictal physiological events. Arch Neurol 1973; **28**:10–17.
18. Meldrum BS. Metabolic factors during prolonged seizures and their relation to nerve cell death. [In] Delgado-Escueta AV, Wasterlain CG, Treiman DM, Porter RJ, eds. Status Epilepticus. New York, Raven Press, 1983, pp 261–275.
19. Norman RM. The neuropathology of status epilepticus. Med Sci Law 1964; **4**:46–51.
20. Delgado-Escueta AV, Wasterlain C, Treiman DM, Porter RJ. Current concepts in neurology: management of status epilepticus. N Engl J Med 1982; **306**:1337–1340.
21. Painter MJ. General principles of treatment: status epilepticus in neonates. [In] Delgado-Escueta AV, Wasterlain CG, Treiman DM, Porter RJ, eds. Status Epilepticus. New York, Raven, 1983, pp 385–393.
22. Lockman LA, Kriel R, Zaske D, Thompson T, Virnig N. Phenobarbital dosage for control of neonatal seizures. Neurology 1979; **29**:1445–1449.
23. Browne TR. Paraldehyde, chlormethiazole, and lidocaine for treatment of status epilepticus. [In] Delgado-Escueta AV, Wasterlain CG, Treiman DM, Porter RJ, eds. Status Epilepticus. New York, Raven Press, 1983, pp 509–517.
24. Vajda FJE. Valproic acid in the treatment of status epilepticus. [In] Delgado-Escueta AV, Wasterlain CG, Treiman DM, Porter RJ. Status Epilepticus. New York, Raven Press, 1983, pp 519–529.
25. Munari C, Casaroli D, Matteuzzi G, Pacifico L. The use of althesin in drug-resistant status epilepticus. Epilepsia 1979; **20**:475–483.
26. Harvey PKP, Higenbottam TW, Loh L. Chlormethiazole in treatment of status epilepticus. Br Med J 1975; **2**:603–605.
27. Opitz A, Marschall M, Degen R, Koch D. General anesthesia in patients with epilepsy and status epilepticus. [In] Delgado-Escueta AV, Wasterlain CG, Treiman DM, Porter RJ. Status Epilepticus. New York, Raven Press, 1983, pp 531–535.
28. Goldberg MA, McIntyre HB. Barbiturates in the treatment of status epilepticus. [In] Delgado-Escueta AV, Wasterlain CG, Treiman DM, Porter RJ. Status Epilepticus. New York, Raven Press, 1983, pp 499–503.