

Management of status epilepticus

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Status epilepticus is due to a range of insults to the central nervous system and results in significant mortality rates, especially in the elderly. We review the current management of this disorder in light of the latest developments from recent trials and guidelines. Important principles in management includes early recognition of status epilepticus, identification of the underlying cause and prompt treatment to terminate seizures and reduce complications. The differentiation diagnosis, role of electroencephalographic monitoring and different treatment regimes are examined. (*Hong Kong j.emerg.med.* 2002;9:206-212)

Keywords: Complications, electroencephalography, management, Status epilepticus

Introduction

Status epilepticus (SE) is a medical emergency.¹ In the United States and Europe an estimated 5-20 patients per 100,000 residents develop SE every year.²⁻¹⁰ The annual incidence shows a bimodal distribution with peaks in neonates, children and the elderly. It can develop in patients with and without a history of epilepsy, in which case they are mostly secondary to acute cerebral disturbances. Not only is it important to stop the convulsions but identification and treatment of any underlying cause is a central part of management. Age, seizure type, aetiology, female sex, duration of SE, and duration from onset to treatment have been reported as determinants of prognosis.⁹⁻¹³ The incidence is higher, in descending order, in African Americans, Whites, Hispanics and Asians; the

higher rate in the Black population has been attributed to reduced anti-epileptic drug compliance and increased alcoholism.⁷ Epidemiological data show that the aetiology of SE can be categorized into acute or chronic processes and are summarized in Table 1. SE in the elderly is mostly secondary to cerebrovascular disease, hypoxic damage secondary to cardiac dysfunction and dementia. The mortality is higher in the elderly whereas in general children have a better prognosis.^{2,10-13}

Definition and classification

Early recognition is imperative to avoid delay in treatment. Generalized tonic-clonic (GTC) status is the most readily recognized form of SE, occurring in 44-74% in surveys but other types of SE can occur.⁵⁻⁹ Table 2 shows an abbreviated classification system based on whether seizures have a motor component (convulsive versus non-convulsive) and whether they affect one part of the body or the whole (partial versus generalised). Other less commonly encountered types such as electrical status epilepticus during slow wave sleep (ESES) and Landau-Kleffner syndrome are not included.

SE is defined physiologically as epileptic activity without complete normalization of neurochemical and

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Table 1. Aetiology of status epilepticus.

Tumour
Anticonvulsant-withdrawal
Chronic epilepsy
Alcohol-related
Cerebrovascular disease
Trauma
Metabolic
Idiopathic
CNS infection
Drug toxicity
Anoxia

Table 2. Classification of status epilepticus.

	Convulsive	Non-convulsive
Generalised	Tonic-clonic	Absence
	Tonic	
	Myoclonus	
Partial	Somatomotor	Complex partial
	Sensory	
	Autonomic	
	Aphasia	

physiological homeostasis and has a wide spectrum of clinical symptoms with a variable pathophysiological, anatomical and aetiological basis.

Traditionally operational definitions of SE consist of: 1) Recurrent seizures without full and complete recovery of consciousness and 2) Single prolonged convulsion lasting over 30 minutes. This allows a distinction to be made between isolated or serial attacks and SE. The time specification is derived from an estimate of the duration after which permanent changes would be established.¹ Recent publications suggest that irreversible damage may occur sooner. The experience of video- electroencephalographic (EEG) monitoring from patients during episodes of seizures is that the tonic and clonic components last one to two minutes and rarely persist for more than five.¹⁴ The threshold for regarding a person as being in SE has therefore come down.¹⁵ Overt generalized tonic-

clonic is easily diagnosed but patients who have been in prolonged SE and who are paralysed may only exhibit subtle motor activity: eyelid/ocular twitching, focal jerks, fluctuation in responsiveness or confusion.¹⁶⁻¹⁸ Non-convulsive SE is increasingly recognised; patients may have bizarre or automatic behaviour (e.g. lip-smacking, face rubbing), appear confused or have isolated aphasia. In one prospective study approximately 5% of all comatose patients were diagnosed with this form of status, which requires EEG confirmation.¹⁶

Pathophysiology

A number of physiological changes develop in SE: during phase 1, compensatory mechanisms, such as increased cerebral blood flow and cardiac output, increased cerebral oxygen, glucose utilization and catecholamine release prevent cerebral damage while in phase 2 the ability of the body to adapt is reduced and the risk of permanent damage increases.^{19,20} The reasons for a failure of mechanisms to abort a seizure are unknown, but excessive activation of excitatory amino acid receptors and failure of inhibition are implicated. Contamination of seafood with domoic acid, an analogue of glutamate, an excitatory neurotransmitter, can cause SE. Pro-convulsants such as penicillin, which antagonise gamma-aminobutyric acid (GABA) receptors are used to study the effects of SE in animal models. Prolonged exposure of N-methyl-D-aspartate (NMDA) receptors to excitatory glutamate results in a marked increase in intercellular calcium; this initiates a biochemical cascade that results in cell damage.

Management

The objective in management is to stop epileptic activity as rapidly as possible in order to protect neurons from seizure-induced damage. Preventing recurrences, managing precipitating factors and treating complications (Table 3) should be carried out at the same time.²¹

Table 3. Complications of status epilepticus.

Cerebral	
	Raised intracranial hypertension
	Cerebral oedema
	Cerebral venous and arterial thrombosis
	Cognitive dysfunction
Renal failure	
	Myoglobinuria, rhabdomyolysis
Respiratory failure	
	Apnoea
	Pneumonia
	Hypoxia, hypercapnoea
	Respiratory failure
Release of catecholamines	
	Hypertension
	Pulmonary oedema,
	Arrhythmia
	Glycosuria, pupillary dilatation
	Hypersecretion, Hyperpyrexia
Cardiac	
	Hypotension, cardiac failure, thromboembolism
Metabolic and systemic	
	Dehydration
	Acidosis
	Hyper/hypoglycaemia,
	Hyperkalaemia, hyponatraemia
	Multi-organ failure
Miscellaneous	
	Fractures, thrombophlebitis, disseminated intravascular coagulation

The following primarily refers to the treatment of generalised tonic-clonic SE. Whether second-line therapy should be initiated as aggressively in partial or non-convulsive SE is a matter of controversy.

General measures

The initial priority is to stabilize airway, breathing and circulation. Place the patient in the recovery position and insert an endotracheal tube if the airways are compromised (there is no need to force open the mouth when the mouth is tightly clenched shut). A careful history from witnesses/relatives may suggest the aetiology, such as drug overdose or recent changes

in anticonvulsants. Electrolyte imbalance should be sought and renal, liver function tests, calcium levels, arterial blood gases and glucose concentration obtained. If hypoglycaemia is suspected or when there is documented hypoglycaemia, intravenous glucose (50 ml 50% glucose) should be given, with 100 mg thiamine intravenously beforehand to reduce the likelihood of Wernicke's encephalopathy. Routine injection of glucose is not advised as hyperglycaemia may worsen neuronal damage. Check drug levels as non-compliance with anti-epileptic drugs or drug withdrawal are important causes of SE. Complete blood picture, blood and urine cultures should be performed to look for evidence of systemic infection. Respiratory and/or metabolic acidosis is common but should not be treated unless the pH has dropped to below 7.0 as the use of bicarbonate may lead to alkalosis which would reduce threshold for seizures.

During the initial half to one hour of SE, most patients are hypertensive. Low blood pressure is common after this phase, especially as most drugs induce hypotension and therefore clinicians should be prepared to initiate treatment with vasopressor agents. Once the patient is stabilized and the seizures are controlled the second phase of investigations should begin. Brain imaging, in practice computed tomography, is sufficient to identify intracranial haemorrhage, herniation and tumours and should be performed first in adults.

If CNS infection is suspected and lumbar puncture cannot be performed immediately, antimicrobials should be initiated at once, after blood cultures have been obtained. Note that a low-grade fever is a frequent result of SE itself, as well as a "post-ictal" pleocytosis. Passive cooling should be initiated if there is fever. Liberal hydration with normal saline is recommended to reduce the risk of dehydration and rhabdomyolysis.

Specific treatment

First line therapy consists of benzodiazepines. They enhance GABAergic inhibition by binding to the BZD-GABA-phenobarbital complex. Intravenous

lorazepam is emerging as the most effective initial agent in abolishing overt convulsive SE. In a large, multicentre, randomized controlled trial (RCT) 570 patients, mainly male US veterans who fulfilled the criteria for SE were enrolled into the study and randomized to four groups, receiving either lorazepam, phenobarbitone, diazepam plus phenytoin or phenytoin alone.²² (Table 4) Lorazepam was the most successful agent in stopping seizures. However there was no significant difference in the intention-to-treat analysis, in outcome at 30 days and among those with subtle SE. In another RCT comparing the efficacy of benzodiazepines and placebo given outside a hospital environment among 205 patients, seizures were terminated in 60% of those given lorazepam and 43% in the diazepam treated group.²³

Lorazepam has a lower volume of distribution compared with diazepam and therefore has a longer duration of action, which is preferable in this situation. Diazepam is highly lipid soluble and will distribute to other body fat stores; twenty minutes after an initial dose, the plasma concentration of diazepam drops to 20% of the maximal concentration. The onset of action and rate of cardiorespiratory depression (around 10%) of lorazepam is the same; in addition inadvertent arterial injection leads to arterial spasm and possibly gangrene in severe cases. Midazolam at 0.2 mg/kg/hr intravenously has been used; it has the advantage that it can be given as an intramuscular injection or buccal instillation. Buccal midazolam, 10 mg instilled between the cheeks and gums, is equally efficacious as rectal diazepam; this is useful outside hospital where intravenous (iv) access is not immediately achievable.

Table 4. Results from RCT of first line agents in status epilepticus.²²

Drugs	Dose (mg/kg)	Percentage success
Lorazepam	0.1	65%
Phenobarbitone	15	59%
Diazepam + Phenytoin	0.15+18	56%
Phenytoin	18	44%

Loading with a long-acting anticonvulsant should take place simultaneously with benzodiazepines (Table 5). Phenytoin is given at 18-20 mg/kg at a rate of not more than 50 mg/hr by slow iv push or infusion. A further loading dose of 5-10 mg/kg may be added if seizures recur. Side effects include hypotension (28-50%) and cardiac arrhythmia (2%) and are more common in the elderly. Parental phenytoin contains propylene glycol, alcohol and sodium hydroxide; it should be injected with a large-gauge needle followed by saline flush to avoid local irritation: thrombophlebitis and "purple glove syndrome". Dextrose should not be used to dilute phenytoin otherwise precipitation would lead to the formation of micro-crystals.²¹

Fosphenytoin (Cerebyx) is a water-soluble prodrug with a 15-minute conversion half-life to phenytoin. After enzymatic conversion, 150 mg fosphenytoin results in 100 mg phenytoin so that a dose of 150 fosphenytoin is labeled as 100 mg phenytoin equivalent. It can be administered more rapidly than phenytoin and also intramuscularly. Infusion site reactions are less common due to its lower pH (9 as opposed to 12 for phenytoin) but the rate of cardiac side effects are comparable.

Table 5. Management algorithm.

0-5 min

ABC, Administer oxygen, iv access
Lorazepam 4-8 mg (0.1mg/kg) or diazepam 5-10 mg (0.2 mh/kg) over 2 to 3 minutes
Investigations: electrolytes, drug levels, full blood count, blood cultures

5-10 min

Monitor vital signs, cardiac monitor
Drugs: 100 mg Thiamine, 40 ml 50% Glucose if hypoglycaemic
Anticonvulsants: phenytoin loading
Repeat benzodiazepines if required

30-45 min

Treat medical complications
Find cause (Drugs, metabolic, CNS pathology)
Transfer to ICU
Consider second-line agents

Although valproate can be given intravenously, there is limited experience when administered for this indication and it is not licensed for this condition. One observational study showed that valproate was effective in 19 out of 23 cases of SE and did not have significant cardio-respiratory side-effects.²⁴

The decision to start chronic oral anti-epileptic treatment should be individualized. Patients with underlying structural brain pathology should be given maintenance anticonvulsants but those who develop SE as a consequence of a reversible cause such as hyponatraemia would not require maintenance therapy once this is corrected.

Monitoring

If the person remains deeply unconscious or seizures recur despite benzodiazepines and phenytoin loading, transfer to an intensive care unit is required for ventilatory and haemodynamic support and monitoring. Patients may have aspirated or have marked secretions so airway support with pulse oximetry and supplemental oxygen is required. Loss of unconscious can be due to SE, the underlying cause or drug effect as all first-line drugs depress respiration. Neurogenic pulmonary oedema is another indication for ventilation.

Serum phenytoin levels should be monitored but it is important to be aware that the therapeutic window does not equate with clinical efficacy. Patients may require "high" or suprathreshold levels to control seizures – in this situation, side-effects such as dizziness and ataxia are not of immediate concern. Serial drug levels are particularly important in patients with altered pharmacokinetics due to renal and liver dysfunction.

EEG monitoring should be used for those who remain unconscious or have received a long-acting paralytic agent. Reviewing the electrophysiological response to treatment in SE is just as crucial as electrocardiographic

monitoring in the therapy of life-threatening cardiac arrhythmias. Among cases whose clinical signs have been successfully abolished, 15% continue to have electrographic seizures. EEG can identify those patients who have unsuspected sub-clinical seizures and those who may have an alternative cause for persistent loss of consciousness (e.g. metabolic encephalopathy).^{25,26} In patients who appear unconscious or have continuous motor activity, a totally normal sleep and awake EEG suggests the diagnosis of psychogenic seizures.

Treiman has described the evolution of EEG in status although this classical description is not seen in every case. Initially after a period of discrete electrographic activity, seizure activity merges and then becomes continuous. This is followed by an intermittent low-voltage flat tracing and finally periodic epileptiform discharges are seen.²⁷ Monitoring can gauge the effect of therapy and the adequacy of drug-induced coma. Achieving a burst-suppression pattern has traditionally been an end-point but an isoelectric recording or an EEG where epileptic discharges are abolished is probably equally appropriate as the important point is to confirm the cessation of electrical seizure activity.²⁸ EEG can also give prognostic information; patients with tracings showing persistent periodic discharges have a poorer outcome.²⁹

Refractory status epilepticus

Nine percent to 40% of cases go on to have persistent seizures despite first line drug treatment.^{30,31} Patients with recurrent or continuous seizures for over 60 minutes are regarded as being in refractory SE. Persistent seizures develop for a number of reasons. Inadequate drug therapy may be due to failure to initiate anti-epileptics or sub-therapeutic doses. Additional medical factors such as recurrent hypoglycaemia or persistent hypocalcaemia may continue to provoke attacks. Misdiagnosis is another possibility - tremor, rigors and psychogenic attacks may simulate epileptic seizures.

The mortality of refractory SE is higher compared with those who respond to first-line agents – 23% versus 14%.³¹ The use of second-line agents is not standardized. These include midazolam, propofol, phenobarbitone and thiopentone infusions.^{32,34} (Table 6) There is a dearth of comparative data; if phenytoin is unsuccessful some experts opt for midazolam or propofol and reserve thiopentone as a third-line drug.

Anecdotal cases of surgical treatment have been reported in individuals who have recurrent seizures despite multiple courses of cerebral suppressant therapy: focal resection and multiple subpial transection of the epileptogenic zone, corpus callosotomy to prevent seizure generalisation in those without a resectable focus and also vagal nerve stimulation.^{35,36}

Once the patient remains free of behavioural seizures and epileptic activity on EEG for 12 to 24 hours, second line treatment can be tapered off. If seizures recur these drugs should be re-administered and a further search of any reversible underlying precipitant and cause should be instigated again. Pyridoxine deficiency is a potentially reversible cause in children.

Conclusions

The overall mortality is 25% despite advances in intensive care and pharmaco-therapy. A number of series have shown that as the duration of SE increases, seizures become more difficult to control. Mortality is higher among cases in which treatment was delayed. The success rate of lorazepam and diazepam in

stopping seizures in the out-of-hospital study was as high as that found in the landmark hospital-based trial even though lower dosages were used. This result may have been due to the early administration of benzodiazepines. These facts emphasise the importance of early recognition of SE and prompt treatment.

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Table 6. Commonly used second-line agents

Drug	Initial dose (bolus)	Rate	Infusion(maintenance)
Diazepam	10-20 mg	≤5 mg/min	8 mg/hr
Midazolam	5-10 mg	≤4 mg/min	0.05-0.4 mg/kg/hr
Thiopentone	100-250 mg, then 50 mg bolus until seizures controlled	30 seconds	3-5mg/kg/hr
Phenobarbitone	10-40 mg/kg	≤100 mg/min	1-4 mg/kg/hr
Propofol	2 mg/kg	Slow push	5-10 mg/kg/hr initially; later 1-5 mg/kg/hr

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