Special Article

Update on Status Epilepticus

Andrew CF Hui FRCP*,
KM Chow FHKAM*, Richard Kay MD, FRCP*

** Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong SAR*

Status epilepticus is a medical emergency and is secondary to a range of insults to the central nervous system. The authors reviewed the current management of this disorder in light of the latest developments from recent trials and guidelines. Important principles in management include early recognition of status epilepticus, identification of the underlying cause and prompt treatment to terminate seizures and reduce complications. The role of electroencephalographic monitoring and different treatment regimens are examined.

Keywords : *Status epilepticus, Electroencephalography, Management, Complications*

J Med Assoc Thai 2007; 90 (3): 599-605
Full text. e-Journal: *http://www.medassocthai.org/journal*

Status epilepticus (SE) is defined physiologically as epileptic activity without complete normalization of neuro-chemical and physiological homeostasis and has a wide spectrum of clinical symptoms with a variable pathophysiological, anatomical and etiological basis. Clinicians require a more concrete guideline and therefore in every day practice SE is defined as: 1) Recurrent seizures without full and complete recovery of consciousness and 2) Single prolonged convulsion lasting over 30 minutes[1]. However, the authors know from observation of patients undergoing video-electroencephalography (EEG) monitoring that during episodes of seizures, the tonic and clonic components last one to two minutes and rarely persist for more than five[2]. The threshold for making this diagnosis has therefore come down to five to ten minutes[1].

Epidemiology

In the United States and Europe an estimated 5-20 patients per 100,000 residents develop SE every year[3-9]. The annual incidence shows a bimodal distribution with peaks in neonates, children and the elderly[4-10]. It can develop in patients with or without a history of epilepsy. Not only is it important to stop the convulsions but identification and treatment of any underlying cause is a central part of management. Based on the results from one large series, the incidence is said to be higher, in descending order, in African Americans, Whites, Hispanics and Asians[6]. Epidemiological data show that the etiology 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. In resource poor countries, as epilepsy is more common and as many patients are not treated or under-treated, the incidence is presumably higher[11].

Correspondence to : ACF Hui, Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong SAR. Phone: (852) 2632-3131 / 2632-3133. Facsimile: (852) 2637-5396, E-mail: huicf @yahoo.com

Clinical features

It is important to recognize status at an early stage to avoid delay in treatment. Generalized tonic-clonic (GTC) status is the most common form of SE, occurring in 44-74% in surveys but other types of SE can occur[6-10]. During statuses, seizures may or may not have a motor component (convulsive or non-convulsive) and they can affect one part of the body or the whole (partial or generalized)[12-16]. Forty years ago, Gastaut suggested there was a status equivalent for every seizure type and in the last proposed classification, over 20 types of status are now listed[17]. Other conditions such as electrical status epilepticus during

Table 1. Identifiable causes of status epilepticus

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

Table 2. 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, pupilliary 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

slow wave sleep (ESES) and Landau-Kleffner syndrome occur more commonly in children and are not discussed in the present review.

Overt GTC seizures are readily diagnosed, but patients, who have been in prolonged SE and who are paralyzed, may only exhibit subtle motor activity: eyelid/ocular twitching, focal jerks, fluctuation in responsiveness or confusion[12-16]. Non-convulsive SE is increasingly recognized; patients may have bizarre or automatic behavior (e.g. lip-smacking, face rubbing), appear confused or have isolated aphasia. In one study approximately 20% of all comatose patients were diagnosed with this form of status, which requires EEG confirmation as there are no or minimal convulsive movements[18].

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. In phase 2, the ability of the body to adapt is reduced and the risk of permanent damage increases[19,20]. Recent publications suggest that irreversible damage may occur earlier than 30 minutes. 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 antagonize 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 2) should be carried out at the same time[21].

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

General measures

The initial priority is to stabilize airway, breathing and circulation. There is no need to force open the mouth if it is tightly clenched shut. A careful history from witnesses/relatives may suggest the etiology such as drug overdose or recent changes in anti-convulsants. Renal, liver function tests, calcium levels, arterial blood gases and glucose concentration should

be determined to exclude electrolyte imbalance and as a baseline. If hypoglycemia is suspected or there is documented hypoglycemia, 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 hyperglycemia 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 the 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.

Once the patient is stabilized and the seizures are controlled the second phase of investigations should begin. SE is usually secondary to a systemic or neurological event. Brain imaging, in practice-computed tomography, is performed to identify any structural cause for status.

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, which 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, multicenter, a controlled trial with 570 patients fulfilling the criteria for SE, were randomized to four groups, receiving either lorazepam, phenobarbitone, diazepam plus phenytoin or phenytoin alone (Table 3)[22]. 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 randomized controlled trial comparing the efficacy of benzodiazepines and placebo given by paramedics before the patient arrives in the emergency department, 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 spasms and possibly gangrene in severe cases. Midazolam at 0.2mg/kg/hr intravenously has been used; it has the advantage that it can be given as an intramuscular injection or buccal instillation. Buccal midazolam, 10mg instilled between the cheeks and gums, is equally efficacious as rectal diazepam; this is useful outside the hospital where iv access is not immediately achievable.

Loading with a long-acting anti-convulsant should take place simultaneously with benzodiazepines (Table 4). Phenytoin is given at 18-20 mg/kg at a rate of not more than 50mg/hr by slow IV push or infusion[21]. 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 hydoxide; it should be injected with a large-gauge needle followed by saline flush to avoid local irritation: thromboplebitis and "purple glove syndrome". Dextrose should not be used to dilute phenytoin, otherwise, precipitation would lead to the formation of microcrystals. Serum phenytoin levels should be monitored but beware that the therapeutic window does not equate with clinical efficacy. Patients may require "high" or supra-threshold levels to control seizures - in this situation side effects such as dizziness and ataxia are not of immediate con-

Table 3. 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%

Table 4. Management algorithm[21]

0-5 min
ABC, Administer oxygen, iv access,
Lorazepam 4-8mg (0.1mg/kg) or diazepam 5-10mg (0.2mh/kg) over 2 to 3minutes
Investigations: electrolytes, drug levels, full blood count, blood cultures
5-10 min
Monitor vital signs, cardiac monitor
Drugs: 100mg Thiamine, 40ml 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

cern. Serial drug levels are particularly important in patients with altered pharmacokinetics due to renal and liver dysfunction.

Although valproate can be given intravenously, there is limited experience 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].

Role of EEG

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 hemodynamic 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 is due to SE or drug effect as all first-line drugs depress respiration. Neurogenic pulmonary oedema is another indication for ventilation.

EEG monitoring should be instituted 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. Even when clinical seizures have been successfully abolished, 15% of patients continue to have electrographic epileptic activity[25]. 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). In patients who appear unconscious or have continuous motor activity, a totally normal sleep and awake EEG suggests the diagnosis of psychogenic seizures.

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[25,26]. EEG can also give prognostic information; patients with tracings showing persistent periodic discharges have a poorer outcome[27].

Refractory status epilepticus

Patients with recurrent or continuous seizures for over 60 minutes despite first-line drug treatment with two to three anti-epileptics AEDs. This occurs in 9-40% of cases[28,29]. Seizures persist for a number of reasons such as sub-therapeutic doses of AED, recurrent hypoglycemia or persistent hypocalcemia. Misdiagnosis is another possibility-tremor, rigors and psychogenic attacks may simulate epileptic seizures. Mortality in refractory SE is higher compared with those who respond to first-line agents-23% versus 14%[29]. If initial treatment with benzodiazepine and phenytoin is unsuccessful, some experts would try AEDs that can be given intravenously (i.e. valproate or phenobarbitone) while others would give anesthetic agents such as midazolam, propofol or thiopentone[30-33]. However, the use of these second-line agents is not standardized, as there is a dearth of comparative data (Table 5).

Once the overt seizures have stopped and epileptic activity on the EEG has been abolished for 12

Table 5. 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	3-5 mg/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

to 24 hours, anesthetic agents 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.

Conclusion

Age, seizure type, etiology, female sex, duration of SE, and duration from onset to treatment are significant prognostic factors[34-39]. Mortality is high in the elderly and in general, low in children[34-36]. For most patients, in particular if they are properly treated, the main determinant of outcome is the underlying condition behind status itself rather than prolonged seizures[39].

Given that the overall mortality is 25% despite advances in intensive care and drug therapy and that outcome is poorer in cases where treatment was delayed, it is essential that SE is recognized early and treated promptly.

References

1. Lowenstein DH, Bleck T, Macdonald RL. It's time to revise the definition of status epilepticus. Epilepsia 1999; 40: 120-2.
2. Theodore WH, Porter RJ, Albert P, Kelley K, Bromfield E, Devinsky O, et al. The secondarily generalized tonic-clonic seizure: a videotape analysis. Neurology 1994; 44: 1403-7.
3. DeLorenzo RJ, Hauser WA, Towne AR, Boggs JG, Pellock JM, Penberthy L, et al. A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. Neurology 1996; 46: 1029-35.
4. Hesdorffer DC, Logroscino G, Cascino G, Annegers JF, Hauser WA. Incidence of status epilepticus in Rochester, Minnesota, 1965-1984. Neurology 1998; 50: 735-41.
5. Coeytaux A, Jallon P, Galobardes B, Morabia A. Incidence of status epilepticus in French-speaking Switzerland: (EPISTAR). Neurology 2000; 55: 693-7.
6. Wu YW, Shek DW, Garcia PA, Zhao S, Johnston SC. Incidence and mortality of generalized convulsive status epilepticus in California. Neurology 2002; 58: 1070-6.
7. Lowenstein DH, Alldredge BK. Status epilepticus at an urban public hospital in the 1980s. Neurology 1993; 43: 483-8.
8. Waterhouse EJ, Garnett LK, Towne AR, Morton LD, Barnes T, Ko D, et al. Prospective population-based study of intermittent and continuous convulsive status epilepticus in Richmond, Virginia. Epilepsia 1999; 40: 752-8.
9. Knake S, Rosenow F, Vescovi M, Oertel WH, Mueller HH, Wirbatz A, et al. Incidence of status epilepticus in adults in Germany: a prospective, population-based study. Epilepsia 2001; 42: 714-8.
10. Hui AC, Joynt GM, Li H, Wong KS. Status epilepticus in Hong Kong Chinese: aetiology, outcome and predictors of death and morbidity. Seizure 2003; 12: 478-82.
11. Diop AG, Sene-Diouf F, Boissy L, Preux PM, Ndiaye IP. Prognosis of epilepsy in Africa. In: Jallon P, editor. Prognosis of epilepsy. Paris: John Libbey Eurotext; 2003: 135-46.
12. Chow KM, Wang AY, Hui AC, Wong TY, Szeto CC, Li PK. Nonconvulsive status epilepticus in peritoneal dialysis patients. Am J Kidney Dis 2001; 38: 400-5.
13. Thomas P, Beaumanoir A, Genton P, Dolisi C, Chatel M. 'De novo' absence status of late onset: report of 11 cases. Neurology 1992; 42: 104-10.
14. Tomson T, Svanborg E, Wedlund JE. Nonconvulsive status epilepticus: high incidence of complex partial status. Epilepsia 1986; 27: 276-85.
15. Towne AR, Waterhouse EJ, Boggs JG, Garnett

LK, Brown AJ, Smith JR Jr, et al. Prevalence of nonconvulsive status epilepticus in comatose patients. Neurology 2000; 54: 340-5.
16. Hui AC, Tong PY, Wong A, Leung TW, Kwan P, Wong LK. Simple partial status epilepticus in Chinese adults. J Clin Neurosci 2005; 12: 902-4.
17. Rona S, Rosenow F, Arnold S, Carreno M, Diehl B, Ebner A, et al. A semiological classification of status epilepticus. Epileptic Disord 2005; 7: 5-12.
18. Claassen J, Mayer SA, Kowalski RG, Emerson RG, Hirsch LJ. Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. Neurology 2004; 62: 1743-8.
19. Lothman E. The biochemical basis and pathophysiology of status epilepticus. Neurology 1990; 40: 13-23.
20. Simon RP. Physiologic consequences of status epilepticus. Epilepsia 1985; 26(Suppl 1): S58-66.
21. Working Group on Status Epilepticus. Treatment of convulsive status epilepticus. Recommendations of the Epilepsy Foundation of America's Working Group on Status Epilepticus. JAMA 1993; 270: 854-9.
22. Treiman DM, Meyers PD, Walton NY, Collins JF, Colling C, Rowan AJ, et al. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. N Engl J Med 1998; 339: 792-8.
23. Alldredge BK, Gelb AM, Isaacs SM, Corry MD, Allen F, Ulrich S, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. N Engl J Med 2001; 345: 631-7.
24. Giroud M, Gras D, Escousse A, Dumas R, Venaud G. Use of injectable valproic acid in status epilepticus: a pilot study. Drug Invest 1993; 5: 154-9.
25. DeLorenzo RJ, Waterhouse EJ, Towne AR, Boggs JG, Ko D, DeLorenzo GA, et al. Persistent nonconvulsive status epilepticus after the control of convulsive status epilepticus. Epilepsia 1998; 39: 833-40.
26. Krishnamurthy KB, Drislane FW. Depth of EEG suppression and outcome in barbiturate anesthetic treatment for refractory status epilepticus. Epilepsia 1999; 40: 759-62.
27. Nei M, Lee JM, Shanker VL, Sperling MR. The EEG and prognosis in status epilepticus. Epilepsia 1999; 40: 157-63.
28. Mayer SA, Claassen J, Lokin J, Mendelsohn F, Dennis LJ, Fitzsimmons BF. Refractory status epilepticus: frequency, risk factors, and impact on outcome. Arch Neurol 2002; 59: 205-10.
29. Bleck TP. Refractory status epilepticus in 2001. Arch Neurol 2002; 59: 188-9.
30. Lowenstein DH, Aminoff MJ, Simon RP. Barbiturate anesthesia in the treatment of status epilepticus: clinical experience with 14 patients. Neurology 1988; 38: 395-400.
31. Kumar A, Bleck TP. Intravenous midazolam for the treatment of refractory status epilepticus. Crit Care Med 1992; 20: 483-8.
32. Pitt-Miller PL, Elcock BJ, Maharaj M. The management of status epilepticus with a continuous propofol infusion. Anesth Analg 1994; 78: 1193-4.
33. Meierkord H, Boon P, Engelsen B, Gocke K, Shorvon S, Tinuper P, et al. EFNS guideline on the management of status epilepticus. Eur J Neurol 2006; 13: 445-50.
34. Shorvon S. Prognosis and outcome of status epilepticus. In: Shorvon S. Status epilepticus: its clinical features and treatment in children and adults. Cambridge: Cambridge University Press; 1999: 293-312.
35. Maytal J, Shinnar S, Moshe SL, Alvarez LA. Low morbidity and mortality of status epilepticus in children. Pediatrics 1989; 83: 323-31.
36. Hui AC, Lam AK, Wong A, Chow KM, Chan EL, Choi SL, et al. Generalized tonic-clonic status epilepticus in the elderly in China. Epileptic Disord 2005; 7: 27-31.
37. Hui AC, Cheng C, Lam A, Mok V, Joynt GM. Prognosis following postanoxic myoclonus status epilepticus. Eur Neurol 2005; 54: 10-3.
38. Towne AR, Pellock JM, Ko D, DeLorenzo RJ. Determinants of mortality in status epilepticus. Epilepsia 1994; 35: 27-34.
39. Logroscino G, Hesdorffer DC, Cascino GD, Annegers JF, Bagiella E, Hauser WA. Long-term mortality after a first episode of status epilepticus. Neurology 2002; 58: 537-41.

ภาวะชักแบบต่อเนื่อง

แอนดรู ฮุย, เคเอม ชาว, ริชาร์ด เค

ภาวะชักแบบต่อเนื่อง (status epilepticus) จัดเป็นภาวะฉุกเฉินทางอายุรกรรม ที่เป็นผลจากความผิดปกติทางระบบประสาทส่วนกลางในหลายรูปแบบ บทความนี้ได้รวบรวมความรู้เกี่ยวกับการดูแลรักษาภาวะชักแบบต่อเนื่องโดยอาศัยข้อมูลจากการศึกษาที่ได้มีรายงานในปัจจุบัน และแนวทางปฏิบัติซึ่งเป็นที่ยอมรับกันโดยทั่วไป ประกอบด้วยการตระหนักถึงภาวะดังกล่าวตั้งแต่ในระยะเริ่มแรก การค้นหาสาเหตุ และการรักษาอย่างรวดเร็วเพื่อระงับอาการชักอันจะช่วยลดภาวะแทรกซ้อนต่าง ๆ ที่จะเกิดตามมารวมทั้งบทบาทของการเฝ้าตรวจคลื่นสมองและแนวทางการรักษาในรูปแบบอื่น ๆ