Status epilepticus: an evidence based guide

Matthew Walker

Writing this article enabled Matthew Walker to revisit the few randomised controlled trials of status epilepticus. This confirmed how poor the data are and that there is little evidence to support one treatment regimen over another

This article is based on a module that is available on the BMJ Learning website (www.bmjlearning.com). Access to the site is free but registration is required

Institute of Neurology and the National Hospital for Neurology and Neurosurgery, London WC1N 3BG
Matthew Walker
senior lecturer and honorary consultant neurologist

mwalker@doctors.org.uk

BMJ 2005;331:673-7

Status epilepticus is a prolonged seizure of any type. This article focuses mainly on the prolonged convulsion (convulsive status epilepticus) rather than non-convulsive status epilepticus.

Though there is some debate about how long a convulsion has to last before being classified as status epilepticus, 30 minutes is generally accepted.¹ Treatment should begin sooner, however, and a convulsion lasting longer than five minutes, or two convulsions without full recovery of consciousness in between, should usually receive emergency treatment.

Who gets it?

The incidence of status epilepticus is 10-60 per 100 000 person years, with the higher incidences occurring in poorer populations.²⁻⁵ Half of these patients have convulsive status epilepticus.

Over half the patients with status epilepticus do not have a diagnosis of epilepsy, and often status epilepticus is precipitated by an acute illness. In children, the major cause of status epilepticus is infections accompanied by fever.³ In adults the main acute causes are:

- Stroke
- Hypoxia
- Metabolic derangements
- Alcohol intoxication or withdrawal (the most common cause in young adults).

In people with a diagnosis of epilepsy, status epilepticus can be precipitated by drug withdrawal, due either to poor concordance or to a doctor stopping the drug.

It is critical to remember that people with epilepsy may have an acute cause for their status epilepticus.

How do I diagnose it?

Diagnosing convulsive status epilepticus is generally straightforward, but it needs to be differentiated from pseudostatus epilepticus (non-epileptic attacks with a psychological basis). Non-epileptic attacks are often prolonged and can be confused with status epilepticus.

In an audit of patients transferred to a specialist neurological intensive care unit for further treatment of their status epilepticus, around half were not in status epilepticus. Instead they were in either pseudo-

Summary points

Emergency treatment of patients with repetitive seizures will prevent the occurrence of status epilepticus

Emergency treatment of patients with status epilepticus involves closely monitoring respiratory and cardiovascular function

First line treatment for patients with convulsive status epilepticus is a benzodiazepine (lorazepam or diazepam) followed by phenytoin

If first line treatment fails, you should transfer the patient to an intensive care unit and give an anaesthetic agent

Refer patients with non-convulsive status epilepticus (continuous seizure activity without convulsive movements) to a neurologist as soon as you suspect the diagnosis

status or drug induced coma (usually secondary to large amounts of chlormethiazole).⁶ Admitting doctors often failed to recognise the possibility of pseudostatus.

You should consider pseudostatus if an episode of status epilepticus does not respond promptly to initial treatment (especially if the seizures are atypical). The clinical features of non-epileptic attacks often include:

- Poorly coordinated thrashing
- Back arching
- Eyes held shut
- Head rolling
- Pelvic thrusting.

Although rises in serum prolactin can be used to differentiate a convulsion from a non-epileptic attack, serum prolactin concentrations are not useful in status epilepticus because they normalise with prolonged seizure activity.

Non-convulsive status epilepticus

Non-convulsive status epilepticus is often difficult to diagnose.⁷ As patients in a coma may present no

Clinical tip

Status epilepticus in patients with a history of epilepsy will often resolve if you restart a medication that has been withdrawn or which the patient has not taken. All health professionals who care for patients with epilepsy should ensure that patients do not suddenly stop their medications

specific clues of seizure activity, all patients in an unexplained coma should have electroencephalography.

In non-comatose patients, non-convulsive status epilepticus can present as confusion, personality change, and even psychosis, with minimal or no clinical clues that there is ongoing seizure activity. Hippus (fluctuations in pupillary size), nystagmus, and cyclical stereotypical motor manifestations may arouse suspicion. The diagnosis of non-convulsive status epilepticus is therefore critically dependent on the results of electroencephalography. When suspicions are raised, you should refer the patient to a neurologist.

How should I treat it?

Convulsive status epilepticus causes considerable physiological compromise. To prevent potentially fatal complications, as well as giving antiepileptic drugs, you should start treatment⁸:

- Giving oxygen
- Monitoring and maintaining blood pressure
- Replacing fluids
- Giving glucose (if you suspect hypoglycaemia) in combination with high potency thiamine (250 mg, for example as the parenteral formulation Pabrinex) in patients likely to have poor nutrition.

People who do not respond to first line treatment (see below) will need to be transferred to an intensive care unit.

Drug treatment varies according to stage:

- Premonitory stage—increasing numbers of seizures often precede convulsive status epilepticus. Treatment at this stage is usually successful and prevents status epilepticus and its associated morbidity and mortality
- Established status epilepticus—this stage needs emergency intravenous treatment
- Refractory status epilepticus—this stage needs intensive care management.

The drugs proposed for use in status epilepticus include clonazepam, chlormethiazole, and valproate. But they have not been tested satisfactorily in randomised controlled trials and can't be recommended currently in management protocols.

Diazepam*Benefit*

You can use diazepam by rectal route in the premonitory phase or as first line treatment intravenously during the established stage. Rectal diazepam will stop recurrent seizures in around 70% of patients.^{9–12} Intravenous diazepam will terminate status epilepticus in 60–80% of patients.^{13–16}

Although diazepam has a long elimination half life (30 hours), when given acutely diazepam rapidly redistributes to fat and muscle, leading to a redistribution

half life of less than 30 minutes. This short plasma half life leads to a rapid fall in plasma levels and a 50% chance of seizures recurring within two hours.¹⁷

Side effects

Side effects of diazepam are:

- Sedation
- Respiratory depression
- Hypotension.

Respiratory depression is largely unreported in randomised studies of rectal diazepam in acute seizures. In a study comparing intravenous diazepam, intravenous lorazepam, and placebo for out of hospital treatment of status epilepticus, placebo was associated with twice as many complications (hypotension, cardiac dysrhythmias, or respiratory intervention).¹⁸ This suggests that ongoing status epilepticus is likely to have greater cardiorespiratory complications than benzodiazepine treatment.

Evidence

Three randomised studies have compared rectal diazepam with placebo for the treatment of recurrent seizures,^{9–11} and one compared rectal diazepam with buccal midazolam.¹² They showed that rectal diazepam is more effective than placebo and as effective as midazolam. No serious complications were reported.

A study of 205 patients with more prolonged seizures (> 10 minutes) in the community found that intravenous diazepam and intravenous lorazepam were more effective than placebo at preventing the evolution to or continuation of status epilepticus.¹⁸ There is no evidence for determining how intravenous diazepam compares with rectal diazepam in the community.

Five randomised studies of status epilepticus have compared diazepam alone or in combination with phenytoin against lorazepam,^{13–14} phenobarbitone,¹⁵ intramuscular midazolam,¹⁹ or lorazepam, phenytoin, and phenobarbitone.¹⁶ These studies have not established that diazepam is superior to any other regimen, nor does diazepam result in significantly greater side effects than any other treatment regimen.

Dose

Rectal diazepam should be given at a dose of 10–20 mg (rectal gel). Intravenous diazepam should be given at a dose of 10–20 mg at 2 mg/min.

Lorazepam*Benefit*

You should use intravenous lorazepam as first line treatment during the established stage. Intravenous lorazepam will terminate status epilepticus in 60–90% of patients.^{13–16}

Lorazepam may be preferable to diazepam as first line treatment because of its longer redistribution half life, leading to a smaller chance of recurrence of seizures. This has not been evaluated in a randomised controlled trial. The randomised studies that have looked at this question were inadequately powered to detect a significant difference.¹⁴

Side effects

Side effects of lorazepam are:

- Sedation

- Respiratory depression
- Hypotension.

In a study comparing intravenous diazepam, intravenous lorazepam, and placebo for out of hospital treatment of status epilepticus, placebo was associated with twice as many complications (hypotension, cardiac dysrhythmias, or respiratory intervention).¹⁸ This suggests that ongoing status epilepticus is likely to have greater cardiorespiratory complications than benzodiazepine treatment.

Evidence

In an out of hospital study of 205 patients with prolonged seizures (>10 minutes), intravenous diazepam and intravenous lorazepam were more effective than placebo at preventing the evolution to or continuation of status epilepticus.¹⁸

Three randomised studies of lorazepam use for status epilepticus compared lorazepam with diazepam,^{13 14} and lorazepam with phenytoin and diazepam, phenytoin alone, and phenobarbitone.¹⁶ They established that lorazepam is superior to phenytoin alone and can be given more rapidly than regimens containing phenytoin or phenobarbitone. Lorazepam did not cause significantly greater side effects than the other drugs tested.

Dose

Intravenous lorazepam should be given at a dose of 4 mg at 2 mg/minute.

Midazolam

Benefit

Midazolam given by the buccal route in the premonitory phase has a 75% chance of preventing further seizures.¹² In early stages it can be given intramuscularly when intravenous access is difficult to attain.¹⁹ There are also reports supporting its use as a continuous infusion in refractory status epilepticus.

Side effects

Side effects of midazolam are:

- Sedation
- Respiratory depression
- Hypotension.

When midazolam was given by the buccal route, no clinically important adverse events were noted in a small randomised trial.¹²

Evidence

The randomised trials of the efficacy of midazolam were carried out in children, and care must be taken when extrapolating these data to adults.

Buccal midazolam has been compared with rectal diazepam in children with serial seizures in a randomised study. No significant difference between these two drugs was found, but the study investigated 79 episodes in only 28 patients, and almost half the episodes occurred in only two patients.¹²

Intramuscular midazolam was compared with intravenous diazepam in a small study (24 patients) in children with motor seizures lasting longer than 10 minutes. Efficacy did not differ significantly, but intramuscular midazolam was more quickly administered because of difficulties getting intravenous

access.¹⁹ Nasal midazolam has been suggested as an alternative route, but there are no randomised controlled trials.²⁰

Dose

Buccal or intramuscular midazolam should be given at a dose of 10 mg.

Phenytoin

Benefit

Phenytoin should be given in established status epilepticus as an adjunct to a benzodiazepine. Around half the patients who have not responded to the initial benzodiazepine will respond with the addition of phenytoin.²¹

Side effects

Side effects of phenytoin are:

- Sedation
- Respiratory depression
- Hypotension
- Rash
- Purple glove syndrome (danger of extravasation).

Blood pressure and electrocardiogram need to be monitored during phenytoin infusions. Giving phenytoin alone, rather than with diazepam, does not reduce the risk of respiratory depression.¹⁶ The phenytoin prodrug fosphenytoin reduces the small risk of purple glove syndrome (ischaemia of the hand).²²

Evidence

One randomised study compared lorazepam, phenytoin alone, phenytoin and diazepam, and phenobarbitone in status epilepticus.¹⁶ Phenytoin alone was the least effective of the drugs at stopping status epilepticus, and the only significant difference in efficacy was between lorazepam and phenytoin alone.

No randomised controlled data supporting phenytoin as a second line treatment are available, but one uncontrolled study suggested that 50% of patients not successfully treated with a benzodiazepine alone would respond to a second line treatment (usually phenytoin).²³

In purple glove syndrome a blue-purple discoloration appears around the intravenous site two to 12 hours after phenytoin has been given, followed by oedema and, in some cases, necrosis. A prospective study found an incidence of purple glove syndrome of 1.7%, which probably does not justify the widespread use of fosphenytoin (a water soluble prodrug of phenytoin that does not cause purple glove syndrome).²²

Dose

Phenytoin should be given as a bolus of 15-20 mg/kg at 25-50 mg/minute. Because of the dangers of precipitation, it should not be given through the same line as other medication and should not be given with glucose solutions. Fosphenytoin (a phenytoin prodrug) should be given at a dose of 15-20 mg phenytoin equivalents/kg at 150 mg/minute.

Phenobarbitone

Benefit

Phenobarbitone can be given in established status epilepticus: it gives a 60-70% chance of stopping the status epilepticus.^{15 16}

Side effects

Side effects of phenobarbitone are:

- Sedation
- Respiratory depression
- Hypotension
- Rash.

Reports that the combination of phenobarbitone and a benzodiazepine can lead to cardiorespiratory compromise, along with concerns about its hypotensive and respiratory depressant effect, mean that phenobarbitone is used less commonly as a first line treatment. These opinions are not supported by randomised controlled trials, which suggest that side effects with phenobarbitone are no greater than with other regimens.¹⁶

Evidence

Two randomised studies compared phenobarbitone with diazepam against lorazepam, phenytoin alone, or diazepam and phenytoin.^{15 16} These studies established that phenobarbitone is as efficacious as other regimens tested and does not result in significantly greater side effects.

Dose

Intravenous phenobarbitone should be given at 10-20 mg/kg at 100 mg/minute.

Refractory status epilepticus

If the status epilepticus continues despite a benzodiazepine and an adequate loading dose of phenytoin, further management should take place on the intensive care unit, with anaesthesia to control the epileptic activity. In addition to anaesthesia, antiepileptic drug treatment should continue. You should monitor the patient with an electroencephalograph at least once a day.

Anaesthesia can be induced by barbiturate or non-barbiturate drugs. Several anaesthetics have been recommended; the most commonly used anaesthetics are the intravenous barbiturates thiopentone and pentobarbitone, the intravenous non-barbiturate propofol, and continuous midazolam infusion.^{24 25}

No randomised controlled trials have compared these treatment options. A meta-analysis of reports of these treatment regimens showed no difference in terms of mortality, but that pentobarbital was slightly more effective than midazolam, at the expense of greater hypotension.²⁵ These data need to be interpreted with caution because the studies were not randomised, had different outcome measures, and had considerable reporting bias (the reports are mostly retrospective). Propofol and midazolam have pharmacokinetic advantages over the barbiturates, which readily accumulate in fat and muscle, leading to prolonged action after stopping the infusion.

What tests should you do?

Tests in patients with status epilepticus are used to help with management and identify the cause. In all patients, you should take blood urgently for analysis of

- Glucose
- Blood gases
- Renal function

- Liver function
- Calcium and magnesium concentrations
- Full blood count
- Blood clotting measures
- Anticonvulsant concentrations.

It is often useful to store blood for further investigation, including tests for illicit drugs.

Electrocardiography, blood pressure, and blood gas monitoring are usually necessary. Other investigations depend on the clinical circumstances. The ranges of causes of status epilepticus determine the investigations required.

Emergency computed tomography is needed in most circumstances. Magnetic resonance imaging and examination of cerebrospinal fluid are also often necessary, depending on clinical circumstance.

When should I refer my patient?

Patients with suspected non-convulsive status epilepticus should be referred to a neurologist, and all patients with status epilepticus that has not responded to first line treatment (benzodiazepine and phenytoin) should be referred to a neurologist for further management.

What's the outlook?

The prognosis for convulsive status epilepticus is poor, with a mortality of 10-20%.¹⁻⁵ The risk of cognitive

Sample questions

Here is a small sample of the questions that you can find at the end of this module. To see all the questions and to get the answers, go to <http://www.bmjlearning.com/> and search for "status epilepticus"

1. A 60 year old man has a seizure in the casualty department. He receives lorazepam and an intravenous glucose infusion. His CT brain scan is normal and he slowly wakes up. But on the fourth day of his hospital admission he becomes confused and develops nystagmus. What is the most likely diagnosis?
 - a. Vitamin B-1 deficiency
 - b. Vitamin B-2 deficiency
 - c. Vitamin B-12 deficiency
 - d. Vitamin B-6 deficiency
2. Which of the following adverse events is not associated with intravenous phenytoin?
 - a. Dyskinesia
 - b. Rash
 - c. Hyperammonaemia
 - d. Purple glove syndrome
3. A 30 year old woman with a history of anxiety disorder has a seizure. She is given rectal diazepam by the paramedics and her seizure stops. On arrival in casualty she is unconscious. Her eyes are shut, and there is intermittent poorly coordinated jerking of her arms with arching of her back, and rolling of her head from side to side. What is the most likely diagnosis?
 - a. Non-epileptic attack
 - b. Status epilepticus
 - c. Neuroleptic malignant syndrome
4. A 52 year old man in status epilepticus that is resistant to benzodiazepines and phenytoin is transferred to the intensive care unit. His wife asks what the outlook is. What is his chance of dying?
 - a. There is a 10-20% chance he will die
 - b. There is a 30-50% chance he will die
 - c. There is a 60-80% chance he will die

decline and development of epilepsy (late spontaneous seizures) is increased.

Mortality for refractory status epilepticus has been estimated to be as high as 48%, with only 29% of patients returning to their premorbid functional baseline.²⁰ Morbidity associated with refractory status epilepticus usually consists of cognitive decline, but other neurological deficits, including persistent vegetative state and hemiparesis, have been described.

Competing interests: MW has received speaker fees from Johnson and Johnson, Pfizer and UCB pharma and consulting fees from UCB pharma and Eisai. He has also received research funding from Johnson and Johnson and UCB pharma.

- Shorvon SD. *Status epilepticus: its clinical features and treatment in children and adults*. Cambridge: Cambridge University Press, 1994.
- Coeytaux A, Jallon P, Galobardes B, Morabia A. Incidence of status epilepticus in French-speaking Switzerland: (EPISTAR). *Neurology* 2000; 55:693-7.
- 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.
- Hesdorffer DC, Logroscino G, Cascino G, Annegers JF, Hauser WA. Incidence of status epilepticus in Rochester, Minnesota, 1965-1984. *Neurology* 1998;50:735-41.
- 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.
- Walker MC, Howard RS, Smith SJ, Miller DH, Shorvon SD, Hirsch NP. Diagnosis and treatment of status epilepticus on a neurological intensive care unit. *i* 1996;89:913-20.
- Walker MC. Diagnosis and treatment of nonconvulsive status epilepticus. *CNS Drugs* 2001;15:931-9.
- Simon RP. Physiologic consequences of status epilepticus. *Epilepsia* 1985;26 (suppl 1):S58-66.
- Cereghino JJ, Mitchell WG, Murphy J, Kriel RL, Rosenfeld WE, Trevathan E. Treating repetitive seizures with a rectal diazepam formulation: a randomized study. The North American Diastat Study Group. *Neurology* 1998;51:1274-82.
- Dreifuss FE, Rosman NP, Cloyd JC, Pellock JM, Kuzniecky RI, Lo WD, et al. A comparison of rectal diazepam gel and placebo for acute repetitive seizures. *N Engl J Med* 1998;338:1869-75.

- Milligan NM, Dhillon S, Griffiths A, Oxley J, Richens A. A clinical trial of single dose rectal and oral administration of diazepam for the prevention of serial seizures in adult epileptic patients. *J Neurol Neurosurg Psychiatry* 1984;47:235-40.
- Scott RC, Besag FM, Neville BG. Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence: a randomised trial. *Lancet* 1999;353:623-6.
- Leppik IE, Derivan AT, Homan RW, Walker J, Ramsay RE, Patrick B. Double-blind study of lorazepam and diazepam in status epilepticus. *JAMA* 1983;249:1452-4.
- Appleton R, Sweeney A, Choonara I, Robson J, Molyneux E. Lorazepam versus diazepam in the acute treatment of epileptic seizures and status epilepticus. *Dev Med Child Neurol* 1995;37:682-8.
- 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; 38:202-7.
- Treiman DM, Meyers PD, Walton NY, Collins JE, 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.
- Prensky AL, Raff MC, Moore MJ, Schwab RS. Intravenous diazepam in the treatment of prolonged seizure activity. *N Engl J Med* 1967;276: 779-84.
- Allredge 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.
- Chamberlain JM, Altieri MA, Futterman C, Young GM, Ochenschlager DW, Waisman Y. A prospective, randomized study comparing intramuscular midazolam with intravenous diazepam for the treatment of seizures in children. *Pediatr Emerg Care* 1997;13:92-4.
- Kendall JL, Reynolds M, Goldberg R. Intranasal midazolam in patients with status epilepticus. *Ann Emerg Med* 1997;29:415-7.
- 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.
- Burneo JG, Anandan JV, Barkley GL. A prospective study of the incidence of the purple glove syndrome. *Epilepsia* 2001;42:1156-9.
- 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.
- Walker MC, Smith SJ, Shorvon SD. The intensive care treatment of convulsive status epilepticus in the UK. Results of a national survey and recommendations. *Anaesthesia* 1995;50:130-5.
- Claassen J, Hirsch LJ, Emerson RG, Mayer SA. Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. *Epilepsia* 2002;43:146-53.

Teaching the teacher a lesson

As senior lecturer in the Department of Anaesthesia at Malawi's medical school, I am responsible for organising a three week module in anaesthesia and intensive care medicine for the fourth year medical students. I quickly abandoned any unrealistic goal for complete coverage of our syllabus in the eleven days that remained of our module, after loss to bank holidays and funerals (one local and one in Rome). I designed a module to show our wide variety of subspecialty interests and to give the students some relevant practical skills of use in their future roles as interns. We stretched the department's staffing resources to teach by rotation in small groups around tutorial and skill stations, and sought the help of visiting lecturers from the Netherlands and the United States.

I felt that things were progressing fairly well until the second Friday of the module. As I was starting the introduction to the section on intensive care medicine, I was stopped by the appearance of a letter from the second row of the class. I was told I should read the letter, which had been signed by all 24 students, before continuing the session. As I read the first line, "Concerns on the Critical Care and Anaesthesia Module," I feared the worst and decided to read the letter aloud in order to deal with each area of concern in turn.

The letter was as bad as I could have imagined: the students took issue with the style of teaching, the use of a bell to signal the end of a station (which they found demeaning), and the requirement to carry their theatre clothes to and from the college each day (which they found a hardship). They complained that the overshoes that I'd provided made them look

like elves and, they felt, made them the laughing stock of the hospital. They threatened a walkout unless these issues were addressed immediately. I was shocked, disappointed, but most of all furious, especially as I had just introduced Dr Kamana Mbekeani, who had travelled from Chicago to contribute to the course.

Unfortunately the only part of the letter that I hadn't read was the date: 1 April 2005. I was on the verge of adding a list of four letter words to the course content for the day, when the students erupted in unison and shouted, "April fool." Pandemonium ensued as I crumpled back into my seat. I explained the term "Hook, line, and sinker" to the class, and after 15 minutes or so, I felt able to limp on with my talk. I was impressed to be caught out by such a convincing wind-up: I, for one, didn't even know that Malawians recognised "April fools" (although I certainly know they recognise one now).

Bruce McCormick senior lecturer in anaesthesia, College of Medicine, Blantyre, Malawi (brucemcc@doctors.org.uk)

We welcome articles up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake*, or any other piece conveying instruction, pathos, or humour. Please submit the article on <http://submit.bmj.com> Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.