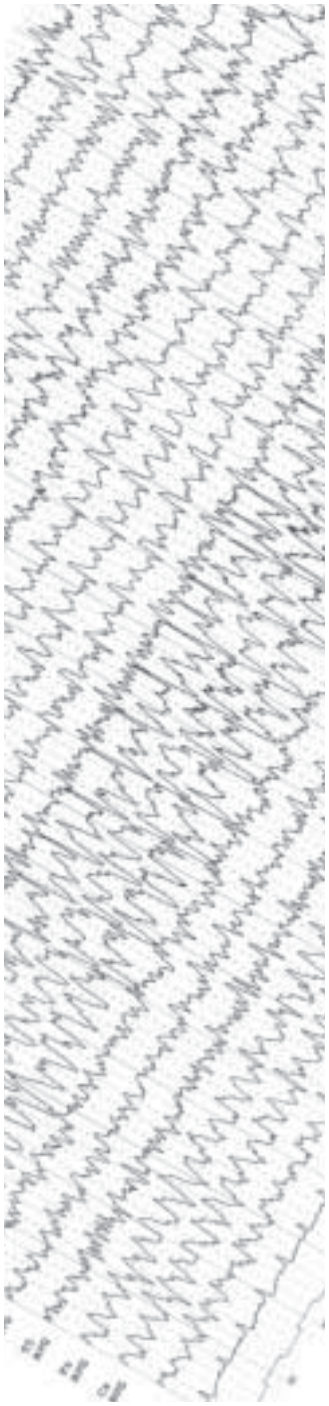
REVIEW

Status ep



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INTRODUCTION

Epilepsy is the most common serious neurological disorder, affecting approximately 1 in 150 people in the UK (Sander 2003), and status epilepticus is sometimes described as the maximal expression of epilepsy, being associated with both short- and long-term significant mortality and morbidity. Learning about its treatment should represent a significant portion of training in acute general internal medicine, and a good understanding is essential for any general or epilepsy neurologist. In this review we will discuss the epidemiology, treatment and outcome of status epilepticus, in the context of best available evidence and nationally and internationally agreed guidelines. Although there are almost as many types of status as there are of seizures (Table 1), we will concentrate on tonic-clonic status but will also make some mention of non-convulsive status epilepticus and epilepsia partialis continua. Forms of status epilepticus specific to childhood (e.g. febrile status) will not be discussed in any detail.

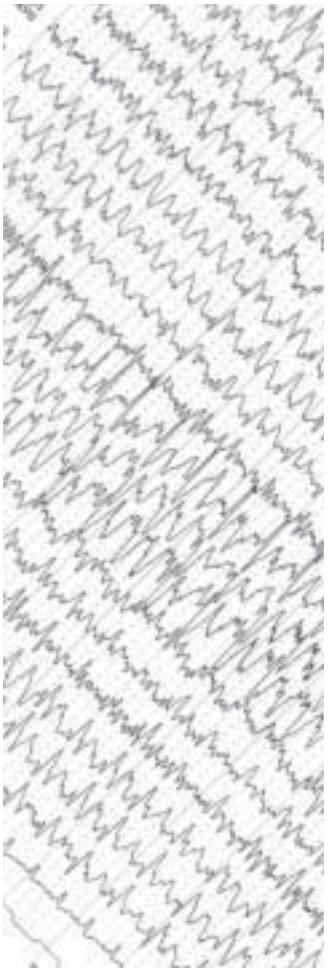
DEFINITIONS

Status epilepticus has been defined as 'a condition in which epileptic activity persists for 30 min or more' (Shorvon 2000). This can manifest as continuous clinical seizure activity, or intermittent seizures without recovery of consciousness in between. However, from a pragmatic perspective, emergency treatment and investigation along status epilepticus guidelines should be initiated for any convulsion lasting more than about 10 min. Furthermore, in many patients, an increase in the usual frequency or severity of their seizures may precede status epilepticus – often referred to as premonitory status, a useful term conveying as it does the need for emergency management

Table 1 Classification of status epilepticus (adapted from Shorvon 2000)

Early childhood only
Neonatal status epilepticus
Status epilepticus in specific neonatal epilepsy syndromes
Infantile spasms
Later childhood
Febrile status epilepticus
Status in childhood partial epilepsy syndromes
Status epilepticus in myoclonic–astatic epilepsy
Electrical status epilepticus during slow wave sleep
Landau–Kleffner syndrome
Children and adults
Tonic–clonic status epilepticus
Absence status epilepticus
Epilepsia partialis continua
Status epilepticus in coma
Myoclonic status epilepticus
Simple partial status epilepticus
Complex partial status epilepticus
Specific forms of status epilepticus in mental retardation
Adults only
De novo absence status

epilepticus



along status guidelines to be at least considered if not instigated. Almost certainly status epilepticus is an instance where prevention is better than cure (although there is little direct evidence to support this).

Once established, status epilepticus is a condition that continues to evolve and change over time. Working definitions of early (up to 30 min), established (30–60 min) and refractory (greater than 60 min) status are commonly applied, and derive from the known pathophysiological evolution of status epilepticus (Fig. 1). Cerebral metabolic demand is generally sustained during phase 1 tonic-clonic status, but

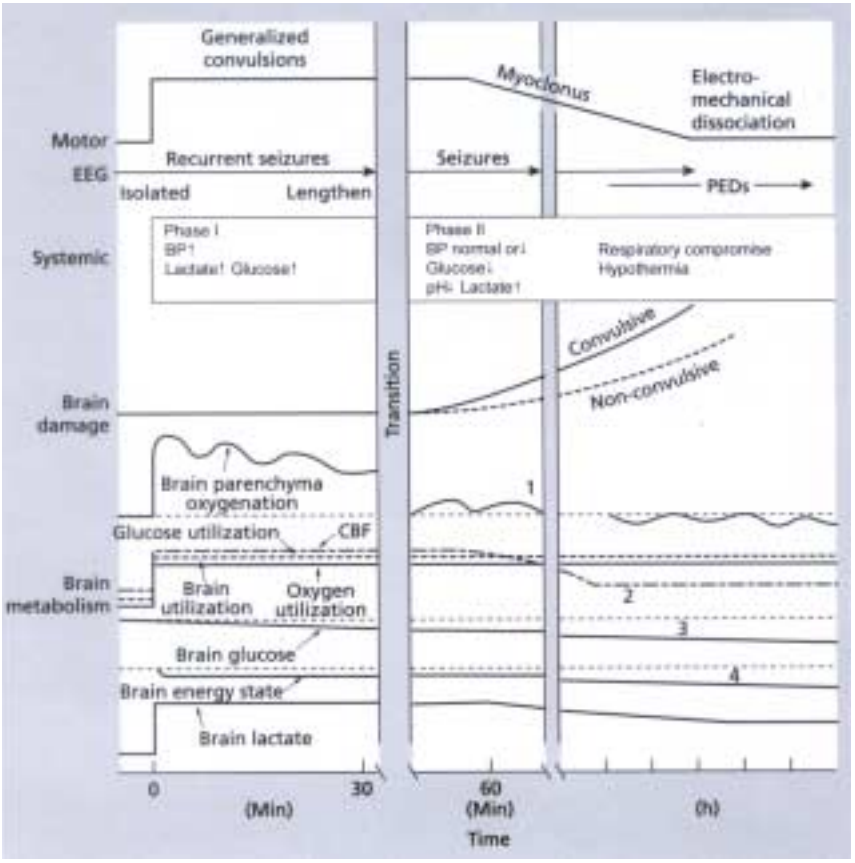


Figure 1 Pathophysiology of status epilepticus (with permission from Lippincott, Williams and Wilkins, original publication Lothman E (1990). The biochemical and pathophysiology of status epilepticus. *Neurology* **40: Suppl 2**, 13–23). Phase I: an increase in the cerebral metabolic demand, and homeostatic mechanisms are recruited. Cerebral blood flow (CBF) rises, systemic and cerebral lactate levels rise, anaerobic respiration is used to maintain energy demands, and blood pressure (BP), heart rate, temperature and other autonomic activities all increase. Phase II: decompensated status. Cerebral autoregulation ceases, CBF is compromised by systemic hypotension and increased intracranial pressure. Autonomic dysfunction, hypoxia and abnormalities of cardiac rhythm often develop, and neurogenic pulmonary oedema can occur. The degree of brain damage increases markedly as decompensation occurs. General tonic–clonic convulsions predominate initially, changing to myoclonus, then complete cessation of clinical seizure activity (electromechanical dissociation). Ongoing EEG seizures are replaced by periodic epileptic discharges (PEDs), and then generally slowed background activity.

A confident diagnosis is not always possible on clinical grounds alone, the biggest problem being functional non-epileptic seizures that may closely resemble epileptic seizures

not during phase 2, which is accompanied by profound metabolic complications. As will be discussed later, the combination of metabolic decompensation and the direct neurotoxic effects of ongoing seizure activity contribute to an association between long duration of status and poor outcome, hence the slogan 'time is brain'.

HISTORY

Descriptions of status epilepticus appear throughout the historical medical literature (Shorvon 1994). As early as the 7th century BC, an account of status epilepticus appears in the Sakikku cuneiform (a Babylonian textbook of medicine, dating from the 10th century BC), although the frequency of reports over the centuries has been far less than might be expected from its current incidence, despite numerous references to self-limiting epileptic seizures. The advanced study of status epilepticus started in the 19th century, in London (at the newly created National Hospital for the Paralysed and the Epileptic) and in Paris (at the Salpêtrière and Bicêtre hospitals). The classical descriptions of untreated status come from such luminaries as Charcot, Bourneville, Hughlings Jackson and Gowers, who not only identified the natural course of untreated status, but also described the subtypes of status, and recognized that they may represent different diseases. However, it was not until the 1920s, with the invention of the electroencephalogram (EEG), that the electrographic manifestations of status epilepticus were described, and this 'dominated research for the next 50 years' to the neglect of pathological studies (Shorvon 1994). In the past 20 years, however, interest has resurfaced in the pathological correlates of status, in particular the effects on the brain, the neuropathological correlates of prolonged seizures, and the neuropharmacology of status.

HOW COMMON IS IT?

Epidemiological observations have been complicated by inconsistent definitions and different classifications. Furthermore, until recently most published data were restricted to tonic-clonic status, and even here incidence and prevalence figures are of doubtful accuracy. The best available evidence has recently been comprehensively reviewed (Table 2). However, given that many cases of non-convulsive status often go unrecognized, particularly in the learning disabled population, the quoted incidence may well be an underestimate. Status epilepticus is the first manifestation of seizures in approximately 50% of adults, with stroke and infection being the commonest causes, whereas in children the proportion of *de novo* cases is higher, particularly if febrile status epilepticus is included. Conversely, up to 10% of patients with known epilepsy experience status at some point (Lennox 1960). Low anti-epileptic drug (AED) levels are a common cause in both children and adults; younger patients, children and those with learning disability or structural pathology, especially in the frontal lobes, are at highest risk. Status epilepticus clearly presents a significant medical problem.

WHY DOES IT MATTER?

In addition to significant case fatality (Table 2), status (particularly tonic-clonic status) is associated with considerable morbidity, in terms of cognitive and neurological deficit. Furthermore, in *de novo* cases the patients are at high risk of subsequently developing epilepsy. Much of the outcome is determined by aetiology and

Table 2 Epidemiology of status epilepticus: summary of data as reported by Chin *et al.* 2004

		Children	Adults
Incidence		3.86–38/100 000/year (135–156/100 000/year in children < 1 year)	4–27/100 000/year (14.6–86/100 000/year in elderly)
Ethnicity		White: non-white 2–3: 1	
Gender		Male: female 1–2: 1	
Aetiology	Acute symptomatic	46–66%	52–72%
	Remote symptomatic	18–38%	20–31%
	Idiopathic	5–13%	3–15%
Co-existing epilepsy		16–38%	42–50%
Case fatality	Short-term	7.6–22% (all ages)	
	(< 30 days)	3–9%	22–38% – elderly
	Long-term	43% (all ages)	
	(within 10 years)	7%	82% – elderly

age, but long duration of status, whilst often difficult to separate from confounding factors (such as aetiology, hypoglycaemia, hypoxia, acidosis), is associated with poor outcome, and importantly is a potentially modifiable factor. It is also increasingly recognized that, in addition to the undoubtedly harmful physiological decompensation mentioned above and illustrated in Fig. 1, persistent seizure activity in itself may damage the brain. This is well established in experimental models: following status epilepticus a characteristic pattern of neuronal damage is associated with behavioural and memory deficits (Holmes 2002). In man, a small number of post mortem reports (Pohlmann-Eden *et al.* 2004) and serial imaging studies (Wieshmann *et al.* 1997) support the same consequences in at least some patients. It is also likely that status in itself plays a role in epileptogenesis: many of the animal models of chronic epilepsy use chemically or electrically induced status to trigger the later development of spontaneous recurrent seizures, without necessarily any additional structural insult (White 2002). In man, around 12% of patients with epilepsy have status at presentation, and episodes of status can change seizure type in established epilepsy (Shorvon 2002).

MANAGEMENT OF TONIC-CLONIC STATUS EPILEPTICUS

Diagnosis

A confident diagnosis is not always possible on clinical grounds alone, the biggest problem being functional non-epileptic seizures that may closely resemble epileptic seizures, even to the most experienced observer. The diagnosis and management of functional non-epileptic seizures are outside the scope of this review and have been comprehensively covered elsewhere (Reuber & Elger 2003). To complicate matters further, some patients with tonic-clonic status have only minor motor features. Fever, tachycardia, leucocytosis and acidosis are often present, but are non-specific, and anyway tend to occur late. As will be discussed later, in an ideal world EEG would be available at this early point in making the diagnosis, but certainly in the UK this is not often achievable.

The inappropriate treatment of non-epileptic seizures carries a significant risk of avoidable iatrogenic complications, including respiratory arrest and admission to ITU (with attendant consequences of invasive treatment there). However, delayed treatment of tonic-clonic status can be equally dangerous. On balance, where there is doubt, so long as the possibility of functional attacks has been considered but is felt less likely than the risks of inappropriate treatment (and is documented as such), prompt and adequate treatment as for tonic-clonic status is probably the best option. That said, identification of normal alpha rhythm in the unconscious patient between convulsive movements effectively excludes tonic-clonic status, and the distinction between this and postictal slowing is recognizable with limited training (Fig. 2). The diagnosis of non-

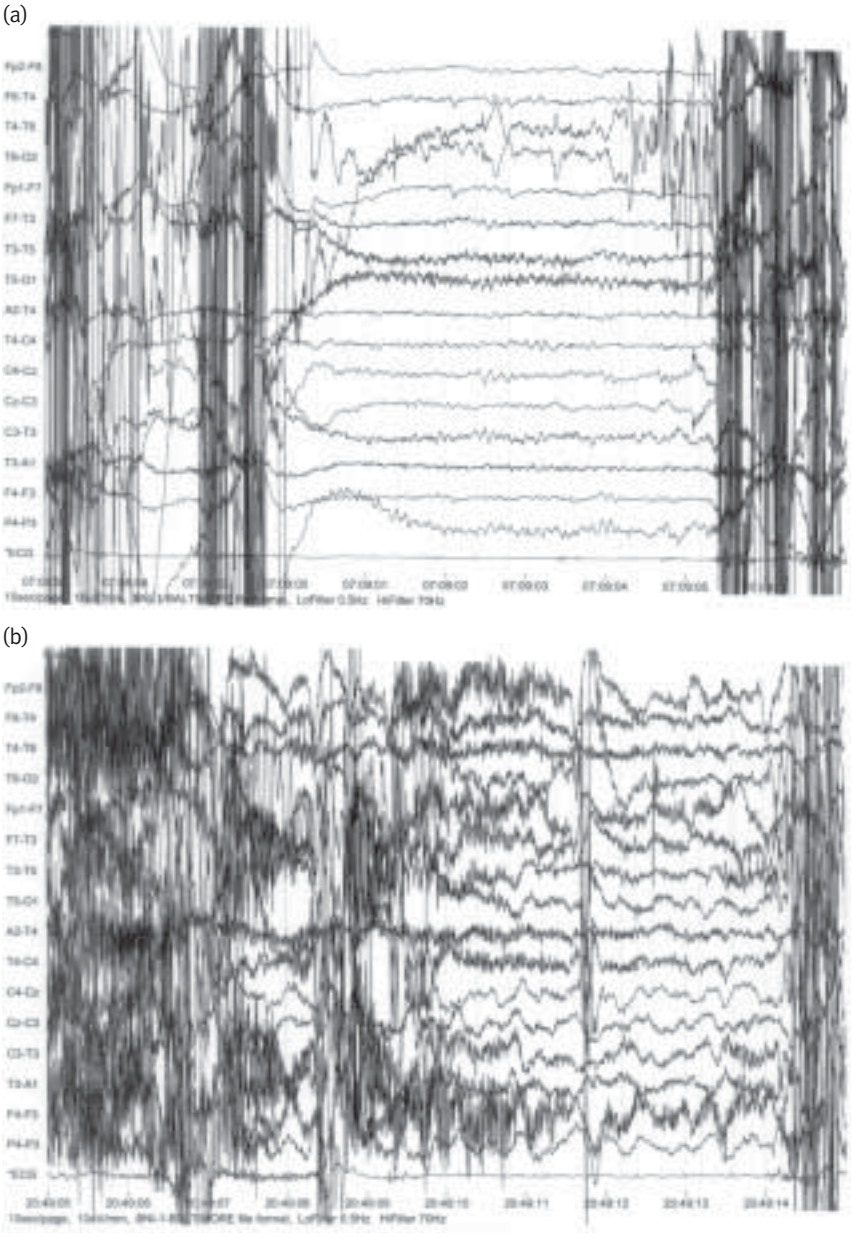


Figure 2 EEG in non-epileptic seizures. (a) Normal alpha rhythm can be clearly seen interspersed with high-amplitude movement artefact, caused by the non-epileptic seizure. Compare this with (b), where similar movement artefact is followed by grossly abnormal slowing (in the delta range) of the background EEG, as seen in epileptic tonic–clonic status.

convulsive status (discussed below) certainly requires EEG expertise outside the scope of general neurology and acute medicine. However, given the shortage of clinical neurophysiologists and EEG technicians in the UK, limited training in EEG for some emergency staff should be considered, specifically aimed at distinguishing epileptic from non-epileptic rhythms in patients with convulsive movements. This suggestion may be controversial but is perhaps worthy of further study, and as neurologists become increasingly involved in acute service provision in the UK, local neurologists may themselves want to explore this further.

Have a protocol

It is now widely accepted that protocols for the treatment of acute medical conditions save lives: proof of this is starkly evident in the dramatic difference that the advanced life support protocol has made to survival from cardiac arrest (Henderson & Ballesteros 2001). Additionally, in an audit of treatment of status epilepticus, 44% of patients presenting to ITU had received inadequate prior doses of AEDs (Walker *et al.* 1996), mainly due to underestimating the amount of phenytoin necessary as a loading dose. The development and implementation of a clear protocol, with ongoing training and specialist support, speed up and rationalize the delivery of treatment in both acute medical and specialist neurological settings, and as such are recommended in all current epilepsy guidelines (Royal College of Physicians Edinburgh 2003; Scottish Intercollegiate Guidelines Network 2003; NICE 2004). To a certain extent, the detailed content is probably less important than the process, particularly given that in many instances there is little evidence on which to make specific drug choices. However, at the very least the implementation of a structured generic treatment plan allows for audit of delivery and response. A standard protocol is shown in Fig. 3.

Out of hospital treatment in patients with recurrent status epilepticus

For those patients with a history of recurrent status, early out of hospital treatment should be considered. It is known that the longer a seizure goes untreated, the less likely treatment will be successful. Thus rapid intervention probably prevents the development of many cases of established status (Shorvon 1994).

When to initiate treatment will vary for individuals, but might include preventative treatment (e.g. clobazam 10–20 mg/day orally) during known high-risk periods (e.g. menstruation or infection), or parenteral treatment if a prolonged (> 5 minute) convulsion occurs. In this latter situation all current guidelines recognize the place of rectal diazepam (diazepam rectal gel, 10–20 mg in adults) in the out of hospital treatment of prolonged seizures. However, although effective, this is inconvenient and undignified, particularly in a convulsing adult where on a practical level it may be impossible.

An alternative is buccal midazolam (midazolam, parenteral preparation, 5–10 mg). NICE (2004) and SIGN (Royal College of Physicians Edinburgh 2003; Scottish Intercollegiate Guidelines Network 2003) both recommend

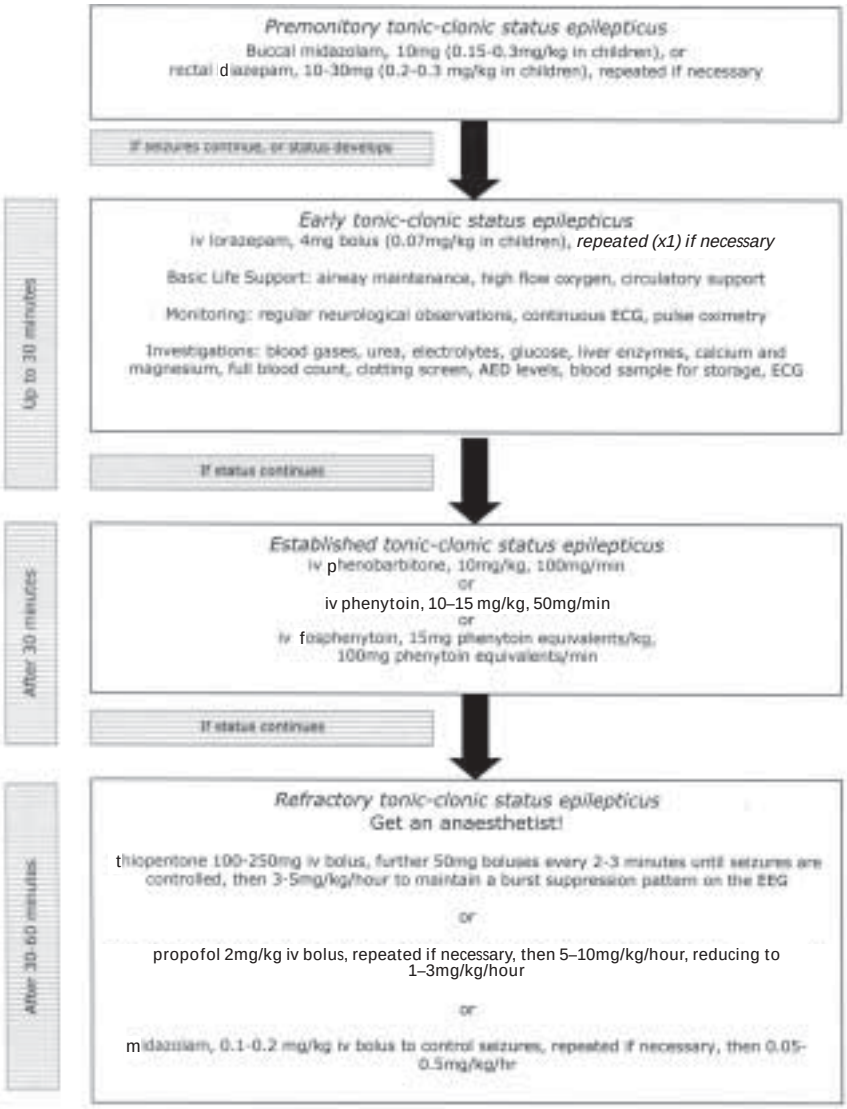


Figure 3 Management of status epilepticus. As recommended by NICE (2004), SIGN (2003) and the Royal College of Physicians Consensus Statement (2003). 'Time is brain' – prepare and use a protocol! In all patients, in parallel with emergency management, maintenance AED therapy must be reviewed/initiated within the first few hours.

this 'where appropriate training is available', and several studies conclude that it is as safe and effective as rectal diazepam (Scott *et al.* 1999). Unfortunately, the lack of a licensed preparation has prevented its wide-scale implementation, to the detriment of patient care. However, many centres operate a 'shared-prescribing' system, with training and implementation provided by specialist services at the outset, transferring to the family doctor once it is established, which is probably the best interim solution.

Basic investigation and general medical management

Nursing care should be directed at preventing injury (e.g. cot sides up), and monitoring and maintenance of basic physiological parameters such as heart rate and rhythm, respiratory rate, blood pressure and BM stick testing for blood sugar (as a diagnostic tool). High-flow oxygen should be provided, the airway secured (trismus of the masseter muscles may make this difficult, in which case a nasopharyngeal airway is a reasonable alternative), a wide-bore cannula inserted, and fluid resuscitation started.

Initial investigations should include full blood count, urea and electrolytes, calcium, magnesium, liver enzymes, blood sugar, and blood cultures if infection is suspected. Serum for drug levels should always be taken at the outset, even if at that stage there is no detailed history. Specific AED levels, or screening for recreational drug use, can easily be requested later on stored serum, and might provide essential information about the cause of the status.

If there is any suspicion of hypoglycaemia, then 50 mL of 50% iv dextrose should be given. Similarly, if alcohol dependence is suspected, then thiamine replacement (e.g. Pabrinex©; Link Pharmaceuticals, Horsham, UK) should be given iv, particularly if iv glucose has also been prescribed (sudden glucose loads can precipitously lower circulating thiamine levels).

Initial antiepileptic drug treatment (Fig. 3)

This is one area where we do have good evidence on which to make a decision. Lorazepam is the drug of choice (look for it in the fridge – it has to be stored at 4°C!), once intravenous access is available, in all current guidelines (Royal College of Physicians Edinburgh 2003; Scottish Intercollegiate Guidelines Network 2003; NICE 2004). Intravenous diazepam has been used traditionally, and although it has a rapid onset of action, it is quickly redistributed into fatty tissue, often leading to rebound seizures. Anyone with emergency experience will recognize the scene where the patient stops fitting on the end of the needle, only to start again 10 minutes later. Repeated doses, often administered in this situation, then lead to accumulation, with the risk of the unpredictable (and often rapid) development of sedative adverse effects, including respiratory depression and arrest. Chlormethiazole, usually given as an infusion, has similar problems, and is not recommended.

Lorazepam is the drug of choice, once intravenous access is available, in all current guidelines

In contrast, iv lorazepam has a smaller volume of distribution, a fast onset of action, and a longer therapeutic half-life. In practice this means it is at least as effective at stopping the seizures, but buys more time to sort out maintenance therapy and whatever is causing the status, making it on the whole a safer and more effective drug in this situation. This is supported by a number of diazepam versus lorazepam comparative studies, including two double-blind randomized trials (Alldredge *et al.* 2001; Appleton *et al.* 1995; Cock & Schapira 2002). The fact that many patients will have received rectal diazepam before arrival at hospital does not preclude the subsequent use of lorazepam, although thought should be given to the total benzodiazepine load when making subsequent decisions (Shorvon 1994). In this context, the frequent habit of writing 'as required' benzodiazepines on the drug chart when patients are admitted with status should in our view be stopped, and replaced by a limited number of single dose entries with clear instructions and guidelines. Without this, patients coming under initial control run the risk of receiving numerous doses, sometimes over several days, without medical review. We once encountered a patient who had received 40 mg of lorazepam, 90 mg of diazepam and over 250 mg of clobazam over one weekend during an episode of initially premonitory, but subsequently refractory tonic-clonic status, before neurological advice was sought.

Established status

If benzodiazepines fail, currently licensed treatments for established status include phenytoin, phenobarbitone and fosphenytoin (Fig. 3). There are numerous case series and much published expert opinion, but the only large randomized controlled trial of any significance in this area (n = 518) was a non-blinded comparison of four different options for the initial treatment of status (lorazepam alone, phenytoin alone, phenytoin plus diazepam, and phenobarbitone

alone) (Treiman *et al*. 1998). In terms of seizure control, all were effective, and the only significant difference was between the best (lorazepam alone, 52% success) and the worst (phenytoin, 37% success, $p = 0.002$). Thus we know that all three agents work, but we do not have any good evidence that one is better than the others, particularly where a benzodiazepine has already been given. There are, however, differences in adverse events, and the practicalities of administration.

Phenytoin has a very high pH (~12), so can cause significant cellulitis if extravasation occurs, and it must be diluted in 0.9% saline (rather than dextrose) to avoid crystallization. Also it must be administered through a side-arm (or a separate iv line) to avoid reaction with other iv drugs and fluids, usually over 20 min or so. All these factors can mean several minutes between the decision to give phenytoin, and the patient receiving, never mind finishing, it. There is also a risk of cardiac arrhythmias and hypotension with parenteral phenytoin, particularly if given quickly, and patients require cardiac monitoring. This is standard in the emergency department, but can in our experience result in potentially dangerous treatment delays if the patient has been moved to a general ward at the point when phenytoin treatment is instigated. Purple hand syndrome, a rare skin reaction to parenteral phenytoin (consisting of swelling, pain and discolouration of the skin) is a potential problem, but this can be avoided by the use of proximal, large-calibre veins for the iv infusion, and in any event it is probably much less common in modern times than once thought (Burneo, Anandan, & Barkley 2001).

Fosphenytoin was devised to overcome many of the problems associated with phenytoin. It has a lower pH (and thus causes fewer problems in solution), it does not cause purple hand syndrome, and there is less risk of cardiac and hypotensive complications (although cardiac monitoring is still recommended during its administration). It can be given much more quickly than phenytoin, and even intramuscularly if iv access is not available (DeToledo & Ramsay 2000). However, the dosage nomenclature (1.5 g fosphenytoin = 1 g phenytoin = 1 PE, or phenytoin equivalent), designed to facilitate its use as a phenytoin replacement, has sometimes led to confusion and administration errors. Taking this into consideration, along with its cost (it is at least 10 times more expensive than phenytoin) (Touchette & Rhoney 2000), it has never become popular in the UK, although there is substantial clinical experience with it elsewhere (Rosenow, Arzimanoglou, & Baulac 2002).

Phenobarbitone, one of the oldest AEDs available in the UK, has a number of practical advantages: it requires less dilution and can be injected more quickly (iv push directly over 10 min) – an important consideration when time matters; and although it also has the potential for hypotension, there are fewer local adverse effects, and it may have faster brain penetration and onset of action than phenytoin. In support of this, an open study in 36 patients comparing diazepam plus phenytoin, and phenobarbitone plus optional phenytoin (Shaner *et al*. 1988) found a significantly shorter response time in controlling seizures (up to 14 min faster) with phenobarbitone, without more complications.

That phenytoin is far more widely accepted and used than phenobarbitone possibly reflects that historically it replaced phenobarbitone as oral maintenance therapy. However, as phenytoin is no longer a recommended first line agent for maintenance in epilepsy, this theoretical advantage has probably now been lost. The bottom line is that there is no good evidence suggesting that any one agent has superior efficacy or tolerability over another. Our advice therefore is to pick your drug, it probably does not matter which, but agree local guidelines and make sure that you know how to use it, and what its problems are. More importantly, whichever you do use, use enough! Studies from the UK (Walker *et al*. 1996) and the USA (Cascino *et al*. 2001) suggest that initial loading is potentially inadequate in around 70% of patients, and not surprisingly adequacy of treatment is highly predictive of efficacy.

Intravenous valproate is used in some centres in the USA, and has been shown to be safe and effective in case series of status epilepticus (Wheless *et al*. 2004; Limdi *et al*. 2005), including patients refractory to conventional treatments, or considered too cardiovascularly unstable to have phenytoin. Unlike phenytoin and phenobarbitone, valproate is also a first line option for oral maintenance therapy, which might be an advantage. An iv preparation of levetiracetam is expected shortly, but there are no comparative trial data for either this drug or valproate.

Refractory status epilepticus

When it comes to refractory status, there is even less evidence on which to base treatment decisions. Expert consensus and all current guidelines advise that if treatment is still not controlling seizures at this stage (between 30 and 60 min), the patient should be transferred to ITU for general anaesthesia, both to suppress seizures and for the management of the systemic adverse effects of the epilepsy and the drugs being used to suppress it. This reflects the fact that patients by this stage are usually metabolically and physiologically compromised, and at risk of serious brain damage if control is not quickly achieved. General anaesthesia, at sufficient doses if tolerated, in principle should at least suppress the electrical and motor activity in all patients.

This advice is not new, but surveys support our personal experience that this is often not what happens in practice. In European surveys of epileptologists, critical care neurologists (Holtkamp *et al*. 2003) and intensivists (Walker *et al*. 1995), over 60% would try a third anti-epileptic agent before considering general anaesthesia.

Our advice therefore is to pick your drug, it probably does not matter which, but agree local guidelines and make sure that you know how to use it, and what its problems are

It is probably more important to initiate anaesthesia without undue delay than to spend time arguing with your local anaesthetists and intensivists about the best choice of drug

Amongst USA critical care neurologists and epileptologists the figure is still 43% (Claassen *et al.* 2003), most opting to try phenobarbitone (on top of phenytoin) before anaesthesia. There is no direct evidence that this is harmful, but it will inevitably mean delay in achieving seizure control for some patients, which as discussed previously might be at the expense of further brain damage.

The guidelines are clear, and generally agreed, but implementation (as is so often the case) appears to be the main hurdle. One reason for hesitancy with respect to anaesthesia is the controversy over which agent to use, and this is another area in which randomized controlled trials to inform practice are urgently needed. Three agents are in common use at present: thiopentone (pentobarbitone in the USA), propofol and midazolam (Fig. 3).

Thiopentone is an effective anti-epileptic agent (Parviainen *et al*. 2002), but tends to cause hypotension and many patients require vasopressor support. It also has an extremely long elimination half-life, and its saturable pharmacokinetics means that blood level monitoring is required to avoid toxicity with long-term (> 48 h) administration.

Propofol is used increasingly – its superior pharmacokinetics and favourable adverse-effect profile make it the drug of choice for many ITU physicians, and, despite some early concerns about a pro-convulsant effect in animals, it appears to have efficacy in terms of seizure control (Rossetti *et al*. 2004). It is delivered in a lipid vehicle (being highly lipid-soluble), and thus there is a theoretical risk of hyperlipaemia with prolonged infusions. In a recent case series of 31 patients treated with propofol, however, only one patient developed high triglyceride levels, but was asymptomatic, so the real risk is probably small.

Midazolam is an effective, short-acting benzodiazepine that when given as an infusion certainly has efficacy in refractory status epilepticus, including potentially at subanaesthetic doses. However, breakthrough and recurrent seizures may be a problem (Claassen *et al*. 2002).

The best comparative information comes from a meta-analysis (Claassen *et al*. 2002). Despite obvious methodological limitations (different outcome criteria, case selection biases), the conclusions reflect anecdotal and personal clinical experience, and suggest that barbiturate anaesthesia is better than the other two drugs in terms of breakthrough seizures and seizure recurrence. There was a slight excess of hypotension in the patients treated with barbiturates, but in an ITU setting this is easily managed, and the risk of *refractory* hypotension was similarly low in all treatment groups.

It is probably more important to initiate anaesthesia without undue delay than to spend time arguing with your local anaesthetists and intensivists about the best choice of drug, so again we recommend a pragmatic approach of agreeing local practice and administration guidelines, and, more importantly, sticking to them.

In most UK units EEG monitoring is not available initially (although recommended), so the level of anaesthesia has to be judged clinically, aiming for complete abolition of clinical seizures. Paralysing neuromuscular blocking agents necessarily mask motor manifestations, so should be avoided, meaning in practice that the level of anaesthesia will also need to be sufficient for the endotracheal tube to be tolerated. Beyond this, the level of anaesthesia that is necessary for control of status, and for how long it should be maintained, is unclear. In most patients who have reached the ITU stage, it will take 12–24 h to determine any precipitating causes and/or make the necessary adjustments to maintenance anti-epileptic treatment, following which anaesthesia should be slowly withdrawn to avoid rebound seizures. This occurs naturally when barbiturates are stopped (because of their long redistribution half-life, patients may take days to wake up after prolonged barbiturate anaesthesia) and might be considered a potential advantage, but must be balanced by the risks and costs associated with longer ITU stays. With propofol and midazolam, we advise that infusions should be gradually tapered (e.g. 5% of the infusion rate per hour, or over 24 h).

Maintenance anti-epileptic drugs

In parallel with emergency management, attention must be given to maintenance anti-epileptic therapy. In patients known to have epilepsy, their usual AED regime should be maintained throughout, using iv or nasogastric tube administration in those who are unconscious for any prolonged period. Adjustments may be required, depending perhaps on AED levels, and, unless there is an obvious remedial precipitant, most patients should have an urgent review of their treatment by a neurologist. Telephone advice from someone who knows the patient from a distant centre may be preferable to local neurological review in some instances. In patients presenting *de novo*, because the underlying cause may not be completely reversible, and because of the high risk of developing epilepsy following an episode of status, most experts recommend AEDs for at least 3–6 months, often longer and even in the absence of recurrent seizures depending on the cause. Where iv phenytoin or phenobarbitone has been used, this can in principle be continued as oral maintenance therapy, but as discussed previously neither is now recommended in this context. Our preference, unless relatively short-lived treatment is anticipated, is to initiate oral maintenance therapy [e.g. valproate or carbamazepine (Jackson 2005)] in line with current guidelines within the first few hours after presentation, in anticipation that by the time the acute situation has resolved and phenytoin or phenobarbitone levels have dropped, there will be sufficient of the maintenance AED on board to 'take over' control. Although start-

ing immediately at standard doses (e.g. 600–800 mg/day of either drug) as opposed to slow titration can result in adverse effects, these are usually transient and a small price to pay in the overall scheme of the emergency management of status.

When to use the EEG and what to look for

As discussed previously, in an ideal world EEG would be available acutely to assist in the diagnosis of any case where non-epileptic status is suspected, or in cases of non-convulsive or subtle motor status epilepticus. However, many hospitals, particularly in the UK, do not have on-site EEG facilities (Shorvon 1999), and national shortages of EEG technicians and clinical neurophysiologists mean getting an urgent EEG outside normal working hours can be difficult even in regional neuroscience centres. In most patients, when control is quickly achieved without seizure recurrence, urgent EEG then becomes irrelevant in any event. However, up to 50% of patients with 'refractory status' have no ongoing epileptic activity on the EEG (the two most common misdiagnoses being non-epileptic status and drug-induced coma), and may have been treated inappropriately with powerful anaesthetic drugs with alarming consequences (Walker *et al.* 1996). In such cases, an EEG is essential to clarify the diagnosis and monitor response to treatment. Current guidelines recommend that when seizures are difficult to control or are recurrent despite first and second line agents (i.e. when general anaesthesia is required), the patient should be transferred to a unit with EEG monitoring (Royal College of Physicians Edinburgh 2003; Scottish Intercollegiate Guidelines Network 2003; NICE 2004). If seizure activity is confirmed (Fig. 4), common practice is to aim for a burst suppression pattern on the EEG (Fig. 5), but we do not really know if this is necessary (Shorvon 2000). If continuous EEG monitoring is not easily available, we suggest as a minimum monitoring until electrographic seizures are controlled, followed by intermittent EEGs at 12–24 h intervals until anaesthesia is withdrawn.

What to do if nothing works

Not surprisingly, for the patient where all of the above has been undertaken appropriately, yet seizures recur when any attempt to withdraw anaesthesia is made, there is effectively no evidence-based advice. Certainly the diagnosis should be revisited, both in terms of whether this is truly epilepsy (necessitating EEG in the unconscious patient), and with respect to aetiology. Even in patients with known epilepsy, magnetic resonance imaging, and cerebrospinal fluid (CSF) examination, should be undertaken or repeated to exclude new pathology. The possibility of anoxic/metabolic brain damage, and of postanoxic myoclonus rather than true status epilepticus should also be considered, and can usually be distinguished on the EEG. Adequate serum levels of both maintenance and newly added agents should also be confirmed.

In the absence of any remedial factor (or alternative diagnosis), common practice is to reinstate anaesthesia, aiming for a longer, deeper level than before, e.g. for 24–48 h before again attempting withdrawal. During this period, alternative AEDs should be considered, and, if not previously tried, iv valproate is certainly an option. We have experience of both nasogastric topiramate and of nasogastric levetiracetam being followed by a good outcome in this situation, where conventional agents, including valproate, have failed. Whether this was a therapeutic response to the new agent, or just the natural history of the status, is uncertain.

OTHER TYPES OF STATUS EPILEPTICUS

We have concentrated on tonic-clonic status, but will mention the other well-recognized and common status syndromes,

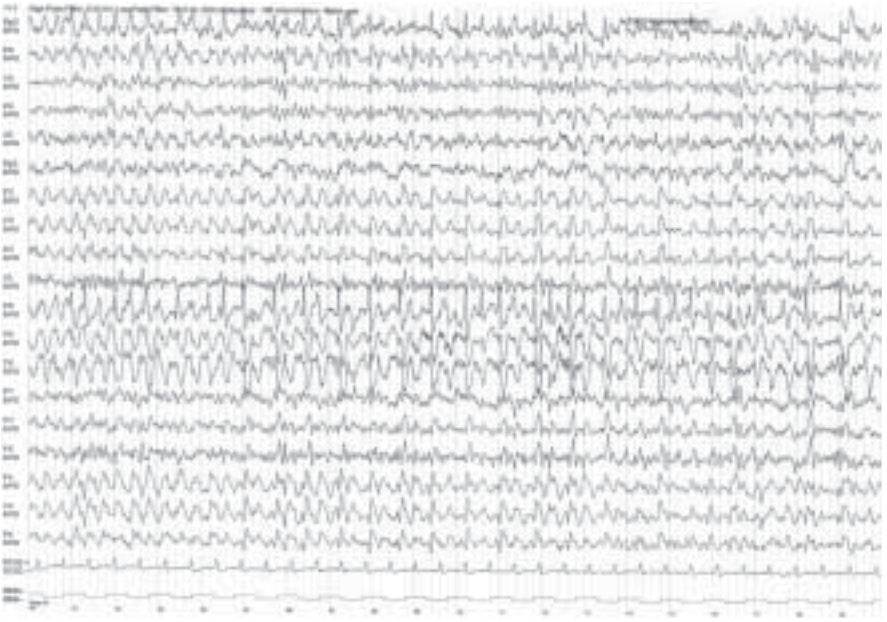


Figure 4 Electrical status epilepticus. An EEG showing rhythmic, generalized, synchronized high-amplitude sharp wave activity, consistent with electrical status epilepticus. This patient had been paralysed for ventilation, hence the lack of movement artefact on the EEG, but similar appearances can be seen in the later stages of tonic–clonic status, when electromechanical dissociation can occur, or in non-convulsive status.

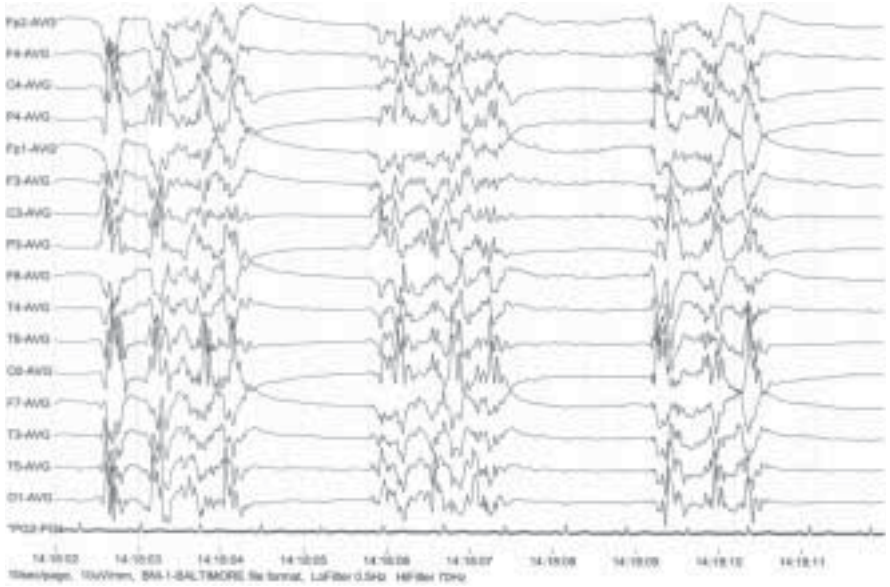


Figure 5 Burst suppression. Profound low-amplitude EEG activity is interspersed with bursts of higher amplitude polymorphic slow-wave activity, which can contain sharp components. Outside the context of deep anaesthesia, this is pathological in all except very premature babies, and usually represents anoxic brain damage or gross metabolic derangement.

because their presentation may be confusing, and the treatment is often different.

Non-convulsive status epilepticus

This is relatively common and often under-recognized (Haffey *et al.* 2004). It may account for up to 25% of all cases of status epilepticus, may persist unrecognized in up to 14% of patients after control of convulsive seizures is secured, and is present in around 8% of all comatose patients with no external signs of seizure activity. In general, the outcome after non-convulsive status is better than after convulsive status, although in some patients, particularly those with temporal lobe pathology, the seizure activity in itself may contribute to cognitive and behavioural decline as previously discussed. As with tonic-clonic status, patients with an underlying acute medical condition have a higher case fatality, largely related to the aetiology, and those with idiopathic generalized epilepsies, in the absence of comorbidities, have a good prognosis. The main problem is making the diagnosis in the first place – undertaking an EEG on every patient with an unexplained altered mental state is certainly not practical. A recent prospective study (Husain *et al.* 2003) found that a combination of remote risk factors for seizures (previous stroke, brain tumour, meningitis, neurosurgery or coexistent dementia) and ocular movement abnormalities (any of nystagmus, hippus or sustained eye deviation) was 100% sensitive in predicting non-convulsive status in a general hospital non-ITU setting, and this deserves further study. Where EEG is not possible, clinical assessment by an experienced neurologist may be sufficient in the first instance.

Contrary to common opinion, non-convulsive status epilepticus can often be the presenting symptom of epilepsy, particularly in the elderly and learning disabled populations (in up to 50% of cases) (Haffey *et al.* 2004).

Non-convulsive status can be subdivided into typical absence status, atypical absence status and complex partial status.

Typical absence status epilepticus

Absence seizures are most frequently observed in children, but absence status is more commonly seen in adults with a primary generalized epilepsy syndrome. It may also occur in the learning disabled patient with Lennox–Gastaut syndrome. Between 3% and 9% of patients with a history of typical absences will experience an episode of absence status at some point. Inappropriate AEDs such as tiagabine (Knake et al. 1999) or carbamazepine (Callahan & Noetzel 1992) are recognized precipitants in some cases. Absence status has also been reported as a *de novo* presentation in the context of benzodiazepine withdrawal in patients treated for anxiety or drug problems, with no history of epilepsy (Thomas et al. 1993).

Change in conscious level can vary from mild clouding of consciousness to profound stupor, and in its most mild manifestation, memory of events between frequent discrete seizures may be retained. A typical episode consists of slowed responses and a trance-like expression, with facial or eyelid myoclonus, but sometimes more generalized myoclonus or atonia is present. The EEG is diagnostic, showing bilateral, synchronous, continuous spike and wave activity. There is little evidence that absence status is dangerous or harmful in itself, though it may terminate with a tonic-clonic seizure if untreated (Shorvon 2000). Typical absence status characteristically responds to iv benzodiazepines, or iv valproate.

Atypical absence status epilepticus

Atypical absence status epilepticus can also occur (e.g. in Lennox–Gastaut syndrome), often with a gradual onset and offset, but

is less likely to develop into a tonic-clonic seizure. The course may fluctuate, lasting in some cases for months, with a typically poor response to medication, and atypical EEG abnormalities (hypsarrythmia, focal abnormalities, irregular and slow spike and wave) (Shorvon 2000). Although regarded as a separate entity to absence status, there is considerable overlap between them (and to some extent with complex partial status, certainly clinically and therapeutically) and the disorders may be regarded as being on a spectrum.

Complex partial status epilepticus

Complex partial status epilepticus is often either misdiagnosed or mislabelled as absence status (and the reverse) by the inexperienced, but there are important therapeutic and prognostic differences. Clinically, the patient is likely to be confused (although up to 25% may initially appear aware, and be able to obey simple commands), with speech and language deficits, behavioural changes, and motor and autonomic features. Fluctuating symptoms are common. A typical episode lasts for several hours, and may follow a tonic-clonic convulsion, but is unlikely to be terminated by one (unlike typical absence status). Episodes may be recurrent, often following a pattern. The EEG is usually abnormal, but the changes may be subtle or variable (continuous or frequent spike/wave, episodes of desynchronization, paroxysmal spike and slow-wave activity). The choice of drug is not as limited as for convulsive status, but ideally it should be a drug where an effective dose is easily and quickly optimized, and this will depend on the patient's previous AED regime. If the level of consciousness is significantly impaired, then iv loading, as in convulsive status, may be appropriate, but is often not necessary. There is little consensus on how aggressively (or not) complex partial status should be managed, and an individualized approach is probably required, guided by the presence of any additional convulsions, underlying aetiology, and severity and duration of the seizures. The response to treatment (intravenous or oral, depending on the level of consciousness) is frequently poor (Shorvon 2000), and this condition may be remarkably refractory to treatment.

Myoclonic status

Myoclonus, whether part of a generalized epilepsy syndrome, or multifocal as in progressive myoclonic epilepsies, is generally not life-threatening in itself, but may be a warning of impending tonic-clonic seizures or tonic-clonic status, so it should not be ignored. In addition, in our experience patients presenting with episodes of myoclonic status, particularly in the context of juvenile myoclonic epilepsy, may be misdiagnosed as having non-epileptic or panic attacks, given the combination of sometimes quite florid jerky movements with preserved consciousness, typically presenting in teenage or young adult life. Such patients often respond to oral or intravenous benzodiazepines such as clobazam or lorazepam. An alternative emergency treatment would be iv valproate.

Focal motor status epilepticus

This is also called epilepsia partialis continua, and is defined as 'spontaneous regular or irregular clonic muscle jerking of cerebral cortical origin' (Cock & Shorvon 2002). Either it can affect a single muscle group or several, characteristically distal groups are more frequently involved, but more proximal group involvement (including the facial muscles) is well recognized. The jerks can be spontaneous or stimulus-induced (touch, auditory or startle), and may have a wide-ranging frequency, from one per 5 min to several per second. The possible aetiologies are diverse, from focal cortical disturbances (such as stroke) to more generalized disturbances of brain function (such as infectious encephalitis, metabolic or neurodegenerative disorders). Episodes can be chronic (lasting up to years), and are typically refractory to treatment, as has been comprehensively reviewed elsewhere (Cock & Shorvon 2002). To date there is no universally effective treatment, although the recent success of focal drug delivery in animals might offer new approaches in the future (Nilsen & Cock 2004; Nilsen *et al*. 2005).

WHAT IS THE ROLE OF THE NEUROLOGIST IN ALL THIS?

Status epilepticus might well be described as 'an orphan condition', at least in the UK. The doctors with most practical experience of it are those trained in emergency medicine who, on the whole, have little knowledge (or interest) in the complexities of epilepsy, and its changing management. Intensive care departments have some first-hand experience of the condition, but the unending pressure on beds means that often their priority is discharge, and they do not have the time or the resource to continue management beyond the most acute stage. In contrast, neurologists are (theoretically) ideally placed to take the lead: we have the training, experience and interest to look after the patients properly, both acutely and afterwards (indeed we may already be looking after them). However, at present in the UK, grossly inadequate workforce provision generally precludes direct care by a neurologist, certainly in the acute stage. What we can and should do, however, is take the lead in ensuring locally agreed protocols, education, implementation and audit strategies in collaboration with emergency medicine, general medical and ITU staff. In addition, we recommend that all patients should be reviewed as soon as possible after presentation by a neurologist, to consider the aetiology, past history and formulation of an appropriate treatment plan, also facilitating effective handover to neurological services for subsequent out-patient management. In some instances telephone advice from a neurologist who knows the patient might be both preferable and more readily achievable, and sometimes more appropriate as already discussed.

CONCLUSIONS

- Status epilepticus is a serious medical condition with both short- and long-term neurological and general medical consequences.
- As a condition, it has been well defined: the physiological mechanisms are well understood, and the underlying cellular pathophysiology is under ever-increasing scrutiny.
- Good evidence for the choice of drug treatment is not always available, but principles and guidelines are largely agreed.
- National guidelines now exist and should be locally implemented and audited.
- However, there are significant barriers to implementation, particularly with respect to availability of EEG.

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