Status epilepticus: pathophysiology and management in adults

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As in Clark and Prout's classic work, we identify three phases of generalised convulsive status epilepticus, which we call impending, established, and subtle. We review physiological and subcellular changes that might play a part in the transition from single seizures to status epilepticus and in the development of time-dependent pharmacoresistance. We review the principles underlying the treatment of status epilepticus and suggest that prehospital treatment is beneficial, that therapeutic drugs should be used in rapid sequence according to a defined protocol, and that refractory status epilepticus should be treated with general anaesthesia. We comment on our preference for drugs with a short elimination half-life and discuss some therapeutic choices.

Introduction

In this review we will focus exclusively on major motor (convulsive) status epilepticus in adults. Complex partial and other forms of status epilepticus are well covered in Simon Shorvon's *Status Epilepticus*,[1] in several recent reviews,[2–9] and in an upcoming volume edited by one of us.[10]

The earliest known description of status epilepticus was in the 25th and 26th tablets of the Sakikku cuneiform of the Neo-Babylonian era, written during 718–612 BC.[1] Status epilepticus is Bazire's latin translation of "Etat de mal",[11] a term coined by the patients of Bicetre and the Salpêtrière, and introduced in published medical work in Louis Calmeil's doctoral thesis.[12]

In 1876, Bourneville defined status epilepticus as more or less incessant seizures.[13] Clark and Prout[14] described the natural course of status epilepticus in 38 patients unaffected by anticonvulsants. They recognised three phases: an early pseudostatus phase (described as aborted, imperfect, or incomplete); convulsive status; and stuporous status. Data[15,16] support Clark and Prout's concept, and we propose calling the three phases impending, established, and subtle status epilepticus.

Gastaut[17] stated that "there are as many types of status as there are types of epileptic seizures" and defined status epilepticus as "a term used whenever a seizure persists for a sufficient length of time or is repeated frequently enough to produce a fixed or enduring epileptic condition".[18] However, status epilepticus is never truly "fixed", and this definition is not easily translated into clinical trials or into everyday practice. Furthermore, research with animals shows that repetitive seizures become self-sustaining and pharmacoresistant within 15–30 min[15,19] and can lead to neuronal injury at about the same time.[20] The duration of what is accepted as status epilepticus has been shrinking progressively from 30 min in the guidelines of the Epilepsy Foundation of America's Working Group on Status Epilepticus[21] to 20 min,[22] to 10 min in the Veterans Affairs Status Epilepticus Cooperation Study,[16] and most recently, a length of 5 min was proposed.[23–25] This trend indicates the need to find an "operational" definition of status epilepticus—eg, a time when the patient should be treated as having status epilepticus, even if not all such patients are in established status epilepticus.

Definition of status epilepticus

Early or impending status epilepticus

The operational definition of status epilepticus is an empirical compromise dictated by therapeutic needs, because treatment should not be delayed until patients are in established status epilepticus, when neuronal injury and time-dependent development of pharmacoresistance have occurred. However, a better name would recognise that treatment is needed even though not all patients are in established status epilepticus. We propose the term "impending status epilepticus", defined as continuous or intermittent seizures lasting more than 5 min, without full recovery of consciousness between seizures. Previous authors have used a similar concept—eg, "early heralds of status"[14] or "early status epilepticus".[26] These definitions recognise the need to treat those patients intravenously with high-dose anticonvulsants, because their risk of developing status epilepticus is high, but they also acknowledge that not all of those patients are in status epilepticus. The Richmond study[27] provides support for this concept; more than 40% of the seizures lasting from 10–29 min stopped spontaneously without treatment, and overall mortality was 2·6% versus 19% for status epilepticus lasting over 30 min ($p<0·001$). By adopting a new category of impending status epilepticus, these patients will receive proper urgent medical care but will not contaminate morbidity and mortality statistics, outcome measures, or clinical trials with a subpopulation that is not in status epilepticus. Impending status epilepticus is not a new concept,[14] and fits with Gastaut's definition of status epilepticus as an "enduring epileptic condition",[18] a state which in his view required 30–60 min of seizure activity.[17]

5 min of continuous seizures is the threshold defining impending status epilepticus, which corresponds with the 5 min operational definition of status epilepticus.[23–25] There are strong statistical arguments for using the 5 min criterion. The mean duration of generalised

convulsive seizures in adults ranges from 62·2 s to 52·9 s (SD 14) for the behavioural symptoms, and averages 59·9 s (SD 12) for the electroencephalographic changes.[28,29] None of the seizures recorded lasted 2 min. Therefore, impending status is a disorder in which the duration of seizures is 18–20 standard deviations away from the norm of a single seizure, indicating that something distinctly unusual and severe is happening. This definition matches the almost universal emergency room practice of treating those patients as if they had status epilepticus. This change in terminology is unlikely to generate complacency or delay treatment, because the term impending implies that something substantial and, in this case, dangerous is about to happen.

Impending status epilepticus might be comparable to the pharmacosensitive initiation phase of experimental status epilepticus, and established status epilepticus to its partly pharmacoresistant maintenance phase.[30] However, no direct translation from animal data to care of patients is truly accurate, and clinical studies are needed to validate this concept.

Established status epilepticus

The definition of status epilepticus should revert to clinical or electrographic seizures lasting more than 30 min without full recovery of consciousness between seizures. We recognise that, in reality, impending and established status epilepticus are probably a continuum, but there is good support in experimental and clinical studies for a cut-off at 30 min; this is when status epilepticus has become self sustaining in experimental animals,[15] when status-epilepticus-induced damage is distinct,[20] and when pharmacoresistance has developed.[16,31,32]

By assuming that the transition from seizures to status epilepticus can be modelled by a single exponential curve, the time constant of this transformation is defined by the time point when 63% of patients have completed the transformation. According to the Richmond data,[27] at 30 min about 60% of prolonged seizures have transformed into an enduring epileptic condition. Animal data show that, after 30 min of perforant path stimulation, all animals were in established status epilepticus.[15] Additionally, 30 min of continuous seizures have been accepted as the defining duration of status epilepticus in both clinical practice and clinical trials. Those criteria only apply to major motor status epilepticus in adults and children over age 5 years.

Subtle status epilepticus

This term was coined by Treiman[33] to draw attention to the fact that, during prolonged status epilepticus, both the motor and electroencephalographic expression of seizures become less florid, yet the prognostic and therapeutic implications of that stage are still those of convulsive status epilepticus. This stage is similar to Clark and Prout's idea of stuporous status epilepticus.[14]

Partly treated status epilepticus

In more than 10% of patients treated for status epilepticus, clinical seizures stop or only show subtle symptoms, but electrographic seizures continue.[34] We do not know whether this continuing seizure activity is harmful, but experimental evidence that uncontrolled firing alone can kill neurons[35] suggests that treating them is the prudent thing to do.

Epidemiology

Three important population-based prospective studies were done to investigate the epidemiology of status epilepticus. The incidence of status epilepticus around Richmond (VA, USA) was 41 per 100 000 individuals per year;[36] however, it was 27 per 100 000 per year for young adults and 86 per 100 000 per year in the elderly. This askew distribution of incidence suggests that in an ageing society, such as in the USA as the baby-boom generation ages, status epilepticus will become more frequently encountered in emergency rooms. Alarmingly, mortality was also high in elderly people: 14% for young adults (16–59 years) and 38% for elderly people (60 years and above). These numbers show that available treatments for status epilepticus are not effective enough; identification of optimum treatments is a substantial challenge for neurologists and scientists.

Other studies show comparable incidence, if the methods of data collection and variations of population are considered. The incidence from two prospective studies in Europe was 17·1 per 100 000 per year in Germany[37] and 10·3 per 100 000 per year in the French-speaking part of Switzerland.[38] These findings are similar to the incidence found in an early retrospective study of status epilepticus from 1965–1984 in Rochester, Minnesota, which is 18·1 per 100 000.[39]

Aetiology

The main causes of status epilepticus are low blood concentrations of antiepileptic drugs in patients with chronic epilepsy (34%), remote symptomatic causes (24%), cerebrovascular accidents (22%), anoxia or hypoxia (~10%), metabolic causes (~10%), and alcohol and drug withdrawal (~10%).[36]

Several prognostic factors are important in predicting outcome of status epilepticus: cause, age, seizure duration, and response to treatment. The high mortality groups are patients with anoxia or multiple medical problems. Low mortality is reported in patients with epilepsy and precipitating factors, such as low serum concentrations of antiepileptic drugs.[36] In general, the elderly population bears a higher risk for mortality and morbidity than any other age group. Prolonged status epilepticus and refractoriness to treatment are associated with poor outcome.[16,40]

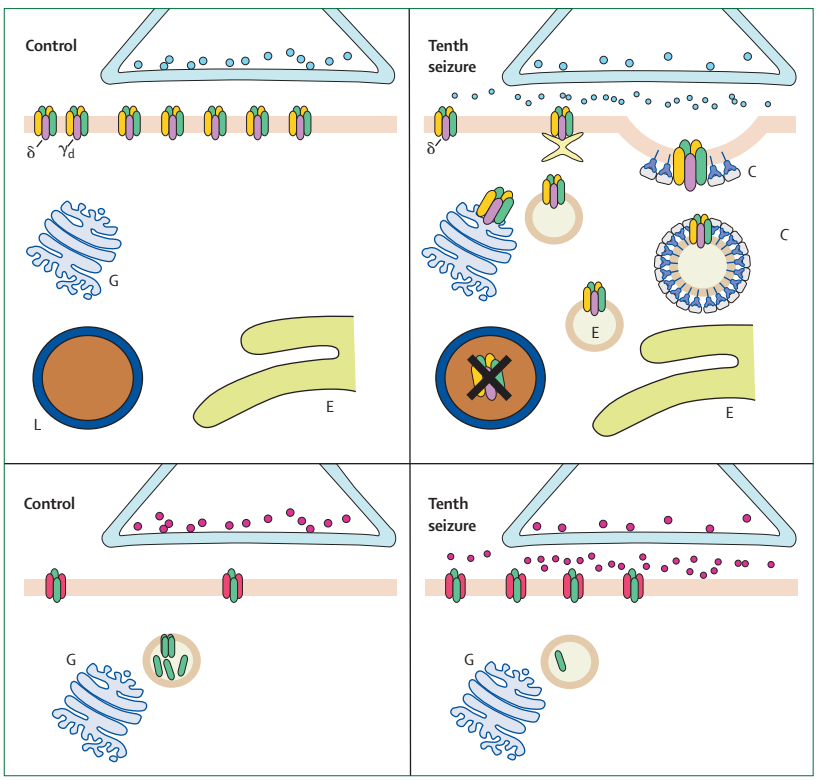

Figure 1: **Model of our hypothesis of receptor trafficking in transition of single seizures to status epilepticus**
Top: after repeated seizures, the synaptic membrane of $GABA_A$ receptors forms clathrin-coated pits, which internalise as clathrin-coated vesicles (C), inactivating the receptors because they are no longer within reach of the neurotransmitter. These vesicles develop into endosomes (E), which can deliver the receptors to lysosomes (L) where they are destroyed, or to the Golgi apparatus (G) from where they are recycled to the membrane. Bottom: by contrast, in NMDA synapses, subunits are mobilised to the synaptic membrane and assemble into additional receptors. As a result of this trafficking, the number of functional NMDA receptors per synapse increases whereas the number of functional $GABA_A$ receptors decreases.[59]

Basic mechanisms, current concepts

Self-sustaining status epilepticus

The tendency of status epilepticus to become self-perpetuating and the fact that it is more than a series of severe seizures were recognised as early as the 19th century: in the words of Trousseau[11] "in the status epilepticus, something happens [in the brain] which requires an explanation". In most models of status epilepticus in awake, free-running animals, seizures rapidly become self-sustaining and continue long after the withdrawal of the epileptogenic stimulus, whether chemical[41–43] or electrical.[15,44,45] Only when seizures are induced under anaesthesia or in very immature brains[46] do they remain stimulus bound. There is no proof that seizures become self sustaining in human beings; however, the age-old observation that seizures that last more than a half hour become very hard to control supports that interpretation. Understanding the mechanisms involved in the transformation from single seizures to self-sustaining status epilepticus might help us to prevent intractable status epilepticus and its consequences, brain damage, and epileptogenesis.

After the serendipitous observation of status epilepticus in animals subject to repeated electroconvulsive seizures,[19] models of self-sustaining status epilepticus were developed by several investigators.[41,47–52] Lothman and colleagues[45] showed that hippocampal stimulation produced long-lasting limbic seizures, which caused brain damage and later chronic epilepsy. Vicedomini and Nadler[53] showed that a series of ten after-discharges were sufficient to trigger self-sustaining status epilepticus. Mechanistic studies of self-sustaining status epilepticus and its consequences have used intermittent stimulation of the perforant path[15] or of the amygdala.[54,55]

The initiation of self-sustaining status epilepticus is easily blocked by many drugs that increase inhibition or reduce excitation.[56] However, once self-sustaining status epilepticus is established, it is maintained by underlying changes that do not depend on continuous seizures activity[57] and it is easily stopped by only a few drugs, all of which directly or indirectly inhibit glutamatergic neurotransmission.[57] Barbiturates and other GABAergic drugs never become totally ineffective but lose potency and can require such high doses that toxic side-effects, such as cardiovascular depression, prevent the delivery of a fully effective treatment.[58]

Another feature of self-sustaining status epilepticus is the progressive, time-dependent development of pharmacoresistance. Kapur and MacDonald[32] showed that the anticonvulsant potency of benzodiazepines can decrease by 20 times within 30 min of self-sustaining status epilepticus. Other anticonvulsants (eg, phenytoin) also lose potency, but more slowly.[31] By contrast, NMDA blockers remain highly efficient in stopping the disorder, even late in its course.[57]

Pathophysiology of self-sustaining status epilepticus

Seizures produce many physiological and biochemical changes in the brain, but a mechanism, that is still highly speculative, has begun to emerge. The first milliseconds to seconds are dominated by the consequences of protein phosphorylation. Ionic channels open and close, neurotransmitters and modulators are released, and receptor desensitisation, in its many forms, takes place. In a framework of seconds to minutes, receptor trafficking causes some key adaptations. Long before any change in gene expression can affect function, the existing receptors can move from the synaptic membrane into endosomes, or be mobilised from storage sites to the synaptic membrane, and this process drastically changes excitability by altering the number of inhibitory and excitatory receptors available in the synaptic cleft (figure 1).[59] In the minutes to hours time range, there are plastic changes in neuropeptide modulators. These changes are often maladaptive, with increased expression of proconvulsive neuropeptides[59,60] and depletion of inhibitory neuropeptides[35,61–64] contributing to a state of raised excitability. Finally, in the hours,

days, and weeks after seizures, there are long-term changes in gene expression. Many changes in gene expression are the result of seizure-induced neuronal death, and of the resulting neuronal reorganisation. Some are the result of plastic adaptation to seizure activity, but because status epilepticus profoundly inhibits brain protein synthesis,[65] many of the acute changes in gene expression are not consolidated.

Transition from isolated seizures to status epilepticus

In hippocampal slices from rats in lithium-pilocarpine induced status epilepticus for 1 h, the number of $GABA_A$ receptors per dentate granule cell synapse is 18 (SD 4), compared with 36 (SD 11) per synapse in controls (figure 1).[59] Immunocytochemical or confocal microscopy studies of the γ_2 and β_{2-3} subunits of the $GABA_A$ receptors show a decrease in the number of subunits present on the synaptic membrane and an increase in the interior of the cell.[59] Endocytosis of the $GABA_A$ receptors might partly explain the failure of $GABA_A$ inhibition[59,66] and the progressive pharmacoresistance to benzodiazepines as self-sustaining status epilepticus proceeds.[31,32] Other mechanisms might also play a part in this loss of GABA-mediated inhibition, including accumulation of intracellular chloride[67,68] or higher bicarbonate (HCO_3^-) permeability. Interestingly, extrasynaptic $GABA_A$ receptors do not endocytose, raising the possibility that stimulation of those extrasynaptic receptors might be useful in the treatment of status epilepticus. At the same time, AMPA and NMDA receptor subunits move to the synaptic membrane where they form additional excitatory receptors (figure 1). This change further increases excitability in the midst of uncontrolled seizures.[69] Immunocytochemical studies show that the NR1 subunits of NMDA receptors move from subsynaptic sites to the synaptic surface, and physiological investigations show an increase in functional NMDA receptors per dentate granule cell synapse from 5·2 (SD 1·2) receptors per synapse in controls to 7·8 (SD 1·2) after 1 h of status epilepticus (figure 1). Not all receptor changes are maladaptive, and trafficking of tachykinin receptors, for example, decreases the amount of receptors, which would be expected to maintain homoeostasis and decrease hyperexcitability.[70] There are also maladaptive changes in synaptic enzyme function. The autophosphorylation of calmodulin kinase II, for example, makes the enzyme calcium-independent, and this increases glutamate release presynaptically.[71]

Maladaptive changes in neuropeptide expression in self-sustaining status epilepticus

During self-sustaining status epilepticus, immunocytochemical studies have suggested a depletion in hippocampus of the predominantly inhibitory peptides dynorphin,[64] galanin,[63] somatostatin,[35,62] and neuropeptide Y,[72] whereas the expression of the proconvulsant tachykinins substance P and neurokinin B is increased, in cells that do not normally express them at detectable concentrations.[60] These changes abate as self-sustaining status epilepticus subsides, and might play a part in maintaining self-sustaining seizures over many hours.

Seizure-induced neuronal injury and death

We have known since the work of Meldrum and colleagues[73,74] that seizures, even in the absence of convulsive activity, cause neuronal loss, and Sloviter[35] showed that this cell death is the result of excessive neuronal firing, through excitotoxic mechanisms. Current models of self-sustaining status epilepticus induce widespread neuronal death, which in adults is mostly necrotic[20] and associated with mitochondrial dysfunction,[75,76] although apoptotic death does happen in several models and locations.[77,78] Evidence that seizures induce neuronal injury in human beings is largely anecdotal: brain damage is often seen in patients who die from status epilepticus;[79] DeGiorgio and colleagues[80] found decreased neuronal density in the hippocampi of five patients who died after status epilepticus compared with that in patients with epilepsy (without status epilepticus) and controls; Rabinowicz and colleagues[81] and O'Regan and Brown[82] identified increased neuron-specific enolase, a marker of neuronal death, in the serum of patients after status epilepticus. Several imaging studies reported acute cerebral oedema and chronic atrophy after status epilepticus[83–86] although others did not.[87] Anecdotal reports describe patients who had a normal brain MRI before status epilepticus, and showed atrophy by MRI after status epilepticus and neuronal loss at autopsy.[88] Patients who developed status epilepticus from domoic acid poisoning showed neuronal loss at autopsy,[89] and focal atrophy has also been recorded in areas of intense seizure activity[90–92] supporting a causal link between seizures and cell loss.

Status-epilepticus-induced epileptogenesis

Status-epilepticus-induced epileptogenesis is common after many types of status epilepticus in several animal species and at different ages.[93–96] The association of this event with the loss of GABAergic interneurons[35,97] or with sprouting of excitatory fibres[98–100] is still debated. Evidence in human beings is remarkably sparse, and subject to diverging interpretations. The risk of unprovoked seizures is 3·34 times higher after acute symptomatic status epilepticus (41%) then after single seizures (13%),[101] and the risk of developing a febrile seizure is much higher after status epilepticus than after simple febrile convulsions[102] but these differences might reflect a more severe illness in patients with status epilepticus, rather than status epilepticus-induced epileptogenesis. Status epilepticus induced by domoic acid is epileptogenic and might offer the closest human approximation to the animal models.[89]

Time-dependent development of pharmacoresistance

The progressive development, during the course of status epilepticus, of pharmacoresistance to benzodiazepines and other anticonvulsants is well documented in animal models.[31,32] In human status epilepticus, early treatment is much more effective than late treatment,[16] and pharmacoresistance is the most likely of several possible explanations for these results.

For readers who are interested in learning more about areas not covered here, or about the different types of animal models used for research on status epilepticus, a recent volume by Pitkänen, Schwartzkroin, and Moshé[103] and several review articles are recommended.[104–110]

Treatment of impending status epilepticus and of status epilepticus

Therapeutic principles: time is brain

Although the optimum treatment of status epilepticus needs to be further defined by controlled clinical trials, several important principles have emerged. Early initiation of intravenous anticonvulsants is crucial to successful treatment of status epilepticus. Clinical data show worsening of outcome with increasing duration of status epilepticus;[40,111] experimental data show time-dependent loss of synaptic $GABA_A$ receptors,[59] and as a consequence, rapid loss of responsiveness to benzodiazepines during status epilepticus.[31,32] The window of effective anticonvulsant therapy is narrow. If a treatment fails, there should be no interval between the end of a failed protocol and the initiation of the next therapy. The tight timetable outlined in the current treatment algorithms is difficult to adhere to but should be followed as closely as clinical circumstances allow.

The safeguarding of homoeostasis is essential for the prevention of neuronal injury, and maximising the supply of oxygen and glucose to the brain, by maintaining cerebral blood flow and blood gases, is as essential as reducing cerebral metabolic needs by restricting seizures and hyperthermia.

The diagnostic assessment is important but should not delay treatment. A trained clinician should be able to establish the diagnosis of impending or established status epilepticus on clinical grounds alone and begin treatment. In general, an electroencephalogram is not needed before the initiation of anticonvulsant therapy. Even when electroencephalography is being done, it should not delay treatment. The same is true of other laboratory studies.

Treatment varies enormously from hospital to hospital,[112,113] and most emergency rooms and intensive-care units do not have a status epilepticus-protocol ready for implementation, which might be one of the reasons why treatment is generally "too low, too slow", with delays initiating treatment,[40] delays between drugs, and timorous dosing possibly contributing to the poor outcome.[114] A treatment protocol helps avoid many of these pitfalls and is highly recommended.[112]

Prehospital treatment

Several studies have investigated the feasibility of treatment before hospitalisation. Rectal diazepam is safe and effective in both adults and children in the pre-hospital care of patients with frequent seizures. Serum drug concentrations peak within 3–30 min, and stay therapeutic for at least 8 h.[114] The drug terminated seizures lasting for more than 5 min in eight patients in a long-term care facility.[115] One randomised, double-blind, prospective study[116] showed that, in patients with continuous seizures lasting longer than 5 min, seizures terminated before arrival to the emergency department more commonly in those who were treated with intravenous lorazepam (59·1%) or diazepam (42·6%) than in patients treated with placebo (21·1%). These treatments were reasonably safe, with the rates of respiratory or circulatory complications at 10·3–10·6% versus 22·5% in the placebo group. Unfortunately, well-trained teams of paramedics did these pilot studies, and intravenous treatment might not be as safe in other settings. For safety reasons, in a prehospital setting, where a physician is usually not present, we do not recommend use of diazepam and lorazepam at doses higher than those used in the study. Because the rectal route has not been widely accepted in adults, trials of prehospital treatment with dugs that can be given intramuscularly (eg, midazolam) and trials using the nasal or buccal route in adults are needed. Recent controlled clinical trials in children gave encouraging results.[116–118] Whenever feasible, however, giving either rectal diazepam or intravenous lorazepam or diazepam before arrival at emergency rooms is beneficial.

Medical management

The first goal of treatment, before giving anticonvulsants, is to maintain airway and blood pressure; this done, anticonvulsants should be given before doing a full diagnostic work-up. Careful diagnosis and management of medical complications is essential throughout the course of status epilepticus.[10,119] Hyperthermia, tachycardia, systemic and pulmonary hypertension, pulmonary oedema, high-output failure, cardiac arrhythmias, metabolic acidosis, hypoxia, hyperkalaemia, hyperglycaemia, blood and cerebrospinal fluid leucocytosis are commonly noted.[10] These parameters should be closely monitored in an intensive-care unit. Control of hyperthermia is neuroprotective.[120,121] Continuous monitoring of vital signs, electrocardiogram, pulse oxymetry, and frequent checks of electrolytes, acid-base balance, and serum anticonvulsant concentrations are useful. Substantial changes should be treated appropriately. The presence of hypoxaemia and respiratory acidosis is an indication for intubation in most cases. Because cerebral blood flow has become pressure-dependent, cerebral metabolic needs remain high, and arterial blood pressure commonly falls late in

the course, systolic pressure should be maintained above 120 mm Hg if possible, and should not be allowed to fall below 90 mm Hg, even if this requires the use of vasopressors. In a third of adults in status epilepticus, arterial pH falls below 7;[122] the main contribution to this change is lactic acidosis from skeletal muscle,[19] which responds well to oxygen and control of convulsive activity. Our practice has been to treat with bicarbonate if the patient is hypotensive and arterial pH is <7 due to metabolic acidosis. Massive release of insulin[123] can rarely lead to hypoglycaemia, which critically restricts glucose delivery to the brain in infants[124] and should be corrected. More often, catecholamine release and other factors cause hyperglycaemia, which does not need correction in most cases,[125] and is not as harmful to the brain during status epilepticus as in ischaemia, because circulation can carry lactate out of the brain.[126,127] Mild acidosis might be an anticonvulsant[128] and neuroprotective.[129]

Treatment of seizures

Only three controlled, double-blind, clinical studies of the treatment of status epilepticus have been published. Leppik and colleagues[130] compared lorazepam with diazepam and found no difference. Treiman and colleagues[16] compared phenytoin, lorazepam, diazepam and phenytoin, and phenobarbital, and there was no significant differences except that lorazepam was superior to phenytoin. Alldredge and colleagues[116] found both intravenous diazepam and lorazepam efficacious in prehospital treatment. Because of the paucity of type 1 evidence, many treatment protocols are used. Among 107 physicians surveyed in the Santa Monica meeting, 16 different protocols were used.[10] A British survey yielded similar results.[112]

Therapeutic principles for anticonvulsants

The paucity of controlled studies condemns us to the old-fashioned use of pathophysiology and pharmacokinetics in many of our therapeutic decisions. Because one of the reasons for the poor results of current treatment[131,132] is that anticonvulsant use tends to be "too low, too slow", we advocate the rapid, sequential use of anticonvulsants with a short elimination half-life. In the Veterans Affairs Cooperative Study,[16] when the first drug failed, 7·3 % of patients responded to the second drug, and only 2% to the third drug, but many patients might not have received a full dose of the third drug, and this could have been a factor in their failure. When using anticonvulsants with a long elimination half-life (eg, diazepam, lorazepam, or phenobarbital), giving a full dose of the third drug without dangerously depressing blood pressure may not be possible. With drugs that have short half-lives, when treatment fails the drug is rapidly eliminated and a full dose of the next drug can be given without being limited by lingering cardiovascular depression.

One or two drugs?

Type-1 evidence shows that lorazepam alone, phenobarbital alone, or phenytoin combined with diazepam, are all effective, and therefore all three represent acceptable initial treatments of status epilepticus.[16] However, the VA Cooperative Study[16] compared lorazepam 0·1 mg/kg, with phenytoin and diazepam 0·15 mg/kg. Because lorazepam is several times more potent than diazepam, the comparison was between an adequate dose of lorazepam, and phenytoin plus an ineffective dose of diazepam, and the question of whether it is better to deliver two drugs simultaneously or sequentially remains unanswered. We initiate treatment with two drugs that have different mechanisms of action (figure 2), for two reasons. First, the time-dependent loss of potency of benzodiazepines documented experimentally[31,32] suggests that those drugs should not be used alone when status epilepticus is treated more than 30 min after seizure onset, because 30 min of seizures are sufficient to cause a substantial decrease in benzodiazepine potency.[32] Hydantoins lose potency more slowly than benzodiazepines,[31] and starting them early should improve therapeutic results. Second, status epilepticus is a heterogeneous disorder, and attacking two mechanisms of action might increase chances of success.

Comparison of benzodiazepines

Type I evidence shows that both diazepam and lorazepam are effective in the treatment of status epilepticus, whereas midazolam has never been used in a double-blind study.[130,133–135] All three drugs achieve effective brain concentrations quickly, although diazepam is slightly faster than the others in this respect. Efficacy and toxicity are similar, although anecdotal evidence slightly favours lorazepam. Pharmacokinetics favour midazolam, which has an elimination half-life of 90–150 min[136,137] compared with 12–24 h for lorazepam and 48 h for diazepam. The half-life of midazolam can increase in subpopulations and during status epilepticus, and its metabolism by the cytochrome P450 3A4 enzymes might make it more susceptible to drug interactions than lorazepam, which is glucuronated.

Comparison of hydantoins

Type I evidence shows that fosphenytoin causes few side effects (pain, phlebitis) at the injection site.[138] The purple glove syndrome is only reported anecdotally for phenytoin (type 4 evidence). This reduction of local toxicity comes at a much higher cost. There is no evidence that either efficacy or the incidence of cardiac arrhythmias differ between drugs, although fewer arrhythmias have been reported with fosphenytoin than phenytoin. Rapid achievement of therapeutic brain concentrations is desirable, whether the drugs differ in this respect is unclear. The 10–15 min needed for dephosphorylation of fosphenytoin is compensated for

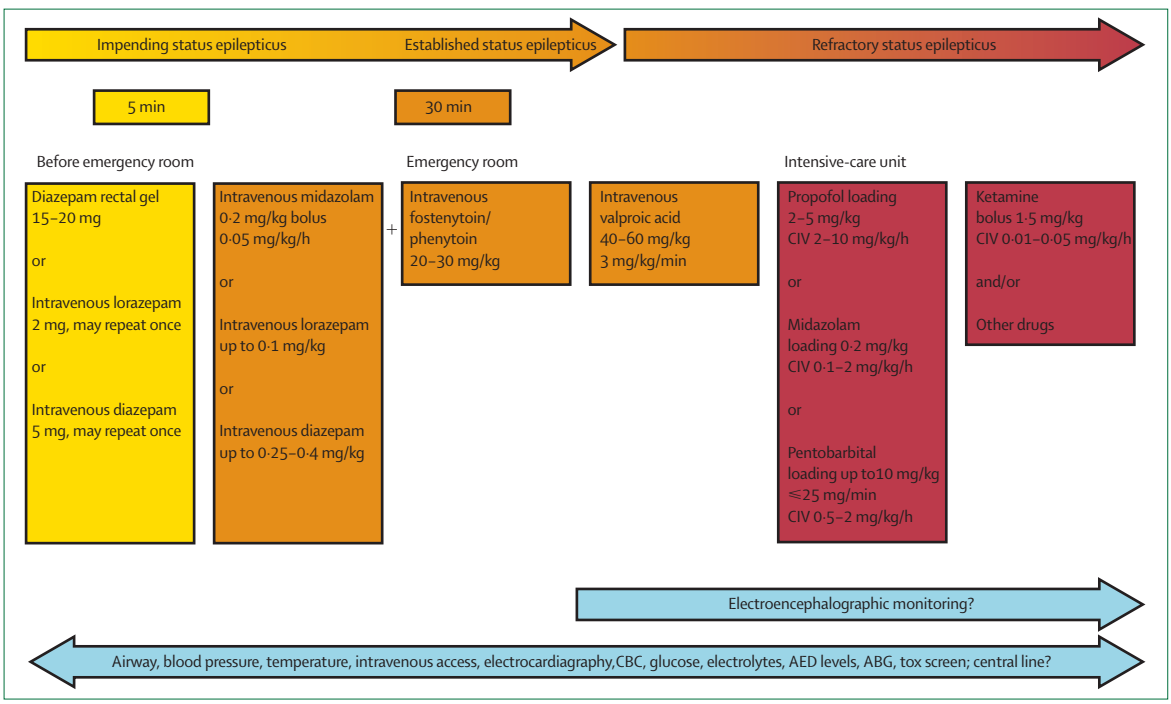

Figure 2: **Management of status epilepticus**
Impending or established status epilepticus: start with 20 mg/kg of fosphenytoin or phenytoin, and if status epilepticus persists, give an additional 10 mg/kg. Follow the flow chart UNLESS there is a history of drug intolerance (eg, allergy to phenytoin or benzodiazepine) then replace by intravenous (IV) valproic acid 40–60 mg/kg or IV phenobarbital 20 mg/kg; UNLESS treatment-induced hypotension slows rate of delivery; UNLESS history of progressive (PME) or juvenile (JME) myoclonus epilepsy (phenytoin/fosphenytoin harmful in PME, ineffective in JME), replace with IV valproic acid or IV phenobarbital; UNLESS tonic status epilepticus with Lennox-Gastaut syndrome (might be worsened by benzodiazepines), replace with IV valproic acid or IV phenobarbital; UNLESS, acute intermittent porphyria, avoid P450 inducers, replace by NG gabapentin (if possible) or by IV valproic acid; UNLESS, focal status epilepticus without impairment of consciousness, IV treatment not indicated, load anticonvulsants orally or rectally. Refractory status epilepticus: IV valproic acid-start with 40 mg/kg and, if status epilepticus persists, give an additional 20 mg/kg. Continous intravenous infusion (CIV) usually starts with the lower dose, which is titrated to achieve seizure suppression and is increased as tolerated if tachyphylaxis develops. Ketamine: rule out increased intracranial pressure before administration. Other drugs: felbamate, topiramate, levetiracetam, lidocaine, inhalation anaesthetics, etc. Dosage and pharmacokinetics of most anticonvulsants must be adjusted appropriately in patients with hepatic or renal failure, or with drug interactions. Some patients in refractory status epiletpcius will need systemic and pulmonary artery catheterisation, with fluid and vasopressors as indicated to maintain blood pressure. CBC=complete blood count; AED=antiepileptic drug; ABG=arterial blood gas.

by the faster infusion rate of fosphenytoin (150 mg/min *vs* 50 mg/min, which for a 70 kg patient receiving 20 mg/kg, would gain 19 min). However, there is one situation when fosphenytoin achieves therapeutic concentrations faster than phenytoin. In patients receiving chronic phenytoin treatment (even if concentrations are slightly subtherapeutic), fosphenytoin displaces phenytoin from its albumin binding sites, rapidly raising the free phenytoin concentration, which is the key to the drug's therapeutic action.

Refractory status epilepticus

This term is defined by the failure of adequate amounts of two intravenous drugs to stop seizures. Because generalised convulsive status epilepticus is a life-threatening disorder with a very poor outcome if it does not respond to the first two drugs,[16] a moderate amount of dose-dependent toxicity (eg, sleepiness, ataxia, and confusion) is a small price to pay for stopping the seizures. Therefore, if the initial treatment does not stop the seizures, the first measure should be to add enough anticonvulsant to reach a high therapeutic or low toxic serum anticonvulsant concentration (eg, phenytoin 30 μg/mL, or valproic acid of 150 μg/mL). There should be no hesitation to depress respiration and intubate, but severe arterial hypotension should be avoided because it will curtail cerebral blood flow. If this additional treatment fails, another therapeutic drug should be given, and possible causes should be carefully examined to make sure that the cause of status epilepticus has been treated.

Intravenous valproic acid has not been objectively assessed for treatment of status epilepticus, but anecdotal reports suggest that it is effective and relatively safe.[139–141] Valproic acid is contraindicated in patients under age 2 years, and by severe liver disease, mitochondrial diseases, pancreatitis, pregnancy, and caution should be used in young children. We currently give this drug before general anaesthesia, although other centres do not use it in refractory status epilepticus because of the risk of delaying general anaesthesia.[142] It can be infused in 15–30 min and if it

Search strategy and selection criteria

References for this review were identified by searches of PubMed with the term "status epilepticus" or "SSSE" in combination with "epidemiology", "GABA", "glutamate", "NMDA", "AMPA", "treatment", "intravenous AND valproate", "midazolam", and "refractory status epilepticus". The last search was done in October 2005. The following publication types were excluded: case report, non-controlled trials, retrospective studies, editorial and reviews. Clinical trials of paediatric patients are largely excluded. In addition, early landmark publications and recent textbooks of status epilepticus are cited.

fails, general anaesthesia should be given as soon as possible.

General anaesthesia

Once the patient has reached this stage, prognosis is poor regardless of treatment choice, and all options entail significant risks. Midazolam is an effective drug,[143–146] but we reserve it for patients who have not received adequate benzodiazepine treatment. There is no objective evidence comparing the risks of the propofol infusion syndrome[147] to the risks of the prolonged cardiovascular depression caused by barbiturates.[148–150] Propofol[151,152] has a short half-life, so that, if it fails, adequate amounts of another drug can be tried. Barbiturate anaesthesia with either pentobarbital or thiopental[119,149,153] (both have a relatively short half-life) has been used extensively and with considerable success. Ketamine, is an attractive "agent of last resort", has proved useful in refractory status epilepticus,[154] is neuroprotective,[155] and is effective in drug-resistant experimental status epilepticus.[57,156] However, because ketamine can raise intracranial pressure, the absence of intracranial masses should be confirmed (by CT scan, for example) before using it. We consider its NMDA antagonist properties as an asset, despite expressed concerns,[157] but limited experience restricts its use to refractory cases.

The stopping of seizures is the holy grail, but most people accept a burst suppression pattern. Anaesthesia is usually stopped once a day, and if seizures recur anaesthesia is resumed for another 24 h. Electroencephalography is useful in determining whether seizures have completely stopped, as well as in diagnosing subtle status epilepticus in patients who do not regain consciousness after clinical seizures stop.

Neuroprotection

Most anticonvulsants that are active against partial seizures have some neuroprotective and antiepileptogenic properties in animal models, but evidence from human beings is too scarce to recommend their use at present. Some of the more potent experimental drugs[43,158–161] might find a place in the future treatment of status epilepticus.

Conclusions

This review highlights the progress made in understanding the nature of status epilepticus in animal models and the paucity of reliable evidence in human beings. We propose a simplified nomenclature of status epilepticus and an aggressive approach to its treatment. For established status epilepticus, available treatments fall far short of what an optimal drug should achieve. New therapies and controlled trials of available drugs are urgently needed.

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Authors' contributions

Both authors contributed equally.

Conflicts of interest

CGW has received research grants from Johnson and Johnson Pharmaceutical Research Institute, UCB Pharma, and Schwartz, Inc. He has been on the Speaker's Bureau of Abbott, GlaxoSmithKline, Novartis, Ortho-McNeill, Pfizer, Shire, UCB Pharma. JWYC has no conflicts of interest.

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