Ulster Med J 2015;**84(2):**88-93

Review

Grand Rounds: An Update on Convulsive Status Epilepticus.

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Accepted: 24 March 2015
Provenance: invited review

ILLUSTRATIVE CASE - A COMMON SCENARIO

A 65 year old man, with no past history of epilepsy or seizures and of weight 80kg, is admitted with sepsis. After a 5 minute generalized tonic-clonic seizure (GTCS) he is given 2mg of intravenous lorazepam. After multiple brief GTCS he is given a further 2 mg of intravenous lorazepam. He becomes obtunded. After a further 10 minutes when he has developed subtle left facial twitching, 1 g of phenytoin is infused over 30 minutes. After a further 15 minutes, by which time his GCS is 8/15, colleagues in anaesthetics are contacted with a view to transfer to the intensive care unit.

INTRODUCTION

Status epilepticus (SE) is the term used to describe an abnormally prolonged state of self-perpetuating and evolving seizure activity, specifically defined by time, as a 5 minute seizure or an episode of briefer seizures with reduced recovery of awareness in between seizures[1].

SE can be convulsive or non-convulsive in type. Non-convulsive seizures represent states of various levels of altered awareness, associated with electroencephalographic (EEG) seizure activity, but without outwardly observable convulsive activity[2]. An important feature of convulsive seizures is their potential for evolution into non-convulsive seizures, where the patient can appear "post ictal" but is having electrical seizures, without obvious convulsive activity[3]. Other types of status epilepticus include simple partial status (with preserved awareness), complex partial status (with impaired consciousness) and myoclonic status (often associated with coma)[4].

Records from antiquity describe SE, but it has only been in the last century that there have been major advances in its understanding and treatment[5]. Many significant questions remain about the pathophysiology and management of this medical emergency which carries a substantial morbidity and mortality. This paper will present the current understanding of SE, identifying gaps in our knowledge. The evidence base for the pharmacological management of SE will be reviewed.

EPIDEMIOLOGY

With an incidence of 6 to 41 per 100,000[6-12] for convulsive SE, between 108 and 738 cases would be expected to occur in Northern Ireland each year. Incidence is bimodal, with peaks in infancy and in the elderly (>60). The overall case fatality rate is between 7.6 and 39%[13]. The mortality rate is higher in the elderly at 38% compared to 14% for younger adults[14].

Over half of SE patients present with de novo seizures[7] and approximately 10% will have recurrent episodes of SE[14]. Patients presenting with SE also have a higher likelihood of developing chronic epilepsy when compared to those who present with a first seizure, that does not fulfill the criteria for SE[15].

CAUSES AND PROGNOSIS

In 50% of cases of SE no cause is identified. The common causes of SE are presented in Figure 1[6-12]. Most episodes of SE are secondary to old structural lesions (e.g. a past stroke), with acute cerebral insults including acute stroke, anoxia, toxic and metabolic causes and alcohol and drug withdrawal, accounting for a significant proportion of the remaining cases. Patients with epilepsy can develop SE for various reasons including reduced serum drug levels from poor adherence with treatment regimens, or the effects of intercurrent

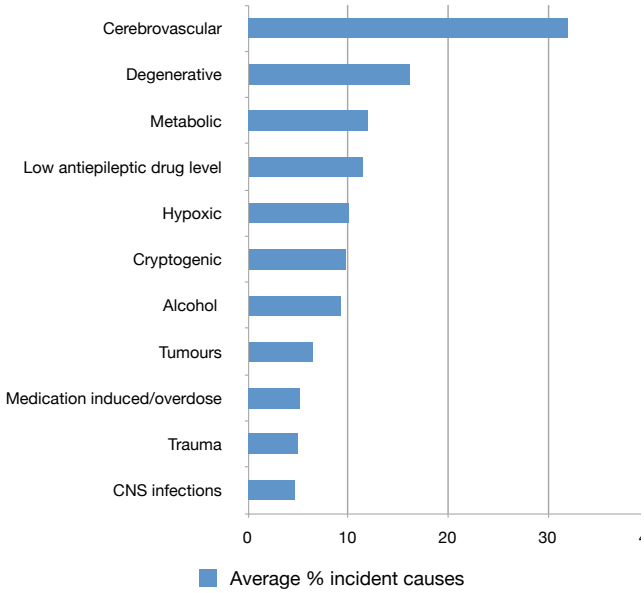

Fig 1. Identified aetiology of status epilepticus across major studies (6-12)

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illnesses and fever. Table 1 summarises the more uncommon causes of SE identified in a recent systematic review[16].

TABLE 1.

The uncommon causes of status epilepticus.16

Category	Examples
Autoimmune disorders	Paraneoplastic disorders, Hashimotos encephalitis, anti NMDA receptor encephalitis, anti VGKC encephalitis, antibody negative limbic encephalitis, thrombotic thrombocytopenia purpura, Rasmussen encephalitis.
Mitochondrial disease	Alpers disease, MELAS, Leigh syndrome, MERRF, NARP, MSCAE
Atypical infections	HSV, bartonella, neurosyphilis, Q fever, HIV, measles, polio, CJD
Genetic disorders	Chromosomal abnormalities (ring chromosome 20), inborn errors of metabolism (porphyria, etc), neuro-cutaneous syndromes, malformations of cortical development, Dravet syndrome, wrinkly skin syndrome.
Toxic	Antimicrobial (beta lactams), antipsychotics, contrast media, cocaine, CO, ecstacy, lead, petrol sniffing, chemotherapy, acute hypo-osmolality.
Medical conditions	Multiple sclerosis, posterior reversible encephalopathy syndrome, Behcets disease, neuroleptic malignant syndrome, neurosurgery, electroconvulsive shock therapy.

The outcome from SE is associated with the underlying aetiology. Anoxia is associated with a substantial mortality (72%). The lowest mortality is in patients with epilepsy who have provoked seizures, for example with low serum anti-epileptic drug levels (mortality rate 4 - 8.6%)[6] Age, duration of SE, whether there have been any prior episodes, depth of coma at presentation, and response to treatment have also been shown to be important[6, 14, 17, 18]. The main modifiable factor is the duration of SE, highlighting the importance of urgent treatment. Duration of seizure activity has been shown to be an important predictor for mortality[19], with seizures lasting less than 30 minutes having a mortality of 2.6%, compared with 19% for those lasting more than 30 minutes.

ACUTE PATHOPHYSIOLOGY - MECHANISMS OF STATUS EPILEPTICUS

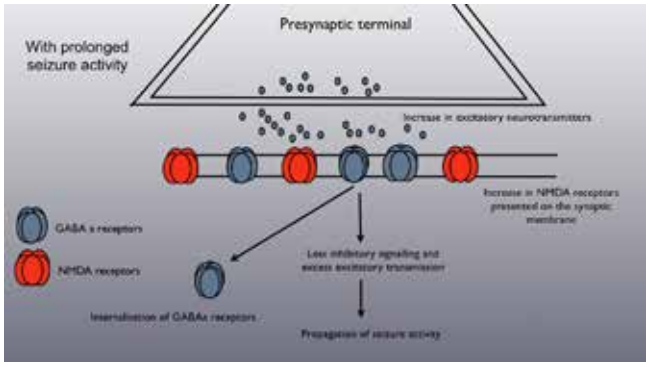

Fig 2. The pathophysiology of status epilepticus[21].

SE is an evolving state with changes in neuronal and synaptic chemistry and systemic physiology resulting in progressive pharmacological refractoriness. For the first 30 minutes physiological compensation occurs to meet the increased metabolic demands. Heart rate, blood pressure and serum glucose level are all elevated to minimize the risk of cerebral damage. After 30 minutes, decompensation occurs with hypotension, hypoxia, metabolic acidosis, cardiac arrhythmias and cerebral auto-regulatory failure ensuing, all of which can lead to neuronal damage. Later complications include rhabdomyolysis, renal failure, pulmonary edema, increased intracranial pressure, and electrolyte disturbance[20].

Within seconds of the development of SE alterations occur in protein phosphorylation at various synapses, ion channel function and neurotransmitter release. Within minutes, receptor expression changes in favour of excitation as a result of progressive reduction in GABA (γ-aminobutyric acid) receptors and an increase in AMPA (α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and NMDA (N-methyl-D-aspartic acid) receptors. (Figure 2). By one hour there is an increase in excitatory neuropeptides. The excess in excitotoxic transmission is a suggested mechanism for neuronal cell death[21].

CLINICAL EVALUATION OF STATUS EPILEPTICUS

In evaluating the patient in SE, the ABC (Airway, Breathing, Circulation) approach to the management of any medical emergency should be employed. After airway and cardio-respiratory stability have been attained, hypoglycaemia must be excluded in all cases. Pabrinex may also be required at this stage, if the patient is at high risk of Wernicke's encephalopathy.

TABLE 2:

Distinguishing seizure from psychogenic non epileptic attacks[22, 23, 24, 25]

Clinical feature	Suggestive of Epileptic Seizures (Status Epilepticus)	Suggestive of Psychogenic non epileptic attacks. (pseudostatus)
Onset	Sudden onset. May have focal seizure activity at onset.	Gradual onset potentially lasting minutes, can have a lead in of panic symptoms (which may not be recalled by the patient). At times can start with sudden onset.
Motor state	Tonic, then evolving into clonic synchronous movements.	Whole body stiffening, with some voluntary movements at times, can be flaccid largely during the ictus (ictal atonia), back arching, side to side head movements, undulating pelvic thrusting.
Evolution	A definite tonic phase, then clonic phase. As progresses the clonic movements become less pronounced, with perhaps nystagmus or subtle twitching as the only manifestation.	Varying, tonic/clonic movements. Not following specific sequence, with pauses during the ictus. Movements usually asynchronous. Subtle eye movements may occur.
Vocalisation	At onset, may have loud guttural cry as air is forced out past a tonic larynx.	May occur in the middle of a seizure, crying and shouting are possible.
Eyes	Eye closure is not typical. Eyes maybe deviated. Pupils tend to be unresponsive.	Eyes are commonly forcibly closed. (This is not always the case). Typically could be deviated away from the observer. Pupils are normal.
Tongue	Can have deep lateral tongue biting.	Typically superficial frontal tip of the tongue location.
Cyanosis	Present	Absent
Responsive?	None. No withdrawal from painful stimulus.	Variable withdrawal from painful stimulus. Limb movements may change with mild restraint.
Consistency	Usually stereotyped seizure episodes.	Variable nature to events.
Recovery	Delayed recovery after event, with amnesia.	Prompt recovery. Non-organic amnesia observed.
Nocturnal seizures	Can happen.	Not recognised. Events can occur from apparent sleep. The only way to be sure is to have EEG confirmed sleep pattern preceding the event.
Ictal incontinence	Not a distinguishing factor	Not a distinguishing factor
Injuries	Common	Common (fractures, head injuries, burns all reported)

Pseudostatus epilepticus (prolonged non-epileptic attacks) should be considered in all patients presenting with apparent SE. Differentiating between the two on clinical grounds alone can be difficult, even for experienced practitioners. Given the limited access to EEG, when the clinical diagnosis is not established beyond reasonable doubt, it is best to err on the side of caution and treat as SE. Clinical features that can help distinguish non-epileptic and epileptic seizures are

detailed in Table 2.[22, 23, 24, 25] The importance of making an accurate diagnosis is all too obvious, to prevent medicalising a psychological condition, to prevent iatrogenic morbidity from anticonvulsant medications, and to reduce morbidity and mortality associated with intubation and ICU stay[26, 27].

Laboratory testing to include a full blood count, biochemistry, liver function tests, electrolytes, glucose, relevant serum antiepileptic drugs levels (to check compliance) and a toxicology screen are recommended as a minimum. Investigations should not delay treatment. In appropriate circumstances, where an infectious cause is suspected, lumbar puncture is necessary. SE can lead to a slightly raised cerebrospinal fluid white cell count[28]. All first presentations of SE should have emergent neuroimaging once the patient is stabilized, utilizing whatever modality is available locally. EEG is invaluable not only for confirming the diagnosis and planning treatment but in the patient who remains obtunded after a seizure, to distinguish a prolonged post ictal state from non-convulsive SE and other causes of reduced consciousness.

STOPPING STATUS EPILEPTICUS

Delays occur at various points in the management of SE, including time to presentation and initiation of first line treatment[29]. In order to minimise these and to reduce variability in practice, SE should be managed with a protocol which provides details on appropriate doses of medications to be given in a timely manner[30]. A simple protocol for the management of SE is given in Figure 3. More detailed guidelines have been published by various groups such as NICE[31], EFNS[32], and the American Society of Neurocritical Care[33] as well as groups of international experts[34].

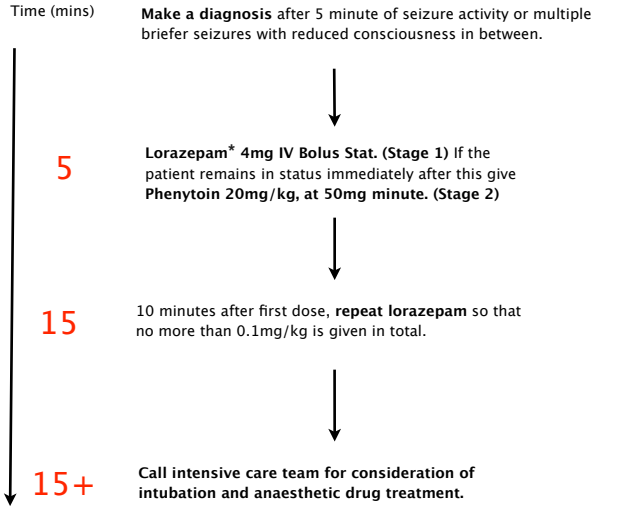

Fig 3. A suggested protocol for management of first and second stage of SE.

Several clinical trials guide the early management of SE[35, 36, 37, 38]. They show that early use of benzodiazepines is important for controlling SE. They work by enhancing the inhibitory GABAergic system, and at higher concentrations limit sustained repetitive neuronal firing[39]. Lorazepam, diazepam and midazolam are the most frequently used.

Diazepam achieves early high brain concentrations and therefore has a very fast onset of action. Unfortunately, it quickly redistributes to fatty tissues, limiting clinical effectiveness to 20-30 minutes and often necessitating repeated dosing which has the potential to lead to accumulation due to its long elimination half-life. While diazepam and lorazepam are equivalent at achieving seizure control[35], lorazepam is the drug of choice in early status due to its favorable pharmacokinetic profile, with a half-life of 12-24 hours. A recent prehospital study[38] compared intramuscular (IM) midazolam and intravenous (IV) lorazepam. It demonstrated that patients received treatment quicker utilizing the IM approach, and that this lead to greater cessation of SE on arrival to the emergency department. Intravenous benzodiazepines have significant side effects including respiratory depression (3-10%), hypotension (<2%), and impaired consciousness (20-60%)[39].

Second line therapies include phenytoin/fos-phenytoin, phenobarbital, valproate, levetiracetam and lacosamide. The best drug to use has not been conclusively demonstrated by a randomized controlled clinical trial.[40] Phenytoin is the most commonly used second line drug in the United Kingdom. It should be given at a dose of 20mg/kg infused at a rate of 50mg/kg. Slower infusion rates are used if cardiac arrhythmia or hypotension occurs. A loading dose can also be given if the patient is taking phenytoin. If the patient presents in SE it is likely that they have a subtherapeutic serum level of phenytoin. Maximum cerebral concentrations are achieved towards the end of the infusion. Side effects include hypotension in 28-50%, bradyarrhythmias and ectopics in <2%. It is important to monitor drug levels after loading with phenytoin, to guide further dosing. Typically maintenance dose will be started the following day at 4-5mg/kg once daily [39, 40].

Other agents used in SE (off license indication) have certain advantages over phenytoin such as faster administration rates, fewer interactions, less side effects and better pharmacokinetics[40]. The second line agents are listed in Table 3 along with their doses, mean efficacy from the results of meta-analyses, side effects and mechanisms of action.

It is presently unclear if some patients should be given one second line drug, or should be rapidly escalated to an initial polytherapy approach, given the fact that treatment of SE becomes more difficult the longer it has occurred[41]. A multi-center blinded comparative randomized control trial using an adaptive design is in the process of being set up which seeks to guide the optimal second line drug choice[42].

For those with epilepsy making sure that they get their regular AEDs in their usual doses at all times, given by whatever means possible (given by nasogastric tube or intravenously)

is also crucial. Maintaining therapeutic doses of any AEDs that have been commenced should also not be overlooked. Both are common reasons for failure to maintain control in those presenting with SE, where seizures have initially been successfully terminated. Treating the underlying cause whenever possible is also important if the best outcomes are to be achieved.

TABLE 3.

Second line management of status epilepticus[40].

Drug	Mean Efficacy (%)	Dose	ADRs	Mode of action
Phenobarbitone	73.6%	20mg/kg IV up to 60mg/min	respiratory depression, hypotension, severe sedation, tolerance and the potential for drug interactions	GABA potentiation
Phenytoin	50.2%	20mg/kg at 50mg/minute (25mg/minute if cardiovascular instability or elderly)	cardio-respiratory risks (cardiac arrhythmia, hypotension, reduced cardiac output, the 'purple-glove' syndrome	Sodium channel modulation
Valproate	75.7%	30-60mg/kg IV up to 3mg/kg/min. Probably safe at 6 mg/kg/min.	Hyperammonaemia. There is a risk of hepatic and pancreatic toxicity, and valproate encephalopathy. bleeding tendency due to its effects on platelets and platelet function	Multiple. Sodium channel modulation, GABA potentiation, glutamate/NMDA inhibition.
Levetiracetam	68.5%	1000 and 3000 mg in young adults, or 20 mg/kg (Infuse at 500mg/minute)	Free of significant adverse-effect	Synaptic vesicle protein 2A
Lacosamide	not available	200-400mg bolus over 5 minutes	Bradycardia, PR interval prolongation	Sodium channel modulation

STATUS EPILEPTICUS IN THE INTENSIVE CARE UNIT

Refractory SE is the state when first and second line therapies have failed, usually 30 minutes into the SE episode. In hospital based series it occurs in 31 - 44% of cases, and has a mortality rate between 16 - 23%[43]. It has been reviewed in several excellent recent articles[44, 45].

Anaesthetic agents used are propofol, midazolam, thiopental or phenobarbital.[46, 47, 48, 49]. These are outlined in Table 4 **in** detail. Often an antiepileptic drug is also given in a loading dose and uptitrated so that once weaning from anaesthetic agents is started there is a background effective antiepileptic agent. The choice of anaesthetic agents is based on small open trials, with no adequately powered prospective randomised controlled trial ever having been completed in this area. Decisions such as treatment duration and target of treatment (either clinical seizure suppression or EEG guided, such as suppression-burst suppression) are thus on an individual patient basis. Usually the patient will be anesthetized for 12-24 hours and then the agents weaned slowly over a period of hours. If after the first wean there are further clinical or electrographic seizures they will require further anesthesia. This situation is then termed super refractory SE[50]

With regards the anaesthetic agents used in SE a number of safety points are worth highlighting. The main clinical concern with propofol is the risk of propofol infusion syndrome (PRIS)[51]. It is characterized by metabolic acidosis, cardiac disturbances, hypertriglyceridaemia, and rhabdomyolysis. The main risk factors appear to be dosage (>83/mcg/kg/minute) and duration of therapy (>48hrs), and simultaneous vasopressor support. It carries a high mortality rate, at least in the early series, and calls for vigilance. The major limiting factors in barbiturate therapy are the risk of haemodynamic instability, immunosuppression, risk of gastrointestinal motility disturbance and nosocomial infection, particularly intestinal infection.

Oher general medical problems can befall the patient in ICU with SE. The main concerns include airway protection, aspiration related to the low GCS, cerebral hypoperfusion, and cardiac dysrhythmia. Hypertension can complicate the first 60 minutes of SE and it is worth bearing in mind that all parenteral anti-epileptic drugs will lower blood pressure, as will sedatives used for intubation. Positive pressure ventilation reduces preload and can also result in the patient ending up becoming hypotensive.

TABLE 4.

Third line agents for status epilepticus.[46, 47, 48]

Drug	Loading dose	Maintenance dose	ADRs	Mode of action	T1/2 after prolonged administration
Midazolam (midazolam paper in neurology)	0.1-0.3mg/kg at 4mg/minute bolus	0.05-0.4mg/kg/hr	Hypotension, tachyphylaxis, increasing does needed with time.	GABAa agonist	6-50h
Propofol	2mg/kg bolus	5-10mg/kg/hr	Propofol infusion syndrome (PRIS) Hypotension.	GABAa agonist	1-2h
Pentobarbital	10-20mg/kg bolus at 25mg/min	0.5-1mg/kg/hr increasing to 1-3mg/kg/hr if required	Accumulation, hypotension, and immunosuppression.	GABAa agonist	15-22h
Thiopenone	100-250mg bolus over 20 secs. 5-mg boluses every 2-3 minutes until seizure control.	Infusion of 2-5mg/kg/hr		GABAa agonist	14-36h

Various parenteral preparations of anticonvulsants are available for use in intensive care units, namely phenytoin, fosphenytoin, valproate, levetiracetem, and lacosamide. Care should be taken in the critically ill patient to ensure that phenytoin and valproate levels are interpreted correctly as often the albumin level is low. Simple conversion tools are available online to help with administration of these drugs (http://www.mdcalc.com/phenytoin-dilantin-correction-for-albumin-or-renal-failure/).

Multiple anti-epileptic drugs will often be tried if patients enter a super refractory state. The duration of anesthesia, using combinations of anaesthetic agents is often prolonged and at times periods of 1 week of anesthesia are used prior to attempting weaning. At this stage attention needs to be directed towards rarer causes of SE (Table 1)[16]. One potentially very treatable group of disorders is the immune encephalopathies. If there is any concern that the cause of SE is one of these disorders a trial of immunotherapy is warranted whilst waiting for corroborative evidence such as the results of autoantibody testing or patterns of abnormalities seen on detailed neuroimaging[50].

Other novel treatments include electroconvulsive therapy (ECT), surgical lesionectomy for example in patients with

complex partial status presumed to originate from an acute structural abnormality e.g. subdural haematoma, hypothermia, and other drugs such as ketamine, lidocaine, and isoflurane. The evidence base for these treatments is currently very limited[51].

The outcome from refractory and super refractory SE is poor, with death in 35% and recovery to baseline in 35%[52]. For those surviving, neurological disability can vary considerably. In one retrospective analysis it was shown that a prolonged duration of SE did not preclude a meaningful functional and cognitive recovery[53]. It is not clear if progressive cognitive decline that can follow SE is due predominantly mainly to the underlying epileptic condition or the underlying aetiology of SE[54].

CONCLUSION FROM ILLUSTRATIVE CASE

The management of the patient in the illustrative case would have been improved by the use of an agreed protocol. After having been diagnosed as having early SE he should have been given 4 mg of lorazepam intravenously, Weighing 80 kg, he should then have been given an infusion of 1600mg of phenytoin, to be given over 32 minutes. If ten minutes after receiving the first dose of intravenous lorazepam he was still showing any signs of seizure activity he should have had a further 4mg of lorazepam, given intravenously. Having completed the infusion of phenytoin any further seizure activity should have prompted immediate referral to ICU.

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