Medical management of status epilepticus: Emergency room to intensive care unit

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ABSTRACT

In convulsive status epilepticus (SE), achieving seizure control within the first 1–2 hours after onset is a significant determinant of outcome. Treatment is also more likely to work and be cost effective the earlier it is given. Initial first aid measures should be accompanied by establishing intravenous access if possible and administering thiamine and glucose if required. Calling for help will support efficient management, and also the potential for video-recording the events. This can be done as a best interests investigation to inform later management, provided adequate steps to protect data are taken. There is high quality evidence supporting the use of benzodiazepines for initial treatment. Midazolam (buccal, intranasal or intramuscular) has the most evidence where there is no intravenous access, with the practical advantages of administration outweighing the slightly slower onset of action. Either lorazepam or diazepam are suitable IV agents. Speed of administration and adequate initial dosing are probably more important than choice of drug. Although only phenytoin (and its prodrug fosphenytoin) and phenobarbital are licensed for established SE, a now considerable body of evidence and international consensus supports the utility of both levetiracetam and valproate as options in established status. Both also have the advantage of being well tolerated as maintenance treatment, and possibly a lower risk of serious adverse events. Two adequately powered randomized open studies in children have recently reported, supporting the use of levetiracetam as an alternative to phenytoin. The results of a large double blind study also including valproate are also imminent, and together likely to change practice in benzodiazepine-resistant SE.

1. Introduction

That status epilepticus (SE) requires emergency treatment has been embedded in practice for decades, and the 2015 ILAE definition [1] emphasises both the need for rapid initiation of treatment and the risk of permanent damage if seizures are not promptly controlled. There are however many types of SE, and it is recognized that outcome is also significantly influenced by seizure type and etiology, as well as the patient’s age and comorbidities. In this review we will focus on the management of early and established convulsive SE for which there is most evidence to guide practice, though management of other types of SE will also be briefly discussed. The management of refractory SE, where seizures have not been controlled by first or second line treatment, is covered in a subsequent article in this supplement.

2. Does speed really matter?

It is widely acknowledged that age and etiology are the biggest determinants of outcome in SE. However, historical uncertainty about the influence of duration as an independent predictor has now been addressed by several large case series. It is clear that achieving seizure control within the first 1–2 hours of onset is a significant determinant of outcome [2] as summarized in Table 1. Systemic compromise [3], and brain damage, thought to be caused by a combination of direct damage from seizure-related activity and the secondary effects of the associated metabolic cascade, both contribute to morbidity and mortality. Furthermore, the earlier treatment of SE is instituted, the more likely it is to be successful. In one recent prospective study in children with refractory convulsive SE, benzodiazepine administration beyond the first 10 minutes was independently associated with a higher frequency of death, use of continuous infusions, longer convulsion duration, and hypotension [4]. Unsurprisingly prompt intervention, including pre-

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hospital, is also likely to reduce healthcare costs [5]. Although no individual study can definitively prove cause and effect, a clear message is coming through.

3. General management and diagnostic issues

3.1. First aid and general medical considerations

Key management considerations are summarized in Fig. 1. Given the importance of speed it is important to check the time at seizure onset and estimate duration if receiving handover from bystanders or emergency medical services. Guidelines then advocate an ‘ABC’ approach, necessitating that the airway be secured in the first instance. During convulsions, it is muscle (including laryngeal) spasm that restricts air entry, so this is best achieved by stopping the seizures. Any attempt to insert an oral airway may cause injury in an actively seizing patient. Airway manoeuvres such as head tilt and jaw thrust can be helpful post-ictally, though many patients will require a nasopharyngeal airway with oxygen therapy to maintain adequate saturations.

Vital signs should be monitored and cardiac monitoring instituted. Cardiac complications are not infrequent [3], and some of the drugs used, particularly phenytoin can also have cardiac side effects. Intravenous access should be established early, alongside checking blood glucose, with further blood samples sent (see Fig. 1) to investigate the potential cause and consequences of SE. Investigations are also covered in the preceding article in this supplement. If there are concerns regarding alcohol excess or poor nutrition, 250 mg IV thiamine should be given followed by 50 mL of 50% glucose IV if the patient is hypoglycaemic.

The above management should all be instituted as rapidly as possible, ideally within the first few minutes of arrival at hospital or pre-hospital where possible. For this reason, amongst others, it is also important to seek help early so that these steps can be carried out in parallel by different members of the multi-disciplinary team.

3.2. Are you sure it’s epileptic status epilepticus?

Whilst not the topic of this article, the importance of considering the
possibility that persistent or recurrent convulsions might be dissociative (psychogenic non-epileptic seizures) rather than epileptic status epilepticus must not be overlooked. Frequent admissions should be considered a red flag, and a reported diagnosis of epilepsy is not uncommon – either due to prior misdiagnosis, or a dual diagnosis. There is no fool-proof clinical marker, but key features which can help distinguish from epileptic seizures are summarized in Table 2. Emergency physicians may be insufficiently experienced to confidently distinguish the two. Perhaps inevitably, the team may initially manage as for epileptic status epilepticus. However, if there is any diagnostic doubt at all, early video recording of the events in parallel with treatment can be extremely helpful to the specialist later called in to advise on longer term management. As with any form of imaging, whilst there is often concern about the sensitive nature of a video, and inability to take consent in this context, video should be considered a critical diagnostic test, and is justifiable as a best interests intervention to inform management [59]. EEG is rarely available in the emergency setting, but is an agnostic test, and is justifiable as a best interests intervention to inform management [59].

4. Initial pharmacological treatment of convulsive status epilepticus

First line medical treatments for status epilepticus may be instituted in the community, by emergency medical services or in the hospital. Whilst the focus of this review is on hospital treatment, much of the evidence around initial treatment of convulsive SE comes from prehospital studies. The most appropriate drug route will vary depending on the setting and consequent practicalities and safety considerations. There have been dozens of adult and paediatric studies published on the efficacy and safety of benzodiazepines via various routes and several recent systematic reviews/meta-analyses. Methodological heterogeneity, including in study populations, trial design, primary outcome definitions and approaches to analysis contribute to some differences in conclusions between individual studies. Nevertheless, there is broad consensus to guide first line treatment, as summarized in Fig. 2. The majority of trials have focused on the use of benzodiazepines, specifically lorazepam, diazepam, midazolam and clonazepam. The main questions addressed relate to which particular benzodiazepine is preferable in terms of speed of onset and duration of action, safety, and impact of route of administration.

4.1. Intravenous benzodiazepines

For all agents, there is consensus that if intravenous (IV) access is already in place, IV administration of benzodiazepines leads to shorter time to seizure termination [17]. IV lorazepam has been found to be at least as effective as IV diazepam in all meta-analyses performed [18-20] whether in adult or paediatric populations. A potential advantage of lorazepam is its longer duration of action compared with diazepam. Some earlier studies report fewer patients needing repeat doses or additional AEDs to terminate SE, but there is not strong evidence to support superiority of lorazepam. IV midazolam has also been shown to be as effective as both IV lorazepam and IV diazepam, although in practice this has rarely been used as initial treatment [18]. IV clonazepam, which has a long half-life and rapid onset of action, is also widely used across parts of Europe, although the evidence was until recently based only on uncontrolled case series [21]. A randomized prehospital trial in in 2016 [22] evaluated the use of IV clonazepam plus either levetiracetam or placebo for the initial treatment of SE. Seizures were stopped within 15 minutes of Clonazepam plus placebo in 84% of patients, so it is clearly effective but has not been compared with other IV benzodiazepines in a clinical trial setting.

4.2. Non-intravenous benzodiazepines

In or out of hospital, unless IV access is already in situ, non-IV routes may be preferable as faster administration can offset the slightly slower onset of action, meaning shorter time to seizure cessation overall. This was demonstrated most clearly in the RAMPART trial, which though set up as a non-inferiority (10% difference) study demonstrated that intramuscular (IM) midazolam is superior to IV lorazepam in the prehospital setting [23]. 893 adults were randomized to either drug. 73% of those receiving IM midazolam (10 mg in adults, 5 mg in children) were seizure-free when arriving in the emergency department vs 63% receiving IV lorazepam (4 mg in adults, 2 mg in children), with the main advantage being shorter time to treatment initiation. Intranasal midazolam and buccal midazolam are also effective non-intravenous options for initial management of SE [24], however the existing comparative evidence for these is less strong than for IM midazolam [18]. Arya et al evaluated the efficacy of various non-venous medications for acute convulsive seizures, incorporating data from 16 trials [25]. They concluded that IM and intranasal midazolam exhibit the best efficacy data for treatment of SE in the absence of IV access. Rectal diazepam is also well-established and relatively cheap, effective option. However, non-IV forms of midazolam are not only associated with shorter time to seizure termination but are also more practical and often more socially acceptable to patients and care-givers than rectal medications [24,26].

There are a number of studies looking at non-IV lorazepam, including intranasal, sublingual or rectal administration [25]. Some studies suggest similar efficacy, but with less consistent data and smaller numbers thus far, such that none are yet recommended as first line options [17].

Overall, the evidence supports use of a non-IV benzodiazepine, preferably Midazolam where IV access is not already present, with choice of agent overall being less important than speed of administration, particularly once IV access is established.

4.3. Non-benzodiazepines as initial therapy for SE

A few studies have looked at alternatives to benzodiazepines as initial treatment in SE. Drugs evaluated include phenobarbital, levetiracetam, sodium valproate and phenytoin. One of the earliest, large
randomized control trials in SE [27] demonstrated that IV lorazepam 0.1 mg/kg has similar efficacy to both IV phenobarbital 18 mg/kg and to combined IV diazepam 0.15 mg/kg with phenytoin 18 mg/kg. IV lorazepam was significantly more effective than phenytoin alone. Phenobarbital may therefore be an effective option for initial treatment, however in practice this is rarely used due to concerns about long term side effects and potential respiratory depression. Evidence from this trial suggests that phenytoin alone should not be recommended as a first line treatment.

There are no trials comparing sodium valproate alone with a benzodiazepine for initial treatment of SE. Three trials have been undertaken comparing sodium valproate with phenytoin, either alone [28,29], or in combination with diazepam [30] as first line treatment. All are small and underpowered. One [27] suggested valproate was more efficacious than phenytoin, and one suggested phenytoin had more adverse events [29]. Levetiracetam has also been evaluated as an initial treatment of SE. In an open pilot study IV lorazepam (0.1 mg/kg) controlled seizures in 75.6% of patients, compared to 76.3% given IV levetiracetam 20 mg/kg as initial treatment of convulsive status [31]. Seizure freedom at 24 hours was also comparable between the two groups. Lorazepam was associated with significantly higher need for intubation and ventilation. Rates of hypotension were also higher with lorazepam administration, though not significantly so. A more recent double-blinded randomized trial analyzed efficacy of levetiracetam with clonazepam vs clonazepam with placebo [22]. In the modified intention to treat analysis, seizures were terminated by 15 minutes in 87% of 68 patients treated with clonazepam and placebo compared with 74% of the 68 pre-hospital patients receiving levetiracetam and clonazepam. There was no significant difference between the two groups.

Thus, as we will go onto discuss, although sodium valproate and levetiracetam may be safe and effective, there is not enough evidence to recommend them as first line treatments of SE, unless and until such time as any clear advantages compared to benzodiazepines are demonstrated which is not yet the case. That both require IV access is also a significant disadvantage as first line treatment.

5. Second line antiepiletics for established SE

Although there is consensus and good evidence to support benzodiazepines as the drug of choice for initial treatment of SE, until recently there was much less evidence to help choose which AED should be used in established SE, when benzodiazepines have failed.

Choice of AED has been largely dictated by availability of IV formulations given the clinical context. Historically only phenytoin or phenobarbitone were used and remain (including fosphenytoin) the only currently licensed medications in established SE. Phenytoin in combination with a benzodiazepine, and phenobarbinate are both effective as evident by the Trieman study cited in 4.3 [27]. However, there is accumulating data suggesting clinical equipoise between phenytoin and newer AEDs such as sodium valproate or levetiracetam. Each has specific potential advantages and disadvantages depending on the clinical context as summarized in Fig. 3, with a considerable body of evidence supporting their use in practice. However, prior to 2019 much of the published data was retrospective, and any clinical trials in established SE had substantial methodological limitations, making it difficult to draw firm conclusions. The best comparative data was from meta-analysis [32]. This estimated the efficacy of levetiracetam to be 68.5% (95% CI: 56.2%–78.7%), phenobarbital 73.6% (95% CI: 58.3%–84.8%), phenytoin 50.2% (95% CI: 34.2%–66.1%) and valproate 75.7% (95% CI: 63.7%–84.8%). However, the quality of evidence is such that this can’t be considered definitive. Most studies had been underpowered; inclusion criteria were variable (many including a mix of convulsive, non-convulsive and focal SE); definitions of treatment efficacy also varied; some included a high proportion with acute symptomatic epilepsy and consequent better outcomes; and most of the existing trials had been open label.
5.1. Phenytoin and fosphenytoin

Phenytoin is one of the oldest drugs used in established SE. As summarized in section 6, current efficacy data suggest a potentially lower efficacy than alternatives. Non-linear kinetics can result in subtherapeutic drug levels, despite recommended dosing at 18-20 mg/kg. To what extent this might impact on reported efficacy is uncertain, with levels often not evaluated in trials, but in practice this is still a relevant consideration. Commonly occurring side effects include thrombophlebitis, cardiac arrhythmias (occasionally fatal) and hypotension, particularly in more elderly patients [34]. Of particular note, from reports to the UK National Patient Safety Agency over 5 years [60], phenytion was the only drug in which loading dose errors were associated with fatalities. It also has the disadvantage of exacerbating seizures in some patients with idiopathic generalised epilepsies such as juvenile myoclonic epilepsy.

Its prodrug fosphenytoin has a number of comparative advantages [35], including fewer infusion site reactions, and availability of an intramuscular formulation allowing for potentially quicker and easier administration. It is considerably more expensive than phenytoin, though levels often not evaluated in trials, but in practice this is still a relevant consideration. Commonly occurring side effects include thrombophlebitis, cardiac arrhythmias (occasionally fatal) and hypotension, particularly in more elderly patients [34]. Of particular note, from reports to the UK National Patient Safety Agency over 5 years [60], phenytion was the only drug in which loading dose errors were associated with fatalities. It also has the disadvantage of exacerbating seizures in some patients with idiopathic generalised epilepsies such as juvenile myoclonic epilepsy.

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5.2. Sodium valproate

Sodium valproate is also a well-established first generation anti-epileptic drug, though it was not available as an IV formulation until 1993. Doses ranging between 25–40 mg/kg have been shown to be both safe and effective in SE [38]. Overall valproate is well tolerated with a low frequency of adverse events (<10%). In some patients it can cause dizziness, mild hypotension and mild thrombocytopenia. In light of the latter, it may be best avoided in acute stroke. It should also be avoided in patients with known liver disease and/or metabolic encephalopathy. Sodium valproate can be hepatotoxic with the potential to cause an encephalopathy, either with or without raised ammonia. It is also best avoided in patients aged less than 2 years old, particularly if as part of polytherapy, due to increased potential hepatic dysfunction and as yet undiagnosed metabolic problems [39].

Several open label trials have been published comparing sodium valproate with phenytoin for treatment of benzodiazepine-resistant SE [28,29,40]. Although meta-analysis demonstrated only a non-significant trend towards valproate being more efficacious [32], but with fewer adverse events, especially less hypotension, compared to phenytoin. For patients who are already taking oral sodium valproate for epilepsy, given that poor adherence is a common provoker of SE, it could be considered the drug of choice. Similarly, it may be preferable in patients with contraindications to phenytoin such as brady-arrhythmias or in those with genetic/idiopathic generalised epilepsy where sodium channel blockers can be aggravating. As such, it is already incorporated in some International SE guidelines [17] as an effective alternative to phenytoin.

5.3. Levetiracetam

Levetiracetam is a 2nd generation well-tolerated anti-epileptic drug which has been available as an IV formulation since 2006. Again, meta-analysis [32] suggests at least similar efficacy to valproate and phenytoin, typically with reported loading doses of at least 20–30 mg/kg, totalling between 1–3 g. A subsequent small open label study adds to this evidence, with seizure cessation achieved in 78.6% of 30 patients [41]. Adverse events occur in <10%. They tend to be mild and...
transient, but can include drowsiness, thrombocytopenia, agitation and post-ictal psychosis [42]. Levetiracetam is possibly thus best avoided in patients with known brain injury or mood disorders as it may exacerbate behavioural disturbance. The drug is renally excreted, and so dose adjustments are also recommended in renally impaired patients. Levetiracetam has been shown to be safe when given at much higher doses (40–60 mg/kg), with the potential to be more effective than existing studies have demonstrated. Based on current evidence, international guidelines recommend levetiracetam as an option in established SE, with doses of 60 mg/kg up to a ceiling of 4500 mg [17], despite that, as with valproate, it is not yet licensed for this indication [43,44,61].

5.4. Recent randomised controlled trials

Two phase IV, well powered open randomized controlled trials reported during 2019 [44,45], with results from the pivotal USA double blinded ESETT in adults and children [46,47] expected imminently. All enrolled individuals with ongoing convulsive SE despite minimum adequate benzodiazepines, and relied on a clinical decision that convulsive SE had ended without other anticonvulsant medication as the primary outcome. Other key methodological differences and the primary outcome results where available are summarised in Table 3. Thus far no significant differences in efficacy have been found. The incidence of key safety endpoints such as life threatening hypotension or arrhythmia was very low, with expected rates of endotracheal intubation, again with no significant differences between the agents. There are methodological pros and cons with each of the studies, too numerous to detail here. However, taking into account the broader safety profiles of each of the agents given in the acute situation together with the practicalities of administration suggests levetiracetam at least may be preferable to phenytoin in most cases, pending the release from ESETT. Both levetiracetam and valproate can for example be given in less than 5–10 minutes even in a large adult, have fewer drug interactions in a patient group who often have comorbidities or complications needing other treatments, and are commonly used maintenance treatments thereafter.

5.5. Phenobarbitone

Phenobarbitone is also an effective and established drug for treatment of both initial and established SE, with efficacy and safety demonstrated in older [27] and more recent studies, [44]. It was first used as an AED in 1912, and has subsequently been developed in formulations for rectal, IV and subcutaneous administration. It is cheap with doses up to 9 mg/kg are typically required to achieve therapeutic concentrations during 2019 [44,45], with results from the pivotal USA double blinded ESETT in adults and children [46,47] expected imminently. All enrolled individuals with ongoing convulsive SE despite minimum adequate benzodiazepines, and relied on a clinical decision that convulsive SE had ended without other anticonvulsant medication as the primary outcome. Other key methodological differences and the primary outcome results where available are summarised in Table 3. Thus far no significant differences in efficacy have been found. The incidence of key safety endpoints such as life threatening hypotension or arrhythmia was very low, with expected rates of endotracheal intubation, again with no significant differences between the agents. There are methodological pros and cons with each of the studies, too numerous to detail here. However, taking into account the broader safety profiles of each of the agents given in the acute situation together with the practicalities of administration suggests levetiracetam at least may be preferable to phenytoin in most cases, pending the release from ESETT. Both levetiracetam and valproate can for example be given in less than 5–10 minutes even in a large adult, have fewer drug interactions in a patient group who often have comorbidities or complications needing other treatments, and are commonly used maintenance treatments thereafter.

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Table 3

<table>
<thead>
<tr>
<th>Trial [ref]</th>
<th>Treatment arms (dose mg/kg, infusion minutes)</th>
<th>Age (n)</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>EcLiPSE [44]</td>
<td>PHT (20,20), LEV (40,5)</td>
<td>6 months &lt; 18 years (286)</td>
<td>Clinical cessation seizures 5 minutes after infusion completed</td>
</tr>
<tr>
<td>ConSEPT [45]</td>
<td>PHT (20,20), LEV (40,5)</td>
<td>3 months – 16 years (233)</td>
<td>Absence of clinically evident seizures and improving consciousness 1 hour after infusion</td>
</tr>
<tr>
<td>ESETT fosPHT (20,10), LEV (60,10)</td>
<td>1 – 94 years (400)</td>
<td>Imminent</td>
<td></td>
</tr>
</tbody>
</table>

PHT = phenytoin; LEV = levetiracetam; VPA = valproate. N = total number recruits, equally randomised between treatment arms; *none significant.
is likely to be many years if ever before there is sufficient evidence to consider them earlier in the treatment pathway.

6. Other types of SE

A comprehensive review of treatment for other types of SE is beyond the scope of this article. Absence status, and myoclonic status in the context of an idiopathic generalized epilepsy should be treated, though at least for Absence SE there is less urgency, and ideally with confirmation using EEG. As for convulsive SE, benzodiazepines are first line, followed by either valproate or levetiracetam. In older patients, absence status may present de novo, often precipitated by benzodiazepine withdrawal and will usefully respond to a small dose (e.g. 1 mg of Lorazepam), repeated if needed. Initial steps for Focal SE follow the same algorithm as for SE, but usually with sequential trials of alternative intravenous AEDs sometimes over days or longer before response to sedation. Focal Motor SE (Epilepsia partialis continua) is often drug resistant, and whilst irritating and disabling, rarely dangerous, meaning the risks of sedation may not be justifiable. For nonconvulsive SE, EEG confirmation will usually be required, but appropriate timing and aggressiveness of treatment is controversial, and informed by the frailty, cause and potential outcome for the individual [56]. For patients in NCS without coma, most would try to avoid ICU if possible. For those with coma, ICU management will often be inevitable, and ongoing management is covered by other articles in this issue.

7. Future potential areas for research

Given the results of the two open trials already published in 2019 [43,44], and pending the blinded ESETT results [35,61], whether there will be an appetite for further large adequately powered studies in established SE remains to be seen. There is emerging interest in the potential for rapid EEG in the emergency setting, likely of benefit in identifying dissociative non-epileptic seizures (clear alpha rhythm in an unresponsive patient, between convulsive movements excludes epileptic SE as the cause). This could also potentially detect ongoing subtle status in those patients who fail to wake, and prompt administration of additional AEDs, though whether this would influence outcome remains uncertain.

One ongoing concern not yet resolved is how best to support the delivery of evidence-based treatment in routine clinical practice. Despite well established guidelines, numerous studies in multiple settings [57], includwing in the ESETT study [62] have demonstrated a culture of initial underdosing and delays in the management of convulsive SE, as well as cumulative overdosing with benzodiazepines negatively impacting on patient outcomes. One root cause analysis study exploring this on a paediatric unit [58] identified inconsistency and delays in physician decision making as a key determinant, improved by use of electronic timed “power plans”. Identifying barriers and quality improvement work should be a priority.

8. Conclusions

Speed is of the essence in treatment of SE. Based on current evidence, IV lorazepam or diazepam, or non-IV midazolam remain first choice for initial treatment of SE. Although pheno- and barbiturals have been used traditionally, levetiracetam and potentially sodium valproate may be preferable in the majority of patients on current evidence.

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