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Pharmacologic management of convulsive status epilepticus in childhood

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The incidence of convulsive status epilepticus in children is approximately 20–50/100,000/year, and is an emergency requiring prompt medical intervention. Prolonged seizures lasting over 5 min are unlikely to stop spontaneously, and time-to-treatment influences treatment response. Prolonged seizures should thus be treated as early status epilepticus. Mortality and morbidity increase significantly with the length of ongoing seizure activity, especially after 60 min. Benzodiazepines remain the first-line drug therapy due to their rapid onset of action. Recent studies imply that buccal midazolam is more effective and easier to administer than rectal diazepam. Phenytoin/fosphenytoin and phenobarbital administered intravenously remain the second-line treatments of choice, whilst barbiturates and midazolam as intravenous anesthetics are used for third-line treatment. Electroencephalogram monitoring is essential to evaluate the electrophysiologic treatment response and depth of anesthesia, especially in refractory status epilepticus. In the future, more individualized protocols and pathways are needed in order to optimize treatment responses. Randomized clinical trials are needed to evaluate new treatment protocols, which should not only stop the seizures more effectively but also be safer and include some neuroprotective elements to halt the cascade of neuronal injury and minimize the risk for neurologic morbidity caused by the convulsive status epilepticus.

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The hallmarks of status epilepticus (SE) are continuous or rapidly repeating epileptic seizures and the time point at which a seizure becomes unlikely to end spontaneously is the main characteristic for SE. SE occurs in children of all ages and is a neurologic emergency requiring active, prompt and monitored pharmacologic and supportive medical intervention. Any seizure type can present as SE and therefore the current International League against Epilepsy proposal for classification of SE follows the classification of epileptic seizures [1]. A simplified classification for convulsive, nonconvulsive and neonatal SE has been used when treatment recommendations have been outlined [2], since these three forms of SE have very different clinical presentations, etiologies, pathophysiologies and medical outcomes. This review focuses on convulsive (C)SE, which is the most common and potentially harmful form of the disorder.

Background

The overall incidence of CSE is estimated to be approximately 20–50/100,000/year in children under the age of 15 years [3,4]. The incidence is highest in infants and young children under the age of 4 years and 4–8 out of 1000 children are expected to experience an episode of CSE before the age of 15 years [5]. CSE as the first seizure in developing epilepsy occurs in approximately 30% of patients and approximately 15–40% of all SE episodes occur in patients with diagnosed epilepsy [6,7]. In others, CSE represents an isolated episode related to either acute symptomatic or febrile etiology. Etiology of the CSE episode is also highly age-bound, being acute symptomatic in infants, febrile in young children and in school-aged children and adolescents remote symptomatic and idiopathic/cryptogenic etiologies predominate [8].

The duration and factors that contribute to the duration of a single convulsive seizure are not well known. Isolated epileptic seizures in adults usually last for 1–2 min [9]. In children, seizures that last longer than 5 min are unlikely to stop spontaneously and it has been suggested that once a seizure has lasted for a 7 min it is very likely to became self-sustaining, which means that the longer the seizure lasts the less likely it is to stop spontaneously [10]. Increased seizure duration is commonly regarded as an important factor for increased morbidity and mortality. The time from seizure onset to initial treatment is presumed to be critical in attaining seizure control, and the administration of effective treatment is essential in preventing cerebral injury and neurologic sequelae [11].

Mortality and morbidity due to CSE in children has declined since the 1970s, and current studies show mortality rates of between 0 and 3% [7,12–14] and permanent neurologic sequelae between 10 and 20% [12,13,15]. Outcome after SE is influenced by the interaction between several factors, including age, etiology and total duration of the seizures, and the concomitant physiologic disturbances [16]. The risk of brain damage and mortality increases with the length of ongoing seizure activity, especially after the SE has lasted for 60 min [17,18] and the risk progressively increases after 1–2 h of continuous status [19]. Acute mortality and morbidity related to SE is usually due to systemic and metabolic disturbances, and also to the direct excitotoxic effect of the seizure discharges. Lower mortality and morbidity figures may be partly due to current treatment practices since more aggressive algorithms for prolonged convulsive seizures are currently recommended for children and adults [20–23].

Management of convulsive status epilepticus in children

Time to treatment

The goal of CSE treatment is to terminate both the clinical and electrical seizure activity as rapidly as possible. In adults, response of initial treatment of SE has been shown to decline from 80% in patients whose treatment began within 30 min from the onset of seizures, to less than 40% in patients with treatment initiated 2 h or later from seizure onset [24]. In children, 40–80% of patients receive their first treatment within 30 min of seizure onset [4,11], and the risk of poor treatment response also appears to increase as the seizure endures; over 30 min treatment delay of convulsive seizures in children has been shown to be independently and significantly associated with delayed treatment response in a population-based study [4].

On the other hand, in children with epilepsy, prolonged seizures can be stressful events for parents and they may be too frightened to clearly assess the situation and determine the proper course of action, or they may call for emergency assistance unnecessarily since, given the currently available treatment options for seizure emergencies, not every seizure or cluster warrants a visit to the emergency department. Therefore, patient and family education is crucial for the practical management of epilepsy and families of people with epilepsy should have an individualized emergency plan in place, including how long to wait before initiating treatment and when to call for medical assistance [11].

Early convulsive status epilepticus: first-line treatment

Early SE can be defined as an epileptic seizure abnormally prolonged for over 5 min; there is operational need for emergency drug treatment to abort the seizure activity. Benzodiazepines (BDZs) are preferred as initial drug therapy for CSE since they have a rapid onset of action. The effect of BDZs is mediated via their interaction with the BDZ binding site on the γ-aminobutyric acid $(GABA)_A$-receptor, resulting in enhanced GABA-mediated inhibition. Rectal diazepam (DZP) has been the golden standard for out-of-hospital pharmacologic management of CSE and it has been reported to be effective in acute repetitive and prolonged seizures [25]. Generally, the recommended dose is 10 mg for children over 15 kg, and 0.5 mg/kg for children under 15 kg, repeated once if necessary. The use of other rectally administered BDZs (e.g., lorazepam [LZP]) has been studied, without significantly better response rates compared with DZP [26]. The risk of treatment-related side effects (respiratory depression) has been shown to increase with more than two doses of BDZs and treatment guidelines are suggested to be modified so that prehospital treatment is also taken into account when further treatment is evaluated [27].

An alternative route of administration of BDZs as a rescue medication is with an intravenous preparation or buccal liquid (where available) of midazolam (MDL) used buccally, but this treatment is currently unlicensed for this indication. However, randomized or controlled studies comparing buccal MDL with rectal DZP [28,29], and a case report of effectiveness and convenience of use [30], have shown buccal/nasal MDL to be a potential alternative. In the first randomized, controlled trial, buccal MDL was more likely than rectal DZP to stop acute tonic–clonic seizures within 10 min (65 vs. 41%, $p < 0.001$) in children at the hospital emergency room and the use of MDL was not associated with an increased incidence of respiratory depression. Buccal MDL was also found to be easier and more acceptable to administer, a view shared by nursing staff and parents. However, if this treatment is used, an individual preplanned protocol and careful instructions (i.e., dose and method of application) for parents and caregivers must be provided for each patient.

The most commonly used first-line intravenous BDZs are LZP and DZP. Randomized, controlled studies show that these two drugs have similar onsets of action and adverse effects (respiratory depression and impaired consciousness), and they are both clinically efficient in 2–3 min [26]. Since LZP has a longer duration of action (12–24 h) than DZP (15–30 min), current treatment algorithms usually recommend LZP as initial intravenous treatment. The recommended dose for intravenous LZP is 0.05–0.1 mg/kg up to 4 mg and the dose can be repeated after 5 min if the seizures continue. The recommended dose for intravenous DZP is 0.2–0.4 mg/kg up to 10 mg and this dose can also be repeated once. The efficacy of first-line treatment

(BDZs, either rectally or intravenously) for prolonged convulsive seizures (over 5 min) in children was 58% in a retrospective population-based study [7].

Established convulsive status epilepticus: second-line treatment

Established CSE is defined as a condition in which epileptic seizure persists for 30 min or more, but second-line therapies should be considered earlier, as soon as it becomes evident that CSE persists after the administration of BDZs. A third (33%) of children with prolonged seizures need second-line pharmacologic treatment [7]. Intravenous phenobarbital (PB) has been shown to be effective as second-line drug treatment for CSE in children [31], the anticonvulsant effect being mediated through enhanced GABA-inhibition via binding with the barbiturate site of the $GABA_A$-receptor. The intravenous loading dose in children is 15–20 mg/kg and the maintenance doses of 2.5 mg/kg at 24 h and 48 h has been considered to be sufficient in maintaining serum concentrations within the therapeutic range for 72 h [32]. The monitoring and support of vital functions is essential due to the depressant effects of PB on respiration, level of consciousness and blood pressure.

Phenytoin (PHT) has been shown to be effective in terminating SE in adults, but its utility as an initial therapy is limited by the slow rate of the drug administration and the attendant delay in attaining the anticonvulsant effect. The major mechanism of action of PHT is blockage of voltage-gated sodium channels. Intravenous fosphenytoin (fosPHT) as a PHT prodrug is an alternative (although more costly) and is currently preferred over PHT due to its water solubility and normal pH, allowing more rapid administration and less infusion-related side effects [22]. The fosPHT dose required to obtain therapeutic serum levels in adults for 24 h is 18 mg PHT equivalent (PE)/kg given as a loading dose at a maximum rate of 150 mg PE/min [33]. In children, the loading dose of 15 mg PE/kg may be effective and safer, but controlled trials are lacking. Cardiac complications and allergic reactions can occur with fosPHT due to its conversion into PHT but the risk for hypotension may be lower.

In children in which PHT/fosPHT or PB cannot be used due to allergic reactions, other medical conditions (e.g., progressive myoclonus epilepsy) or the type of CSE (e.g., myoclonic SE), the use of valproate (VPA) is favored, and this drug has been used intravenously [34], although there is no official approval for its use in SE. The loading dose is 15–40 mg/kg with an infusion rate of 3 mg/kg/min or 200 mg/min. In the presence of enzyme-inducing drugs (e.g., carbamazepine, PHT and PB) the VPA doses need to be up to 40 mg/kg as a loading dose [35]. The intravenous maintenance dose for VPA in children is 7.5 mg/kg administered four-times daily [36]. There is no marked depression of consciousness and respiration, but hypotension has been described in pediatric patients [37]. There are no controlled clinical trials comparing the safety and efficacy of VPA with other medical treatments for SE and the place of VPA in the management of SE in general is currently unknown.

Refractory convulsive status epilepticus: third-line treatment

SE that does not respond to first-line BDZs or second-line antiepileptic drugs (e.g., PHT/fosPHT or PB), and lasts over 60–120 min is usually considered refractory CSE and requires an even more aggressive treatment. In a retrospective population-based study in children, 9% of the CSE episodes could be regarded as refractory SE [7]. The optimal treatment for refractory CSE has not been defined [38]. The pharmacologic treatment of refractory CSE is general anesthesia with continuous intravenous anesthetics administered in doses, which abolish all clinical and electrographic epileptic activity often requiring sedation to the point of burst suppression in the electroencephalogram (EEG). Burst suppression pattern on the EEG provides a physiologic target for the titration of the intravenous treatment. If burst suppression is the target, the drug dosing is commonly set at a level with interburst intervals between 2 and 30 s [21].

Barbiturate anesthetics (pentobarbital in the USA and thiopental in Europe and Australia) have been the most used and highly effective general anesthetics for refractory SE both for children and adults, and they probably remain the only way to stop seizure activity with certainty in severe refractory cases. However, myocardial depression, hypotension, delayed postinfusion respiratory recovery and ileus necessitating total parenteral nutrition as well as increased susceptibility to Gram-positive infections are the limitations [21]. Pentobarbital is used as a 10–15 mg/kg bolus followed by continuous infusion of 0.5–1 mg/kg/h and thiopental as 3–5 mg/kg initial bolus with 1–2 mg/kg additional boluses within 3–5 min up to clinical response with a maximum of 10 mg/kg and then continuous infusion at the rate of 3–5 mg/kg/h [16,39]. In individual cases, higher continuous infusion rates may be needed (≤7.5 mg/kg/h) [40].

MDL as an imidazobenzodiazepine drug has been used intravenously in the treatment of SE with a loading dose of 0.2 mg/kg, repeated until clinical response up to a maximum of 2 mg/kg and continued with infusion at the rate of 0.05–2 mg/kg/h [21]. The most common disadvantage of MDL treatment is breakthrough seizures, which may be managed with an additional bolus and increase in the intravenous rate by 20% [22]. Other problems include tachyphylaxis and a prolonged half-life. The clinical response can usually be observed between 10 min and 1 h, and if seizures continue, more effective (suppressive) treatment options should be considered [23].

Intravenous propofol, which has been used for the treatment of refractory CSE, acts at a location other than the BDZ binding site and modifies the chloride channel in a way that is different from BDZs and barbiturates [22]. However, in critically ill patients, propofol infusion syndrome (e.g., rhabdomyolysis, acidosis and cardiac arrhythmias) associated with doses over 5 mg/kg/h for prolonged sedation has been described [41]. The risk for propofol infusion syndrome appears to be far greater in children than adults [42] and the use of propofol for sedation has been contraindicated in many countries (e.g., USA, Canada and the EU) in children under the age of 16 years.

Regardless of drug selected, the patient should be managed in an intensive care unit setting since artificial ventilation, hemodynamic support and invasive monitoring is often necessary. Additionally, EEG monitoring is essential during the treatment of refractory CSE. Without EEG monitoring, the response of antiepileptic drug (AED) treatment is difficult to verify since subclinical, electrographic seizure activity may persist after the control of clinical symptoms. Once seizures have been controlled for at least 12 h, intravenous therapy should be gradually tapered off if the drug is MDL. Gradual tapering is probably not necessary with pentobarbital or thiopental. However, intravenous anesthetics should be reintroduced if CSE recurs during or shortly after tapering off of the treatment.

Prevention of recurrence

In order to prevent the recurrence of CSE, intravenous PHT, fosPHT or VPA administration should be continued to ensure an adequate baseline for AED medication before withdrawal of the continuous intravenous anesthetics. In addition to PHT/fosPHT/VPA, levetiracetam (LEV) may also become available for clinical use as an intravenous formulation [43]. AEDs that are only available in an enteral form can be given via a nasogastric tube or by percutaneous endoscopic gastrostomy and, although enteral AEDs may not always be sufficiently absorbed and can reach unpredictable serum levels in critically ill patients, these medications are important for preventing breakthrough and withdrawal seizures, particularly directly prior to the tapering off of intravenous anesthetics [23]. Children with epilepsy should have their earlier medications continued, but doses should be optimized. If additional medication is needed, the best AEDs to be started quickly in this setting are gabapentin for focal seizures and LEV and topiramate for all seizure types [44]. All these drugs can be safely initiated with high dosages without an increased risk of idiosyncratic reactions.

Conclusions

CSE is a neurologic emergency that requires prompt recognition and aggressive pharmacologic management. The goal of the treatment is to terminate the clinical and electrical seizure activity as soon as possible. BDZs are initial drug therapy since they are potent and have a rapid onset of action. The evident risk for the refractoriness of seizures lasting over 30 min should underline the need for rapidly proceeding into the next stages of the treatment protocol; PHT/fosPHT and PB are established second-line intravenous drugs. The patients refractory for first- and second-line treatments need even more aggressive intervention, which often requires sedation to the point of burst-suppression in the EEG, and the patients have to be managed in an intensive care unit setting. EEG monitoring is essential to evaluate the electrophysiologic treatment response and the depth of anesthesia, especially in refractory CSE. It is essential for each emergency and intensive care unit to have a general algorithm for the treatment of CSE.

Expert commentary

In early CSE, the different BDZs probably have equal efficacy, but the route of administration (e.g., rectal vs. buccal) may be crucial for compliance of the parents and caregivers and facilitate early intervention. According to present knowledge, the availability of nonrectal application routes favors the use of MDL (buccally) – although it is currently unlicensed for this indication and should be used only following training according to individualized instructions drawn by the specialist. The intravenous use of LZP has pharmacologic advantages over DZP (e.g., longer duration of action) and it may be regarded as first-line intravenous treatment for CSE, even by paramedics in the out-of-hospital setting, but the safety of intravenous BDZs in this setting needs further study.

In established CSE it would be rational to choose consecutive AEDs with different modes of action. Since both BDZs and PB act via GABAergic binding sites and have an additive respiratory depressant effect when combined, the intravenous drugs with other modes of action, such as PHT/fosPHT (which block the sodium channels) may be safer and more effective in seizures unresponsive to BDZs, although controlled studies supporting this are lacking. As the administration of more than two doses of BDZs also increases the risk for adverse effects, such as respiratory depression, it is important to move forward in the treatment protocol to second- or third-line treatment options in the hospital, if adequate doses of BDZs have already been given in the prehospital setting.

In refractory CSE, adverse effects of propofol limit the options for anesthetics in children. Barbiturates probably remain the only agent to ensure the abortion of both clinical and electrographic seizure activity with minimal risk of breakthrough seizures (problem with MDL) and immediate relapse after drug withdrawal or severe adverse reactions (problems with propofol). Barbiturates may also have beneficial effects on the secondary physiologic disturbances associated with CSE, such as the risk of increased intracranial pressure, and they are reported to also exhibit protective properties related to cerebral blood flow and oxygen consumption.

Five-year view

Time-to-treatment is crucial in the management of CSE. In optimal cases the treatment is administered as soon as it becomes evident that the seizure is not going to end spontaneously, is repeated, or otherwise atypical, for a given child. In the future, ideally, the treatment steps will be undertaken earlier using adequate doses of effective drugs applied through accessible routes of administration, with rapid procession to the next step if earlier steps are ineffective (TABLE 1). On the other hand, treatment should be administered according to the length of the seizure estimated in each case individually, which means that rapidly proceeding from first-line medication straight to third-line treatment may be necessary in newly admitted patients if the duration of the CSE without cessation has, out of hospital, already exceeded 60 min or the clinical situation otherwise indicates the need for this.

Table 1. Current schematic treatment phases of early, established and refractory convulsive status epilepticus and how they might be optimized in the future with drug options available at the moment.

	Early SE		Established SE	Refractory SE
	First-line		*Second line*	*Third line*
	Step 1	*Step 2*	*Step 3*	*Step 4*
Time	>5 min	>5 min	>30 min	>60 min
Drug administration	Out of hospital/nonmedical persons (e.g., parents)	Out of hospital/medical personnel (e.g., paramedics)	In hospital/emergency room or department	In hospital/intensive care unit
Drugs currently used	None or rectal DZP only	Rectal DZP	Intravenous BDZ and/or intravenous PHT/fosPHT, PB, VPA	General anesthesia
Drugs used in optimal situation in future	Buccal MDL	Intravenous LZP	Intravenous PHT/fosPHT, PB, VPA	General anesthesia

BDZ: Benzodiazepam; DZP: Diazepam; LZP: Lorazepam; MDL: Midazolam; PB: Phenobarbitone; PHT: Phenytoin; SE: Status epilepticus; VPA: Valproate.

In the future, the individualization of the treatment will become important. This means adjusting general algorithms into individualized treatment protocols and pathways that will take into account, for example, the individual responses to different drugs, especially for those with repetitive CSE episodes. In pediatric epilepsy, a predecided individual emergency plan should also be in place in order to minimize the emotional stress of families and children associated with seizure emergencies. This plan should include, for example, how long to wait before initiating treatment and when to call for medical assistance [11].

In the future, randomized clinical trials will hopefully determine the best treatment for CSE in children. These trials should include the randomizations between the different anesthetics, such as barbiturates and MDL, but also take into account the goal of treatment; cessation of seizures versus suppression of EEG activity. There is also a need for new treatment options for CSE. These new drugs should stop the seizures more effectively and be safer than those currently used. They should also include some neuroprotective elements to halt the cascade of neuronal injury and minimize the risk for neurologic morbidity caused by the CSE.

Key issues

- Convulsive status epilepticus is a medical emergency requiring prompt medical intervention.
- Convulsive seizure lasting over 5 min should be regarded as early status epilepticus and treated as such.
- Time to treatment influences treatment response.
- Mortality and morbidity increase with the length of ongoing seizure activity, especially after 60 min.
- Electroencephalogram monitoring is essential in order to evaluate the electrophysiologic treatment response and the depth of anesthesia.
- Benzodiazepines (e.g., buccal midazolam and intravenous lorazepam) as first-line, phenytoin/fosphenytoin and phenobarbital intravenously as second-line, and intravenous anesthetics (barbiturates, midazolam) as third-line drugs form the core for general treatment algorithms.
- In the future, individualized treatment protocols and pathways are needed in order to optimize individual responses to drugs and minimize the emotional stress of families and children associated with acute seizure episodes.
- Randomized clinical trials are needed to determine the best treatment in children.
- New treatment options that would stop the seizures more effectively, be safer and include some neuroprotective elements are needed for convulsive status epilepticus.

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