Medical Treatment of Pediatric Status Epilepticus

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Status epilepticus (SE) is a common pediatric neurologic emergency that refers to a
prolonged seizure or recurrent seizures without a return to baseline mental status between
seizures. Appropriate treatment strategies are necessary to prevent prolonged SE and its
associated morbidity and mortality. This review discusses the importance of a rapid and
organized management approach, reviews data related to commonly utilized medications
including benzodiazepines, phenytoin, phenobarbital, valproate sodium, and levetiracetam,
and then provides a sample SE management algorithm.
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Status epilepticus (SE) is a common pediatric neurologic emergency that refers to a prolonged seizure or recurrent seizures without a return to baseline between seizures. Appropriate treatment strategies are necessary to prevent prolonged SE and its associated morbidity and mortality. This review focuses on the management of SE with anticonvulsant medications and addresses both out-of-hospital and in-hospital approaches. An evaluation to determine the etiology of SE[1] and attention to systemic complications must proceed simultaneously.

Types of SE

Initially, SE was defined as a seizure lasting longer than 30 minutes or a series of seizures without a return to baseline level of alertness between the seizures, largely based on data that these seizures could produce lasting pathologic changes. Although this remains an appropriate definition for outcome studies and animal models, there is increasing recognition that most seizures are brief (3-4 minutes),[2] and medication administration delay is associated with more refractory seizures. This has led to a change in clinical practice that has shortened the seizure duration of SE over the last decade to a seizure lasting longer than 5 minutes.[3] Recent commentaries have proposed that aggressive management be initiated even earlier than 5 minutes.[4] Immediate aggressive management may be particularly important in postoperative neurosurgical and cardiac surgical patients, patients with or at risk for elevated intracranial

pressure (traumatic brain injury, brain tumor, and central nervous system infections), children with malignant hyperthermia, and children with multisystem organ failure.[5] SE occurs frequently in children being treated with therapeutic hypothermia after cardiac arrest[6] and is a risk factor for poor outcome in adults,[7] so early recognition and aggressive management may also be warranted in these children.

SE may be categorized based on etiology, seizure type, or timing. Attention to the timing stage of SE ensures management proceeds without delay. In the initial 5 minutes of seizure, a period referred to as the prodromal or incipient stage, it is unknown whether the seizure will self-terminate or evolve into SE. Persisting SE may be divided into early SE (5-30 minutes), established SE (>30 minutes), or refractory SE (RSE) (seizures that persist despite treatment with adequate doses of an initial 2 or 3 anticonvulsant medications).

Systemic Management

Systemic changes occur during SE and may worsen the underlying brain lesion in acute symptomatic SE. In early SE, brain glucose and oxygen use increases, but delivery may also increase because of a rise in blood pressure and cerebral perfusion. In later SE, blood pressure may decrease, sometimes to hypotensive levels, and respiratory compromise may occur. These changes may result in brain hypoxia, hypoglycemia, and acidosis.[8] Hyperthermia and rhabdomyolysis may also develop.[9] Furthermore, seizures may elevate intracranial pressure, and if cerebral autoregulation is already disturbed by the underlying lesion or by SE, autoregulatory mechanisms may be further compromised.[10] Rarely, SE is associated with ictal bradycardia, stress cardiomyopathy, neurogenic pulmonary edema, rhabdomyolysis and related renal failure, or bone fractures.

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Treatment Overview

Many SE management algorithms have been developed.[5,11,12] The initial management uses benzodiazepines with slight differences in benzodiazepine preference and dosing. Second-line drugs are more variable and generally include phenytoin (PHT), phenobarbital, valproic acid (VPA), and levetiracetam (LEV). Third-line drugs are even more variable, with some algorithms suggesting trials of additional second-line drugs and some proposing pharmacologic coma induction. Despite small differences in the clinical algorithms, there are certain important common principles discussed below.

Rapid Treatment of SE Is Important

A number of studies have suggested that the rapid treatment of SE is associated with a higher efficacy of anticonvulsants and possibly a better outcome. A prospective observational study of 182 children with convulsive SE found that for every minute delay between the SE onset and emergency room arrival there was a 5% cumulative increase in the risk of having SE last more than 60 minutes.[13] Several clinical studies showed that anticonvulsants are more effective when administered early rather than later during the seizure.[14-18] For example, a retrospective study of 154 children with SE compared children with aborted SE and RSE. Of the 71 children who continued to seize despite first- and second-line anticonvulsants, seizures were terminated by a third anticonvulsant in 100% when it was administered within 60 minutes of the first anticonvulsant and only 22% if administered more than 1 hour after the initial anticonvulsant.[14] One explanation for this finding may be that with the increasing duration of SE, inhibitory GABA receptors are internalized, making benzodiazepines less effective.[19-21]

Longer seizures may also be associated with a worse outcome. In the retrospective study comparing aborted and RSE described earlier, RSE was associated with higher mortality, less return to baseline functioning, and an increased risk of long-term deficits and epilepsy.[14] Even after adjusting for RSE status, having longer seizures (both when eventually aborted and when refractory) was associated with a significantly worse outcome. Furthermore, children who received a third anticonvulsant within an hour of treatment initiation returned to baseline significantly more often than those with more delayed administration of a third anticonvulsant (81% vs 0%).[14] Similarly, a partially retrospective and partially prospective study evaluated 307 adults and children (122 children) with SE and compared patients with seizures lasting 10 to 29 minutes with those with seizures lasting 30 minutes or longer. Despite similar etiologies in the 2 groups, those with seizures lasting longer than 30 minutes had a statistically higher mortality than those with shorter durations (19% vs 3%). However, this difference was seen in adult and elderly patients, and there was no significant difference in mortality in just the pediatric group.[22] Together these studies suggest that early treatment may be associated with higher anticonvulsant efficacy and possibly better outcome.

Home Management Plans Are Important

Most episodes of early SE have onset outside the hospital,[23] and early SE is a critical period for terminating the seizure. Ten percent of children with epilepsy may eventually develop SE,[24] and 16% of those with a first episode of SE may have recurrence within a year.[23] A retrospective study reported that out-of-hospital management with diazepam (DZP) (rectal or intravenous [IV]) was associated with shorter duration of SE (32 vs 60 min) and a decreased risk of recurrent seizures in the emergency department (ED).[25] A lack of prehospital treatment with DZP has been associated with a significantly increased risk of SE lasting longer than 60 minutes in both retrospective[25] and prospective[13] studies. Furthermore, benzodiazepine dosing was lower than recommended in 75% of episodes, both when administered by parents and paramedics.[13] This suggests that out-of-hospital management is important and that detailed plans are required to ensure appropriate dosing. A recent survey reported that 79% of parents had a rescue medication care plan, 75% of those who had been prescribed a rescue medication reported using it, and most parents reported that it was always or often effective in terminating seizures and avoiding hospitalization.[26] A home plan must take into account the seizure history, the distance to medical care, and the medical sophistication of the family.[27]

An In-Hospital Management Plan Is Important

Although an ideal, evidence-based SE management algorithm has not been developed yet, ensuring that some plan is in place may help guide management and avoid treatment delays. A recent consensus document from an international colloquium on SE recommended that "all units should have a written protocol" and that "the protocol should be staged with a clear structured timeframe." Furthermore, it advocated for educational incentives and set the goal that at least 80% of children with SE be treated appropriately.[28]

Unfortunately, recent studies have documented that in current practice in-hospital treatment delays and inappropriate dosing are common. A large retrospective multicenter study reported that even once in the ED, the median time to administer a second-line anticonvulsant to a seizing child was 24 minutes and that for each doubling in the duration of prehospital seizure there was only a 6% reduction in the time taken to administer second-line anticonvulsants.[29] Inappropriate benzodiazepine dosing is also reported, with both high and low dosing causing problems. Both prospective observational[30] and retrospective[31] studies have reported benzodiazepine dosing outside the standard range in 22% to 45% of children. Low dosing may not terminate SE. High dosing is also problematic and often occurs when prehospital doses are not considered. Both prospective[13] and retrospective[31] studies of children with SE showed that extra doses given in the ED are associated with an increased risk for respiratory depression. A retrospective case series of 47 children admitted to a hospital with SE showed that children who were not managed with a SE protocol more often received extra ben-

zodiazepine doses and were more likely to require intensive care unit admission than those managed with a protocol.[32]

Initial Benzodiazepine Management

In current practice, there is substantial variability in the initial management of SE. A survey of physicians in Australia and New Zealand reported that first-line management of SE without IV access included rectal DZP (49%), intramuscular midazolam (MDZ) (41%), and buccal MDZ (9%), whereas first-line management of SE with IV access included MDZ IV (50%) and DZP IV (44%).[33] A large number of studies have compared various benzodiazepines and routes of administration. These studies suggest that if IV access is not available, the use of intranasal MDZ (0.2 mg/kg),[34,35] buccal MDZ (0.2 mg/kg),[36] or intramuscular MDZ (0.2 mg/kg)[37,38] may be good alternatives to placing an IV line and then administering IV DZP (0.3 mg/kg). Furthermore, some of these studies have indicated that intranasal MDZ (0.2 mg/kg)[39-41] and buccal MDZ (0.5 m/kg)[42-45] may be more or equally effective than rectal DZP (0.2-0.5 mg/kg). However, if IV access is already available or can be established quickly, then an IV infusion of DZP (0.2-0.3 mg/kg)[35] or lorazepam (LZP) (0.1 mg/kg)[13] may be preferable. A prospective randomized controlled trial of 178 children with SE showed that LZP (0.1 mg/kg) was as safe and effective as DZP (0.2 mg/kg) and PHT (18 mg/kg) combined,[46] so LZP may be the preferred IV medication.

Second-Line Management

Although initial benzodiazepine management is effective in a large number of patients, many have persisting seizures and require additional medications. For example, a retrospective, multicenter descriptive study of 542 convulsive SE episodes reported that first-line treatment was effective in only 42%.[29] A second retrospective study of 154 children with SE reported that SE was terminated by a first line benzodiazepine in only 39%, and 46% continued seizing despite first and second line medications.[14] A recent survey of pediatric emergency medicine physicians reported that PHT was chosen as the second-line agent by 88% of respondents.[33] This is consistent with other surveys that targeted neurologists.[47] Third- and fourth-line agents were more variable and included phenobarbitone, thiopentone, paraldehyde (not available in the United States), and MDZ.[33] A number of recent case series have suggested that valproate sodium[17,48-52] and LEV[53-60] may be useful second- or third-line agents.

PHT and Fosphenytoin

PHT or fosphenytoin (FOS) (the water-soluble prodrug of PHT) are effective in terminating early SE. A single-center, open-label, descriptive cohort study of 122 children managed using an SE protocol involving MDZ (0.1 mg/kg IV followed later by continuous infusion if needed) and PHT (20 mg/kg) reported seizure termination in 89%, and SE etiology did not impact the intensity of anticonvulsant treatment

needed to terminate SE.[61] A randomized controlled study of 178 children with SE reported that a combination of DZP and PHT terminated SE in 100% of children, which was equal in efficacy to LZP.[46]

Fosphenytoin dose, solution concentration, and infusion rates are expressed as phenytoin equivalents (PE). IV FOS may be administered more rapidly than PHT (maximum of 150 mg PE/min or 3 mg PE/kg/min in children vs 50 mg/min in adults or 1 mg/kg/min in children) and, thus, despite the need for conversion from the prodrug, it is expected to reach therapeutic concentrations in the brain in the same amount of time as PHT (about 15 minutes).

Cardiac arrhythmias are rare but may occur with PHT or FOS,[62] usually with more rapid administration. If IV infiltration occurs, FOS is associated with less tissue injury than PHT. Although PHT and FOS are effective in treating most types of SE, they may be ineffective in treating SE related to generalized epilepsy, such as absence status (spike wave stupor) and myoclonic SE. Critically ill children may have toxic free levels of PHT despite normal total levels, suggesting that in some patients free levels must be followed.[63] Drug interactions must be considered because PHT and FOS interact with many medications commonly used in critically ill children.[64]

Phenobarbital

Phenobarbital (PB) is commonly used as a first-line agent to treat neonatal seizures and SE[65] and is often considered a third- or fourth-line drug in pediatric SE algorithms. However, there has been little rigorous study of PB in SE management. A prospective, randomized, nonblinded study of 36 children with SE indicated that PB monotherapy terminated seizures in 11 of 18 children and was faster than a combination of DZP and PHT (5 vs 9 minutes), with similar frequencies of intubation, hypotension, and arrhythmia.[66] Retrospective case series have reported that high-dose PB may be useful in RSE management.[67-70] The major limitation of the use of PB is the potential for sedation, respiratory depression, and hypotension.

Valproate Sodium

Valproic acid (VPA) is a broad-spectrum anticonvulsant and has been reported to be safe and highly effective in terminating SE[17,48-50] and RSE[51,52] without adverse effects. A retrospective case series of 18 children with SE reported that a loading dose of VPA (25 mg/kg) terminated seizures in 100% within 20 minutes without adverse effects.[48] A retrospective case series of 17 children with a seizure indication (but not necessarily SE) used a loading dose (mean, 28.5 mg/kg) followed by a continuous infusion (1 mg/kg/h) and reported seizure termination in 65% without adverse effects.[49] A prospective, single-center, open-label study described 48 patients (5 younger than 15 years) with SE refractory to DZP and phenobarbitone and reported that IV VPA (30 mg/kg) terminated seizures in 87.5% of patients within 1 hour; none recurred in the next 12 hours, and no adverse effects were noted.[50] A prospective randomized study of adults and chil-

Management

Out-of-hospital or No IV Access Available
    Buccal midazolam (0.2 mg/kg), intranasal midazolam (0.2 mg/kg) or rectal diazepam (0.3 mg/kg).
 	
Emergency Room
    Lorazepam 0.1 mg/kg IV (max5mg) over 1 min
    Allow 5 minutes to determine whether seizure terminates.
 	
Give oxygen. Stabilize airway, respiration, and hemodynamics. Obtain IV access. Check bedside glucose.
Begin EKG monitoring. Avoid hyperthermia, hypoglycemia, and hyperglycemia.
 	
If hypoglycemic, administer bolus of 2ml/kg 50% glucose. Consider thiamine 100mg IV first.
 	
Repeat benzodiazepine administration if patient has not received 2 doses of benzodiazepines. (Be sure to
consider pre-hospital dosing).
 	
Administer 2nd anticonvulsant:
    Fosphenytoin 25-30 mg PE/kg IV at 3 mg PE/kg/min (max 150 mg PE/min) (PE = phenytoin equivalents)
    Phenytoin 25-30 mg/kg IV at 1mg/kg/min (max 50mg/min)
 	
If < 2 years, consider pyridoxine 100mg IV push.
 	
Testing to be considered:
    Bedside Glucose, Basic Metabolic Panel, Magnesium, Phosphate, Complete Blood Count, Liver Function
    Panel, Coagulation Tests, Anticonvulsant Levels, Toxicology, Cultures, Head CT.
 	
Draw phenytoin level (~10 min after infusion completed)

If seizure continues 10 minutes after fosphenytoin/phenytoin infusion then patient has refractory SE
regardless of time elapsed.
 	
Administer 3rd anticonvulsant:
    Levetiracetam 40 mg/kg IV at 5mg/kg/min.
        Consider in patients with hemodynamic instability or possible metabolic/liver disease. OR
    Valproate Sodium 40 mg/kg at 5mg/kg/min.
        Contraindicated if liver disease, thrombocytopenia, or possible metabolic disease. OR
    Phenobarbital 30 mg/kg IV at 2 mg/kg/min (max rate 60mg/min).
        May cause respiratory depression and hypotension.

If seizure continues 5 minutes after 3rd anticonvulsant, then consider administered a different third-line anticonvulsant, or proceed directly to pharmacologic coma initiation. Admit to PICU. Prepare to secure airway, mechanically ventilate, obtain central venous access and continuous hemodynamic monitoring through arterial line. Once clinical seizure terminates may need EEG monitoring to assess for non-convulsive seizures.
Initiate coma with midazolam 0.2 mg/kg bolus (max 10mg) over 2 min and then initiate infusion at 0.1 mg/kg/hr. If clinical seizures persist 5 min after initial midazolam bolus then administer additional midazolam bolus of 0.2 mg/kg bolus. Continue infusion. If clinical seizures persist after another 5 minutes, then administer another midazolam bolus of 0.2 mg/kg and increase infusion to 0.2 mg/kg/hr. Repeat as needed. If seizure persist at maximum midazolam (generally 2-3 mg/kg/hr) or midazolam infusion is not tolerated, then consider transition to pentobarbital (3-5mg/kg bolus followed by maintenance infusion of 0.3- 3 mg/kg/hr, up to 10 mg/kg/hr). Other options include: Isoflurane or Propofol. Consider addition of topiramate, valproicacid, levetiracetam, or ketamine.
Continue pharmacologic coma for 24 hours after last seizure with EEG goal of burst-suppression. Continue initial medications and check levels: Ensure an additional anticonvulsant is administered to provide coverage during weaning coma.
Reduce midazolam by 0.05 mg/kg/hr every 3 hours with frequent EEG review. If no clinical or electrographic seizures then wean until off. Continue EEG for at least 24 hours after end of infusion to evaluate for recurrent electrographic seizures.
If clinical or subclinical seizures occur then re-institute coma with midazolam for 24 hours. Start midazolam at infusion rate that achieved burst suppression (approximately 50/50) and increase according to suggested midazolam titration algorithm. Add additional anticonvulsants (topiramate, levetiracetam, ketamine, high dose phenobarbital). Additional imaging (3 Tesla MRI, consider Magnetoencephalography) and surgical evaluation.

Left margin labels: **Impending/Established Status**, **Refractory Status**, **Malignant Status**

Right margin labels: Airway, Breathing, Hemodynamics, Temperature, Glucose Levels; EEG Monitoring
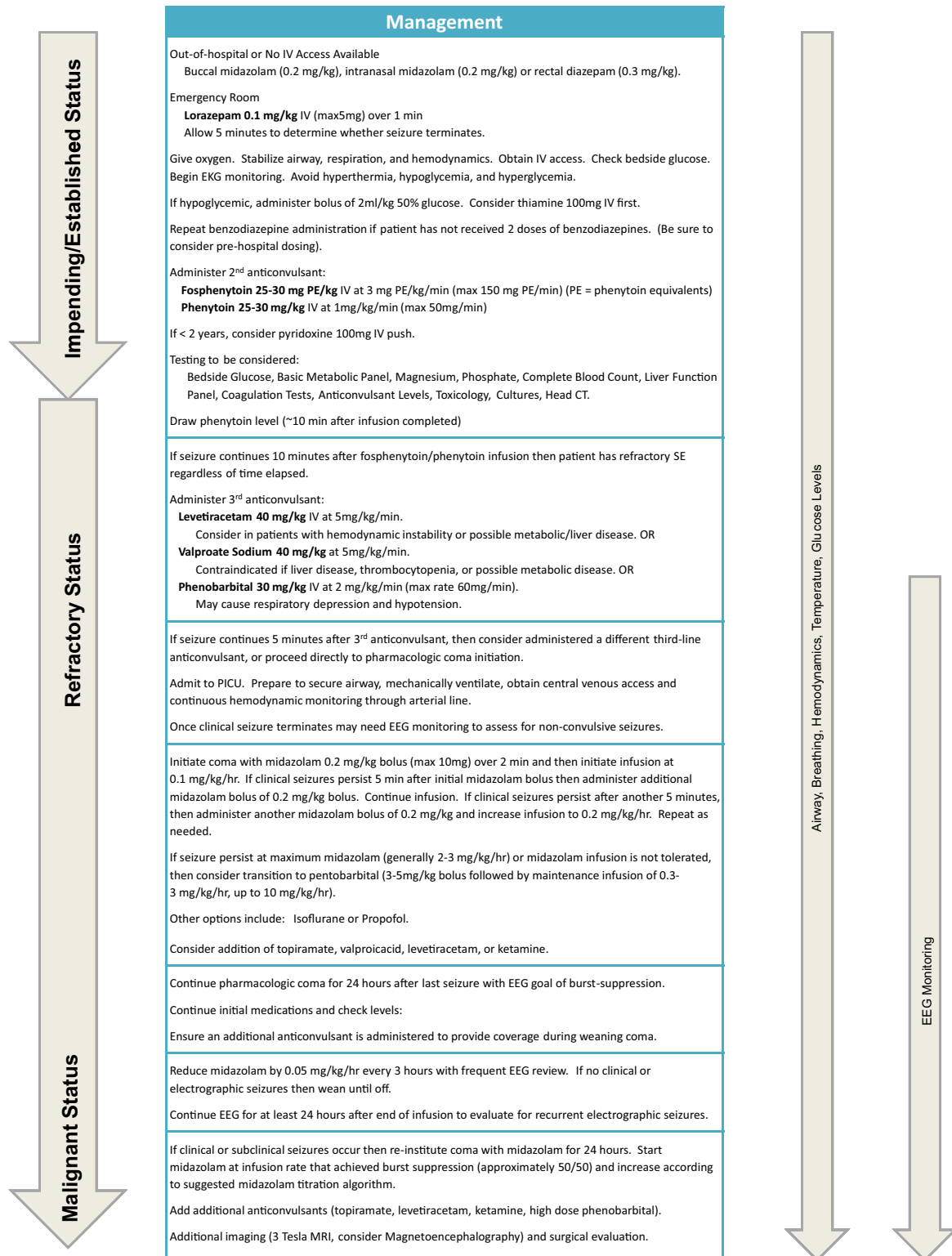
Figure 1 Status Epilepticus Management Algorithm. (Color version of figure is available online.)

dren (median age, 27 years) with SE refractory to IV DZP compared IV VPA (20 mg/kg) with IV PHT (20 mg/kg) and found no difference in seizure termination (88% vs 84%). There was no significant difference in the number of adverse effects, but the type of adverse affects differed with PHT causing hypotension and respiratory depression and VPA causing transient serum glutamic oxaloacetic transaminase (SGOT) elevation.[17]

Two studies have reported on the use of IV VPA in RSE. A retrospective, single-center, open-label large case series of 41

children with RSE reported that a VPA load of 20 to 40 mg/kg followed by a 5-mg/kg/h infusion terminated RSE in 78%, with 66% terminating within 6 minutes. Higher efficacy was noted with higher loading doses (30-40 mg/kg). No adverse effects were reported.[51] A prospective, randomized open-label study of 40 children with RSE compared IV VPA (30 mg/kg loading dose followed by another 10 mg/kg in 10 minutes followed by an infusion of 5 mg/kg/h) and DZP (infusion started at 10 μg/kg/min and increased to a maximum of 100 μg/kg/min) and showed that seizures were terminated in 80% with VPA and 85% with DZP. RSE was controlled more quickly with VPA than DZP (5 vs 17 minutes) and was not associated with adverse effects.[52]

Larger studies in adults have also shown the utility of VPA in SE management. Several studies have compared VPA and PHT in adults with SE or acute repetitive seizures and have shown that VPA was more effective[71] or equally effective[17,72] to PHT and may have fewer adverse effects.[72]

Although VPA is often loaded slowly (<20 mg/min), recent studies have shown that faster infusion may be safe. A prospective safety study in 18 children reported that when VPA was administered intravenously at 1.5 to 11 mg/kg/min, 1 patient experienced burning pain with infusion but there were no severe infusion site complications. There were no arrhythmias, bradycardias, or hypotensive episodes noted.[73] A prospective safety study of 40 adults with epilepsy (not actively seizing) administered a faster infusion (6-10 mg/kg/min) and showed that even though infusion site pain, burning, and paresthesias occurred in 81% of subjects, they only lasted several minutes and were not associated with signs of redness, irritation, or phlebitis. There were no changes in vital signs or in the level of consciousness.[74] VPA has not been associated with changes in blood pressure or heart rate in children.[17,48-52] A retrospective case series reported that even in patients with known cardiovascular instability VPA loading appeared to be safe.[75] VPA rarely causes thrombocytopenia or hepatotoxicity,[76] but this has not been reported after a first loading dose.

Levetiracetam

LEV is a broad-spectrum anticonvulsant and although there have been no prospective studies comparing LEV with other anticonvulsants, a growing number of retrospective, single-center, open-label case series and case reports have provided increasing evidence that LEV may be safe and effective for treating both SE and acute repetitive seizures in children.[53-60] The first series described 32 children treated with IV LEV (50 mg/kg over 15 minutes) for acute seizures (16 with SE) and reported that all patients had seizure termination within 25 to 30 minutes of infusion. This included 59% of patients who had seizures refractory to FOS. There were no immediate adverse effects.[60] The second series reported 10 children who received IV LEV for non-convulsive SE (NCSE), RSE, or acute repetitive seizures using loading doses of 6.5 to 31 mg/kg and reported NCSE termination in 2 of 2 with NCSE secondary to hypoxic ischemic encephalopathy, acute repetitive seizure termination in 4 of 4, and temporary (12-24 hours) seizure

termination in 3 children with RSE. No patients experienced hypotension, hypertension, bradycardia or tachycardia, rash, or respiratory compromise.[53] The third series reported 10 children who received IV LEV and described SE termination in 1, SE improvement in 1, and acute repetitive seizure termination in 2 without any adverse effects.[58] The fourth series of children who received LEV (IV in 6 and nasogastric in 5) at starting doses of 1 to 70 mg/kg (mean, 30 mg/kg) for RSE described that with a median latency of 1.5 days, 45% either had resolution of RSE or could at least be weaned from continuous infusions with a median latency of 1.5 days without adverse effects. All responders received at least 30 mg/kg/d.[57] Case reports in children have also shown that LEV resulted in improvement in NCSE,[55,56,77] myoclonic SE,[59] migrating partial seizures of infancy,[78] and neonatal RSE.[54]

LEV clearance is dependent on renal function, and maintenance dosage reduction is recommended in patients with renal impairment. LEV completely avoids hepatic metabolism, which may be beneficial in critically ill patients with liver dysfunction or metabolic disorders or in patients at risk for drug interactions. In comparison with other IV anticonvulsants, LEV has few known adverse effects, including a low risk of sedation, cardiorespiratory depression, or coagulopathy, and is thus potentially useful in critically ill children. As described earlier, recent small retrospective case series of IV LEV in critically ill children have reported no adverse effects,[53,57,58,60] and this is consistent with larger studies of critically ill adults.[79-84] A prospective safety study in children and young adults with epilepsy (not actively seizing) who received IV LEV boluses of 20, 40, and 60 mg/kg over 5 to 6 minutes found no significant changes in blood pressure, no local infusion site reactions, and no electrocardiogram abnormalities. These rapid loading doses achieved serum levels of more than 100 mg/mL.[85] There are rare case reports of elevations in liver enzymes,[82] fulminant hepatic failure,[86] and thrombocytopenia.[84,87]

Conclusions

SE is a common medical emergency. There is increasing evidence that early intervention improves response to treatment and outcome. This necessitates the development of out-of-hospital management plans and the implementation of rapid in-hospital management algorithms. Benzodiazepines are considered the first-line medication for SE. If IV access is available, LZP or DZP are appropriate choices although some data favor the use of LZP. If IV access is not available, then the use of nasal, buccal, or rectal benzodiazepines is appropriate. Although PHT is generally considered the second-line medication, there is growing evidence that other anticonvulsants may be good alternatives. A prospective study of second-line medications is needed to better define the roles of PHT, VPA, and LEV in SE management. Although definitive data regarding the optimal management approach to pediatric SE are lacking, the development of organized management algorithms using available data should improve management. The current SE management algorithm used at the Children's Hospital of Philadelphia, Philadelphia, PA, for convulsive SE

in children aged 1 month to 18 years is provided (Fig 1) and is similar to algorithms proposed by physicians at other large pediatric centers.[5,12]

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