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Treatment of convulsive status epilepticus in childhood: Recommendations of the Italian League Against Epilepsy

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Summary

The Italian League Against Epilepsy Commission Guidelines Subcommittee on Status Epilepticus (SE) has published an article on the management of SE in adults, and now presents a report on the management of convulsive status epilepticus (CSE) in children, excluding the neonatal period. Children's greater susceptibility than adults to epileptic seizures results from many factors. Earlier maturation of excitatory than inhibitory synapses, increased susceptibility and concentration of receptors for excitatory neurotransmitters, peculiar composition of the receptor subunits resulting in slower and less effective inhibitory responses, all cause the high incidence of SE in the pediatric population. The related morbidity and mortality rates, although lower than in adults, require immediate diagnosis and therapy. The division into focal and generalized, nonconvulsive and convulsive SE is applied in children and adolescents, as is the distinction in the three different stages according to the time elapsed since the start of the event and the response to drugs (initial, defined, and refractory SE). In children and adolescents, an "operational definition" is also accepted to allow earlier treatment (starting at 5–10 min). Maintenance and stabilization of vital functions, cessation of convulsions, diagnosis, and initial treatment of potentially "life-threatening" causes are the objectives to be pursued in the management of children with CSE. The need for early pharmacologic intervention stresses the need for action in the prehospital setting, generally using rectal diazepam. In hospital, parenteral benzodiazepines are used (lorazepam, diazepam, or midazolam). When first-line drugs fail, sodium phenytoin and phenobarbital should be used. As alternatives to phenobarbital, the following can be considered for treatment of refractory CSE: valproate, levetiracetam, and lacosamide. In cases with refractory CSE, pharmacologic options can be thiopental, midazolam, or propofol in continuous intravenous infusions to suppress electroencephalographic bursts and convulsive activity. These drugs need to be administered in intensive care units to ensure the monitoring and support of vital signs and brain electrical activity.

KEY WORDS: **Epileptic status, Treatment.**

Definition, Classification, Epidemiology, and Etiology

Definition of status epilepticus

Several definitions have been proposed and published over the last 50 years to define the concept of status epilepticus (SE). However, there is still no universally accepted definition, particularly about the duration of clinical seizures that is necessary and sufficient to define SE. In 1993, the International League Against Epilepsy (ILAE; Commission on Epidemiology & Prognosis, International League Against Epilepsy, 1993) and the Epilepsy Foundation of America (Epilepsy Foundation of America's Working Group on Status Epilepticus, 1993) defined SE as a condition in which a single attack or more seizures continue for >30 min without recovery of function/consciousness. Similarly, the study group of the Italian

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League Against Epilepsy (LICE)—within the guidelines of SE in adults—adopted the following definition:

> SE is a clinical situation characterized by continuous seizure activity (generalized or partial, with or without motor manifestations) lasting for more than 20 min or seizures recurring at very short intervals (<1 min) establishing a persisting epileptic condition.

(Minicucci et al., 2006). The essential element of these definitions is the chosen time criterion. Clinical and experimental evidence has suggested that persistent epileptic activity (particularly longer than 20–30 min), especially if convulsive, has the potential not only to cause direct neuronal damage (even when brain oxygenation is adequate), but also to induce systemic effects potentially damaging to the central nervous system (CNS) (Meldrum & Brierley, 1973; Meldrum & Horton, 1973; Meldrum et al., 1973; Meldrum, 1983; Nevander et al., 1985; Lothman, 1990; VanLandingham et al., 1998; DeLorenzo et al., 1999). In addition to these so-called "injury based" definitions, useful in epidemiologic research, the evidence that a single seizure rarely lasts for longer than 2–10 min (Kramer & Levisohn, 1992; Theodore et al., 1994; Shinnar et al., 2001) has suggested the possibility of incorporating a working definition ("operational definition") that allows treatment to be started promptly (Lowenstein et al., 1999) and that limits the temporal criterion. Shinnar suggests that a cutoff of 5–10 min may be appropriate for the definition of SE in relation to the appropriate timing for starting treatment (Shinnar & Hesdorffer, 2010).

Classification

SE can be classified according to different parameters: clinical features, duration and etiology of the seizures. Although there have been several classifications of SE based on the underlying epileptic syndrome over the years (Gastaut, 1983; Engel, 2006; Shorvon, 2010), a first, fundamental distinction is between convulsive (CSE) and nonconvulsive SE (NCSE). The latter, including different situations involving mainly an impaired state of consciousness (absences, obnubilation, psychomotor slowing), with absent or minor motor activity (focal rhythmic clonus, repeated blinking, simple or complex gestural automatisms), is not the subject of this article. It should be borne in mind that the initial drug treatment of CSE can prevent or blunt motor manifestations, whereas ictal electric activity consistent with NCSE may persist.

The distinction between general and partial status epilepticus is based on the presence of unilateral or bilateral motor manifestations, as well as on focal or generalized ictal electrical activity. This distinction is fundamental in directing an appropriate diagnostic workup.

Depending on the duration of the event, which reflects the response to treatment, CSE can be divided into initial CSE (duration <20–30 min); defined CSE (duration 30–60 min); refractory CSE (lasting >60 min) (Lothman, 1990).

Several etiologic classifications of CSE have been proposed (Gastaut, 1983; Commission on Epidemiology & Prognosis, International League Against Epilepsy, 1993; Riviello et al., 2006; Chin et al., 2006) with different prognostic implications (see Etiology).

Epidemiology

Epidemiologic studies in children, mainly retrospective, have analyzed the frequency and the risk factors for CSE in patients younger than 15 years of age (Hussain et al., 2007; Nishiyama et al., 2007; Stroink et al., 2007; Singh et al., 2010). The frequency of CSE is affected by socioeconomic factors and race.

Only one population-based prospective study has been carried out on CSE in pediatric patients (Chin et al., 2006). This two-year study enrolled 226 children with CSE living in north London, aged between 1 month and 15 years. Approximately 22% had other episodes of CSE over the following 2 years. The annual incidence of CSE was 17–23 episodes per 100,000 individuals, more than in adults (4–6 per 100,000 individuals). The incidence was higher in the first year of life (51/100,000 children/year) than in older age groups (29, 9, 2/100,000/year, respectively in the age ranges 1–4, 5–9 and 10–15 years). This is probably related to the fact that in the first year of life the brain is more susceptible to seizures in response to acute insults (electrolyte imbalance, fever, infections, and so on). Fever is the most common cause in children younger than 1 year of age (Raspall-Chaure et al., 2007).

Approximately 15% of pediatric patients with a previous diagnosis of epilepsy have at least one CSE in the course of their history (Sillanpää & Shinnar, 2002); CSE is the mode of onset in 10–20% of cases (Chin et al., 2006). During the 12 months after a first episode of CSE approximately 16% of patients have a second episode, regardless of etiology. The relapse rate, however, is three times higher among those with existing neurologic diseases than among neurologically healthy subjects (Chin et al., 2006).

Two years after the first episode of CSE, the risk of developing epilepsy, usually focal, is estimated at 20–30% in children (Metsäranta et al., 2004)

Neurologic sequelae, mainly cognitive deficits related to both the duration and etiology of CSE, are present in variable percentages of patients (Scott, 2009). The mortality rate within 1 month from the CSE ranges from 3–8% and is related, in children, to the etiology rather than the duration of the CSE (Neville et al., 2007).

Etiology

Pediatric CSE has several causes. The identification of these causes is important to the overall therapeutic approach to the child's illness and the formulation of prognosis.

On the basis of the etiology, children with CSE can be divided into the following subgroups (Commission on

Epidemiology & Prognosis, International League Against Epilepsy, 1993; Berg et al., 2004; Chin et al., 2006; Riviello et al., 2006; Singh & Gaillard, 2009; Singh et al., 2010):

1 Previously healthy children with a first prolonged febrile convulsion;
2 Previously healthy children with an existing diagnosis of prolonged febrile convulsion;
3 Previously healthy children at the first manifestation of an idiopathic epilepsy;
4 Previously healthy children with an existing diagnosis of idiopathic epilepsy;
5 Children with an existing diagnosis of symptomatic epilepsy (both generalized and focal);
6 Children with a history of previous neurologic disorder in the absence of seizures;
7 Previously healthy children with an acute CNS insult;
8 Children with a first episode of CSE, not included in any of the above groups.

The most common etiologies are prolonged febrile seizures, acute CNS insults, and remote neurologic disorders (Berg et al., 1999; Chin et al., 2006; Singh et al., 2009, 2010). In 8.5 to 47.8% of cases, depending on the case series, the cause of the CSE remains unknown.

Although low blood levels of antiepileptic drugs can be detected in up to one third of children being treated for epilepsy presenting to the emergency department with CSE (Riviello et al., 2006), it is not always easy to determine whether this has any causal relationship with the CSE.

The prognosis in children depends mainly on the CSE etiology, although many aspects of the outcome remain uncertain (Neville et al., 2007). Anoxia, CNS infections, and severe head injury are associated with higher mortality, whereas prolonged febrile convulsions and CSE in children with idiopathic epilepsy are associated with significantly lower mortality and morbidity (Arzimanoglou, 2007; Raspall-Chaure et al., 2007) .

The abrupt discontinuation of antiepileptic drugs may lead to a worsening in seizure frequency and to a CSE (Barry & Hauser, 1994; Shorvon, 1994; Maytal et al., 1996). If CSE occurs in patients with existing epilepsy, previous antiepileptic treatment should be continued.

Research Methods and Analysis of the Literature

A task force, appointed by LICE and represented by the authors of this article, performed a literature search through PubMed for the period from 1990–2012 for reports dealing with the diagnosis and treatment of CSE. The findings from a similar LICE document relating to SE in adults, and other documents prepared by members of the working group were also taken into account (Minicucci et al., 2008; Vecchi et al., 2009).

This background material was used for the preparation of a document later examined by the Task Force Coordinator and, finally, by the LICE executive committee before being approved and published on the LICE website.

We used the following three levels of recommendation (PNLG, 2002) based on six levels of evidence:

Grade A

Level 1: Evidence from meta-analysis of randomized controlled trials (RCTs);

Level 1B: Evidence from at least one RCT;

Grade B

Level 2: Evidence from at least one prospective nonrandomized controlled trial;

Level 2B: Evidence from at least one other type of well-designed, quasi-experimental study;

Level 3: Evidence from nonexperimental descriptive studies such as comparative retrospective studies, correlation, and case–control;

Grade C

Level 4: Evidence from expert committee opinions or clinical experience of respected experts, in the absence of good-quality studies.

Diagnostic and Therapeutic Approaches

General criteria

In CSE, prevention of CNS injuries and systemic complications related to prolonged convulsive activity should be achieved. In this effort, diagnosis and treatment are closely related and should be prompt.

Maintenance or stabilization of vital functions, cessation of seizure activity with antiepileptic drugs; diagnosis and initial treatment of potentially "life-threatening" CSE causes (hypoglycemia, meningitis, intracranial hypertension, electrolytic imbalance); and admission, if necessary, to a pediatric intensive care unit for the continuation and monitoring of care are the objectives.

Management of SE in the Prehospital Setting

CSE, especially if generalized, is an emergency that must be dealt with promptly and adequately to reduce morbidity and mortality (Alldredge et al., 2001). Where possible, treatment should begin before arrival at the hospital, even if no venous access is available. Benzodiazepines used in the prehospital setting in the event of a seizure lasting longer than 5 min improve the outcome (Chin et al., 2008). Rectal diazepam (0.5 mg/kg) has been the treatment of choice in the prehospital setting for years.

Buccal transmucosal midazolam (0.5 mg/kg) is at least as effective than rectal diazepam (0.5 mg/kg), is equally safe, and is more socially acceptable (Appleton et al., 2008; Mpimbaza et al., 2008; McMullan et al., 2010; Scott et al., 2012). Nasal transmucosal midazolam (0.2 mg/kg) is more effective and safer than rectal diazepam (Fişgin et al., 2002; Holsti et al., 2007) and as safe and effective as intravenous diazepam (0.3 mg/kg) (Lahat et al., 2000; Mahmoudian & Zadeh, 2004) with an overall shorter time of seizure resolution.

In Italy midazolam has been recently registered for this purpose. Intramuscular midazolam is as safe and effective as intravenous diazepam (Chamberlain et al., 1997; Shah & Deshmukh, 2005) with overall shorter resolution time.

A recent randomized, controlled double-blind study found that midazolam injected intramuscularly by paramedics was as effective as, and safer than, intravenous lorazepam (Silbergleit et al., 2012). The use of intravenous midazolam has been recently authorized in Italy for the treatment of SE.

At present, if rectal diazepam and midazolam have been just administered by medical staff trained in first aid, without cessation of the seizure, minimal interventions to preserve vital functions are recommended (placing the patient supine in a safe place, establishing and maintaining a clear airway, draining secretions and vomit from the mouth, and ensuring a correct position of the head).

Synthesis and recommendation 1 (see Summary)

An epileptic seizure should be treated as early as possible, even in the prehospitalization stage (Level 1B, Grade A). To improve the outcome, caregivers and medical emergency staff should be properly trained in the prehospital management of seizures in patients without venous access (Level 2, Grade B).

Although diazepam formulated for rectal use is currently the drug most commonly used in this context (available in Italy and registered for the purpose), there is recent evidence that midazolam by buccal transmucosal and intramuscular routes could be a safe and effective alternative (Level 1B, Grade A).

Management of SE in the Hospital Setting

General measures

Assessment and stabilization of vital functions in the ABC sequence:

Airway

1 Establish and maintain airway patency;
2 Position the head (if trauma jaw thrust);
3 Aspirate secretions/vomit (mouth-to-nose);
4 Insert oropharyngeal airway tube, in special situations;
5 Ensure a patent airway and administer oxygen (O_2).

Breathing

1 Ensure effective ventilation;
2 Administer O_2;
3 If spontaneous ventilation is ineffective, consider ventilation with Ambu (after positioning nasogastric tube) if necessary;
4 If ventilation with Ambu is ineffective, consider intubation (to protect the airway, ensure adequate ventilation and oxygenation).

Circulation

1 Maintain adequate perfusion
2 Wrist monitor (if any external chest compression pulse and vital signs absent);
3 Monitor blood pressure (BP);
4 Ensure venous access.

Positioning of monitors for heart rate (HR), respiratory rate (RR), blood pressure (BP), O_2 saturation.

Blood sample for: blood glucose test (hemoglucotest), blood gases, electrolytes, serum calcium, serum magnesium, C-reactive protein (CRP), urea and creatinine, complete blood count.

Administration of antiepileptic drugs.

Administration of saline (maintenance).

Treating hypoglycemia/hypovolemia/fever/acidosis/electrolyte imbalance.

Vital signs must be reassessed in the ABC sequence during all phases (pay attention to cardiorespiratory depression induced by antiepileptic drugs). On shifting from initial SE to defined SE, every attempt must be made to establish the cause of SE, correct any metabolic abnormalities, and monitor and treat pathologic changes in blood pressure. In addition, start monitoring the electroencephalography (EEG), if it is not already being done, to confirm the diagnosis and assess the effectiveness of therapy and the need for admission to the intensive care unit for further treatment.

Drug treatment

Initial CSE

Benzodiazepines are the first-line drugs for the treatment of initial CSE (Leppik et al., 1983; Shaner et al., 1988; Appleton et al., 1995; Treiman et al., 1998; Hubert et al., 2009; Sreenath et al., 2010). In the pediatric population, intravenous lorazepam is as effective as intravenous diazepam. Children receiving lorazepam intravenously are less likely to (1) require additional doses of anticonvulsant drugs to stop the seizures; (2) develop respiratory depression; and (3) require admission to an intensive care unit (Appleton et al., 1995, 2008).

Intramuscular midazolam is as effective and safe as intravenous diazepam (Chamberlain et al., 1997; Shah & Deshmukh, 2005), with a shorter overall time of seizure resolution (considering the time required for positioning the venous access), and is as safe and effective as intravenous lorazepam (Silbergleit et al., 2012).

Giving more than two consecutive doses of benzodiazepines can increase the risk of respiratory depression (Stewart et al., 2002; Chin et al., 2004a,b).

Synthesis and recommendation 2

Intravenous lorazepam or diazepam is indicated for the initial treatment of CSE in children. Intravenous lorazepam, if available, is preferred, with a lower risk of relapse and respiratory depression (Level 1B, Grade A). If no intravenous access can be located, intramuscular midazolam is an alternative to intravenous benzodiazepines (Level 1B, Grade A). This drug has been recently authorized in Italy for the treatment of SE.

Benzodiazepines can cause respiratory failure, as well as sedation. It is advisable to avoid administration of more than two doses of benzodiazepines (including the dose administered in the pre-hospital setting) (Level 3, Grade B).

Dosage

Available venous access:

Intravenous lorazepam: 0.1 mg/kg (maximum dose 4 mg)

Or:

Intravenous diazepam: 0.5 mg/kg (maximum dose 10 mg);

Intravenous midazolam: 0.2 mg/kg (maximum dose 5 mg) (recently registered for this use in Italy).

No venous access available

Buccal midazolam 0.5 mg/kg (maximum dose 10 mg) (pending registration for this use in Italy)

Intramuscular midazolam: 0.2 mg/kg (maximum dose 5 mg)

Buccal lorazepam: 0.1 mg/kg (maximum dose 2.5 mg)

Definite CSE

Sodium phenytoin and phenobarbital are the options to consider if benzodiazepines fail. There are no comparative studies in children of phenytoin and phenobarbital. In adults, phenobarbital is more effective than phenytoin, but is just as effective as phenytoin associated with diazepam (Treiman et al., 1998). Except in neonatal infants, phenytoin is usually preferred to phenobarbital as it has fewer side effects in terms of cardiovascular depression, sedation, and risk of cardiorespiratory depression than phenobarbital given after benzodiazepines (Appleton et al., 2000; Milh et al., 2009).

In some therapeutic CSE protocols in childhood, sodium phenytoin and phenobarbital are not used sequentially, but alternating (Appleton et al., 2000; Advanced Life Support Group, 2004; New South Wales Department of Health, 2006). When used in sequence, as suggested by the present protocol, generally phenytoin precedes phenobarbital on account of its better safety profile and the lower likelihood of cardiorespiratory depression, especially when benzodiazepines have already been used (Appleton et al., 2000).

The decision to use them in sequence or alternately, preferring one drug to the other, must take into account the following: (1) the practice and experience of the medical personnel in the use of one of the two drugs; and (2) their ability to manage the side effects.

Other drugs (not yet registered with this indication in Italy) have been reported for the treatment of definite SE as an alternative to sodium phenytoin and phenobarbital: valproic acid, levetiracetam, and lacosamide (see section "Nondrug options"). Two randomized-controlled trials (RCTs) including children showed that valproic acid was equivalent (Agarwal et al., 2007) or more effective (Misra et al., 2006) than phenytoin in the treatment of CSE after failure of benzodiazepines, with no significant difference in side effects.

In a recent randomized, double-blind study in children younger than 2 years with persistent CSE after intravenous diazepam, intravenous bolus injection of valproic acid was more effective and better tolerated than intravenous bolus injection of phenobarbital (Malamiri et al., 2012).

Synthesis and recommendation 3

After failure of benzodiazepines, phenytoin is the preferred drug, possibly followed by phenobarbital (Level 2B, Grade B). Valproic acid offers a valid alternative to phenytoin and phenobarbital (Level 1B, Grade A). It should be used with extreme caution, however, particularly in young children, when a possible metabolic etiology has not been ruled out.

Intravenous Sodium Phenytoin

1 Recommended dosage: 18–20 mg/kg (maximum dose 1 g);
2 Must not be injected faster than 1 mg/kg/min (i.e., usually at least 20 min);
3 Must be diluted in saline because it does not dissolve in glucose solution;
4 Should be diluted to a concentration not exceeding 10 mg/ml
5 Should be infused using an independent venous access in a large caliber vessel (if possible) to reduce the risk of phlebitis (depending on the child's age);
6 Heart rate and blood pressure should be monitored;
7 Can cause side effects such as sedation (rare), hypotension, cardiac arrhythmias, "purple glove syndrome," and skin reactions of varying severity up to Stevens-Johnson syndrome;
8 Respiratory depression is possible, but very rare;

9 Is contraindicated in patients with grade II atrioventricular block or severe hypotension;

Phenytoin may be replaced by fosphenytoin, phenytoin prodrug, given by intravenous or intramuscular injection. Fosphenytoin has fewer side effects than phenytoin; in particular it has a lower risk of reaction at the injection site. However, this drug is still not available commercially in Italy.

Intravenous Phenobarbital

1 Recommended dosage: 15–20 mg/kg (maximum dose 1 g);
2 Must not be injected faster than 1 mg/kg/min (i.e., usually at least 20 min);
3 Must be diluted to a concentration not exceeding 10 mg/ml with water for injections;
4 Can cause side effects such as sedation, respiratory depression, or hypotension;
5 In spontaneously breathing patients it should be administered with a resuscitator and/or trained medical personnel available to support advanced ventilation (through ventilation with Ambu and mask and oral or nasotracheal intubation) and treat hypotension;
6 Heart rate should be closely monitored with a monitor including, electrocardiography, and blood pressure.

Refractory CSE

If, after all above actions, seizures persist, the patient should be transferred to an intensive care unit for induction of coma (midazolam, barbiturates, propofol).

In children, EEG monitoring of refractory CSE follows the same rules as in adults. The induction and management of drug-induced coma should be complemented by continuous EEG monitoring of brain activity. It is best to achieve an alternating suppression-burst pattern with respect to the suppression of electrical activity in order to avoid side effects such as CNS hypotension (Gilbert et al., 1999; Krishnamurthy & Drislane, 1999).

Refractory CSE carries high mortality rates, mainly related to the underlying etiology (Chin et al., 2006; Raspall-Chaure et al., 2007; Lambrechtsen & Buchhalter, 2008; Kravljanac et al., 2011). Prognosis is more severe when CSE occurs in the course of encephalitis (Kramer et al., 2005).

There are no randomized trials for the treatment of refractory SE in children, but retrospective reviews can be found about the type of drug used (midazolam, sodium thiopental, propofol), as well as expert opinions and guidelines (Van Gestel et al., 2005; Morrison et al., 2006; Mehta et al., 2007; Abend & Dlugos, 2008; Prasad, 2009; Lampin et al., 2010; Friedman, 2011; Loddenkemper & Goodkin, 2011; Schreiber & Gaillard, 2011; Shearer & Riviello, 2011; Mastrangelo & Celato, 2012; Sasidaran et al., 2012) correct. The guidelines differ from country to country depending on the sedatives commercially available and the legislative regulations. In CSE refractory to first- and second-line drugs, the alternative use of midazolam, has been recently authorized in Italy.

Synthesis and Recommendation 4

After the failure of first- and second-line drugs (benzodiazepines, phenobarbital, and/or phenytoin), 30 min after parenteral CSE treatment, patients should be admitted to the intensive care unit and, taking into account their general conditions, underlying etiology and the possible drug side effects coma should be induced with midazolam, thiopental sodium, or propofol (Level 4, Grade C).

The induction and management of drug-induced coma requires continuous EEG monitoring for the attainment of a suppression-burst pattern (Level 4, Grade C).

Intravenous Sodium thiopental

1 Induction of barbiturate coma: bolus of 3 mg/kg, repeated after 2 min, followed by maintenance (1–15 mg/kg/h) to control seizures and/or achieve "suppression-burst "EEG activity (increasing 1 mg/kg/h every 2 min);
2 The subsequent maintenance infusion should continue for 12–48 h;
3 During the infusion, continuous EEG monitoring should be maintained;
4 Usually causes respiratory depression when induction is carried out in intubated and ventilated patients; can also induce hypotension and heart failure, and sometimes pharmacologic support for pressure and circulation is necessary;
5 Contraindicated in the presence of hypotension, cardiogenic shock, sepsis.

Notes: short half-life, need for continuous infusion due to redistribution to other tissues, especially adipose tissue, and its slow metabolism; the sedative effect frequently persists after discontinuation.

Intravenous Propofol

1 1–5 mg/kg bolus (repeatable) followed by continuous infusion up to a maximum of 5 mg/kg/h;
2 Requires continuous EEG monitoring;
3 Can cause hypotension and arrhythmias, so heart rate and rhythm and blood pressure must be monitored to implement compensatory pharmaceutical measures;
4 When used at high doses and for prolonged periods, may cause "propofol syndrome" involving metabolic acidosis, rhabdomyolysis, arrhythmias, heart failure, kidney failure, hepatomegaly, and possible death (Harrison et al., 1997; Riker et al., 2009);
5 Liver problems may arise (Rason & Ko, 2009), either isolated (hypertriglyceridemia) or together with systemic problems.

Note: short half-life, need for continuous infusion. Not subject to tachyphylaxis or accumulation effect, so on discontinuation the patient wakes faster. The optimal dose

has not yet been established, so the maximum dose recommended is continuous infusion of 5 mg/kg/h; because of possible serious side effects, its use requires careful assessment of benefits and risks for each individual patient.

Intravenous midazolam

1 Bolus of 0.2 mg/kg; if clinical and/or electrical seizures cease continue with maintenance of 0.06 mg/kg/h;
2 If there is no response after 15 min, inject a second bolus of 0.2 mg/kg and start infusion at 0.5 mg/kg/h;
3 If there is no response after another 15 min, increase infusion to 1 mg/kg/h and assess response;
4 Requires continuous EEG monitoring to assess response and decide tapering;
5 Can lead to respiratory depression in spontaneously breathing patients;
6 Can lead to metabolic acidosis, reversible on discontinuation, and hypotension.

Note: rapid duration of action, subject to tachyphylaxis, so needs continuous infusion; induces accumulation with prolongation of drug half-life if used for long periods. Does not induce respiratory depression when medical care is adequate (anesthesiologists) and when administered for a short time; can be used as first drug for refractory CSE. Its use has recently been authorized for the treatment of SE in Italy

Given the absence of clear evidence, the decision to use the first or other sedative medications must take into account the patient's general condition, weighing the risks and benefits against the potential adverse effects of the medication, and the medical staff 's experience in the use of these drugs and their ability to manage the side effects (Koul et al., 1997; Holmes and Riviello 1999; Brevoord et al., 2005; Tasker, 2006; Hayashi et al., 2007; Federman et al., 2009).

Should these drugs fail or be contraindicated, other pharmacologic options are given in the section "Other pharmacologic options" (high-dose phenobarbital, levetiracetam, lacosamide, topiramate, isoflurane, and ketamine).

These drugs are not always reported in protocols in the literature, but can be effective.

Other pharmacologic options

Valproic acid

Two RCTs including children have shown that valproic acid is equivalent to (Agarwal et al., 2007) or more effective than (Misra et al., 2006) phenytoin in the treatment of CSE after the failure of benzodiazepines, with no significant difference in side effects. In a recent randomized, double-blind study in children younger than 2 years with persistent convulsive SE after intravenous diazepam, intravenous valproic acid bolus was more effective and better tolerated than intravenous phenobarbital bolus (Malamiri et al., 2012).

Synthesis and recommendation 5

After the failure of benzodiazepines, valproic acid may be an alternative to phenytoin and phenobarbital (Level 1B, Grade A), although the drug is not registered in Italy for the treatment of SE. It should be used with caution, however, particularly in young children when a possible metabolic etiology has not been ruled out.

With the preceding recommendation, after the failure of benzodiazepines and second-line drugs for SE (phenytoin or phenobarbital) and when there is delay or difficulty in intubation and starting mechanical ventilation, valproic acid may be an effective alternative, based on experts' opinions (Level 4, Grade C).

1 Dosage: bolus 30–45 mg/kg (maximum dose 1.5) as a 15-min intravenous infusion (some protocols suggest more rapid infusion but the rate should always be less than 200 mg/min); the bolus can be followed by continuous infusion of 1–2 mg/kg/h depending on clinical course;
2 Valproic acid has the advantage of rarely inducing hypotension, respiratory depression, or excessive sedation (occasional hypotension/respiratory depression may be seen during infusion);
3 This drug is not registered in Italy for the treatment of SE;
4 This drug is contraindicated in cases with liver disease, or suspected metabolic disease, and must be avoided or used with extreme caution in children, especially those younger than 3 years, if the SE etiology is not known.

Intravenous high-dose phenobarbital

Anecdotal cases or small case series are reported in the literature about the use of high doses of phenobarbital in refractory CSE after failure of first- and second-line drugs. Effectiveness is reached with a mean plasma level of 114 μg/ml (Crawford et al., 1988; Lee et al., 2006).

Synthesis and recommendation 6

In cases with refractory CSE and contraindications to the use of sodium thiopental and propofol, high-dose phenobarbital can be considered for induction of coma (Level 4, Grade C).

1 Dosage: bolus of 20 mg/kg followed by maintenance to achieve plasma levels at least higher than 100 μg/ml (maximum daily dosage 80–120 mg/kg);
2 In patients intubated and ventilated after failure of first- and second-line drugs;
3 Possible side effects: hypotension, respiratory infections;
4 Possible prolonged sedative effect on discontinuation.

Levetiracetam

There are no RCTs on the use of levetiracetam in pediatric CSE, but retrospective reports can be found of small groups of patients (aged 2 days to 18 years) presenting

refractory SE and treated intravenously or by oral bolus (Patel et al., 2006; Goraya et al., 2008; Abend et al., 2009; Gallentine et al., 2009; Gámez-Leyva et al., 2009; Kirmani et al., 2009). Advantages of levetiracetam are good tolerability, possibility of administration in a relatively short time, and absence of hemodynamic and sedative effects. Further studies are needed to compare its effectiveness in defined SE in comparison with phenytoin and phenobarbital. Levetiracetam is not registered in Italy for the treatment of SE.

Synthesis and recommendation 7

Levetiracetam in intravenous formulation may be a therapeutic option in SE, especially if other drugs are contraindicated and/or the SE is refractory, but it is not yet registered in Italy for this indication (Level 4, Grade C).

1 Dosage: bolus of 13–70 mg/kg (maximum dose 4 g), typical starting dose 30 mg/kg in 15-min intravenous infusion (from 5 to 60 min) for a total of 100 ml (but at high concentration and low volume: 50 mg/ml);
2 The drug can be administered through a nasogastric tube;

In cases where it was effective, seizures stopped in 25–30 min after intravenous injection and in 1.5 days when given through a nasogastric tube;

1 This drug can be used for continued oral therapy, does not cause significant side effects, and needs no preliminary check of renal function;

Topiramate

There are anecdotal case reports, retrospectively evaluated, of children (age 2 months to 11 years) with refractory CSE treated with oral topiramate. It was reported to result in rapid CSE resolution (<24 h) with no hemodynamic or sedative side effects (Kahriman et al., 2003; Blumkin et al., 2005; Perry et al., 2006; Perucca, 2009; Akyildiz & Kumandaş, 2011).

Synthesis and recommendation 8

Topiramate administered by nasogastric tube in refractory CSE can induce rapid resolution, with no significant side effects (Level 4, Grade C).

1 Dosage: administration through nasogastric tube in refractory CSE at an initial dose of 5–10 mg/kg/day for two days followed, if there is a response, by maintenance at 5 mg/kg/day;
2 Possible efficacy in 24–48 h;
3 Possible side effects: metabolic acidosis, decreased sweating, glaucoma.

Isoflurane

Anesthetics such as isoflurane have been effective in refractory CSE in children (individual case reports and small series of adults and children) (Kofke et al., 1989). The authors agree on the use of these drugs only after the failure of others or when serious side effects may result from the use of other drugs.

Synthesis and recommendation 9

In CSE refractory to barbiturate and other drugs the anesthetics can be used, taking into account the risks and benefits, and in the presence of personnel trained in the use of such drugs. (Level 4, Grade C).

1 Dosage: administered to 0.8–2 vol%, with possible variations to maintain;
2 "suppression-burst" EEG activity;
3 Can induce hypotension so close hemodynamic monitoring is necessary, with inotropic therapy;
4 Can lead to atelectasis, paralytic ileus, and deep vein thrombosis.

Lidocaine

Data on the use of lidocaine in pediatric patients are insufficient, so it is not recommended and its use should be limited to cases of refractory CSE.

1 Dosage: 2 mg/kg intravenous bolus, not to exceed 50 mg/min. The bolus may be repeated once if necessary and followed by maintenance of 2 mg/kg/h.
2 Possible hypotonia, hallucinations, and bradyarrhythmias.

Ketamine

Ketamine acts as an *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonist, and can be useful in refractory CSE. There are anecdotal reports of oral or intravenous use (Sheth & Gidal, 1998; Mewasingh et al., 2003; Kramer, 2012). However, given the limited experience and possible side effects (hypertension, cerebellar toxicity) its use should be limited to cases of refractory CSE.

Synthesis and recommendation 10

The use of ketamine should be limited to CSE cases refractory to sedatives, barbiturates or not, in which risks and benefits have been thoroughly assessed (Level 4, Grade C).

1 Possible oral use at 1.5 mg/kg/day for 2–5 days;
2 Possible intravenous use at 2 mg/kg followed—in the event of effectiveness—by intravenous maintenance at maximum 7 μg/kg/h;
3 Can cause high blood pressure, so it is contraindicated in cases with intracranial hypertension, tachycardia, and respiratory depression; possible cerebellar toxicity.

Lacosamide

Anecdotal pediatric CSE cases successfully treated with lacosamide are reported. The bolus dose has not been established. Lacosamide at a dose of 25 mg × 2/day was effective in a single case of pediatric CSE. In Italy, however, lacosamide is registered only for the treatment of drug-resistant partial seizures in patients older than

16 years of age. It may prolong the PR interval, so its use should be carefully evaluated in patients with heart concerns.

Nondrug options

Alternatives to drug treatment are resective surgery, vagus nerve stimulation, ketogenic diet, hypothermia, and electroconvulsive treatment, the use and outcome of which in the literature is limited to anecdotal cases. Prospective studies are needed to assess the real efficacy and safety of these treatment options in refractory CSE.

Summary and Recommendations

Synthesis and recommendation 1

Treatment of CSE should be performed as early as possible already during the prehospitalization phase (Level 1B, Grade A).

To improve outcome, caregivers should be properly trained in the prehospital treatment of seizures in the absence of venous access (Level 2, Grade B).

Although the drug commonly used in this context (as available in Italy and registered for this purpose) is currently represented by diazepam in its formulation for endorectal use, recent evidence shows that buccal and intramuscular midazolam could be a safe and effective alternative (Level 1B, Grade A).

Synthesis and recommendation 2

Intravenous lorazepam or diazepam is indicated for the initial treatment of CSE in children. Intravenous lorazepam, if available, is the preferred choice, with a lower risk of relapse and of respiratory depression (Level 1B, Grade A).

If no intravenous access can be readily located, intramuscular midazolam is a valuable alternative to intravenous benzodiazepines (Level 1B, Grade A). The use of midazolam for the treatment of SE has been recently authorized in Italy.

Benzodiazepines can cause respiratory depression, as well as sedation. It is advisable to avoid more than two doses of benzodiazepines (including the dose administered in the prehospital setting) (Level 3, Grade B).

Synthesis and recommendation 3

After failure of benzodiazepines, phenytoin is the preferred treatment, possibly followed by phenobarbital (Level 2B, Grade B).

Valproic acid offers a valuable alternative to phenytoin and phenobarbital (Level 1B, Grade A), although it is not registered in Italy for the treatment of CSE. It should be used with extreme caution, however, particularly in young children, if a possible metabolic etiology has not been ruled out.

Synthesis and recommendation 4

If first- and second-line drugs are ineffective (benzodiazepines, phenobarbital, and/or phenytoin) 30 min after the parenteral treatment of the CSE, coma should be induced (midazolam, thiopental sodium, propofol), with the patients in the intensive care unit and taking into account the general condition, the underlying etiology and the possible side effects of these drugs (Level 4, Grade C).

Induction and management of drug-induced coma requires continuous EEG monitoring for the attainment of suppression-burst EEG activity (Level 4, Grade C).

Synthesis and recommendation 5

After the failure of benzodiazepines, valproic acid may be an alternative to phenytoin and phenobarbital (Level 1B, Grade A), even if the drug is not registered in Italy for the treatment of CSE. It should be used with extreme caution, however, particularly in young children if a metabolic etiology has not been not ruled out.

With the above recommendations, after the failure of benzodiazepines and second-line drugs (phenytoin or phenobarbital) and when there is delay or difficulty in intubation and starting mechanical ventilation, valproic acid may be a valuable treatment option, based on expert opinions (Level 4, Grade C).

Synthesis and recommendation 6

In cases with refractory CSE and contraindications to the use of sodium thiopental or propofol, high-dose phenobarbital can be used to induce coma (Level 4, Grade C).

Synthesis and recommendation 7

Levetiracetam and lacosamide in intravenous formulation may be a therapeutic option in SE, especially if other drugs are contraindicated and/or the CSE is refractory, and taking into account that they are not registered for this indication in Italy (Level 4, Grade C).

Synthesis and recommendation 8

Topiramate administered by nasogastric tube in refractory CSE can induce rapid seizure resolution, with no significant side effects (Level 4, Grade C).

Synthesis and recommendation 9

In the case of CSE refractory to barbiturates and other drugs, anesthetics should be considered, taking into account their risks and benefits, if medical personnel trained in their use are available (Level 4, Grade C)

Synthesis and recommendation 10

Ketamine and lidocaine should be used only in cases with CSE refractory to the other drugs previously indicated and where the risks and benefits have been assessed (Level 4, Grade C)

Disclosures

The authors declare no conflicts of interest.

We confirm that we have read the Journal position on issue involved in ethical publication and affirm that this report is consistent with these guidelines.

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