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Consensus paper

Standards of care for adults with convulsive status epilepticus : Belgian consensus recommendations

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Abstract

Status epilepticus (SE) is a significant health problem, affecting approximately 1,000 to 4,000 individuals per year in Belgium. A workshop was convened by a panel of neurologists from major Belgian centers to review the latest information relating to the definition, diagnosis and treatment of convulsive SE. The panelists sought to make recommendations for practising neurologists, but also primary care physicians and physicians in intensive care units when initiating emergency measures for patients with convulsive SE.

As there is an association between prolonged seizures and a poor outcome, the importance of early (within the first 5 minutes of seizure onset) and aggressive treatment is to be stressed. In addition to general systemic support (airway, circulation), intravenous administration of the benzodiazepines lorazepam or diazepam is recommended as first-line therapy. Intramuscular midazolam may also be used. If SE persists, second-line drugs include phenytoin or valproate, and third-line drugs the barbiturate phenobarbital, the benzodiazepine midazolam, or the anaesthetics thiopental or propofol, or eventually ketamine. If the patient does not recover after therapy, monitoring of seizures should involve an electroencephalogram to avoid overlooking persistence of clinically silent SE. As a general rule, the intensity of the treatment should reflect the risk to the patient from SE, and drugs likely to depress respiration and blood pressure should initially be avoided.

If initial treatment with a benzodiazepine fails to control seizures, the patient must be referred to the emergency unit and a neurologist should be contacted immediately.

Key words : Epilepsy ; seizures ; status epilepticus ; antiepileptic drugs ; consensus.

Objectives of the workshop

On the 22nd of December 2004 and 26th of January 2005, a two-part consensus meeting was held in Brussels with the purpose to discuss the current state-of-the-art in the definition, diagnosis and treatment of convulsive status epilepticus. At present, there are several guidelines dealing with this important topic, while at the same time important new information from clinical studies have become available. A group of 8 invited experts in the field of epilepsy discussed the current state of knowledge. On the basis of the available information, the expert panel aimed to make pragmatic consensus recommendations for neurologists, but also for general physicians and physicians in emergency and intensive care units. The present paper focuses on SE in adults and is limited to the convulsive form. Further recommendations will be elaborated on non-convulsive SE.

Introduction

Seizures are usually self-terminating. If seizures are so frequently repeated or so prolonged as to create a “fixed and enduring epileptic condition”, they are termed status epilepticus (SE) (1). SE encompasses a wide range of seizure types with different clinical presentations, pathophysiologies, treatment modalities, and outcomes.

SE is a medical and neurological emergency. The most dramatic and life-threatening form is generalized convulsive SE. Given the significant risk of mortality, and the possibility of successful intervention, it is essential for all physicians to effectively identify and treat patients in SE.

Definition

There is no generally agreed definition of SE. Basically, it is based on the clinical manifestation (a prolonged seizure or a series of seizures during which the patient has incomplete recovery of consciousness) and duration (2). The International League Against Epilepsy was unspecific in their 1981 definition of SE, describing the time elements as “sufficient length” and “frequently enough” (3). About a decade ago, the Epilepsy Foundation of America’s Working Group on Status Epilepticus defined the condition as two or more sequential seizures without full recovery of consciousness between seizures, or more than 30 minutes of

continuous seizure activity" (4). While this definition is generally accepted (5), it is impractical in daily routine conditions. By the same token, a more suitable, operational definition was proposed by Lowenstein *et al.*, defining SE as a continuous, generalized, convulsive seizure lasting greater than five minutes (in an adult or a child older than five years), or two or more seizures during which the patient does not return to baseline consciousness (6). The recent hallmark studies (Veterans Administration Cooperative Trial (7), Pre-Hospital Treatment of SE (8)) investigating the treatment of SE used seizure times of ten and five minutes, respectively.

The Belgian consensus group recommends that any person who exhibits persistent seizure activity for five minutes or more should be considered to be in SE. For practical purposes, any person still seizing upon arrival of medical help should be considered to be in SE.

Classification

At present, there is no generally accepted international consensus on a classification system for SE (5). Many schemes have been generated that rely on both clinical and electroencephalographic (EEG) findings.

It is important to note that virtually all seizure types may become prolonged, thereby fulfilling the definition of SE. In other words, as there are many types of seizures, there are many types of SE (9). It has been recognized increasingly that SE is a dynamic state that changes over time even within one episode (10).

The Belgian consensus group encourages using a simple, clinical approach. From a clinical perspective, the most elemental division is that of convulsive and non-convulsive SE (9). Nonconvulsive seizures and SE are subtle with a variety of clinical manifestations such as coma, confusion, somnolence, altered affect, fugue status, aphasia, delusions, hallucinations and paranoia (11). The focus of the present recommendation is on convulsive seizures and SE that are easily recognisable.

Aetiology

There are various causes for SE. The most frequently noted aetiology in adults in a hospital or community setting are non-compliance or withdrawal of antiepileptic drugs (25% of cases), followed by cerebrovascular disease (23%), remote symptomatic causes (19%), alcohol withdrawal (15%), metabolic disorders (13%), hypoxia (12%), and infectious disorders (8%) (12).

Epidemiology and mortality

In the US, annual incidence rates of SE in adults of 18-41 in 100,000 individuals have been reported (13, 14). An important new contribution from the EPISTAR study in the French-speaking cantons of Switzerland, which reports the only European data on this topic, found a substantially lower rate of 10 in 100,000 inhabitants per year (15). The discrepancy may stem from the lack of a homogeneous, rigorous, and pragmatic definition of SE and the efficient management of acute repetitive seizures in this area (15). When translating these US and Swiss data to the Belgian population, about 1,000 to 4,000 individuals in Belgium experience a SE event annually.

A bimodal distribution is noted, with SE occurring most frequently during the first year of life and after the age of 60 years. In the latter group, the incidence is about 86 in 100,000 per year (13, 14).

The mortality from SE, defined as death within 30 days of event, is substantial. In the Richmond study, the rate in adults was 26%, while the elderly population had the highest rate of mortality at 38% (13, 16). The primary determinants of mortality in persons with SE were duration of seizures, age at onset, and aetiology (16). While patients with anoxia and stroke had a very high mortality rate, patients with SE due to alcohol withdrawal or low levels of AEDs had a relatively low mortality rate (5).

The general systemic effects of SE are described in Table 1.

Pharmacological treatment

The ideal antiepileptic drug (AED) has well defined properties : it should be easy to handle and to administer, available via the parenteral route, have a high availability in the CNS and a rapid onset of action, while having favourable pharmacokinetics. In addition, it should be well tolerated and safe.

The following section reviews the pharmacological classes of medications (summarized in Table 2) and the rationale for their use in SE.

Benzodiazepines (BZD) are among the most effective drugs in the initial treatment of acute seizures and SE. The BZD most commonly used to treat SE are diazepam, lorazepam, and midazolam. By binding to high-affinity sites on the neuronal membrane adjacent to the γ-aminobutyric acid ($GABA_A$) receptor, they enhance the affinity of the receptor for its ligand. This results in enhanced hyperpolarisation and reduction of sustained and repetitive neuronal firing (17), which is a mechanism similar to that of phenytoin and carbamazepine (18). Important side effects include respiratory depression, sedation and hypotension. Therefore the clinician should be prepared to intubate or to give pressors if indicated (2).

Diazepam (Valium®), is highly lipid soluble, crosses the blood-brain barrier rapidly, and may have an

Table 1

Overview on the systemic effects of status epilepticus

Body system	Effects	Reference
Lungs	Metabolic and respiratory acidosis _ pH of arterial blood gases often ↓ (clinical significance or prognostic value unknown)	(46)
	Pulmonary vascular pressure ↑, may contribute to pulmonary edema[a]	(47, 48)
Heart	Tachycardia due to sympathetic overdrive. Potentially fatal arrhythmias	(49)
Muscle	Lactate acidosis due to anaerobic metabolism	(50)
Blood chemistries	White blood cell count often ↑, hyperglycemia followed by hypoglycemia	(46)
Vital signs		
Blood pressure	Systemic blood pressure ↑. In prolonged SE, normalisation of BP or hypotension.	(46)
Temperature	With progression of SE : ↑	(46)
Respiratory rate	Transient change in respiratory rate and tidal volume	(46)
	Central hypoventilation[a]	(51)

Adopted from Bassin *et al.* 2002 (2). ↓ Decreased / below normal. ↑ Increased / above normal.
[a] Animal studies.

Table 2

Drugs used in the treatment of status epilepticus in alphabetical order

Drug	Route of administration	Typical dose in SE		Main adverse effects	Advantages	Disadvantages
		loading	maintenance			
Diazepam	IV (IR)	0.15 mg/kg	4-8 mg/h	respiratory depression hypotension decreased levels of consciousness		short duration of action needs second-line drug
Ketamine	IV	50-100 mg/kg ?	?		theoretical neuroprotective effects	Risk of intracranial hypertension
Lorazepam	IV	0.1 mg/kg	–	see diazepam	ready-to-use formulation ; compared to diazepam, longer duration of action and higher efficacy	need for refrigeration
Midazolam	IV, IM, IB, IN	0.2 mg/kg	1-5 µg/kg/min	see diazepam	hydrosoluble, IM route effective	short duration of action needs additional drug, otherwise high SE recurrence rate
Phenobarbital	IV	20 mg/kg	100-300 mg/d then TDM	respiratory depression hypotension decreased levels of consciousness	long acting	long sedation
Phenytoin	IV	15-20 mg/kg at 50 mg/min elderly : 20 mg/min	300 mg p.o. 4 h after the load then TDM	hypotension QT prolongation	effective as second-line	phlebitis, local necrosis
Propofol	IV	1-3 mg/kg	2-10 mg/kg/h		short duration	propofol infusion syndrome, lipid load
Thiopental	IV	100-200 mg (within 20 sec)	3-5 mg/kg/h	see phenobarbital	see phenobarbital	see phenobarbital
Valproate	IV	30 mg/kg at 3 mg/kg/min	1-5 mg/kg/h then TDM	toxic encelopathy	ease of administration well tolerated compared to alternatives lack of cardiovascular and respiratory depression less sedation	

Adapted from Gaitanis 2003 (9), Manno 2003 (18), Sirven 2003 (5). ? = questionable ; IV = intravenous, IM = intramuscular, IR = intrarectal, IN = intranasal, IB = intrabuccal ; p.o. = per os. ; TDM = therapeutic drug monitoring (according to plasma levels).

antiepileptic effect within as little as one minute (9). However, the drug redistributes rapidly to peripheral fat stores, which reduces its clinical anticonvulsant effectiveness to only 20-30 minutes and accounts for a large relapse rate. For this reason, diazepam use for SE needs to be followed with a second agent (18). Notably, if administered repeatedly, due to its long elimination half-life, diazepam and its metabolites can accumulate, especially in elderly patients.

Intravenous *lorazepam* (Temesta®) is less lipid soluble, binds to the GABAergic receptor more tightly, and has a longer duration of clinical effect than diazepam. It also has a broad spectrum of efficacy, terminating seizures in up to 80% of cases in the Veterans Affairs Status Epilepticus Cooperative Study Group trial (7). Thus, it is the preferred BZD for the acute management of SE (5, 9, 19). The anticonvulsant effects of lorazepam last 6 to 12 hours, and its side effect profile is identical to that of diazepam.

Midazolam (Dormicum®) unlike other BZD is water soluble in acidic solutions, but becomes lipid soluble at physiologic pH. The drug can be administered intramuscularly which makes it an attractive choice when secure intravenous access cannot be obtained (20). Alternative routes of administration are intrabuccal and intranasal. However, clinical experience with these routes is limited. In view of the extremely short duration of action and high recurrence rate of seizures, midazolam is rarely used in first-line treatment (5, 18).

Phenytoin (Diphantoine®) is an antiepileptic drug that limits the repetitive firing of action potentials through the slowing of the rate of recovery of voltage-activated sodium channels (18). Because of its efficacy, absence of sedation or respiratory suppression, intravenous phenytoin has largely replaced phenobarbital (phenobarbitone) as the second agent of choice (following the administration of a benzodiazepine) in the treatment of convulsive SE. While the efficacy of phenytoin is well established, the parenteral formulation of phenytoin has several inherent shortcomings which compromise its tolerability and limit the rate of administration. Intravenous phenytoin has been associated with fatal haemodynamic complications, cardiac arrhythmia and serious reactions at the injection site including skin necrosis and amputation of extremities (21).

Valproate (Depakine®) is a broad spectrum AED, being effective against all seizure types (22). Its pharmacological effects involve a variety of mechanisms, including increased GABAergic transmission, reduced release and/or effects of excitatory amino acids, blockade of voltage-gated sodium channels and modulation of dopaminergic and serotoninergic transmission. Intravenous valproate has been used in several case series and small studies in nonconvulsive and convulsive SE with favourable outcomes (23-27).

Phenobarbital and thiopental (Pentothal®) are barbiturates that prevent seizure activity by increasing $GABA_A$-mediated cellular inhibition, which is similar to the mode of action of BZD (but may involve different isoforms of the $GABA_A$ receptor) (28). The drugs are extremely effective in producing coma and achieving burst suppression on EEG (2). However, as they depresses respiration and central cardiovascular function, they may trigger a shock-like condition requiring medical support (9). Phenobarbital is sometimes considered as another option for initial therapy after Benzodiazepines and phenytoin or valproate. However, because $GABA_A$ receptors may turn out to be progressively unresponsive as status becomes prolonged, there is an evolution of treatment protocols and Phenobarbital should be relegated to use at high doses in refractory cases or replaced by another anaesthetic agent.

Propofol (Diprivan®) is a unique, nonbarbiturate, anesthetic agent possessing anticonvulsant properties, although the exact anticonvulsant mechanism is unknown (29). Several case reports and two small, open, uncontrolled studies have described the efficacy of propofol in refractory SE. Most of these clinical reports discuss the utility of propofol after traditional treatment regimens have failed or are not tolerated. Advantages of propofol compared with traditional barbiturate anaesthetic agents include better cardiovascular tolerability and a more favourable pharmacokinetic profile, allowing for rapid assessment of efficacy and neurological assessment upon drug withdrawal (29). However, due to its short half-life, there is a substantial risk of rebound seizure. Propofol has been associated with a variety of neuroexcitatory adverse events such as opisthotonos, muscle rigidity, and choreoathetoid movements (29). Long term infusion (propofol infusion syndrome) causes marked hyperlipidaemia and may result in acidosis, and rhabdomyolysis, especially in children (30).

Ketamine (Ketalar®) is an N-methyl-d-aspartate (NMDA) receptor antagonist, with a potent anaesthetic effect. The drug produces a state of “dissociative anaesthesia”, amnesia, and at the same time, it maintains an effective respiratory drive and does not depress the systemic arterial blood pressure (31). Ketamine has a place in therapy as a later option only for prolonged and intractable SE (32, 33). However, it induces limbic seizures in up to 50% of epileptic patients (34). Side-effects include the increase of salivar and bronchial secretions, and the possible increase of pulmonary pressures. Ketamine is contraindicated in patients who are at risk for increased intracranial pressure.

Practice recommendations for the management of patients with SE

Convulsive SE is a medical emergency. It is associated with the significant medical complications, as shown in Table 1 (35). SE treatment should proceed on four fronts : termination of SE, prevention of recurrence, management of potential precipitating causes, and management of SE complications and underlying conditions (36). The intensity of the treatment should reflect the risk to the patient from SE, and drugs likely to depress respiration and blood pressure should initially be avoided.

General measures

Table 3 summarizes the recommended treatment algorithm in the management of convulsive SE. Initial management of SE follows the principle of life support (4, 37). Since most patients with SE maintain adequate ventilation as long as an adequate airway is present, this must be ensured as first priority (38). A nasal cannula or bag mask ventilation are usually adequate to avoid hypoxia, however, supplemental oxygen, if available, is useful. Most patients with prolonged seizures or those receiving large doses of BZD or other sedatives will require tracheal intubation (18).

Obtaining intravenous (IV) access is the next step, as it is needed to provide drugs and fluid, as well as for resuscitation measures. Blood should be drawn for the routine laboratory evaluation of serum electrolytes, blood urea nitrogen, glucose, magnesium, calcium, liver function tests, complete blood cell count and antiepileptic drug levels. Toxic drug screen should be considered. Isotonic saline infusion should be initiated. A bedside glucose level should be attained as soon as possible. Thiamine 100 mg should be given as a preventive measure, because glucose infusion increases the risk of Wernicke's encephalopathy in susceptible patients (5). As hypoglycaemia may precipitate SE and is quickly reversible, 50 ml of 50% glucose should be given immediately if hypoglycaemia is suspected (5). In case of doubt, glucose can be given empirically but not systematically as nonketotic hyperglycemia may cause SE in 6 to 25% of cases (39, 40).

All patients should have continuous electrocardiographic monitoring and pulse oximetry, as cardiac arrhythmias and hypoxemia are not uncommon in SE. Blood pressure should be measured regularly, especially after anticonvulsants have been administered.

Electroencephalography

EEG is extremely useful in the diagnosis and management of SE and should be recorded without delay, if available (5). It can help to establish and confirm the diagnosis in unclear cases and help to confirm that an episode of SE has actually ended. Physicians should be aware that in nearly half of the patients electrographic seizures continue in the absence of clinical seizures (41). Importantly, in these patients vigorous AED treatment must be continued until disappearance of the ictal activity in the EEG. Any patient with SE who fails to recover rapidly and completely should be monitored with EEG for at least 24 hours (5).

Early pharmacological management

SE is a neurological emergency requiring prompt pharmacological intervention. The goal of pharmacotherapy is the immediate cessation of all seizures and the prevention of recurrence (18). Recent advances in the treatment of SE include the introduction of treatment algorithms that are tailored more specifically to clinical situations, a trend towards more aggressive therapies if initial treatment with front-line agents fails (37). Pharmacological treatment should not be delayed for diagnostic tests. It has been suggested that treatment failure may reflect delayed administration of second-line or third-line medications (42), which also underlines the need for prompt pharmacological management. The parental route is preferable.

First-line, second-line and third-line drugs

The recommended treatment protocol lists BZD as *first-line* drugs. Lorazepam should be used in the first place in accordance with evidence from prospective, double-blind studies showing lorazepam to be effective for controlling seizures in more than half of the cases and at least equal to if not more effective than, other approaches (7, 8, 43). Diazepam is the other first-line option or midazolam (especially when the IV route is not available), however, both agents are less efficacious than lorazepam (8) and need a second-line drug (7, 43).

Second-line treatment options comprise repeated administration of lorazepam or diazepam, or the add-on of IV phenytoin or valproate. Notably, there are no prospective trials to date investigating this approach, but the add-on of phenytoin has been shown efficacious in clinical practice (38). Phenytoin is less effective in direct comparisons with lorazepam or phenobarbital in first-line treatment of generalised convulsive SE (7), but its potential to terminate SE is well established (7, 8, 44). However, several caveats apply : phenytoin must be diluted only in saline (not in glucose) ; phenytoin should be avoided if hyperglycaemia is suspected, and the appropriate rate of administration should be respected. Cardiac monitoring is mandatory during the infusion.

Table 3

Checklist for management of status epilepticus (generalized tonic-clonic seizures)

Time flow and non AED measures	Recommended AED regimens
At : 0-5 minutes	
• Out-of-hospital : call ambulance • Initiate general systemic support : ◦ secure airway, give O2 ◦ assess cardiac and respiratory function regularly ◦ check temperature frequently • Collect blood ◦ bedside blood glucose monitoring and full blood count, urea, electrolytes, liver function tests, calcium, clotting, AED levels. ◦ Measure blood gases to assess extent of acidosis	• Start pharmacological measures : ◦ secure IV access in large vein and administer isotonic saline at low infusion rate ◦ administer n lorazepam at 0.1 mg/kg IV OR n diazepam 10mg IV (if no IV access : give 10-20 mg IR) OR (if IV not accessible) n midazolam 0.1 mg/kg IM, IN or IB (0.5 mg IR)
At : 10 minutes	If SE persists ….
• Contact neurologist • Determine aetiology of SE and treat appropriately ◦ if suggestion of alcohol abuse or impaired nutritional status : give thiamine 100 mg ◦ if suggestion of hypoglycaemia : give 50 ml glucose 50% IV • EEG, when available, monitoring until end of SE • ECG monitoring	◦ administer n repeat lorazepam or diazepam (or midazolam) (dosage as above) OR n administer phenytoin 15-20 mg/kg IV (ECG monitoring mandatory) OR n valproate bolus 30 mg/kg, then 1-5 mg/kg/h
At : 30 minutes	If SE persists ….
◦ Refer to intensive care unit and specialist advice	◦ administer n phenobarbital 20 mg/kg IV at $\leq$ 5 mg/min OR n thiopental loading 100-200 mg, maintenance 3-5 mg/kg/h OR n propofol 3-5 mg/kg load, then 5-10 mg/kg/h initial infusion then 1-3 mg/kg/h OR n midazolam 0.2 mg/kg load, 0.25-2 mg/kg infusion OR n Ketamine (if previous treatments are ineffective)

ECG = electrocardiogram, EEG = electroencephalography, IV = intravenous, IM = intramuscular, IR = intrarectal, IN = intranasal, IB = intrabuccal.

Injectable valproate has been investigated in a number of uncontrolled case series, indicating easy use, good tolerability and suggesting that it may be efficacious (23-27). It may be of particular benefit in patients who are hemodynamically unstable and cannot tolerate the hypotensive effects of other anticonvulsants, but only if they do not suffer from pre-existing contra-indications as coagulopathy disorder, hepatopathy, pancreatitis, etc. (23).

As for *third-line* treatment, there are very little data on the treatment of SE refractory to a benzodiazepine, phenytoin or valproate. Despite this lack of data many centres today use midazolam or propofol rather than phenobarbital or thiopental in this setting because these compounds have short half-lives and are, therefore, easier to handle (45). Ketamine because of its sympathomimetic effect is an alternative for refractory SE when tachyphylaxis and hypotension preclude use of benzodiazepines or barbiturates. No studies have been done to determine the optimal dose, however.

Conclusion

SE often occurs outside the hospital. In view of the high mortality and potential long-term consequences, it poses a particular challenge to primary care physicians. It is of importance that treatment of the condition occurs early and aggressively, as the duration of SE can be lowered significantly and prognosis be improved substantially. In order not to lose time, it is also important to have a prepared plan to treat SE, and EEG monitoring should be used, if available.

Only few large-scale studies provide evidence for the optimal treatment algorithms, and the existing evidence is largely limited to first-line and second-line therapy. Nonetheless against the background of extensive clinical experience gained over the years, recommendations can be provided. It should be kept in mind, that current available drugs are only effective as first-line therapy in two-thirds of patients treated (10). Hence, future research to optimise therapy is warranted.

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