Antiepileptic Drug Therapy for Status Epilepticus

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Status epilepticus (SE) is one of the most serious neurologic emergencies. SE is a condition that encompasses a broad range of semiologic subtypes and heterogeneous etiologies. The treatment of SE primarily involves the management of the underlying etiology and the use of antiepileptic drug therapy to rapidly terminate seizure activities. The Drug Committee of the Korean Epilepsy Society performed a review of existing guidelines and literature with the aim of providing practical recommendations for antiepileptic drug therapy. This article is one of a series of review articles by the Drug Committee and it summarizes staged antiepileptic drug therapy for SE. While evidence of good quality supports the use of benzodiazepines as the first-line treatment of SE, such evidence informing the administration of second- or third-line treatments is lacking; hence, the recommendations presented herein concerning the treatment of established and refractory SE are based on case series and expert opinions. The choice of antiepileptic drugs in each stage should consider the characteristics and circumstances of each patient, as well as their estimated benefit and risk to them. In tandem with the antiepileptic drug therapy, careful searching for and treatment of the underlying etiology are required.

Key Words status epilepticus, seizure, antiepileptic drugs, benzodiazepines, anesthetics,
 drug therapy.

INTRODUCTION

Status epilepticus (SE) is one of the most serious neurologic emergencies. SE is defined as "a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures…that can have long-term consequences…including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures."[1] This conceptual definition proposed by the International League Against Epilepsy (ILAE) Task Force on classification of status epilepticus also provides two operational time points: the onset of abnormally prolonged seizure (t_1) and the onset of the long-term consequences (t_2). These time points vary depending on the type of seizures.[2] For convulsive SE (CSE), t_1 and t_2 are reportedly 5 and 30 min, respectively.[1] Hence, the ideal treatment of CSE should be completed within the window of 5−30 min in order to prevent long-term consequences.

The heterogeneous classification of SE based on the age at onset, etiology, seizure semiology, or electroclinical characteristics[3-8] has informed the recent classification of SE proposed by the ILAE Task Force based on the following four axes: semiology, etiology, electroencephalography (EEG) correlates, and age.[1] The foundation of the classification system, semiologic classification refers to the classification of the clinical presentation of SE according to two main taxonomic criteria (Fig. 1): 1) the presence or absence of prominent motor symptoms and 2) the degree of consciousness impairment. SE with prominent motor
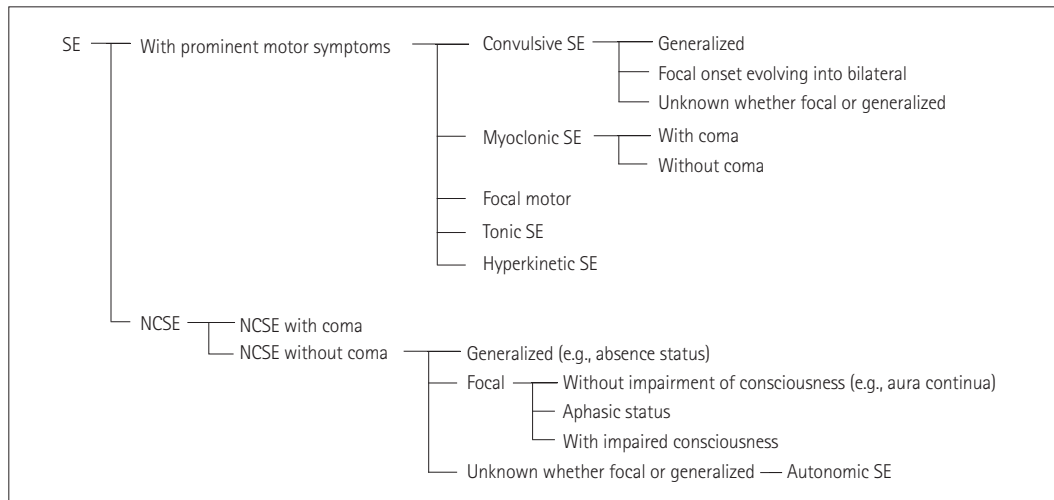
Fig. 1. Classification scheme for status epilepticus proposed by the International League Against Epilepsy Task Force on classification of status epilepticus. NCSE: nonconvulsive SE, SE: status epilepticus.

symptoms and impaired consciousness can be classified as a CSE, also known as tonic–clonic SE. SE without prominent motor symptoms is summarized as nonconvulsive SE (NCSE).

It is noteworthy that the symptoms and signs of SE change dynamically over the course of SE–e.g., bilateral CSE frequently evolve into a coma state with subtle, if any, convulsive movements. This condition is traditionally called subtle SE. If the patient presents to the hospital in this stage, the semiology of SE might be classified as NCSE with coma. Regarding the therapeutic approach to as well as proper classification of SE, however, it is more appropriate to classify SE according to the true initial semiology of seizures, which can only be presumed in some cases. If NCSE with coma is presumed to have evolved from CSE, it is recommended that the patient be treated for the latter.

The primary goal of the treatment of SE is to rapidly terminate epileptic activity, ideally before t_2, in order to prevent long-term consequences. SE, however, is not a single disease entity but rather a condition attributable to wide range of etiologies. Hence, the treatment of SE should encompass both antiepileptic drug therapy to terminate seizures and treatments of the specific etiologies. The Drug Committee of the Korean Epilepsy Society performed a review of the existing guidelines and literature with the aim of providing practical recommendations for antiepileptic drug therapy. As one report of the series of review articles produced by that committee, this article discusses the use of antiepileptic drug therapy to stop epileptic activity. Although the etiology of SE and its treatment are beyond the scope of this article, the importance of ascertaining and treating the etiology of SE should not be overlooked at any point in the course of the treatment for SE.

ANTIEPILEPTIC DRUG THERAPY FOR CONVULSIVE STATUS EPILEPTICUS

CSE can be divided into four stages: early, established, refractory, and super-refractory.[9-12] It is recommended that this stage-based conception of CSE inform treatments of the condition.[13] Seizure activity that persists for more than 5 min is considered early SE, and first-line treatment should be administered at this stage (Fig. 2). The failure of the first-line treatment or the persistence of seizure for more than 10 min indicates the presence of established SE as well as the need to initiate second-line treatment. Refractory SE indicates the failure of the second-line treatment with continuous seizure activity or recurrent seizures without the recovery of consciousness. If SE continues or recurs 24 h or more after the anesthetic therapy, the patient's condition is considered super-refractory.

Early status epilepticus: first-line treatment
The first-line treatment for early SE mainly comprises the administration of benzodiazepines, the most frequently used of which include diazepam, lorazepam, and midazolam. Each of these drugs has been established as an effective first-line treatment for CSE based on randomized controlled trials.[14-20]

Diazepam
Diazepam is the first benzodiazepine used for the treatment of epilepsy and SE. Highly lipophilic and rapidly enters the brain, diazepam can be administered intravenously as a bolus of 0.15−0.2 mg/kg up to 10 mg.[21-23] Considering the relatively long elimination half-life of diazepam, its rapid redis-
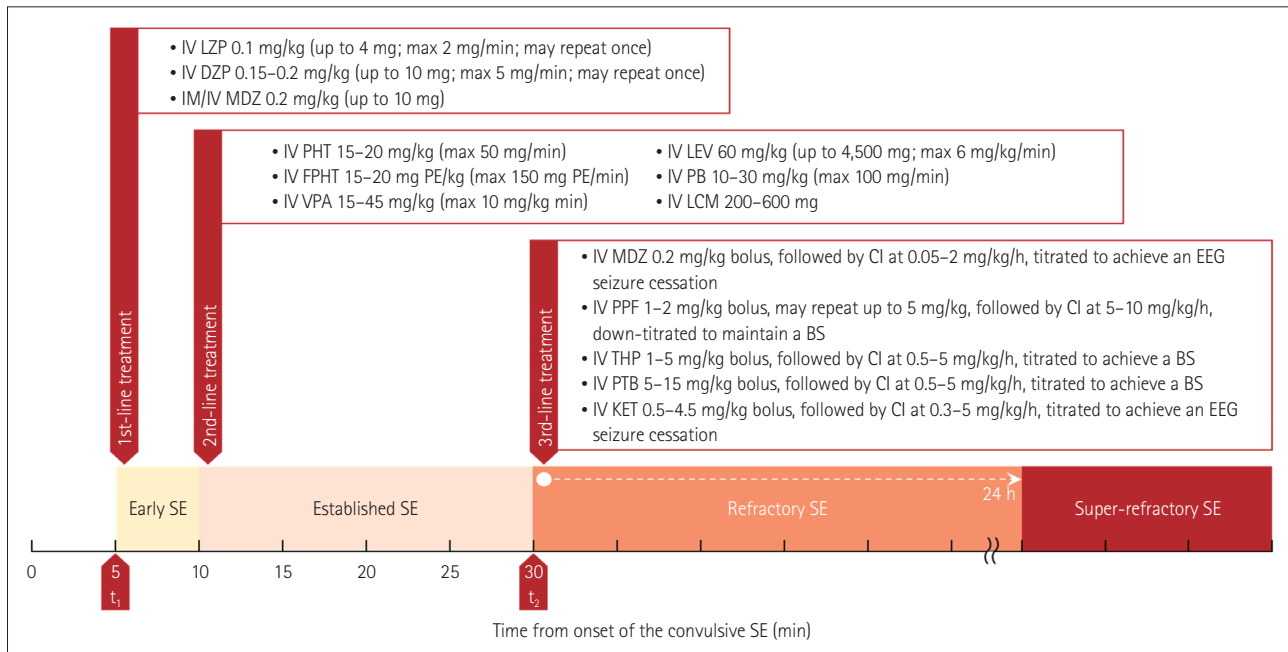
Fig. 2. Treatment options for convulsive status epilepticus at different stages. t_1: the onset of abnormally prolonged seizure, t_2: the onset of the long-term consequences. BS: burst-suppression pattern, CI: continuous infusion, DZP: diazepam, EEG: electroencephalography, FPHT: fosphenytoin, IM: intramuscular, IV: intravenous, KET: ketamine, LCM: lacosamide, LEV: levetiracetam, LZP: lorazepam, MDZ: midazolam, PB: phenobarbital, PE: phenytoin sodium equivalent, PHT: phenytoin, PPF: propofol, PTB: pentobarbital, SE: status epilepticus, THP: thiopental, VPA: valproate.

tribution into peripheral tissues shortens its duration of action; repeated doses or an alternative longer-acting antiepileptic drug is usually required.

Lorazepam

Lorazepam can be administered intravenously. Although lorazepam has a longer onset of action relative to diazepam, it is less lipophilic and does not feature diazepam's rapid redistribution into peripheral tissues; consequently, it acts for a longer duration.[24] This pharmacokinetic property favors its use in early SE. Four randomized controlled trials compared intravenous (IV) lorazepam and IV diazepam.[14,15,17,20] One of these trials showed the superiority of lorazepam at 0.05−0.1 mg/kg in seizure control over diazepam at 0.3−0.4 mg/kg.[15] While the other trials also appeared to favor lorazepam (4, 2, and 0.1 mg/kg, respectively) over diazepam (10, 5, and 0.2 mg/kg, respectively), their findings were not statistically significant.[14,17,20] A meta-analysis of three trials found that lorazepam performed significantly better in lowering the risk of noncessation of seizures compared with diazepam [risk ratio (RR) 0.64, 95% confidence interval (CI) 0.45−0.90] and of continuation of SE requiring a different drug or general anesthesia (RR 0.63, 95% CI 0.45−0.88).[25] The recommended dosage of IV lorazepam is 0.1 mg/kg, up to maximum of 4 mg, administered at 2 mg/min. The dosage may be repeated once.[21-23,26]

Midazolam

Midazolam is a water-soluble benzodiazepine. At a physiologic pH, midazolam undergoes a conformational change to becomes lipophilic.[27] Its water solubility allows midazolam to be administered via multiple routes, including by intramuscular (IM) injection. A randomized controlled trial compared the efficacy of IM midazolam (10 mg for body weight >40 kg, 5 mg for body weight 13−40 kg) as an out-of-hospital treatment with that of IV lorazepam (4 mg for body weight >40 kg, 2 mg for body weight 13−40 kg) (Rapid Anticonvulsant Medication Prior to Arrival Trial).[19] While these two drugs have similar safety, IM midazolam is shown to be superior to IV lorazepam in terms of seizure control. In the treatment of CSE, IV or IM midazolam can be administered at a dose of 0.2 mg/kg up to 10 mg.[21]

Established status epilepticus: second-line treatment

Seizures continue and progress to established SE in about 40% of patients with CSE despite benzodiazepine administration as the first-line treatment. The second-line treatment for established SE consists of a loading dose of antiepileptic drugs. Frequently used antiepileptic drugs include phenytoin or fosphenytoin, valproate, levetiracetam, phenobarbital, and lacosamide. There is no clear evidence for the relative superiority of any of these drugs.[22] A meta-analysis of the efficacy of second-line drugs in terminating seizure activity showed that valpro-

ate exhibited the highest efficacy (75.7%; 95% CI 63.7−84.8%), followed by phenobarbital (73.6%; 95% CI 58.3−84.8%), levetiracetam (68.5%; 95% CI 56.2−78.7%), and phenytoin (50.2%; 95% CI 34.2−66.1%).[28] Lacosamide was excluded from the meta-analysis due to insufficient data. Another recent meta-analysis found that phenobarbital was superior to the others with respect to SE cessation, while lacosamide and valproate performed better in terms of tolerance.[29] However, because the quality of evidence in these meta-analyses was insufficient, the results cannot be considered definitive.

The recent randomized clinical trial Established Status Epilepticus Treatment Trial randomized patients aged >2 years to one of three pharmacotherapeutic regimens: 20 mg PE/kg fosphenytoin, 40 mg/kg valproate, and 60 mg/kg levetiracetam. While the sample size was originally designed to be 1,500 patients, enrollment was discontinued after 400 patients (384 unique patients) because the trial met the predefined criterion for futility of finding one drug to be superior or inferior.[30,31] The primary outcome of the cessation of SE and improvement in the level of consciousness at 60 min occurred in 68 patients assigned to levetiracetam (47%; 95% credible interval 39−55%), 53 assigned to fosphenytoin (45%; 95% credible interval 36−54%), and 56 assigned to valproate (46%; 95% credible interval 38−55%). The incidence rates of adverse events were similar across the treatment arms.

The lack of sufficient evidence for the second-line treatment of established SE means that no single drug is recommended over the others. Each drug has its own advantages and disadvantages depending on the clinical context. The choice of second-line drug relies largely on its availability and the systemic condition of the patient.

Phenobarbital
Phenobarbital primarily acts by enhancing γ-aminobutyric acid (GABA) inhibition. As one of the oldest drugs used to treat SE, the treatment efficacy of phenobarbital has been demonstrated for both early and established SE. In a randomized controlled study that enrolled 384 patients with CSE, phenobarbital (15 mg/kg) was found to be as effective as lorazepam (0.1 mg/kg) as a first-line treatment.[16] However, despite being effective in the treatment of established SE as well as early SE, the unfavorable safety profile of phenobarbital restricts its use–respiratory depression, hypotension, and sedation are commonly encountered adverse events, although serious systemic toxicities are rare. The IV loading dose of phenobarbital is 10−20 mg/kg.[21-23,26] The infusion rate should not exceed 100 mg/min in adults and 2 mg/kg/min in children.

Phenytoin and fosphenytoin
Phenytoin is one of the longest-standing antiepileptic drugs

used in the treatment of SE. When delivered intravenously, phenytoin should be diluted in normal saline and injected directly into a large vein. The concentration of phenytoin in the injected solution should not exceed 10 mg/mL. The usual loading dose is 15−20 mg/kg: 15 mg/kg for older adults and 18−20 mg/kg for younger adults. Two hours after completing the infusion, doses of 15 and 18 mg/kg will increase the phenytoin serum concentrations in adults by approximately 20 and 23 μg/mL, respectively.[32] The serum phenytoin concentration measured 2 h after loading may help to guide the timing of its maintenance dose.[33] The infusion rate should not exceed 50 mg/min in adults and 1 mg/kg/min in children.

Phenytoin is only slightly soluble at a pH of 7 or less, but increases markedly at higher pH values. Parenteral phenytoin is therefore formulated in an aqueous vehicle consisting of 40% propylene glycol and 10% ethanol with a pH of 12. This may cause pain, burning, or itching sensations, and thrombophlebitis at the infusion site. Purple-glove syndrome is a potentially severe complication with an unknown pathophysiology.[34] The IV administration of phenytoin can also cause cardiovascular complications such as hypotension and arrhythmia, including ventricular fibrillation. A high concentration of phenytoin and a rapid rate of administration are related to these complications.[35] The heart rhythm should therefore be monitored during the IV administration of phenytoin.

Fosphenytoin is a water-soluble prodrug of phenytoin. While fosphenytoin itself has no known antiepileptic drug activity, it rapidly and completely converts to phenytoin. After administration, 1.5 mg of fosphenytoin sodium converts to 1 mg of phenytoin sodium. To prevent confusion, fosphenytoin is packed as a milligram phenytoin sodium equivalent (mg PE). Thus, 100 mg PE of fosphenytoin and 100 mg of phenytoin yield the same molar amounts of phenytoin sodium. Fosphenytoin can be diluted in various solutions including dextrose and lactated Ringer solutions. The loading dose of fosphenytoin can range from 15 mg PE/kg to 20 mg PE/kg, and it can be infused at much faster rates of up to 150 mg PE/min. Local reactions and cardiovascular complications associated with IV administration occur significantly less often with fosphenytoin than with phenytoin.[36]

Valproate
Valproate is a broad-spectrum antiepileptic drug exhibiting efficacy against all seizure types. The common IV loading dose is 15−45 mg/kg, with an infusion rate of 6−10 mg/kg/min.[37,38] Valproate is well tolerated, with a low overall incidence of adverse events; dizziness, mild hypotension, and mild thrombocytopenia are the most common. Valproate administration has been associated with encephalopathy char-

acterized by an acute alteration of consciousness. The most feared adverse event is fatal hepatotoxicity, for which young age is a risk factor.[39]

Levetiracetam

Levetiracetam is a broad-spectrum antiepileptic drug with a unique mechanism of action and favorable pharmacokinetic and safety profiles. The minimal plasma protein binding of levetiracetam makes drug interactions unlikely. The recommended loading dose is 60 mg/kg, with a maximum of 4,500 mg.[22] Adverse events are usually mild and transient, and the most common ones include sedation and thrombocytopenia.[40] Levetiracetam can also cause psychiatric adverse events such as agitation and psychosis, but such events are rarely reported when using levetiracetam to treat SE.[41] Levetiracetam is excreted renally, and dose adjustments are recommended in the presence of renal impairment.

Lacosamide

Lacosamide acts primarily by selectively enhancing the slow inactivation of voltage-gated sodium channels without interfering with fast inactivation. Animal models of SE have shown the potential of lacosamide in seizure suppression and neuroprotection.[42] Although the current evidence for the use of lacosamide is limited, the availability of an IV solution has resulted in this drug being increasingly used in the treatment of SE.[43,44] A systematic review estimated the efficacy of lacosamide in the treatment of CSE at 61%;[44] however, that systematic review used retrospective evidence collected from studies performed at heterogeneous therapeutic stages. While the most commonly used loading dose was 400 mg, the most appropriate dose remains to be established. One study suggested using a dose in excess of 5.3 mg/kg to ensure higher efficacy,[45] while another recommended 10−12 mg/kg at an infusion rate of 0.4 mg/kg/min as a safe loading dose.[46] Adverse events associated with lacosamide are usually mild or moderate, and mainly consist of dizziness, abnormal vision, diplopia, and ataxia. A possible concern about lacosamide acting as a sodium-channel modulator is atrioventricular block. Lacosamide was found to prolong the PR interval in a dose-dependent manner.[46]

Refractory and super-refractory status epilepticus: third-line treatment

SE is considered refractory when the first- and second-line treatments fail and seizures continue or recur. Such treatment resistance reportedly occurs in 23% to 43% of patients with SE.[47-50] In-hospital mortality of refractory SE has been reported to range between 17% and 39%. The mainstay of treatment in this stage is the continuous administration of IV an-

esthetic drugs such as midazolam, barbiturates, and propofol. However, there is no clear evidence for guiding the treatment of refractory SE. Furthermore, observational studies have associated the continuous administration of IV anesthetic drugs with independent risks of undesirable events and death.[51-54] Hence, the choice of treatment depends on its estimated benefit and risk to individual patients. Applying a loading dose of another second-line agent can be beneficial in some patients with refractory SE. The intensity and duration of the continuous infusion of IV anesthetic drugs should be guided by continuous EEG monitoring, with a typical regimen involving the maintenance of electrographic seizure cessation or burst suppression for at least 24 h before slowly reducing the anesthetic agents.

Midazolam

Midazolam is widely used for continuous infusions due to its water solubility, rapid onset, and short duration of action. However, tolerance to midazolam can increase the dosing requirement during continuous infusion.[55] Furthermore, the increased volume of distribution associated with continuous infusion will prolong the elimination of midazolam. Respiratory suppression and hypotension are frequently encountered during continuous infusion. A 0.2 mg/kg loading dose of IV midazolam by bolus injection followed by continuous infusion at 0.05−2 mg/kg/h is recommended.[21,56] The infusion rate can be increased gradually under guidance from continuous EEG monitoring.

Propofol

Propofol is an anesthetic agent characterized by a rapid onset and short duration of action. Furthermore, its favorable pharmacokinetic properties and little prolongation of elimination after long-term continuous infusion are major advantages to its use.[57] While its mechanism of action has yet to be fully elucidated, propofol seems to stimulate GABA receptors, block N-methyl-D-aspartate (NMDA) receptors, and reduce calcium influx through slow calcium channels.[58]

Characterized by lactic acidosis, rhabdomyolysis, renal failure, and heart failure, propofol infusion syndrome is a rare but dangerous complication of propofol administration. Risk factors for propofol infusion syndrome include young age, carbohydrate depletion, the concomitant use of corticosteroids, and prolonged infusion at high doses (e.g., for longer than 48 h at dosages exceeding 5 mg/kg/h).[59] Other adverse events include hypotension, respiratory suppression, bradycardia, and hypertriglyceridemia. Propofol can be administered intravenously as a loading bolus of 1−2 mg/kg. If seizures persist, bolus delivery may be repeated until a total dose of 5 mg/kg is reached. Continuous infusion can begin

at a dosage of 5−10 mg/kg/h and then be gradually reduced to a dosage that is sufficient to maintain a burst suppression pattern on EEG.[26]

Thiopental and pentobarbital

Thiopental and pentobarbital are barbiturates that act as GABA$_A$ agonists. These drugs tend to accumulate in the body, resulting in a prolonged duration of action and delayed recovery after discontinuation. Although barbiturates induce strong antiepileptic effects, they have been associated with more adverse events compared with other drugs:[60] A meta-analysis found pentobarbital to be associated with lower frequencies of short-term treatment failure, breakthrough seizures, and changes to the infusion of another medication compared with midazolam and propofol;[61] however, adverse events are reportedly more common when taking barbiturates than either midazolam or propofol.[60-62] Hypotension and respiratory suppression are common with the continuous infusion of barbiturates, and other adverse events include hepatotoxicity and immunosuppression. It is recommended that thiopental be administered at a loading dose of between 1 mg/kg and 5 mg/kg, with continuous infusion at 0.5−5 mg/kg/h.[12,23,63,64] Pentobarbital can be administered at a loading dose of 5−15 mg/kg,[12,21,63] and its infusion rate should not exceed 50 mg/min, with continuous infusion at 0.5−5 mg/kg/h being recommended. For both drugs, continuous infusion should begin at a relatively low rate and then subsequently be titrated to achieve a burst-suppression pattern on EEG.

Ketamine

Ketamine is a noncompetitive NMDA receptor antagonist. Studies suggest that the internalization of inhibitory GABA$_A$ receptors and the mobilization of excitatory NMDA receptors to the membrane are associated with refractory SE.[65,66] As a primary mechanism of action, NMDA-receptor antagonism makes ketamine an attractive option for treating refractory SE. Ketamine can also exert anesthetic and analgesic effects without profoundly impairing consciousness. Furthermore, the administration of ketamine does not necessarily require endotracheal intubation or mechanical ventilation, exhibits sympathomimetic properties that are absent in other third-line anesthetic agents, and can increase the blood pressure. Ketamine has a short half-life of 2−3 h. It is primarily metabolized through the cytochrome P450 system. Although ketamine had been commonly administered to patients with SE refractory to one or more anesthetic agents,[67,68] a meta-analysis found the efficacy of ketamine to be as high as 64% across 3 days when used to address refractory SE, with this efficacy decreasing to 32% across 26.5 days.[69]

Adverse events associated with ketamine include hyper-tension, increased intracranial pressure, arrhythmia, hallucinations, hypersalivation, nausea, and vomiting.[69,70] The recommended loading dose ranges from 0.5 mg/kg to 4.5 mg/kg, and the recommended dosage range for continuous infusion is 0.3−5 mg/kg/h.[23,60,64] The EEG pattern related to the clinical efficacy of ketamine is heterogeneous.[69] The cessation of seizure activities rather than burst-suppression is recommended as a therapeutic target.

ANTIEPILEPTIC DRUG THERAPY FOR NONCONVULSIVE STATUS EPILEPTICUS

NCSE has been broadly classified as two conditions with different prognoses according to the patient's status: 1) ambulatory patients with mild or no impairment of consciousness and electroencephalographic SE (so-called "walking wounded" or NCSE proper) and 2) comatose patients with electroencephalographic SE (so-called "ictally comatose" or comatose NCSE), who have a significantly worse prognosis.[71,72] This dichotomy of NCSE is maintained in the classification of the ILAE Task Force (Fig. 1). NCSE with coma could be a manifestation of either uncontrolled CSE (subtle SE) or NCSE emerging in critically ill patients with coma. The time points of t_1 (after the time at which treatment should be started) and t_2 (before the time at which SE should ideally be terminated) for NCSE would vary considerably among the different subtypes of NCSE. There is little evidence to inform the definition of time points in focal NCSE with impaired consciousness without coma, but a t_1 of 10 min and a t_2 of >60 min have been proposed.[1] No time points have been established for generalized NCSE without coma (i.e., absence SE).

The antiepileptic drug therapy for NCSE is largely inferred from that for CSE. However, because the prognosis differs across the subtypes as well as their diverse etiologies, the treatment of NCSE remains controversial.[73] Moreover, there is no consensus on how aggressively it should be treated. The choice of treatment should take into account the etiology and subtype of NCSE as well as the clinical course of each patient, with a particular emphasis on the risk-to-benefit ratio of treatment.

First- and second-line treatments for NCSE follow the same protocols as those for CSE. If the first- and second-line treatments fail, the administration of additional loading doses of previously unused second-line antiepileptic drugs is recommended before proceeding to the third-line treatment.[73] As for CSE, there is little evidence for the best anesthetic drug to achieve seizure control in NCSE that is refractory to first- and second-line treatments. IV anesthetic drugs are reportedly used to treat from 11% to 69% of patients with refracto-

ry NCSE.[49,53,54,74] It is noteworthy that the risk of IV anesthetic drug therapy is likely to be greater in patients with NCSE, especially in the case of focal NCSE with impaired consciousness without coma.[53,54] The outcome is likely to be better in NCSE without coma than in CSE or NCSE with coma.[72] It is recommended that IV anesthetic drugs be avoided when treating NCSE patients without coma. The administration of newer broad-spectrum antiepileptic drugs might be worth considering in such cases.[73]

CONCLUSION

Based on a review of the guidelines and literature performed by the Drug Committee of the Korean Epilepsy Society, the present review has summarized the recommended approach to administering antiepileptic drug therapy for SE. Due to the lack of high-quality evidence regarding the treatment of SE that has progressed beyond the early stage, many of the present recommendations are based on case series or expert opinions. Furthermore, the controversies in the literature mean that which second- or third-line treatment option is superior remains unclear. Hence, the decisions regarding treatment should consider the characteristics and circumstances of each patient. Novel antiepileptic drugs–especially those with parenteral formulations–may lead to new treatment options for SE.[75] Moreover, early combinations of antiepileptic drugs with different mechanisms of action might be beneficial when treating SE.[75,76] However, evidence for the efficacy of novel antiepileptic drugs or rational polytherapies for SE is still lacking, and so these therapeutic options should be applied based on a sound understanding of the pharmacokinetics, pharmacodynamics, and mechanism of action of each antiepileptic drug whose use is being considered. In tandem with the antiepileptic drug therapy, careful search for and treatment of the underlying etiology are required.

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