Chapter 8
Status Epilepticus

CQ 8-1

What is the definition of status epilepticus?

Summary

Status epilepticus (SE) was defined as "a seizure that persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur" (International League Against Epilepsy: ILAE, 1981)[1]. Regarding the length of seizure, if convulsive seizure persists for 5 minutes or longer, treatment should be started, and if persists for 30 minutes or longer, there is a risk of long-term consequences (ILAE 2015)[2].

Comment

In 2015, ILAE proposed a new definition for SE as follows: "Status epilepticus is a condition resulting either from the failure of the mechanisms for seizure termination or from the initiation of mechanisms provoking abnormally prolonged seizures (after time point t_1). It is a condition, which can have long-term consequences (after time point t_2), including neuronal cell death, neuronal cell abnormality, and alteration of neuronal networks, depending on the type and duration of seizures"[2].

Although the traditional definition did not define the seizure duration, epileptic seizures usually terminate in 1 to 2 minutes in most cases. It has become clear that a prolonged seizure duration is associated with drug resistance. For this reason, it is recommended that if the convulsive seizure lasts more than 5 minutes (t_1)[2, 3], the diagnosis of SE should be made and treatment should be started. In addition, animal experiments have shown that brain damage occurs if the epileptic discharges continue for 30–45 minutes or more. If seizure persists for more than 30 minutes (t_2), there is a risk of serious long-term consequences[2].

■ References

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2) Trinka E, Cock H, Hesdorffer D, et al. A definition and classification of status epilepticus—Report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia. 2015; 56(10): 1515-1523.
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■ Search formula and secondary reference sources

PubMed search: September 12, 2008
Status Epilepticus AND (define* OR definition*) = 136

Additional PubMed search: December 8, 2015
"Status Epilepticus/classification" [Majr] OR "Status Epilepticus/etiology" [Majr] = 24

No references that could serve as evidence were found in Ichushi Web.

CQ 8-2

Which drugs are used for convulsive status epilepticus?

Summary

Figure 1 shows the treatment flowchart for convulsive status epilepticus.

Comment

Early status epilepticus (stage 1) is defined as convulsive seizures persisting for more than 5 minutes. Established status epilepticus (stage 2) is defined as seizures persisting for over 30 minutes without cessation after treatment with benzodiazepines. Refractory status epilepticus (stage 3) is defined as seizures persisting for more than 60–120 minutes despite treatment with intravenous infusion or intravenous injection of antiepileptic drugs[1]. Treatment strategy depends on the disease stage[1-5]. When seizures are not controlled even by general anesthesia and persist for more than 24 hours, the condition is called super-refractory status epilepticus (stage 4), for which no standard treatment strategy has been established[1]. Nonconvulsive status epilepticus treatment generally follows those for convulsive status epilepticus, but the usefulness of general anesthesia is undetermined.

■ References

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3) Mazurkiewicz-Bełdzińska M, Szmuda M, Zawadzka M, et al. Current treatment of convulsive status epilepticus—a therapeutic protocol and review. Anaesthesiol Intensive Ther. 2014; 46(4): 293-300.
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5) Ohsawa M. Treatment for status epilepticus. No To Hattatsu. 2007; 39(3): 185-192. (in Japanese)

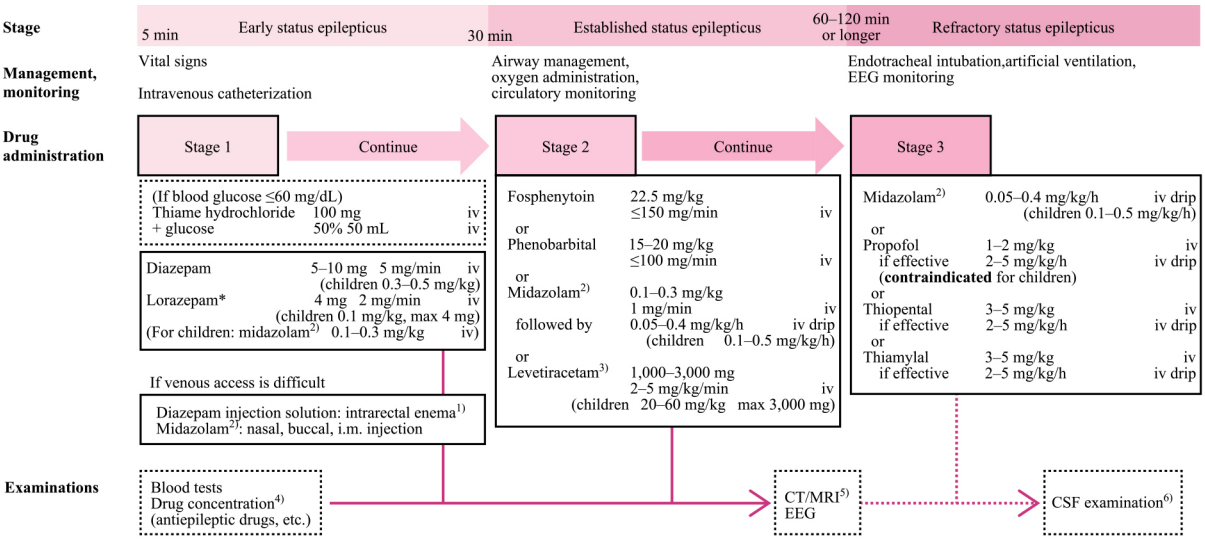
■ Search formula and secondary reference sources

PubMed search: September 9, 2008
Status Epilepticus/drug therapy" AND (first-line OR first choice) = 49

Additional PubMed search: June 26, 2015
(((Anticonvulsants/therapeutic use [Majr]) AND Status Epilepticus/drug therapy [Majr])) OR ((Status Epilepticus/drug therapy [Majr]) AND ((first-line) OR first-choice)) = 242

No references that could serve as evidence were found in Ichushi Web.

Figure 1. Treatment flowchart for status epilepticus (constructed from references 1–5).



[1]: The dose of diazepam injection solution administered as enema is 10–30 mg (for children 0.2–0.5 mg/kg) (not covered by medical insurance)
[2]: When midazolam is administered nasally, buccally, and intramuscularly, use 0.5% injection solution at 10 mg (for children 0.3 mg/kg) (not covered by medical insurance). When administered as intravenous injection or continuous intravenous drip, use of 0.1% injection solution is covered by medical insurance. In the package insert for midazolam 0.1% injection solution, the dose is 0.15 mg/kg for intravenous injection and 0.1–0.4 mg/kg/h for drip. In general anesthesia, adjust dose as appropriate.
[3]: Not covered by medical insurance for status epilepticus.
[4]: If treated with antiepileptic drugs, check blood concentrations of the antiepileptic drugs being taken. If overdose of convulsion-inducing drugs (including theophylline) is suspected, check those blood levels if possible.
[5]: Perform brain MRI or CT as necessary to investigate the cause of seizures. Start treatment as for acute symptomatic seizure if necessary. If possible, continuous EEG monitoring must be done ideally to differentiate psychogenic seizures and evaluate the course of treatment, and even if not possible, it is desirable to record EEGs after treatment to confirm the cessation.
[6]: In cases suspected of meningitis or encephalitis, perform CSF examination. In addition to general CSF examination, bacterial culture and microscopic examination, it is desirable to freeze a portion of the sample for investigation of anti-neuronal antibodies in the future.
*: Lorazepam is not marketed in Japan as of December 2017.

CQ 8-2-(1)

What treatment should be given when intravenous line has not yet been established?

Summary

Intrarectal administration of diazepam injection solution is effective. In children, nasal / buccal administration and intramuscular injection of midazolam are effective (not covered by medical insurance).

Comment

A small-scale prospective open study[1] and a small-scale retrospective study[2] have demonstrated the efficacy of intrarectal administration of diazepam injection solution. The incidence of adverse effects including respiratory depression is low, and is safer compared to intravenous injection.

When diazepam is administered intrarectally, the beneficial effect appears within 10 minutes in most cases[1, 2]. However, to be effective for status epileptics, rather than suppository, gel enema preparation (not available in Japan) or injection solution should be used. Diazepam suppository lacks fast-acting effect, and is usually not effective in controlling on-going convulsions[3].

In addition, diazepam intramuscular injection is not recommended due to the delayed onset of effect and large variability of time course of effects[1].

The use of 10 mg (for children 0.3 mg/kg) of midazolam 0.5% injection solution (note: not 0.1% injection) is effective. In a meta-analysis of a total of 774 children and young adults, non-intravenous midazolam was more effective than intravenous diazepam. In an analysis of 628 patients, buccal midazolam was more effective than rectal diazepam[4]. In a randomized double-blind trial of 893 patients, intramuscular midazolam (73.4%) had equivalent efficacy as intravenous lorazepam (63.4%)[5]. Another report suggests that intrarectal and intranasal lorazepam may also be effective[6] (not available in Japan).

■ References

1) Remy C, Jourdil N, Villemain D, et al. Intrarectal diazepam in epileptic adults. Epilepsia. 1992; 33(2): 353-358.
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■ Search formula and secondary reference sources

PubMed search: September 9, 2008
Status Epilepticus/drug therapy" AND (first-line OR first choice) = 49
Additional PubMed search: June 26, 2015
(((Anticonvulsants/therapeutic use [Majr]) AND Status Epilepticus/drug therapy [Majr])) OR ((Status Epilepticus/drug therapy [Majr]) AND ((first-line) OR first-choice)) = 242

No references that could serve as evidence were found in Ichushi Web.

CQ 8-2-(2)

What are the drugs for stage 1 status epilepticus?

Summary

The therapeutic drug for stage 1 is intravenous diazepam or lorazepam; both drugs are benzodiazepines. However, lorazepam for injection is not available in Japan.

Comment

A prospective, randomized, double-blind study showed that intravenous injection of diazepam 10 mg controlled seizures in 76% of the patients[1]. Diazepam has to be administered intravenously, not intramuscularly. Diazepam should be injected undiluted, because it becomes turbid when diluted with normal saline or glucose. If the first injection is ineffective, additional injection can be given after 5–10 minutes. Pay attention to respiratory depression when giving additional injection. An intravenous injection of diazepam usually has an anti-convulsion effect for 20 minutes[2].

A prospective randomized double-blind trial in 273 children found no difference in efficacy and adverse effects between diazepam and lorazepam[3], but a meta-analysis by Cochrane review of 289 cases showed that lorazepam had a lower rate of ineffectiveness (32/130 cases for lorazepam versus 51/134 cases for diazepam, hazard ratio 0.64, 95% confidence interval 0.45–0.9)[4]. Intravenous preparation of lorazepam is not available in Japan.

As an alternative to intravenous diazepam, midazolam 0.1% injection may be given, and is often used for stage 1 treatment in children.

If the benzodiazepines are ineffective, proceed to stage 2 treatment.

■ References

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PubMed search: September 9, 2008
Status Epilepticus/drug therapy" AND (first-line OR first choice) = 49

Additional PubMed search: June 26, 2015
(((Anticonvulsants/therapeutic use [Majr]) AND Status Epilepticus/drug therapy [Majr])) OR ((Status Epilepticus/drug therapy [Majr]) AND ((first-line) OR first-choice)) = 242

No references that could serve as evidence were found in Ichushi Web.

CQ 8-2-(3)

How effective is intravenous fosphenytoin for status epilepticus?

Summary

Fosphenytoin or phenytoin is used for the treatment of stage 2 status epilepticus.

Comment

Phenytoin has been used for a long time and fosphenytoin was developed to overcome the adverse effects associated with phenytoin. Therefore, fosphenytoin is easy to use in clinical practice.

While intravenous phenytoin should be injected slowly, fosphenytoin can be injected at an usual speed and reaches effective blood concentration more rapidly. In addition, phenytoin is strongly alkaline, causing vascular pain and vascular disorder, and its extravasation induces tissue necrosis. On the other hand, fosphenytoin is almost neutral, and rarely produces the above adverse effects[1].

The effective rate of fosphenytoin is reported to be 44–97%, and a randomized study of 256 emergency patients showed no difference in efficacy between phenytoin and fosphenytoin[1].

Phenytoin is effective for many types of status epilepticus, except absence seizure status epilepticus and myoclonic seizure status epilepticus[2]. In a meta-analysis of 8 studies with 294 patients in total, the effective rate of phenytoin was 50.2% (95% confidence interval 43.2–66.1%)[3]. Phenytoin should be injected intravenously immediately after injection of the fast-acting diazepam, because phenytoin begins to exert its effect approximately 20 minutes after administration[4, 5].

We should follow the instructions shown below when using phenytoin. Inject undiluted phenytoin into to a relatively large blood vessel. Since there is a risk of heart failure due to cardiovascular disturbance (mainly hypotension and arrhythmia), inject the drug slowly while monitoring blood pressure, pulse and electrocardiogram. In addition, phenytoin causes vascular pain and purple glove syndrome due to vascular disorder at an incidence rate of 5.9%[1], and may cause tissue necrosis due to extravasation. Care should be taken, especially for children.

■ References

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■ Search formula and secondary reference sources

PubMed search: September 21, 2008
Status Epilepticus AND (“Diazepam” OR “Phenytoin” OR “Midazolam” OR “Propofol”) = 357
Additional PubMed search: June 26, 2015
(“Status Epilepticus” [Mesh]) AND “Phenytoin/therapeutic use” [Mesh] = 56

No references that could serve as evidence were found in Ichushi Web.

CQ 8-2-(4)

How effective is intravenous phenobarbital for status epilepticus?

Summary

Intravenous phenobarbital is used for the treatment of stage 2 status epilepticus.

Comment

In a prospective randomized controlled trial comparing a combination of diazepam and phenytoin versus phenobarbital, the latter was slightly better in shortening both the duration of convulsion and the time of effect onset (average 5.5 minutes), although there was no difference in adverse effects[1]. In another double-blind comparative study, there was no significant difference in seizure control between diazepam plus phenytoin and phenobarbital[2]. In a meta-analysis of two studies with a total of 43 seizures, the rate of benefit of phenobarbital was 73.6% (95% confidence interval 58.3–84.8%)[3]. Inject phenobarbital intravenously after intravenous diazepam injection[4], or use phenobarbital when a combination of diazepam and phenytoin fails to control seizures[5]. Note that when using phenobarbital after diazepam, the frequency of respiratory depression increases.

■ References

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3) Yasiry Z, Shorvon SD. The relative effectiveness of five antiepileptic drugs in treatment of benzodiazepine-resistant convulsive status epilepticus: a meta-analysis of published studies. Seizure. 2014; 23(3): 167-174.
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■ Search formula and secondary reference sources

PubMed search: September 21, 2008
Status Epilepticus AND ("Diazepam" OR "Phenytoin" OR "Midazolam" OR "Propofol") = 357

Additional PubMed search: June 26, 2015
("Status Epilepticus" [Mesh]) AND "Phenobarbital/therapeutic use" [Mesh] = 18

No references that could serve as evidence were found in Ichushi Web.

CQ 8-2-(5)

How effective is midazolam for status epilepticus?

Summary

Midazolam is used for treating stage 1 and stage 2 status epilepticus, or as a general anesthetic agent.

Comment

Midazolam can be used as a therapeutic agent for stage 1 and stage 2 status epilepticus or as a general anesthetic agent[1, 2]. Midazolam belongs to the benzodiazepines. It is a fast-acting agent and a potent anticonvulsant. When vein access cannot be secured, intranasal, buccal or intramuscular midazolam can be administered[3]. As an alternative to intravenous diazepam, intravenous injection or continuous infusion of midazolam is an option[1]. Midazolam can be infused intravenously, and it has a low risk of respiratory depression or cardiovascular disturbances. Moreover, because of its short half-life, midazolam can be switched to other drugs (such as general anesthesia with barbiturates) when it is ineffective, without wasting time.

In a meta-analysis by Cochrane review, there were no significant differences in efficacy and adverse effects between intravenous midazolam and intravenous diazepam[4]. In the pediatric clinical practice in Japan, midazolam has been used as a therapeutic agent for stage 1 status epilepticus[5]. In addition, midazolam has been reported to be effective for non-convulsive status epilepticus uncontrolled by diazepam and phenytoin[6].

■ References

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■ Search formula and secondary reference sources

PubMed search: September 21, 2008
Status Epilepticus AND (“Diazepam” OR “Phenytoin” OR “Midazolam” OR “Propofol”) = 357

Additional PubMed search: June 26, 2015
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No references that could serve as evidence were found in Ichushi Web.

CQ 8-2-(6)

How effective is intravenous levetiracetam for status epilepticus?

Summary

Intravenous levetiracetam is effective as a therapeutic agent for stage 2 status epilepticus. However, this drug is not covered by medical insurance in Japan.

Comment

Levetiracetam has a mechanism of action different from those of other antiepileptic drugs[1]. This drug is fast-acting, with few adverse effects including respiratory depression and cardiovascular disturbances[1-3], and interaction with other drugs is also uncommon[1].

Comparative studies of levetiracetam with intravenous phenytoin[4] and intravenous lorazepam[5] have reported equivalent efficacy among them. In a systematic review of 7 retrospective studies with a total of 141 cases, the effective rate was 52–94%. In another systemic review of 3 prospective studies with 100 cases, the effective rate was 44–75%[2]. In a meta-analysis of 8 studies with 204 cases, the effective rate was 68.5%[3].

■ References

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■ Search formula and secondary reference sources

PubMed search: December 14, 2015
("Status Epilepticus" [Mesh]) AND "levetiracetam/therapeutic use" [Mesh] = 193

No references that could serve as evidence were found in Ichushi Web.

CQ 8-3

How effective is general anesthesia for refractory status epilepticus?

Summary

Administer general anesthesia as early as possible for refractory status epilepticus. As general anesthetic agent, midazolam, propofol, thiopental or thiamylal can be used.

Comment

Refractory status epilepticus is defined as status epilepticus that is not controlled by stage 1 (such as diazepam) and stage 2 therapeutic drugs (such as fosphenytoin).

Refractory status epilepticus develops in 31–43% of patients with status epilepticus[1]. When seizures are not controlled by stage 1 and stage 2 therapeutic agents, we should administer general anesthetic agent immediately. When convulsive status epilepticus persists for more than 30 minutes, irreversible changes occur in the brain. Based on this result, it is reasonable to use general anesthesia when seizures persist for approximately 30 minutes. However, there is no high quality evidence for the timing to start anesthesia, which general anesthetic agent to use, the depth of anesthesia, or the duration of anesthesia. There are no clear recommendation standards for the above issues[2].

For general anesthesia, midazolam (see CQ 8-2-(5) on page 72), propofol or barbiturate is used.

Propofol has a potent antiepileptic effect and is effective in many patients. Moreover, it is fast-acting with a short half-life, and there is no waste of time when switching to other anesthetics. Its lethal adverse effects have been reported, but the risk is low when used at doses not exceeding 5 mg/kg/hour[3] and terminated within 48 hours[2]. However, general anesthesia with propofol is contraindicated for children.

Thiopental and thiamylal belong to the barbiturates. Thiopental[4] is fast-acting, but takes a long time to arouse after its cessation. The frequency of adverse effects (including hypotension and infections) during anesthesia is high. Thiamylal has a similar profile as thiopental.

In terms of controlling convulsive seizures, thiopental is superior to propofol and midazolam, but there is no association between these anesthetics and prognosis of disease[4]. In a meta-analysis by Cochrane review of only one single-blind trial of 24 cases, there was no clear difference in efficacy between thiopental and propofol[5].

■ References

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■ Search formula and secondary reference sources

PubMed search: September 9, 2008
Status Epilepticus AND (general anesthesia) = 48
Additional PubMed search: June 26, 2015
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No references that could serve as evidence were found in Ichushi Web.

CQ 8-4

Does EEG monitoring during status epilepticus have clinical significance?

Summary

Electroencephalographic monitoring during status epilepticus is useful.

Comment

When seeing patients with suspected status epilepticus, record EEG in parallel with treatment. The EEG examination is useful in (1) exclusion of non-epileptic seizures such as psychogenic nonepileptic seizures (PNES), (2) differentiation between generalized seizures and partial seizures, (3) diagnosis of nonconvulsive status epilepticus (NCSE), (4) evaluation of brain function, and (5) prediction of prognosis.

PNES is not a malingering disorder, and it may cause not only incontinence or self-injury, but also any other symptoms, and some patients with PNES require mechanical ventilator[1, 2]. EEG recording during or immediately after seizure is useful for a definitive diagnosis. When examining patients with suspected PNES, record EEG as far as possible concurrent with treatment (see Chapter 14 on page 123).

For evaluation of treatment, we should confirm not only the clinical improvements but also reduction of epileptic discharges on EEG. A report demonstrated that after anesthesia was stopped, 48% of the clinically controlled patients still had subtle convulsion or electrical status on EEG[3].

Many reports have shown that in status epilepticus, maintaining flat EEG[3, 4] or burst suppression pattern[5] with deep anesthesia using general anesthetic agents improves the final outcome.

Continuous EEG monitoring is useful for the diagnosis of NCSE[6, 7]. EEG monitoring for over 6 hours can detect abnormal findings in 82% of NCSE[8] (not covered by medical insurance). In addition, the occipitally dominant background EEG activity has been reported to be related to clinical outcome[9].

■ References

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■ Search formula and secondary reference sources

PubMed search: September 7, 2008
Status Epilepticus AND "Electroencephalography" = 178

Additional PubMed search: June 29, 2015
((Status Epilepticus [majr]) AND "Electroencephalography" [Mesh]) AND (("Monitoring, Physiologic" [Mesh]) OR monitor*) = 89

No references that could serve as evidence were found in Ichushi Web.