

Concepts for Prehospital and Initial In-hospital Therapy of Status Epilepticus



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ABSTRACT

Status epilepticus is a major neurological emergency requiring immediate anticonvulsive treatment. Rapid and sufficient treatment is essential for optimizing outcome and reducing mortality. Here, we give an overview on concepts for acute prehospital and initial in-hospital treatment of status epilepticus. Options for initial therapy in settings without intensive care monitoring are presented in detail.

Introduction

Status epilepticus (SE) is a major neurological emergency associated with significant lethality and morbidity. SE incidence increases with age; thus, with the demographic shift of an aging population, rises in incidence rates are likely. In Germany, at least 16 000 to 20 000 cases of SE are to be expected annually; the resulting costs of acute in-patient SE treatment amount to over EUR 200 million per year. Mean SE mortality is between 15 and 20 % [1–4].

To treat SE, a large number of anticonvulsants are available which are used in very different therapeutic sequences and in various dosage forms. Whenever possible, SE should be treated in a neurocritical care unit; however, initial treatment should not be delayed by patient transport times to such a unit. Especially in patients with nonconvulsive SE or focal SE who may present with minimal neurological signs and symptoms, an EEG investigation in a clinical neurophysiology department is required to establish the diagnosis. In the prehospital environment, initial treatment needs to be modified to reflect the limited monitoring capabilities available in this setting. This review discusses the options available for prehospital and initial in-hospital treatment of SE (corresponding to stage 1 and stage 2; see below) in non-ICU settings with limited monitoring ca-

pabilities, taking into account the most recent SE definition of the International League Against Epilepsy (ILAE) published in 2015 [5] and the current consensus-based (S2k) Guideline on the Management of SE in Adults, issued by the German Neurological Society (Deutsche Gesellschaft für Neurologie, DGN) in 2012 [6].

Definition

According to the DGN guideline on SE [6], seizures of more than 5 min duration or a series of discrete seizures between which there is incomplete recovery of the previous neurological status is defined as SE and should be treated as soon as possible with sufficiently high doses. The 5-minute time limit dates back to an operational definition proposed by Lowenstein in 1999, aimed at ensuring that patients receive treatment as soon as possible, and which considers any seizure lasting for more than 5 min as SE [7]. The current ILAE definition sets two time points (t₁, t₂); while t₁ defines the transition of a seizure to SE (t₁), depending on semiology, t₂ marks the point in time when neurological injury is likely to occur. Regarding the start of SE treatment (t₁), the time limit is 5 min for generalized convulsive (tonic-clonic) status epilepticus (GCSE), 10 min

for complex focal status epilepticus (focal SE with impaired consciousness) and 10 to 15 min for absence status epilepticus [5]. SE-induced neuronal damage is assumed to occur after a time (t_2) of 30 min with GCSE and after 60 min with complex focal status epilepticus [5]. Thus, the urgency with which to start treatment is also dependent on the type of SE and appears to be most pressing with GCSE. Clinical and experimental data show a correlation between delayed start of treatment and reduced likelihood of successful SE termination with the first treatment attempt [8–10].

Stage-adapted Therapeutic Principles

Clinically, four phases of SE are differentiated [11] which are closely associated with the staged approach to treatment described in the following. The time spans listed below apply to a GCSE:

1. Initial phase of SE: A seizure of 5–10 min duration or continuous seizure activity in EEG. There is still a clinically relevant chance of spontaneous termination. Initial treatment with a benzodiazepine is appropriate.
2. Established status epilepticus: Seizure/epileptic activity in EEG of at least 10–30 (maximum 60) minutes or series of seizures between which there is incomplete recovery of consciousness. In addition to the initial treatment with a benzodiazepine, a conventional anticonvulsant is administered intravenously.
3. Refractory status epilepticus: SE persisting after failure of the first and second treatment, usually 30–60 min after start of seizure activity; escalation of therapy is critical. At this point in time, general anesthesia with endotracheal intubation should be administered to patients with GCSE. In patients with focal SE, there is not the same urgency to initiate aggressive anticonvulsive therapy as with GCSE; thus, further stage 2 treatment options should be used.
4. Super-refractory status epilepticus: Super-refractory SE is assumed when general anesthesia was ineffective [11, 12]. In this situation, several treatment options are available, including steroids, hypothermia, immunoglobulins, inhalation anaesthetics, ketogenic diet, perampanel, stiripentol, among others; however, all of these treatments lack evidence base and some are associated with limited anticonvulsive efficacy [11, 13–15]. Currently, a randomized, double-blind, placebo-controlled study (NCT02477618) on the use of allopregnanolone in patients with super-refractory SE is being performed [16]. Allopregnanolone is a neurosteroid, acting as a positive allosteric modulator of synaptic and extrasynaptic GABA_A receptors [17].

Initial Phase of Treatment (Stage 1)

Strong evidence from both clinical [8, 10] and animal model data [9] emphasizes the critical role of early initiation of treatment in patients with SE, as therapeutic response to most anticonvulsants deteriorates over the course of SE due to progressive decline in GABAergic inhibition [18]. Consequently, anticonvulsant treatment should be started as early as possible, ideally already before arrival at a hospital [10]:

In the initial phase, benzodiazepines are the drug of choice. With its longer intracerebral half-life and the resulting lower risk of seizure recurrence, lorazepam (LZP) is a clinically suitable drug and evidence-based initial treatment for patients with SE; it may be ad-

ministered by paramedics (up to 4 mg) and emergency physicians, or in a hospital setting (up to 0.1 mg/kg body weight [BW] intravenously) [10, 19]. As an alternative to LZP, clonazepam (CLP), another long-acting benzodiazepine, is often used because of its similar pharmacokinetic characteristics [20]; CLP should be slowly administered intravenously as a bolus dose of 0.015 mg/kg BW. However, data from randomized controlled trials are not available for CLP. A cohort study conducted in Lausanne (Switzerland) and Boston (USA) showed that LZP was more frequently underdosed in everyday clinical practice compared with CLP and associated with a higher risk of a more refractory treatment course [21]. Alternatively, other benzodiazepines can be used (for details on individual benzodiazepines refer to ► **Table 1**). When diazepam (DZP) or midazolam (MDZ) are used, concomitant rapid loading with another anticonvulsant (stage 2) is advisable to compensate for their shorter intracerebral half-life and to reduce the risk of seizure recurrence.

The RAMPART (Rapid Anticonvulsant Medication Prior to Arrival Trial) study compared the efficacy of intramuscular administration of MDZ (total dose of 10 mg, administered using an applicator; 5 mg for patients with body weights from 13 kg to 40 kg) with that of intravenous administration of LZP (4 mg total dose, 2 mg for patients with body weights from 13 kg to 40 kg) in the prehospital treatment of SE [22–24]. Intramuscular MDZ was superior to intravenous LZP with regard to the rate of GCSE controlled at the time of admission to hospital. This was primarily due to the shorter time to initial administration and emphasizes the need for rapid administration of benzodiazepines in the treatment of SE [25]. Although the time from drug administration to termination of SE was shorter in the arm treated with intravenous LZP, this did not result in statistical superiority because of the longer time needed to establish a secure intravenous access [22–24].

For initial treatment, especially by nursing staff and family members, additional routes of administration with rapid absorption are available, such as the buccal or intranasal administration of MDZ and the rectal administration of DZP. These routes of administration have been extensively studied, especially in children and adolescents, but are often expensive in daily use. Sublingual administration of LZP orally disintegrating tablets and oral administration of CLP or DZP drops should be avoided in the treatment of SE, as a long absorption half-life of about 20 min can occur.

Several studies showed the equivalence or superiority of intranasal or buccal administration of midazolam (0.2 mg/kg) or lorazepam (0.05 mg/kg to a maximum of 4 mg) compared with intravenous or rectal administration [26–37]. Thus, intranasal or buccal administration of midazolam (5–10 mg, repeated, if necessary, maximum dose approx. 20 mg), intramuscular administration of midazolam (10 mg i.m.) or rectal administration of diazepam (10–20 mg rectally, repeated, if necessary, maximum dose approx. 30 mg) are recommended for the initial treatment of SE in adults.

Among the branded medications, Buccolam is available for buccal administration; however, this product is only approved for the treatment of prolonged, acute, convulsive seizures in infants, toddlers, children and adolescents (from 3 months to <18 years). The missing approval of the product for the treatment of adults is due to the streamlined form of the approval process for pediatric use (PUMA, pediatric-use marketing authorization); however, prescribing this medication to adults in an outpatient setting may mean that

► **Table 1** Summary of benzodiazepines for acute treatment of prolonged seizures and status epilepticus.

	Midazolam	Lorazepam	Clonazepam	Diazepam
Typical initial dose in adults [#]	5 to 10 mg, in 2–3 mg steps	2 to 4 mg [#]	1 mg	10 mg [#]
Recommended intravenous dosage	0.1 mg/kg BW	0.05 bis 0.1 mg/kg BW	0.015 mg/kg BW	0.15 mg/kg BW
Maximum dosage	20 mg	8 mg	3 mg	30 mg
Routes of administration	intravenous, intranasal buccal, intramuscular	intravenous	intravenous	intravenous, rectal
Half-life	3–4 h	12–16 h	30–40 h	20–100 h *
Interactions	few	few	many	many
Tissue toxicity	low	low	low	low

BW: body weight

* short duration of action in CNS due to rapid redistribution

[#]To prevent underdosing, another dose of lorazepam and diazepam, in particular, should be administered in addition to the typical initial dose (1–2 vials) (WARNING: risk of respiratory depression)



► **Fig. 1** Ready-to-use midazolam nasal spray. The nasal spray delivers reproducible and standardized doses of 2.5 mg midazolam in 140 µl solution per puff. Rapid absorption via the nasal mucous membrane is ensured by the low puff volume.

► **Table 2** Formulation of midazolam nasal spray, 5 ml (adapted from [38, 63]).

Midazolam hydrochloride *	99.25 mg
Sodium chloride	32 mg
Benzalkonium chloride	0.5 mg
Sodium EDTA	5 mg
Purified water	to 5 ml

* Midazolam hydrochloride 99.25 mg \triangleq midazolam 89.3 mg; pH of 3.3 achieved with 1 N hydrochloric acid

However, commercially available MDZ vials can be used to administer MDZ via the intranasal route: For this, the solution for injection is to be transferred to a syringe, followed by intranasal administration using an atomizer (mucosal atomization device). Here, it is important to pay attention to the various commercially available MDZ dilutions and vial sizes (MDZ 5 mg/5 ml, 5 mg/1 ml or 15 mg/3 ml). A more convenient method of administration is to use a concentrated MDZ nasal spray which has already been evaluated during video-EEG monitoring and established successfully [38]. It was shown that intranasal administration of MDZ significantly delayed seizure recurrence and reduced the likelihood of generalized tonic-clonic seizures [38]. This concentrated MDZ nasal spray (► **Fig. 1**) can be prepared by pharmacies; for details of the formulation refer to ► **Table 2**. One puff of the spray (volume of 140 µl) contains 2.5 mg MDZ. To dissolve MDZ in an aqueous solution, an acidic pH of 3.3 is required. As a result, up to 5% of cases may experience irritation of the nasal mucosa [38]. The clear and colorless nasal spray can be stored at room temperature in a dark place for up to 3 months; the nasal spray must not be stored in a fridge as this could lead to the formation of precipitations in the solution. Since the separated form contains more than 15 mg MDZ, the prescription of the nasal spray falls under Appendix III of the German

costs are not covered by the statutory health insurances due to the off-label nature of its use in adults. No intranasal dosage form of midazolam has yet become commercially available; currently, such a medication is being evaluated in a clinical trial (NCT01390220).

► **Table 3** Summary of conventional anticonvulsants with intravenous application forms, listed by date of approval.

	Phenobarbital	Phenytoin	Valproate	Levetiracetam	Lacosamide	Brivaracetam
Typical initial dose in adults [§]	500–700 mg	1 200–1 500 mg	2 100 mg	2 000–4 000 mg	400 mg	200 mg
Intravenous dosage	10 mg/kg BW [#]	15–20 mg/kg BW [#]	30 mg/kg BW	30–60 mg/kg BW	5 mg/kg BW 200–600 mg	100–400 mg
Infusion speed	100 mg/min	max. 50 mg/min, max. 30 mg/kg	max. 10 mg/kg/min	max. 500 mg/min	15 min	bolus injection
Target serum concentration	30–50 µg/ml	20–25 µg/ml	100–120 µg/ml	not known	not known	not known
Half-life	60–150 h	20–60 h	12–16 h	6–8 h	13 h	8–9 h
Measuring serum concentration	recommended (toxic from 50 µg/ml)	recommended (toxic from 25 µg/ml)	no (adverse effects from 100 µg/ml)	no	no	no
Interactions	many	many	many	none	none	minimal
Respiratory depression	yes	no	no	no	no	no
Circulatory depression	monitoring required *	monitoring required *	no	no	no *	no
Vigilance	sedation	sedation	somnolence	somnolence	somnolence	somnolence
Tissue toxicity	high	very high	strict IV administration	very low	very low	very low

BW: body weight

* Acute high-dose intravenous phenytoin or phenobarbital should always be administered with ECG and blood pressure monitoring in an ICU setting. ECG monitoring is recommended when lacosamide is administered—especially in combination with sodium channel blockers—as it can cause PR interval prolongation

[#] Treiman et al. administered phenobarbital and phenytoin at doses of 15 mg/kg and 18 mg/kg BW, respectively [44]

[§] Based on a body weight of 70 kg

Narcotics Act (Betäubungsmittelgesetz, BtMG); thus, the nasal spray must be prescribed and documented for each patient individually.

For rectal administration, 5 mg and 10 mg of rectal DZP are available in 2.5 ml rectal solution and approved for the treatment of SE. For decades, DZP has been used in prehospital treatment [39]. However, the rectal administration of medications, especially in the public, is not fully accepted by society and associated with negative psychosocial effects, such as embarrassment and stigmatization [40, 41]. Currently, a trend towards buccal or intranasal administration of benzodiazepine is noted [42, 43].

Treatment with Intravenous Anticonvulsants (Stage 2)

Rapid loading with anticonvulsants is required in patients with persisting SE or after termination of SE with benzodiazepines to prevent seizure recurrence. Intravenous dosage forms, listed according to the approval dates of the various anticonvulsants, are available for phenobarbital (PB), phenytoin (PHT), valproic acid (VPA), levetiracetam (LEV), lacosamide (LCM), and brivaracetam (BRV); refer to ► **Table 3**. The DGN Guideline on the Management of SE in Adults recommends the use of PHT; as alternative medications or

in case PHT is contraindicated, VPA, LEV and PB are taken into consideration [6].

PHT should be administered at a dose of 20 mg/kg body weight (BW) (max. 50 mg/min, max. 30 mg/kg BW) via a secure large-bore IV access, ideally a central venous catheter [44]. PHT is available both as an infusion concentrate (750 mg/50 ml) and as an injection solution (250 mg/5 ml) with distinct PHT doses. The highly alkaline PHT solution must not be diluted with other substances as this could result in the precipitation of free phenytoin base. For the further treatment, it should be attempted to achieve a target phenytoin level of 20 µg/ml (up to max. 25 µg/ml). The comparably slow infusion speed should not be exceeded in the light of PHT's proarrhythmic effect—a disadvantage of this medication. According to its summary of product characteristics, PHT is contraindicated in patients with second- or third-degree atrioventricular block, myocardial infarction during the last 3 months and heart failure with an ejection fraction under 35%. In addition, similar to thio-pental, phenytoin exhibits local tissue toxicity; thus, intravenous access should be large-bore and secure to avoid tissue necrosis associated with extravasation. Irreversible damage of the cerebellum may result from phenytoin intoxication [45]. These toxicities limit the use of phenytoin as a first-line treatment in patients who have no indwelling central venous catheter or where continuous monitoring of vital signs is not available; thus at our hospitals, PHT is

used as drug of 4th choice after LEV, VPA and LCM [3], and other centers pursue similar management strategies [46–48]. Furthermore, this approach reflects the current prescribing behavior in patients with epilepsy in Germany: in over 50% of patients, treatment is started with LEV at first diagnosis [49, 50].

VPA should be infused at a dose of 20–30 mg/kg BW, max. 10 mg/kg/min, to be repeated after 10 min, if necessary, then at a dose of max. 10 mg/kg. For the further treatment, it should be attempted to achieve a target VPA level of 100–120 µg/ml. VPA is available at a concentration of 100 mg/ml in various dose sizes, with 300 mg, 400 mg and 1 000 mg per vial. A major contraindication is known mitochondriopathy. According to the summary of product characteristics, VPA is also contraindicated in patients with insulin-dependent diabetes mellitus or porphyria. Since VPA can cause a platelet dysfunction (thrombocytopenia), its use in patients with increased susceptibility to bleeding and in need of surgical treatment is problematic. Further contraindications include hepatic disorder, pancreatitis and oral anticoagulation with vitamin K antagonists such as warfarin or phenprocoumon (susceptibility to bleeding and INR imbalance). Furthermore, it is often difficult to achieve adequate serum levels in patients with carbapenem antibiotics as co-medication [51].

LEV is to be administered at a dose of 30 mg/kg BW with the maximum infusion speed of 500 mg/min; if required, this can be repeated after 10 min (maximum total dose of 60 mg/kg BW). The target level for LEV treatment has not yet been established. In patients with renal impairment, dose adjustment is required for continuing therapy.

PB can be administered at doses of up to 20 mg/kg BW (max. 100 mg/min) [44]. Higher total doses require intensive care monitoring as well as preparedness for intubation and mechanical ventilation; consequently, as with PHT, its use is contraindicated where adequate monitoring cannot be ensured. In addition, drug-drug interaction as well as intoxication risks have to be taken into consideration when PB is used in combination with VPA. In patients with hepatic impairment, PB should not be used. For the further treatment, it should be attempted to achieve a target PB level of 30–50 µg/ml.

Since 2008 LCM has been available as an intravenous anticonvulsant. According to a recent systematic review, it has been used in more than 500 cases to treat SE; its efficacy was 57% and its tolerability profile was favorable [52]. Usually, a dose of 5 mg/kg BW is administered over ≥ 15 min (initial dose of 200 to 400 mg) [53–55]. As with LEV, LCM has not yet been approved for the treatment of SE. Since PR interval prolongation have been observed with LCM, it should be used with caution in patients with known second-degree or higher AV block and in patients with cardiac disease. Dose adjustment is required in patients with renal or hepatic impairment.

Approved in 2016, BRV is the latest intravenous anticonvulsant that has become available and data on its use to treat SE are limited to just a few cases [56]. Most commonly, starting dosages of 200 to 400 mg are used; in contrast to other intravenous anticonvulsants, undiluted solution can be used for bolus injection, further cutting down the time to treatment in SE. BRV has not yet been ap-



► **Fig. 2** The SE emergency kit used in Frankfurt for the initial treatment of status epilepticus in settings with limited monitoring capabilities.

proved for treatment of SE. All in all, BRV is a well-tolerated antiepileptic drug (AED) with a lower incidence of psychobehavioral adverse events compared with LEV [57, 58]. Switching from LEV to BRV is possible and a ratio between 15:1 and 10:1 can be applied [57]. Dose adjustment is required in patients with hepatic or renal impairment [59, 60]. Since BRV crosses the blood-brain barrier significantly faster than LEV and attains its maximum concentration in the brain within minutes after intravenous administration [61], future studies will have to clarify whether BRV treatment starting with a bolus injection for rapid loading offers advantages in the emergency situation.

Concepts for Management Outside Intensive Care Units

Neither in the prehospital nor in the in-hospital setting should the treatment of SE be unnecessarily delayed. An established local treatment pathway should be in place to ensure that treatment is started immediately after diagnosis, already outside the emergency department or intensive care unit. In patients in whom SE is suspected based on EEG findings, the technician should inform the treating physician experienced in EEG interpretation so that, once the diagnosis of SE is confirmed, treatment can be started. If SE is diagnosed in the clinical neurophysiology department, it has proven to be beneficial to bring along an SE emergency kit (► Fig. 2) so treatment can be started while an EEG is recorded. Midazolam can be administered intranasally if intravenous access is not yet established; once established, conventional anticonvulsants such as LEV, VPA, LCM or BRV should be administered intravenously—the monitoring capabilities of an emergency department or intensive care unit are not required for this step. Further treatment is then provided in an intensive care unit.

Conclusion

In conclusion, besides uncontrollable factors such as etiology, comorbidity and age of patient, rapid initiation of treatment with benzodiazepines and other anticonvulsants in high enough doses is critical for a successful therapy. In prehospital and in-hospital settings outside of intensive care units where monitoring capabilities are limited, the treatment of SE has to be adapted to local conditions. Therapy should be continued in a neurocritical care unit, especially when treatment with PHT or PB or stage 3 or 4 therapy is required. To ensure initial treatment is started without delay, it is critical to establish a local treatment pathway [62] so that the recommended treatment can be provided immediately.

Conflict of interest

L. Kay, A. von Blomberg and L.M. Willems declare that no conflict of interest exists. A. Strzelczyk received consulting and lecture fees and/or support for research projects from Bayer HealthCare, Boehringer Ingelheim, Desitin Arzneimittel, Eisai, LivaNova, Pfizer, Sage Therapeutics, UCB Pharma, and Zogenix. C. Kellinghaus received consulting and lecture fees from Cerbomed, Desitin, Eisai, and UCB Pharma. S. Knake received consulting and lecture fees from Desitin and UCB Pharma. F. Rosenow received consulting fees from GlaxoSmithKline, Eisai, UCB Pharma, Shire, Sandoz, and Pfizer. He received lecture fees from UCB Pharma, GlaxoSmithKline, Eisai, Hexal, Desitin, and Medtronic as well as support for continuing medical education (CME) events from Nihon-Kohden, UCB Pharma, Medtronics, Cyberonics, and Cerbomed.

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