Treatment of Status Epilepticus

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Summary

Status epilepticus treatment involves the use of several pharmacological compounds, which are conceptually divided in three successive and additional lines of action. Benzodiazepines represent the first approach, due to their rapid onset of action; these are followed by classical AED that are administered IV. In refractory episodes, pharmacological coma induction with an appropriate anesthetic agent is advocated. Apart from the fist-line, the level of evidence is limited.

It is important to specifically address etiology in order to maximize the impact of the antiepileptic therapy. Furthermore, the fine tuning of the treatment strategy, including mainly the decision regarding coma induction, should be performed balancing benefits of a rapid SE control with the risks of side effects. While each status epilepticus episode should be treated as rapidly as possible, it appears advisable to reserve coma induction for the forms that have been shown to bear a consistent risk of neurological sequelae, i.e., generalized convulsive status.

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Key words: Benzodiazepines, phenytoin, valproate, levetiracetam, anesthetic agents

Le traitement du statut épileptique

Le traitement du statut épileptique suppose le déploiement d'un arsenal pharmacologique qui se scinde en trois vecteurs d'action conceptuels successifs se complétant. Les benzodiazépines sont engagées en première ligne du fait de leur action rapide ; suivent les anti-épileptiques classiques par application IV. Dans les épisodes réfractaires, l'induction d'un coma pharmacologique au moyen d'un anesthésique approprié est préconisée. Mise à part la première ligne d'action, il manque cependant encore une documentation suffisante pour les autres.

Il est important de définir l'étiologie exacte afin de maximiser l'impact de la thérapie anti-épileptique. De plus, le réglage fin de la stratégie thérapeutique, et notamment de la décision d'induire un coma ou non, devrait se faire en pondérant soigneusement les bénéfices d'un contrôle rapide du statut épileptique versus le risque d'effets indésirables. Car si chaque épisode d'état de mal épileptique nécessite bien une intervention aussi rapide que possible, l'induction d'un coma devrait être réservée aux formes où un risque consistant de séquelles neurologiques, p.ex. un statut convulsif généralisé, a été avéré.

Mots clés : benzodiazépines, phénytoïne, valproate, lévétiracétam, agents anesthésiques

Behandlung des Status epilepticus

Zur Behandlung des Status epilepticus stehen verschiedene pharmakologische Waffen zur Verfügung, die sich in drei sukzessive und sich vervollständigende Handlungsstrategien unterteilen. Erste Priorität haben ihrer raschen Wirkungsweise wegen die Benzodiazepine, gefolgt von den klassischen, IV verabreichten Antiepileptika. Schliesslich wird bei refraktären Episoden eine Komainduktion mit geeigneten Anästhetika vertreten. Wirklich gut bekannt ist dabei nur das erste Behandlungskonzept, die beiden anderen sind noch nicht ausreichend dokumentiert.

Es ist wichtig, die Ätiologie genau zu kenne, um mit der antiepileptischen Therapie das bestmögliche Resultat zu erzielen. Zudem sollten bei der Feinregulierung der Behandlungsstrategie, und insbesondere bei einem Entscheid für oder gegen ein induziertes Koma, die Vorteile einer raschen Kontrolle des SE sorgfältig abgewogen werden gegen das Risiko unerwünschter Nebeneffekte. Natürlich sollte jeder Status epilepticus so rasch als möglich behandelt werden, trotzdem scheint es ratsam, die Komainduktion jenen Formen von SE vorzubehalten, bei welchen ein konsistentes Risiko neurologischer Folgen, z.B. in Form eines generellen konvulsiven Status zu befürchten sind.

Schlüsselwörter: Benzodiazepin, Phenytoin, Valproat, Levetiracetam, anästhetische Wirkstoffe

Pharmacological background and general outline

There is a general consensus on the need to treat status epilepticus (SE) as soon as possible, in order to prevent potentially deleterious sequelae [1 - 4]. The pathophysiologic mechanisms occurring during an episode of SE are characterized, at the beginning, by an imbalance between inhibitory (mostly $GABA_A$) and excitatory (predominantly glutamate-mediated, kainate and AMPA) inputs [1, 5-12]. This represents the rationale to start SE treatment with benzodiazepines, rapidly acting GABA-ergic agents. GABA resistance then develops progressively following receptor trafficking and subunit changes; afterwards, a shift towards self-sustaining glutamate-mediated excitotoxicity occurs, resulting pri-

marily from the activation of NMDA receptors. These changes may explain both refractoriness to benzodiazepines and excitotoxic neuronal damage.

SE treatment aims at stopping seizure activity, and controlling complications [2]. Pulmonary and cardiac function need to be secured; in parallel, a targeted examination and history taking should be performed to detect SE imitators, such as movement disorders (e.g., shivering in the ICU) and psychogenic seizures [13]. Laboratory and neuroradiological work-ups are paramount to address SE etiology, since its specific treatment may greatly influence the success of AED prescription. In general, SE treatment should be performed under EEG control.

Pharmacological SE treatment may be categorized into three phases of antiepileptic drug (AED) administration, generally intravenously: 1. benzodiazepines aiming at rapid SE control; 2. classical AEDs targeting early resistant forms and long term coverage following anticipated control of SE; 3. general anesthetics for refractory SE. This approach should be sequential and additional. A simple protocol with corresponding timing is proposed in the **figure**. Awareness of a protocol greatly facilitates this practical approach, and allows a smooth interplay between the different providers (paramedics, emergency or ICU team, neurologists).

First line

The first-line SE treatment has been better investigated than second- and third-line. A small study in 1983 found a nonsignificant trend toward better response to lorazepam (LZP) as compared to diazepam (DZP) [14]. A pre-hospital trial found that LZP had a nonsignificant superiority over DZP, whereas both treatments were

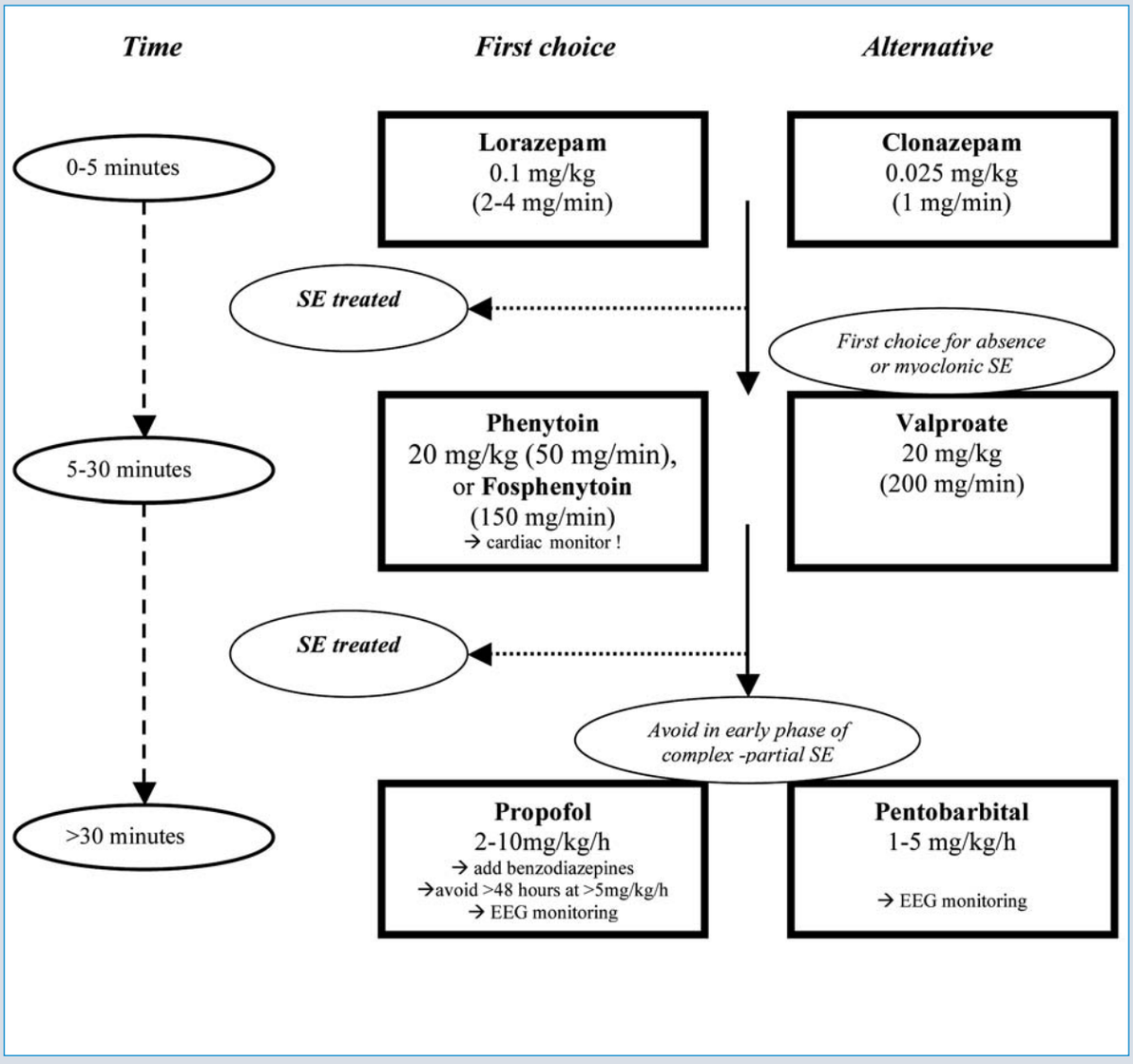

Figure: Pharmacological SE treatment

significantly better than placebo; cardiovascular and respiratory complications did not differ among groups [15]. A large VA trial, focusing on generalized convulsive SE and assessing the efficacy of LZP, phenobarbital (PB), diazepam (DZP) followed by phenytoin (PHT), and PHT alone, disclosed better efficacy of LZP as compared to PHT alone, but not to the other arms [16]. The overall response in overt SE was higher than in subtle SE (about 60% vs. 20%). Nevertheless, as SE becomes more refractory to treatment with time [7], and the first treatment has a far better chance of success than the second or third, regardless of the drug (55% vs. 7% vs. 2 %) [17], it is important to administer IV drugs that act quickly. Therefore, benzodiazepines represent the better option over PB and PHT, although there is usually no contraindication to giving both at essentially the same time. Compounds with a long CNS elimination half-life are desirable, since this avoids rebound seizures as drug levels decline. Note that tonic SE in patients with developmental delay may be aggravated by benzodiazepines.

– *Lorazepam (LZP)* is administered in a slow bolus of 0.1 mg/kg (2mg/min); it enters the brain in less than 2-3 minutes [18] and has a long duration of action (at least 12 h), as it is far less prone to redistribute in the tissue than diazepam [19]. Its elimination half-life is 8-25 h [18, 19].

– *Diazepam (DZP)* is administered at 0.2 mg/kg (5mg/min), it enters readily the brain (less than 10 sec), but its free fraction redistributes in the fat tissue accordingly to its high lipophilia and protein given rectally.

– *Clonazepam (CLZ)* is relatively widely used in Europe. It is administered at a bolus of 0.025 mg/kg. It reaches the brain within 1 min [18], and despite its lipophilia has stable action over time. It has a long half-life (up to 38 h) and moderate protein binding (less than LZP: 65% vs. 90%) [18, 20].

– *Midazolam (MDZ)* has a short half-life (about 2 h), but represents a valuable alternative when IV lines are not available or in children (intranasal or buccal administration). The usual dosage is 0.1-0.2 mg/kg, but doses up to 0.5 mg/kg have been reported [21].

The administration of a benzodiazepine bolus may induce respiratory and circulatory collapse (about 10%-26%) [15, 16], thus, monitoring of these functions is mandatory.

Second line

To date, there have not been any large-scale, prospective comparative assessments among AED used as second- or third-line SE treatment. The VA study included a PHT (which acts principally through sodium channel modulation) and a PB (mainly a $GABA_A$ agonist) arm as initial SE treatment, and found a nonsignificant trend toward a better efficacy of PB (58% vs. 44% [16]). Intravenous valproate has been repeatedly reported to be efficacious for several SE types [22, 23], without cardiovascular adverse reactions, therefore there is no need of concurrent monitoring. Levetiracetam has also been employed in SE treatment [24]; recent availability of an intravenous formulation makes it even a more promising option [25, 26].

– *Phenytoin (PHT)* is the most widely used agent in this context, administered at 20mg/kg (maximal infusion rate, 50mg/min). Maximal concentrations in the CNS are reached after 20 min [19]. The elimination half-life is about 24 h, but is longer at high serum levels. Some rare but serious local reactions (purple glove syndrome) are induced by the alkaline solution, whereas PHT itself is associated with hypotension and bradyarrhythmia (27% and 7% in the VA study group [16]). A slower infusion rate is especially advisable in elderly subjects. Cardiac monitoring should always be available during intravenous PHT administration.

– *Phosphenytoin (PPHT)* is a water-soluble PHT prodrug lacking propylene glycol and therefore safer regarding local reactions. It is administered in PHT-equivalents. Although it can be infused at a much faster rate (150mg PHT equivalents/min), it is questionable whether effective CNS concentrations are reached before PHT administered at optimal rates [27].

– *Phenobarbital (PB)* is administered at 15 mg/kg (100mg/min). It reaches the brain after 20-40 min. Its half-life is around 100 h. It also bears a consistent risk of hypotension (34% in the VA study [16]).

– *Valproic acid (VPA)* is loaded at 20mg/kg, up to 200 mg/min [22, 28], and its elimination half-life is about 15 h. VPA enters the CNS rapidly through active transport [29]. Clinical experience in SE suggests that effective CNS concentrations are reached within 30 min [28, 30]. Its main advantage is the lack of cardio-depressive reactions.

– *Levetiracetam (LEV)* may be loaded up to 20 mg/kg [25]; its plasma half life is about 7 hours, but the bioavailability within the blood-brain barrier is probably longer [31]. It is unclear how fast LEV reaches the brain, but personal observations suggest that an effect occurs within 15 to 30 minutes of IV administration. The most frequent adverse event is mild sedation; no cardiovascular reactions have been reported.

Third line

In generalized convulsive SE, the earliest administered treatment has the greatest chance to be effective [11, 17], therefore the sequential administration of second-line treatments does not appear to have a good rationale, and it seems reasonable to proceed straight to 3rd-line treatment once the 2nd-line (which takes at least 20-30 min to be effective) has failed [2, 32]. An important caveat concerns SE episodes in which patients are at least partly conscious, including absence and several forms of complex partial SE. Indeed, it is unclear

whether prolonged complex partial seizures in humans induce permanent structural neurological damage [33-37], as opposed to generalized convulsive SE, in which damage of limbic structures has been confirmed both pathologically and radiologically [38, 39]. It is thus debatable whether and when coma induction, which may predispose to several complications (e.g., pneumonia, deep vein thromobosis, pulmonary embolism, neuropathy, myopathy, ileus), is warranted in SE forms other than generalized convulsive SE. A recently validated severity score (STESS) may help to orient early treatment strategy in unclear situations [40]. In some instances, it appears advisable to attempt avoiding coma induction by administering non-sedating AED sequentially. SE episodes in patients with idiopathic generalized epilepsy (absence or myoclonic SE) readily respond to benzodiazepines and VPA and should not be intubated. Conversely, postanoxic SE, the expression of a severe underlying encephalopathy, is often refractory to standard treatments; in selected cases, however, after considering other prognostic factors, AED including anesthetics could be prescribed before reassessing the patient [41].

Existing studies on refractory SE are represented by case series. A meta-analysis of barbiturates, propofol, and midazolam [42] did not disclose any significant difference in short-term mortality among these three agents, although some variations were noted in both efficacy and tolerability. A retrospective analysis taking into account possible combinations of anesthetics did not show any notable difference in outcome among the agents, used alone or in association [43]. There is also considerable uncertainty regarding the optimal extent of EEG suppression [43, 44], and the optimal length of treatment. An EEG target of burst-suppression with an interburst interval of about 10 sec, maintained for 24-36 hours, followed by progressive tapering over 12-48 hours, represents a good practical option.

– *Barbiturates*, such as thiopental in Europe or its metabolite pentobarbital (PTB) in North America, show a long half-life after continuous administration (PTB: 15-22 hours) [45]. There is a considerable tendency of this drug to accumulate, prolonging the need for mechanical ventilation. Induction with PTB is performed with boluses of 5-15 mg/kg, and maintenance dose is 1-5 mg/kg/h.

– *Propofol* has a short half-life of about 1-2 hours [46], allowing rapid titration and withdrawal. It may induce the so-called "propofol infusion syndrome", a potentially fatal cardio-circulatory collapse with lactic acidosis, hypertriglyceridaemia and rhabdomyolysis, especially in young children, which has been only exceptionally described in patients with SE [47, 48]. Concomitant benzodiazepines could lower the needed propofol dose, possibly reducing the risk of this complication [49]. Loading dose is 2 mg/kg, followed by maintenance at 2-10 mg/kg/h. Prolonged (over 48 h) administration of doses over 5 mg/kg/h should be avoided.

– *Midazolam (MDZ)* has a half-life of 6-40 hours after prolonged infusion [50], with marked tachyphylaxis developing within 24-48 h [51]. It is loaded at 0.2 mg/kg, then maintained at 0.05-0.6 mg/kg/h.

Other treatment approaches

Other anesthetics, such as ketamine, an NMDA antagonist [52, 53], or isoflurane [54], an inhalation anesthetic, represent alternatives for extremely refractory SE, which is classically encountered in young patients with documented or presumed encephalitis [55], but are not used routinely. Also high-dose oral topiramate may be beneficial at times [56]. Immunomodulatory approaches, such as steroids, IVIG, or plasma exchanges, are often tried those cases [57]. Regarding non-pharmacological treatments, vagal nerve stimulation [58] and hypothermia [59] should be mentioned.

Conclusion

Although several pharmacological options are used in the treatment of SE, there is substantial lack of comparative, high-level, evidence-based information. These issues need to be investigated in well-designed studies. It is paramount to continue SE treatment, together with supportive care, also in those episodes refractory to treatment for prolonged time, as long as clear evidence of irreversible neurological damage is not available [57, 60].

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