Antiepileptic Medication in the ICU: Which Compounds Do We Need?

Alba Sierra-Marcos and Andrea O. Rossetti, Department of Clinical Neurosciences, CHUV, BH07, Lausanne

Summary

The aim of this contribution is to offer an overview of the main antiepileptic treatment options used in the intensive care unit (ICU). Benzodiazepines (BDZ) are gamma-amino-butyric-acid (GABA) receptor agonists, improving the inhibition of signal transmission. Commonly used intravenous (IV) BDZ include diazepam (DZP), midazolam (MDZ), lorazepam (LZP) or clonazepam (CLZ). The main problem with BDZ is the phenomenon of tachyphylaxis, which may result in breakthrough seizures. Classical AED such as phenytoin (PHT), valproate (VPA), phenobarbital (PB), and more recently newer AED such as levetiracetam (LEV) and lacosamide (LCM), are also available in IV formulations. At times, the antiepileptic management includes administration of general anesthetics, mostly thiopental/pentobarbital (THP), propofol (PRO), or midazolam (MDZ). Further pharmacological, such as other anesthetics, as well as topiramate (TPM) or pregabalin (PGB) by nasogastric tube, or non-pharmacological treatments may also come at play in selected situations. Despite all these therapeutic options, the management seizures and status epilepticus in the ICU has a low level of evidence, and there is a lack of randomized controlled trials comparing the different options.

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Key words: Epilepsy, seizure, status epilepticus, treatment, intensive care unit

Antiepileptische Medikation in der Intensivpflege: Welche Antiepileptika brauchen wir?


Schlüsselwörter: Epilepsie, Anfall, Status epilepticus, Behandlung, Intensivstation

Médicaments antéépileptiques dans l’Unité de Soins Intensifs : Quels composés avons-nous besoin?

L’objectif de cette contribution est d’offrir une vue d’ensemble des principales options de traitement antéépileptique utilisées dans l’unité de soins intensifs (USI). Les benzodiazépines (BDZ) sont des agonistes des récepteurs de l’acide gamma-amino-butyrique (GABA), contribuant à l’inhibition neuronale. Les BDZ plus couramment utilisés par voie intraveineuse (IV) comprennent le diazépam (DZP), le midazolam (MDZ), le lorazépam (LZP) ou le clonazépam (CLZ). Le principal problème avec les BDZ est le phénomène de tachyphylaxie. Les AED classiques tels que la phénytoïne (PHT), le valproate de sodium (VPA), le phénobarbital (PB), et plus récemment des nouveaux AED tels que le lévetiracé tam (LEV) et la lacosamide (LCM), sont également disponibles dans des formulations IV. En outre, la thérapie antéépileptique comprend parfois l’administration d’anesthésiques généraux, principalement le thiopental/pentobarbital (THP), le propofol (PRO), ou le mida zolam (MDZ). D’autres approches pharmacologiques, comme d’autres anesthésiques, ainsi que le topiramate (TPM) ou prégabaline (PGB) par sonde naso-gastrique, peuvent se rendre utiles dans quelques situations particulières. En dépit de toutes ces options thérapeutiques, le traitement des crises et de l’état de mal épileptique à l’USI a un très faible niveau d’évidence.
Introduction

Seizures represent a common complication in patients treated in the ICU, not only with neurological, but also with other medical or surgical problems, and may range up to 50% for selected groups of patients; most events are nonconvulsive (reviewed in [1] and in the contribution of JW Lee in this Epileptologie issue). Status epilepticus (SE) represents a frequent challenge in the Intensive Care Unit (ICU), with an estimated short-term mortality varying between 3.45% to 22% in different assessments, depending basically on the age and the underlying etiology [2, 3]. The optimal treatment in this setting involves both the acute cessation of ictal activity and preventing seizure recurrence, ideally by removing or correcting the trigger and providing pharmacological prophylaxis [4]. The aim of this article is to review the main antiepileptic drugs (AEDs) used in the ICU.

The treatment of the different phases of repeated seizures and SE has been extensively reported in the literature [5 - 8], and there are several (mostly similar) protocols advocating the initial use of benzodiazepines (BZD), followed by classical AEDs administration, and finally by anesthetic agents, in successive phases as follows:

- Early-established status (<30-60min)
  - First line: IV BDZ (mostly midazolam, lorazepam, or clonazepam)
  - Second line: IV classical AED (such as phenytoin, valproate, phenobarbital), or more recently levetiracetam and lacosamide

- Refractory status (>30-60 min)
  - Third line: IV drips of thiopental/pentobarbital, propofol, or midazolam
  - Further pharmacological (such as other anesthetics, topiramate or pregabaline by nasogastric tube) or non-pharmacological treatments

First line treatment: Benzodiazepines

These compounds penetrate rapidly into the brain, are potent gamma-aminobutyric acid (GABA) receptor agonists, and thus improve local inhibition of signal transmission. They represent the drugs of first choice for SE and seizures associated with post-anoxic insult or alcohol withdrawal. The main problem with BZD is the phenomenon of tachyphylaxis, resulting in possible breakthrough seizures after an initial response [9]. Commonly used BZD include diazepam, midazolam, lorazepam or clonazepam, each compound having its pharmacokinetic profile.

- **Diazepam (DZP)** is a highly lipophilic drug, which rapidly redistributes from the serum into fat tissue. The anticonvulsant duration lasts less than 30 minutes, whereas its elimination takes many hours. Such kinetics may result in brief seizure control, yet a prolonged sedative effect if large dosages are administered. DZP is rarely used in our environment because of the above mentioned issue, the recommended loading doses range from 0.1 to 0.25 mg/kg.

- **Midazolam (MDZ)** is also a highly lipophilic and short acting drug (2 to 4 hours), and is cleared by the liver – via CYP 3A4 – much more rapidly than DZP, resulting in better correlation between drug effect and clearance [10]. However, MDZ exhibits use-dependent pharmacokinetic changes that may be important clinically in situations that require prolonged therapy, raising the elimination half-life to 50 hours [11]. The efficacy of intramuscular (IM) MDZ versus intravenous (IV) lorazepam as a first-line treatment in the pre-hospital setting has been recently demonstrated in a randomized non-inferiority clinical trial. It adds the advantage of its ease of administration and practicality for paramedic use [12]. Therefore, MDZ 0.15 mg/kg IM is one of the drugs of choice for immediate seizure control, especially in the pre-hospital setting, with a maintenance dose of 0.1–0.4 mg/kg/h.

- **Lorazepam (LZP)**, a compound with greater water solubility that prolongs its serum half-life, is clinically effective for 6-8 hours, and has an elimination half-life of about 20 hours. In a randomized controlled trial, LZP was found to be superior to DZP, phenytoin, and phenobarbital alone in terminating clinical and EEG seizures [13]. The duration of effect reflects LZP low hepatic clearance, small volume of distribution, and absence of active metabolites (unlike DZP and MDZ), with a low risk of drug interactions [14].

- **Clonazepam (CLZ)** is extensively metabolized in the liver into pharmacologically inactive metabolites. It has an elimination half-life of 19 - 60 hours, is largely bound to plasma proteins and it passes easily through the blood-brain barrier, with levels in the brain corresponding with levels of unbound CLZ in the serum. However, plasma levels seem very unreliable, as they can vary as much as tenfold between different patients [15]. The optimal loading dose for the initial treatment of seizures is 0.015 mg/kg IV. This compound is basically used in Europe, especially in French-speaking countries, and is unavailable as intravenous formulation in the US.
Second line treatment: Antiepileptic drugs

If patients are not responsive to BZD, the next step is adding first, second or even third generation AEDs available in IV formulations. Only the oldest drugs have a consensual approval for the second-line treatment of SE; however, the more recent AEDs may offer the advantage of a better tolerance and ease of administration.

- **Phenobarbital (PB)** is the oldest AEDs still in use, as it was commercialized exactly one century ago. It binds to the GABA<sub>δ</sub> receptor, extending the duration of GABA-mediated chloride channel openings. An IV PB bolus remains an effective second-line drug option, although this drug is used less frequently in recent years due to adverse effects, including respiratory depression, sedation, and hypotension (especially with rapid infusion rates and previous treatment with IV BZD). Nevertheless, the prolonged effect may be advantageous. The loading dose is 15 to 20 mg/kg IV and the recommended target serum level is 30-40 mg/L. PB dosage range from 40 to 140 mg/kg/day. A number of drugs can influence the serum concentration of PB, and on its turn PB is a potent enzyme inducer, which does not make it recommendable in polymedicated patients [16].

- **Phenytoin (PHT)** mostly acts by blocking voltage-dependent neuronal sodium channels. Its metabolism takes place in the liver through a non-linear kinetics enzyme. Both PHT and the pro-drug fosphenytoin (which has the advantage of better local tolerability but not available in Switzerland) can be administered intravenously with doses roughly equivalent to the oral route, usually pursuing plasma concentrations between 12 to 20 mg/L. In the ICU, the loading dose is 20 mg/kg (maximal drip rate, 50 mg/min), and it is mandatory to perform a continuous hemodynamic monitoring due to the risk of significant bradyarrhythmias or hypotension. A great number of drugs can influence the serum concentration of PHT, which also is a potent enzyme inducer and has a high protein-binding. The protein-binding of PHT and the pharmacologically active free concentration may increase relative to the total concentration. The major systemic side effects include gingival hypertrophy, hypertrichosis, rash, Stevens-Johnson syndrome, lymphadenopathy and neurotoxic side effects. It is important to remember that PHT may also aggravate absence and myoclonic seizures in Idiopathic Generalized Epilepsy (IGE).

- **Valproate (VPA)** is a broad-spectrum AED with multiple mechanisms of action, including blockage of voltage-dependent sodium channels, increase of GABA concentrations, and suppression of T-type calcium currents. As PHT, VPA is tightly protein-bound and is metabolized in the liver. Therapeutic concentrations are usually in the 50 to 100 mg/L range. Accumulating evidence suggests that IV VPA can be safely infused at rates up to 10 mg/kg per minute and doses of up to 30 mg/kg [17]. A large number of drugs affect the serum level of VPA, which is an enzyme inhibitor. Side effects of VPA include nausea, vomiting, hair loss, tremor, weight gain, obesity, insulin resistance, thrombocytopenia or other coagulation disturbances, subclinical hypothyroidism, pancreatitis and polycystic ovarian syndrome. Indeed, VPA-exposure in utero is associated with major malformations and cognitive impairment; thus, it should be avoided when possible in women of childbearing age and pregnancy. Finally, VPA-related hyperammonemic encephalopathy causes lethargy, increased seizures, and rarely coma and death.

- **Levetiracetam (LEV)** is a more recently developed broad spectrum AED whose mechanism of action includes the binding to the synaptic vesicle protein SV2A, modulating synaptic transmission through alteration of vesicle fusion. Its catabolism (renal excretion and hydrolysis) is independent of the cytochrome CYP450 system, avoiding the potential pharmacokinetic interactions with AEDs or other compounds. However, the dosage must be adjusted for patients with renal impairment. IV formulation confers a relatively rapid onset of action [18], at a loading dose of 30 mg/kg, administered in 5-10 minutes. LEV does not require a titration period, and the IV formulation is bioequivalent to oral tablets; nor recommended serum level known for the ICU setting. There is a lack of randomized controlled trials (RCT) comparing the efficacy of the different AEDs for second line treatment of SE; nevertheless, a tendency to a lower responder rate with LEV compared to PHT or VPA (used as second-line compounds) has been described [19]. Otherwise, a recent randomized pilot study has shown that LEV is comparable to LZP for the first line treatment of SE [20], offering an alternative in patients with respiratory compromise and hypotension. Most adverse events associated with LEV are mild to moderate in intensity and include fatigue, somnolence, dizziness, while psychiatric complaints may be significant, especially (but not only!) in intellectually disabled patients or subjects with baseline behavioral problems [21].

- **Lacosamide (LCM)** has become available as the second IV formulation of a new AED based on bioequivalence to the oral formulation, with also a low potential of drug interactions. More than 100 patients who received IV LCM for a SE or repeated seizures have been reported, mostly using loading doses of 200-400mg, with an overall success rate of 67% [22]; this very high proportion may nevertheless
represent a publication bias. As for LEV, there is a lack of prospective studies or RCT, and target serum levels are not known.

Third line treatment: General anesthetics

When the patient does not respond to the first and second line treatment, a refractory status epilepticus (RSE) is considered, and, especially in cases of generalized-convulsive SE, the therapeutic management requires rapid admission to the ICU and administration of general anesthetics under continuous EEG monitoring and mechanical ventilation [5 - 8] (Tables 1 and 2). The prevalence of RSE – compared to all those in SE – varies from 23% to 43%, in prospective and retrospective cohorts respectively [23, 24]. Despite the high mortality (16 - 39%) and morbidity, the adequate management is not evidence-based, and the treatment is limited by the different side effects, especially regarding hypotension.

- Propofol (PRO, 2,6-diisopropylphenol) is a frequently used compound, in alternative to barbiturates, for the management of patients with RSE. In our institution, PRO is considered the first option at a loading dose of 2 mg/kg and a maintenance of <5 mg/kg/h, administered together with MDZ (which is described in the above section) at 0.2 mg/kg/h in order to reduce its toxicity (which correlates with the total dose). Its mechanism of action includes a modulation of GABA_A receptors at a site different from that targeted by BZDs and barbiturates, a subcortical dopamine agonism (which explains its occasional association with the appearance of dystonia or other abnormal movements) and a glycine antagonism, while its anti-glutamate properties are debated. Metabolized in the liver, it is highly lipid soluble and has very short distribution and elimination half-lives (2-4 min and 30-60 min, respectively). It is important to avoid prolonged infusions (>48 h) for the risk of the so-called propofol-infusion syndrome (PRIS),

<table>
<thead>
<tr>
<th></th>
<th>THP</th>
<th>PRO</th>
<th>MDZ</th>
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<tbody>
<tr>
<td>Mechanism of action</td>
<td>GABA_A&gt;NMDA&gt;Ca channels</td>
<td>GABA_A &gt;&gt; NMDA, Ca and Na channels</td>
<td>GABA_A</td>
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<tr>
<td>t ½ (Half life)</td>
<td>&lt; 36h</td>
<td>0.5-2h</td>
<td>1.5-50h</td>
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<tr>
<td>Cumulation</td>
<td>+++</td>
<td>±</td>
<td>++</td>
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<tr>
<td>Tachyphylaxis</td>
<td>-</td>
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<td>+++</td>
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<td>Hypotension</td>
<td>+++</td>
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<td>+</td>
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<tr>
<td>Loading dose</td>
<td>2 mg/kg</td>
<td>2 mg/kg</td>
<td>0.2 mg/kg</td>
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<tr>
<td>Maintenance</td>
<td>3-5 mg/kg/h</td>
<td>2-10 mg/kg/h</td>
<td>0.05-0.6 mg/kg/h</td>
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<tr>
<td>Control of seizures (SE)</td>
<td>64%</td>
<td>68%</td>
<td>78%</td>
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<tr>
<td>Breakthrough seizures (SE)</td>
<td>0-12%</td>
<td>1-15%</td>
<td>3-51%</td>
</tr>
<tr>
<td>Withdrawal seizures (SE)</td>
<td>9-43%</td>
<td>6-46%</td>
<td>&lt;1-63%</td>
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<tr>
<td>Therapy failure because of side-effects (SE)</td>
<td>3%</td>
<td>6%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Mortality (SE)</td>
<td>19-48%</td>
<td>8-52%</td>
<td>2-46%</td>
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SE=status epilepticus
a potentially fatal complication characterized by hyperlipidemia, rhabdomyolysis (including severe myocardial dysfunction), and lactic acidosis, particularly described in young children, patients with severe brain-injury, and under co-medication with steroids or catecholamines [25].

- **Tiopental (THP)** is now mostly considered in very severe SE cases. As a barbiturate, THP is a non-selective agent that binds to an entire superfamily of ligand-gated ion channels, of which GABA<sub>A</sub> receptor agonism represents the most significant, but also displays glutamate antagonism. It is a highly lipophilic molecule which rapidly crosses the blood brain barrier, with a significant sequestration in fat tissue, leading to marked accumulation. Once redistributed, the free fraction in the blood is metabolized in the liver, mainly to pentobarbital. THP causes cardiovascular and respiratory depression resulting in hypotension, apnea and airway obstruction; paralytic ileus may represent a severe problem, and immunological inhibition is also discussed [26].
The recommended loading dose is 2-3 mg/kg and the maintenance dose is 3-5 mg/kg/h. It is contraindicated in hepatic disease, myasthenia gravis, porphyria, severe hemorrhage or burns, severe cardiovascular disease and adreno-cortical insufficiency.

- **Inhalational anesthetic agents (isoflurane and desflurane):** The antiepileptic effects are likely due to potentiation of inhibitory postsynaptic GABA<sub>A</sub> receptor-mediated currents, and a modulation in thalamocortical pathways. The pharmacokinetic and pharmacodynamic properties (rapid onset of action and elimination) make them effective and easy-to-titrate agents [27]. However, there is a list of potential complications including hypotension, apart from the challenges of providing a tight environment on the patient, to prevent inhalation of the compounds by the caregivers. It has been occasionally reported in refractory SE.

- **Ketamine:** The progressive loss of gabaaergic inhibition with ongoing seizure activity together with the increase of N-methyl-D-aspartate (NMDA) expression may limit the efficacy of agents with predominantly GABAergic mechanisms of action. Ketamine, an NMDA antagonist, has therefore been used to terminate seizure activity in highly refractory cases and, due to its sympathomimetic properties, hypotension associated with other anesthetic agents is prevented [28]. The loading dose is 1-3 mg/kg and the maintenance dose is up to 5-10 mg/kg/h, administered together with BDZ in order to prevent neurotoxic effects. There are surprisingly limited data regarding its use in SE.

Oral AEDs may represent further add-on treatment options for patients not responding to conventional IV AEDs. In particular, topiramate (TPM) and pregabalin (PGB), two second-generation AEDs with good oral bioavailability and fast titration, may be safely administered via nasogastric tube. However, the reported rate of efficacy seems to be low [29 - 31]. There are also several other possible non-pharmacological treatments, such as hypothermia, magnesium, pyridoxine (especially in infants), immunotherapy, ketogenic diet, emergency neurosurgery, electroconvulsive therapy, cerebrospinal fluid drainage, vagal nerve stimulation and deep brain stimulation, but in all cases the efficacy has been described only in individual patients [5 - 7].

In conclusion, despite all the different therapeutic approaches, the adequate management of repeated seizures, SE and RSE in the ICU remains at a low level of evidence [4 - 7, 32]. It is therefore important to address this issue in future by well-designed clinical trials.

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Address for correspondence:
Dr Alba Sierra-Marcos
Service de Neurologie
CHUV-BH07
CH 1011 Lausanne
Tel. 0041 21 314 1220
Fax 0041 21 314 1290
Alba.Sierra-Marcos@chuv.ch