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Epilepsy (E Waterhouse, Section Editor)

Nonconvulsive Seizure Control in the Intensive Care Unit

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Opinion statement

Nonconvulsive seizures (NCS) occur in as many as 20 % of comatose critically ill patients. These seizures need to be treated; however, the urgency with which this must be done and the medications that should be used are unclear. Often, data from treatment of convulsive status epilepticus (SE) is used to determine the best therapy for NCS. This may lead to "overtreatment" with sedating medications that prolongs hospitalization and worsens outcome. Nonsedating antiepileptic drug (AED) use is favored by many neurologists as the side effect profile is superior to sedating medications. Though limited, the available data suggests that valproic acid and lacosamide may be preferable to phenytoin/fosphenytoin and levetiracetam based on efficacy and side effect profiles. Other AEDs such as topiramate and pregabalin have also been used, but their data is even more limited, and they do not have an intravenous formulation. Clinical trials that have recently been completed and those that are ongoing will further inform our decisions about which drugs to use in the future.

Introduction

Nonconvulsive seizures (NCS) are seizures that have subtle or no clinical phenomena in a patient with impaired consciousness. Subtle clinical features may include agitation, nystagmus, sustained eye deviation, facial or limb muscle twitching, catatonia, and psychosis [1]. Nonconvulsive status epilepticus (NCSE) is a condition of ongoing or intermittent seizure activity without convulsions for at least 30 min and without recovery of consciousness in between episodes. NCS/NCSE are often discussed together in papers without difference in their treatment paradigm. NCS are frequently encountered in the neurology intensive care units in patients who have underlying brain tumors, traumatic brain injury, CNS infections, intracerebral hemorrhage, or ischemic stroke [2]. They occur in 10–25 % of patients with acute brain injury and are associated with worse

outcomes [3]. NCS can also be seen in 8 to 30 % of patients presenting with altered mental status to the emergency department [4]. In a recent study, 28 % of elderly patients presenting with delirium were found to have electroencephalographic (EEG) patterns consistent with NCSE [5]. The risk was even higher in patients with preexisting cognitive impairment.

Early detection and treatment of NCS are important given the increased metabolic demand and blood flow associated with ictal activity that may lead to further injury to the brain. NCS after traumatic brain injury have been associated with delayed, prolonged increase in intracranial pressure and lactate/pyruvate ratios [6]. In subarachnoid hemorrhage, NCS have been associated with a proinflammatory state leading to poor outcomes [7]. Short NCS have also been associated with worsening global cognitive function, speed of central information processing, and memory function [8]. Serum neuron-specific enolase levels, a marker for acute neurological injury, have been shown to be elevated in patients with NCSE [9].

The best way to detect NCS is by EEG. Given that NCS are intermittent, a 20–30-min EEG recording is often inadequate, and most patients require continuous EEG (cEEG) monitoring. Previous studies have shown prevalence of about 30 % in patients undergoing monitoring in the intensive care unit (ICU) [10]. More recent studies have shown that 17–27 % of critically ill patients have electrographic seizures [2, 11•, 12•]. Despite the relatively high prevalence of NCS in critically ill patients, there is no consensus about how long patients should be monitored with cEEG when NCS are suspected. In one study, seizures were detected in 88 % of patients within the first 24 h [2]. However, only 15 % were having seizures at the start of the EEG and about 50 % had their seizures within the first hour of EEG monitoring. Conversely, if only diffuse slowing is noted on the initial EEG, cEEG is less likely to show seizures [12•]. A survey of neurologists who perform cEEG monitoring noted that 47 % of respondents would continue EEG for at least 24 h in comatose patients without any evidence of seizures and in patients who have been treated for status epilepticus (SE) [13]. A more recent survey noted that about 50 % of physicians continue cEEG for 24 h when screening for NCS, but given ideal circumstances and infinite resources, 43 % would extend the duration to 48 h [14]. Neurocritical Care Society guidelines recommend cEEG monitoring for at least 48 h in comatose patients to evaluate for NCS [15••].

Treatment

Prospective, randomized, multicenter treatment trials have been conducted for convulsive SE. This has led to development of recommended treatment algorithms. Similar trials have not yet been reported for NCS. Because of this, treatment for NCS has been extrapolated from treatment of convulsive SE; however, the appropriateness of this practice remains unclear. Convulsive SE is recognized as a neurologic emergency and is often urgently treated with high doses of benzodiazepines or other sedating medications. This type of treatment has been used in patients with NCS and NCSE; however, significant adverse outcomes have been noted. In the elderly with NCSE, such aggressive treatment was associated with an increased risk of death [16]. Additionally, aggressive ICU management of these patients was found to prolong hospitalization with added cost without improving outcome. A survey of neurologists noted more frequent use of nonsedating antiepileptic drugs (AED) (such as phenytoin and levetiracetam) and less willingness to intubate for NCS [13].

The treatment options discussed below have been used in patients with NCS and NCSE [17••]. Most studies, however, are retrospective, and the true utility of these AEDs in NCS and NCSE remains uncertain at this time. Prospective studies are underway and data on at least some of these agents should be forthcoming. The following discussion relates to what is known about AED use

in SE, not necessarily NCS as that information may not be available. Note that these treatment options are for NCS and NCSE, not for convulsive SE.

Phenytoin

Phenytoin (PHT) has been used extensively in the treatment of convulsive SE for decades. A randomized convulsive SE study confirmed the utility of PHT when combined with a benzodiazepine; 43.1 % of patients were successfully treated with PHT+diazepam as the first treatment. However, PHT alone was only successful in 36.8 % of patients [18]. A recent meta-analysis evaluated the relative effectiveness of AEDs in benzodiazepine-resistant SE and found the estimated mean efficacy for phenytoin was 50.2 % [19••]. However, given its side effects, it was not recommended as first-line therapy in benzodiazepine-resistant SE. Advantages for PHT include its long duration of action and fast central nervous system (CNS) entry [19••]. The IV formulation contains 40 % propylene glycol and 10 % ethanol to maintain solubility. Because of the propylene glycol, extravasation can cause phlebitis and "purple glove syndrome" [20]. Other significant side effects of PHT include cardiotoxicity, hypotension, hepatotoxicity, leukopenia, thrombocytopenia, pancytopenia, and hepatic enzyme induction [21]. In hopes of reducing some of these side effects, a water-soluble prodrug of PHT was developed, fosphenytoin (fPHT), that did not need propylene glycol to maintain solubility. It was anticipated that fPHT would result in a lower risk of phlebitis, hypotension, and cardiotoxicity [22]. Unfortunately, a recent FDA White Paper noted that fPHT has the same cardiotoxicity and hypotension risk as PHT, but perhaps the risk of purple glove syndrome is lower [23••]. Additionally, the White Paper noted that the recommended fastest infusion rate of 150 mg PE/min was too high and slower rates of infusion should be considered when appropriate. Recently, a prospective, randomized, multicenter treatment trial of fPHT compared to lacosamide (LCM) for NCS was completed, and results will be available soon.

Mechanism of action Use-dependent inhibition of sodium channels is the primary mechanism of action for PHT and fPHT.

Modes of administration PHT is available in PO or IV forms. fPHT is available in IM or IV forms.

Standard dosage Loading dose of PHT in SE is 15–20 mg/kg IV given once, which can be followed by additional 10 mg/kg IV after 20 min if there is no response to the initial dose. Loading dose of fPHT in SE is 18–20 mg PE/kg with a maximum infusion rate of 150 mg PE/min IV. Note that slower rates are often preferred in less urgent situations to reduce toxicity [23••]. Maintenance dose should begin 12 h after loading dose. For PHT, maintenance dose is 100 mg PO/IV q6–8 h [adjusted based on treatment response or blood levels]. Maintenance dose of fPHT is 5 mg PE/kg/day IM/IV divided daily tid.

Contraindications These include hypersensitivity to drug class, sinus bradycardia, SA block, second- or third-degree AV block, and Adams-Stokes syndrome.

Main drug interactions These occur with cytochrome P450 enzyme (CYP) inducers and CNS depressants. PHT also increases thyroid hormone clearance.

Main side effects Adverse effects include nystagmus, ataxia, diplopia, drowsiness, impaired concentration, gingival hyperplasia, hirsutism, acne, hepatotoxicity, and idiosyncratic reactions including lupus-like reactions and aplastic anemia.

Special points There is a FDA warning for purple glove syndrome with IV PHT use. Of note, fPHT can cause just as many cardiovascular side effects as PHT although has a lower risk of purple glove syndrome [23••]. There is a black box warning for cardiovascular risk with rapid infusion; therefore, IV infusion should not exceed 50 mg/min in adults or 1–3 mg/kg/min in pediatric patients.

Cost/cost-effectiveness IV PHT and fPHT are relatively inexpensive drugs. Previously, fPHT was much more expensive, but more recently, its price is similar to PHT. The generic PO PHT is also inexpensive.

Valproic acid

The AED meta-analysis discussed above found the mean efficacy of valproic acid (VPA) to be 75.7 % [19••]. The efficacy lasted beyond the acute treatment period and more patients were seizure free on follow-up. VPA is also efficacious for different subtypes of SE, such as generalized tonic-clonic, focal, absence, and myoclonic with about 70 % response rate [24••]. VPA is well-tolerated even at large doses (~100 mg/kg) and does not have cardiorespiratory side effects. In susceptible patients, there is a risk of hyperammonemia, hepatic and pancreatic toxicity, and valproate encephalopathy with high doses of IV VPA. There is also a theoretical risk of bleeding due to effects on platelets and platelet function, but these side effects have not been reported in SE [19••].

Mechanism of action The precise mechanism of action of VPA is unknown; however, there are multiple proposed actions that include multiple GABA-related actions, NMDA receptor antagonism, and histone deacetylase inhibition.

Modes of administration VPA is available in IV and PO formulations.

Standard dosage The loading dose of VPA in SE is 20–30 mg/kg IV at an infusion rate of 6 mg/kg/min. The maintenance dose of VPA is 10–15 mg/kg/day divided in bid-tid dosing.

Contraindications These include hypersensitivity to drug class, hepatic disease, urea cycle disorders, mitochondrial disorders, and pregnancy.

Main drug interactions VPA may interact with drugs that are metabolized via the CYP pathway, are CNS depressants, have antiplatelet effects, or can cause hyperammonemia or hyponatremia.

Main side effects Adverse effects of VPA include dose-related tremor, hair loss, weight gain, nausea/vomiting, hepatotoxicity, acute hemorrhagic pancreatitis, thrombocytopenia, and hyperammonemia.

Special points VPA is not approved for use in SE by the FDA. Unlike other AEDs, VPA does not have any cardiorespiratory side effects.

Cost/cost-effectiveness IV VPA is slightly more expensive than older AEDs but still relatively inexpensive compared to newer ones.

Levetiracetam

Levetiracetam (LEV) has been shown to be a useful alternative in SE if administered early (<4 days since SE onset) even when given to intubated patients [25]. However, dosages exceeding >3000 mg/day did not provide additional benefit. Estimated mean efficacy of LEV is 68.5 % when given in infusions of 1000–3000 mg in young adults or 20 mg/kg.

Mechanism of action	The precise mechanism of action of LEV is unknown; however, one hypothesis notes that LEV binds synaptic vesicle protein 2A (SV2A).
Modes of administration	LEV is available in IV and PO formulations.
Standard dosage	The loading dose of LEV in SE is 20 mg/kg at an infusion rate of 1.5 mg/kg/min.
Contraindications	This includes hypersensitivity to the drug class.
Main drug interactions	There are no drug-drug interactions with LEV.
Main side effects	Adverse effects of LEV include dizziness, somnolence, asthenia, headache, irritability, behavioral problems, depression, and psychosis.
Special points	LEV is not approved for use in SE by the FDA. It has no reported drug interactions. LEV is renally cleared and therefore requires dose adjustment in patients with renal impairment.
Cost/cost-effectiveness	LEV is relatively inexpensive and in about the same price range as PHT. IV formulation is slightly more expensive than IV PHT.

Pregabalin

A retrospective study of patients with NCS or NCSE showed that 52 % of patients were responders to treatment with pregabalin (PGB) as evidenced by the cessation of seizures within 24 h of initiation of PGB without the addition of another AED [26]. Of note, PGB was significantly more efficacious in aborting NCS (82 %) vs NCSE (18 %). There was also a higher rate of response noted in patients with brain tumors (67 %), and the responders were noted to have a better outcome as well (64 vs 9 % discharged home).

Mechanism of action	The precise mechanism of action of PGB is unknown; however, hypothesis includes that PGB binds to the $\alpha_{2\delta}$ modulatory subunit of voltage-sensitive calcium channels.
Modes of administration	PGB is available in PO formulation only but it can be given via a nasogastric tube as well.
Standard dosage	The typical dose of PGB is 150 mg/day divided in bid-tid dosing.
Contraindications	This includes hypersensitivity to the drug class.
Main drug interactions	PGB has drug interactions with CNS depressants.
Main side effects	Adverse effects of PGB include dizziness, somnolence, and weight gain.
Special points	PGB is not approved for use in SE by the FDA. It has no drug interactions. PGB is renally cleared and therefore requires dose adjustment in patients with renal impairment.
Cost/cost-effectiveness	An IV formulation for PGB is not available. The PO formulation is expensive, priced similar to other new AEDs. A generic version of PGB is not yet available.

Topiramate

Topiramate (TPM) has been studied in patients with refractory NCSE in one study [27]. TPM was administered via a nasogastric tube, and it was found to be effective in all six cases unresponsive to previous trials of various AEDs, including fPHT, lorazepam, phenobarbital, and VPA. TPM was effective in aborting multiple seizure types including generalized convulsive SE and NCSE owing to its multiple mechanisms of action. The only side effect attributed to TPM in that study was lethargy.

Mechanism of action	TPM has multiple mechanisms including blockade of the kainite/α-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid glutamate receptor subtype; blockade of voltage-activated sodium channels; enhancement of GABA-mediated chloride flux at $GABA_A$ receptors; reduction in amplitude of high voltage-activated calcium currents; and activation of potassium conduction.
Modes of administration	TPM is available in oral formulation which can be given via a nasogastric tube.
Standard dosage	The effective doses for TPM ranged from 300 to 1600 mg/day but usually prescribed as 200 mg PO bid.
Contraindications	This includes hypersensitivity to drug class.
Main drug interactions	These include interaction with other drugs that are metabolized via CYP, are CNS depressants, decrease renal perfusion, or alkalize urine.
Main side effects	Adverse effects of TPM include drowsiness, paresthesias, metabolic acidosis, oligohidrosis, renal calculi, impaired language fluency and cognition, weight loss, and rarely acute glaucoma.
Special points	TPM is not approved for use in SE by the FDA. Renal calculi are the most commonly reported idiosyncratic reaction of TPM.
Cost/cost-effectiveness	An IV formulation for TPM is not available. A generic PO formulation is available and priced comparable to generic PO LEV.

Lacosamide

LCM is a relatively new AED that is available in IV formulation. In part because of IV availability, soon after it was approved by the FDA for use as adjunctive therapy for partial-onset seizures, it was used "off label" for treatment of NCS and NCSE. One retrospective study showed that 60 % of patients receiving LCM for NCSE or NCS achieved control of their seizures [28]. Patients with NCS responded more frequently than patients with NCSE. A larger retrospective study that evaluated all published reports of the use of LCM in the treatment of NCS and NCSE reported very similar efficacy [29•]. As noted above, recently, a prospective, randomized, multicenter trial of fPHT compared to LCM in NCS was completed, and results will be available soon [30•].

Mechanism of action	LCM selectively enhances the slow inactivation of voltage-gated sodium channels.
Modes of administration	It is available in PO or IV formulations.
Standard dosage	The loading dose of LCM in SE is 400–600 mg IV. Maintenance therapy is 200–300 mg bid (this was the dose used in the LCM-fPHT treatment trial mentioned above).
Contraindications	This includes hypersensitivity to drug class.
Main drug interactions	Though drugs metabolized via CYP-19 can affect LCM metabolism, the clinical significance of this interaction is uncertain.
Main side effects	These include dizziness, headache, nausea, and diplopia. LCM can also prolong the PR interval.
Special points	LCM is not approved for use in SE by the FDA. The bioavailability of IV LCM is the same as that of the oral formulation.
Cost/cost-effectiveness	The PO formulation is expensive, priced similar to other new AEDs. A generic version of LCM is not yet available. IV LCM is relatively inexpensive, priced comparable to IV fPHT.

Emerging therapies

Various medications are being investigated in prospective trials to determine their efficacy in SE. Recently, the TRENdS (Treatment of Recurrent Electrographic Seizures) trial comparing fPHT and LCM in patients with NCS ended. Results comparing efficacy and side effects of the two drugs will be available soon. Brivaracetam is an AED that has recently completed phase III trials for adjunctive therapy in partial-onset seizures. It has an IV formulation as well and is being tested for its utility in NCS in a prospective, randomized trial. A neurosteroid, allopregnanolone, is being tested in a prospective, open-label study in very late stage SE. Another trial comparing established AEDs, fPHT, VPA, and LEV, in early SE is being considered. It is encouraging to see prospective clinical trials in the treatment of NCS and NCSE.

Pediatric considerations

While there is little data on the treatment of NCS and NCSE in adults, there is even less data on the treatment of these conditions in children. The same medications discussed above have been used in children as well. The efficacy and side effects of any of the AEDs discussed above have not been well established in this population. Moreover, the dose used varies with the investigator and standardized recommendations are not yet available.

Conclusions

NCS and NCSE are common in all types of ICUs. Up to 20 % of comatose patients in an ICU may have NCS. They can be detected only with cEEG monitoring. NCS need to be treated, but how urgently and with which medication are uncertain. Sedative medications used to treat convulsive SE may not necessarily be appropriate. Though many nonsedating AEDs have been tried in NCS, prospective, randomized trials have not been available until recently. Exciting new trials promise to shed more light on how best to treat this condition.

Compliance with Ethics Guidelines

Conflict of Interest
Mariam Wasim declares no conflict of interest.
Aatif M. Husain declares the receipt of grants and personal fees from UCB Pharmaceuticals and grants from Pfizer, outside the submitted work.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by the authors.

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