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Use of pregabalin for nonconvulsive seizures and nonconvulsive status epilepticus

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ABSTRACT

Purpose: To determine the efficacy of pregabalin (PGB) in treatment of frequent nonconvulsive seizures (NCS) and nonconvulsive status epilepticus (NCSE) in critically ill patients.
Methods: In this retrospective study, 21 patients were identified as having received pregabalin for the treatment of NCS as determined by continuous electroencephalographic monitoring. The patients were considered to be responders if their seizures were terminated within 24 h of initiation of PGB without the addition of another antiepileptic agent.
Results: Of the 21 patients who received PGB for treatment of NCS or NCSE, 11 (52%) were responders. PGB was administered via a nasogastric tube or orally and was the 2nd to 4th agent used. The average initial dose and total daily dose of PGB was similar in the responders and non-responders (342 mg vs. 360 mg, respectively). PGB was more effective in aborting NCS (9 patients, 82%) than NCSE (2 patients, 18%). Of the 9 brain tumor patients, PGB resulted in seizure cessation in 67% (6 patients). In contrast, all patients with hypoxic injury (4) did not respond to PGB. The responders were noted to have better clinical outcome (64% vs. 9% discharged home). Most of the patients tolerated the medication without any significant short term adverse effects, except two patients who were noted to have dizziness and sedation.
Conclusions: Pregabalin may be safe option for add-on treatment for nonconvulsive seizures in critically ill patients when conventional therapy fails.

1. Introduction

Nonconvulsive seizures (NCS) and nonconvulsive status epilepticus (NCSE) are common in the neurologic intensive care unit (NICU). Prior studies have documented that 10–48% of patients admitted to medical or neurologic ICUs may be having frequent NCS or be in NCSE.[1]

There are no prospective, randomized controlled trials evaluating antiepileptic drugs (AEDs) for the treatment of NCS and NCSE. Since more data is available for convulsive status epilepticus (CSE), the treatment of NCS and NCSE has reflected that of CSE. Benzodiazepines and phenytoin (PHT) are typical first and second-line treatments, respectively, to abort CSE.[2] When these fail, medications such as propofol, midazolam, phenobarbital, and pentobarbital are often used.[2] Due to central nervous system and respiratory depression, these therapies often require intubation, which can be associated with significant morbidity.

Newer, non-sedating antiepileptic drugs (AEDs) such as pregabalin (PGB),[3,4] lacosamide,[5] levetiracetam (LEV) and topiramate[2] are being increasingly used in patients with NCS as treatment is not deemed to be as urgent as in CSE. Non-sedating AEDs are a particularly attractive alternative to older, sedating AEDs as they avoid the complications (i.e. respiratory depression) associated with sedating AEDs. The goal of this study was to evaluate the efficacy of PGB in NICU patients with NCSE and NCS.

2. Methods

This was a retrospective study in which patients aged greater than or equal to 18 years of age admitted to the NICU at Duke University Medical Center between August and December, 2007 who had received PGB were identified through inpatient pharmacy records. Medical records of these patients were reviewed to determine which patients underwent cEEG monitoring for NCS and NCSE and received PGB for treatment. Previously described definitions of NCS and NCSE are utilized at our institution.[6–9] This study was approved by the Institutional Review Board.

Demographic, clinical and cEEG data was reviewed for patients who had received PGB for NCS and NCSE while undergoing cEEG

Abbreviations: NCS, nonconvulsive seizures; NCSE, nonconvulsive status epilepticus; NICU, neurologic intensive care unit; CSE, convulsive status epilepticus; AEDs, antiepileptic drugs; PHT, phenytoin; PGB, pregabalin; LEV, levetiracetam; LAC, lacosamide; cEEG, continuous electroencephalography.

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Table 1
Demographic information for patients that received pregabalin for the treatment of NCS or NCSE.

	Responders ($n=11$)	Non-responders ($n=10$)	p value
Average age (yrs)	50.9	60.6	0.09
Gender (male) (%)	5 (45.5)	7 (70)	0.69
Average PGB dose (mg)	342 ± 49	360 ± 54	0.80
Pre-existing epilepsy (%)	3 (27.3)	4 (40)	0.57

Table 2
Clinical outcomes and cEEG findings for patients that received pregabalin for the treatment of NCS or NCSE.

	Responders ($n=11$)	Non-responders ($n=10$)	p value
Outcome			0.06
Alive	9 (82%)	4 (40%)	
Dead	2 (18%)	6 (60%)	
cEEG findings			0.009
NCS	9 (82%)	2 (20%)	
NCSE	2 (18%)	8 (80%)	

monitoring. Those patients whose electrographic seizure activity stopped within 24 h of receiving PGB and did not return for at least 24 h were considered responders. Descriptive analysis was obtained for the responder and nonresponder groups. Continuous variables were compared using a two-tailed Student's t-test, and categorical variables were compared using a contingency analysis. The Fisher exact statistic was used due to small sample size. A p value of <0.05 was considered statistically significant.

3. Results

A total of 51 patients were identified that received PGB while admitted to the NICU. Of these, 21 patients received PGB for treatment of NCS or NCSE while undergoing cEEG monitoring. These patients formed the group that was further analyzed. The remaining 30 patients had received PGB while in the NICU for various pain syndromes (13 patients) and for prophylaxis of seizures (17 patients). These latter 17 patients either did not undergo cEEG monitoring or may have undergone cEEG monitoring but did not have electrographic seizure activity and consequently were not included in further analysis.

Of the 21 patients who received PGB for treatment of NCS and NCSE, 11 (52%) had cessation of their electrographic seizure activity (responders) and 10 (48%) did not (non-responders). The demographic and clinical features for these 21 patients are presented in Table 1. There was no significant difference between the two groups in terms of age, gender, and history of epilepsy. Responders and non-responders received similar doses of PGB (average daily dose of 342 mg vs. 360 mg, respectively).

Brain tumor patients were more likely to respond to PGB when compared to patients with infection, hemorrhage, autoimmune disease or hypoxia as the underlying etiology for their seizures. Of the 9 brain tumor patients with NCS or NCSE, PGB resulted in seizure cessation in 67% (6 patients). Conversely, all four patients with hypoxic brain injury did not respond to PGB. The response rates for various etiologies of NCS and NCSE are shown in Fig. 1.

PGB was administered via a nasogastric tube or orally. It was administered as the 2nd agent in one patient and as the 3rd or 4th agent in the rest. In the responder group, AEDs administered prior to PGB include: LEV in 11 patients (average dose 2454 ± 687 mg), PHT in 7 patients (goal free PHT level 1.0–2.0), valproic acid in 1 patient, phenobarbital in 1 patient and midazolam infusion in 1 patient. In the non-responder group, AEDs administered prior to PGB include: LEV in 10 patients (average dose 2600 ± 966 mg), PHT in 6 patients (goal free PHT level 1.0–2.0), midazolam infusion in 7 patients, valproic acid in 2 patients, pentobarbital in 2 patients and propofol in 1 patient. Most of the patients tolerated PGB without any significant short term adverse effects except two patients who were noted to have dizziness and sedation.

CEEG monitoring revealed NCS in 11 patients and NCSE in 10 patients. Of the responders, 9 patients (82%) had NCS and 2 patients (18%) were noted to have NCSE ($p = 0.009$). Among the non-responders, 2 patients (20%) had NCS and 8 patients (80%) had NCSE (Table 2).

PGB responders were noted to have better clinical outcomes (64% vs. 9% discharged home). The mortality rate of the non-responders was high at 60% while the mortality rate of the responders was much lower at 18% ($p = 0.06$) (see Table 2).

4. Discussion

In this retrospective study, PGB was found to be effective in stopping NCS or NCSE in 52% of patients to whom it was administered. This therapy was more effective in aborting NCS (9 patients, 82%) than NCSE (2 patients, 18%), which was statistically significant ($p = 0.009$). PGB was most effective in patients with brain tumors and least effective in patients with hypoxic injury. In brain tumor patients with NCS and NCSE, administration of PGB resulted in seizure cessation in 67% while none of the four patients with hypoxic injury had seizure cessation with PGB. This finding is consistent with a recent retrospective study reported by our institution that found that PGB added to PHT and LEV stopped NCSE in 70% of brain tumor patients with refractory NCSE.[3]

PGB was well-tolerated and no major adverse events were noted. Other studies using PGB,[3,4] topirimate[10,11] and LEV[12] administered orally or via a nasogastric tube have also shown efficacy as add-on therapy for refractory NCS and NCSE. These

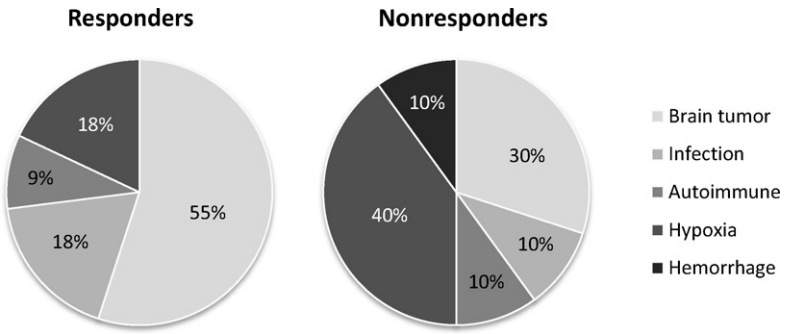

Fig. 1. Graphical representation of NCSE and NCS etiology in patients that received pregabalin.

studies demonstrate that intravenous AEDs are not always necessary to treat NCSE or NCS. Furthermore, aggressive therapy for NCS and NCSE may actually be detrimental. One study found that elderly patients with NCSE who were treated with benzodiazepines had a higher mortality rate when compared to patients treated less aggressively.[13]

Although PGB is only approved for use in the U.S. as adjunctive therapy for patients with refractory partial seizures (and various pain syndromes), it remains an attractive option for the treatment of NCS and NCSE for several reasons. First, PGB can theoretically complement other AEDs via its unique mechanism of action that involves binding to and inhibition of the alpha-2-delta protein of the presynaptic calcium channel. Second, PGB is not metabolized in the liver and does not interact with other AEDs, which are favorable characteristics of medications used in critically ill patients. Lastly, PGB can be administered relatively quickly since it lacks idiosyncratic side effects, has almost complete gastrointestinal absorption and reaches peak levels within 1 h.[14]

There are several limitations of this study. The results are limited by the small sample size and retrospective design. In addition, ideal loading and maintenance doses of PGB in this setting have not been established. Lastly, the patients in this study received at least one other AED before PGB, therefore one cannot be certain which AED resulted in seizure cessation or if spontaneous seizure cessation occurred. PGB was administered as the 3rd or 4th AED in most patients, and seizure cessation may be attributed to a delayed effect of the 1st or 2nd AED rather than PGB. A larger, prospective study is warranted to determine the efficacy and safety of PGB in NCSE and NCS.

Despite the limitations of this study, our results suggest that PGB can be considered as an alternative option for add-on treatment of NCS and NCSE if standard therapy (i.e. benzodiazepines and PHT) is unsuccessful.

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