EEG Patterns Predicting Clobazam Response in Refractory Status Epilepticus in Adults

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SUMMARY

Background. Seizure resolution is often difficult to attain promptly in status epilepticus (SE). Clobazam (CLB) is structurally different from typical benzodiazepines with an affinity to the α2 subunit of GABA-A receptors, rendering unique efficacy in seizure termination.

Aim. To assess the response of clobazam in refractory status epilepticus (RSE) and to correlate this response with EEG patterns.

Materials and Methods. This was a single-center retrospective study conducted at a neurocritical care unit between January 2018 and June 2023. The study included fifty consecutive patients with RSE, out of which sixteen adult patients had continuous EEG monitoring both before and during treatment with clobazam until the resolution of RSE. Patients for whom clobazam was the last anti-seizure medication (ASM) used were included in the study. Thirty-four patients were excluded for various reasons, like lack of continuous EEG monitoring (cEEG), status post cardiac arrest, exclusion of clobazam due to medical issues or adverse events, or admission to the hospice floor.

Results. Out of the sixteen patients included in the study, twelve (75%) had focal nonconvulsive RSE on cEEG and four had focal convulsive RSE when clobazam was administered. Thirteen out of sixteen patients (81.25%) responded successfully to clobazam, with an average time of 23.5 hours since starting the medication. On average, three other ASMs were tried before clobazam, initiated at a mean time of 27 hours since SE onset. The study identified EEG patterns correlated with the use of clobazam :1) lateralised periodic discharges that evolved from 1–1.5 Hz to 2–3 Hz, then evolved to rhythmic theta/delta activity with embedded LPDs; 2) repetitive spikes that evolved to theta and delta frequencies (good responders to CLB), and iii) low voltage faster frequencies and evolved to theta delta frequencies (less responders to CLB).

Conclusion. Rapid pharmacoresistance to first-line benzodiazepines and ASM occurs as seizures persist during SE. Our study provides EEG correlates to the successful use of CLB in RSE based on its unique targeting of the GABA-A subtype receptors involved in postsynaptic phasic inhibition.

Key words: refractory status epilepticus • electroencephalogram • critical care • clobazam • antiseizure medication

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BACKGROUND

Status epilepticus (SE) is a condition resulting from either the failure of the mechanisms that are responsible for seizure termination or the initiation of mechanisms that lead to abnormally prolonged seizures. SE can be efficiently controlled if prompt diagnosis occurs and immediate treatment starts, though this might sometimes be difficult in clinical practice. If established SE is not promptly treated, it may progress to refractory SE (RSE). According to the International League Against Epilepsy (ILAE) guideline, SE is diagnosed based on clinical and/or electroencephalographic evidence of seizure activity with a duration of at least 5 minutes or a series of seizures without interictal clinical recovery (Vasquez et al., 2018). RSE is the persistence of seizures that continue despite the administration of two IV medications, one of which is a benzodiazepine (Marawar et al., 2018).

Previous research surrounding the management of status epilepticus has predominantly focused on the timely administration of antiseizure medications (ASM) to terminate seizures and prevent progression to RSE. Traditional first-line treatments for SE include benzodiazepines, such as lorazepam, diazepam, and midazolam, which act by enhancing the inhibitory effects of gamma-aminobutyric acid (GABA) neurotransmission (Vasquez et al., 2018). However, pharmacoresistance to benzodiazepines can develop rapidly following SE onset, limiting their efficacy over time. This phenomenon is attributed to the internalisation of benzodiazepine-sensitive synaptic γ2-containing GABAA receptors and the concurrent increase in excitatory activity mediated by glutamate receptors, particularly N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Thome-Souza et al., 2016).

Clobazam became FDA-approved in 2011 and is the first and only 1,5 benzodiazepine to be used in the management of epilepsy. It differs from other antiseizure benzodiazepines in that its nitrogen radicals are in positions 1 and 5 rather than 1 and 4 (Thome-Souza et al., 2016). Clobazam is believed to exert its anticonvulsant effects through allosteric modulation of the inhibitory response of GABA, the most common inhibitory transmitter. GABA binds to the ligand-gated GABA-A receptors, which are widely distributed throughout the CNS and are found synaptically and extra synaptically. Postsynaptic GABA-A receptor binding opens negatively charged chloride ion (Cl-) channels, and the inward chloride current results in membrane hyperpolarisation (Maille et al., 2023). This hyperpolarisation results in an inhibitory postsynaptic potential because the membrane potential becomes ‚negative enough' to make action potential more difficult. The resulting transient electrical signal is called phasic inhibition because the channel is rapidly inactivated. Tonic inhibition mediated by extrasynaptic GABA receptors is distinguished from synaptically mediated phasic inhibition in that the signal is a continuous current maintained by low GABA concentrations in extracellular space. This is mediated by high affinity, slowly inactivating extrasynaptic GABA receptors that bind low concentrations of GABA overflowing from synapses (Sankar, 2012).

AIM

Our goal is to correlate the efficacy of clobazam in patients with refractory status epilepticus and continuous EEG (cEEG) patterns associated with response. Through this approach, SE and RSE could be successfully treated during its early stages, preventing progression to a refractory state and subsequent undesired outcomes.

MATERIALS AND METHODS

The project's local Institutional Review Board approval was obtained prior to chart review or data collection. We retrospectively reviewed the medical records of all fifty consecutive RSE patients treated in the Neurocritical Care Unit at an academic tertiary care hospital between January 2018 and June 2023. We included only patients who had continuous EEG monitoring (cEEG) during the entire course of treatment and who received clobazam as the last anti-seizure medication via nasogastric tube. Exclusion criteria included RSE patients with a lack of continuous EEG monitoring or incomplete EEG monitoring during the treatment, those who had hypoxic brain damage (as it was considered an entity of its own with a particularly poor prognosis), those who did not receive clobazam due to other medical issues, or CLB discontinued due to side effects, patients who were already on clobazam before hospital admission, and patients admitted to the hospice floor.

Data from these patients' charts was retrospectively collected, and their cEEG findings, ASM administered, and comorbidities were reviewed. We analysed the following parameters: Modified Rankin Scale (mRS) at ad-

mission and at discharge, days on clobazam treatment, SE type (convulsive and non-convulsive), presence or absence of lateralised periodic discharges (LPDs), EEG ictal patterns, days to start clobazam from SE onset time, and ASM used before clobazam.

Median, mean, standard deviation, range, and upper and lower quartile were used to describe variables. The sign test was used to compare ordinal data and proportion differences to compare qualitative data. All cEEG data was reviewed by a Board-Certified Epileptologist. Response to clobazam was considered if it was the last ASM added with successful weaning off anaesthetic medications without needing reinstituted and no seizures for at least 24 hours in convulsive status patients and avoidance of anaesthetics in non-convulsive status patients).

RESULTS

Sixteen out of fifty patients were identified that met our inclusion criteria from our review: ages 59.5 ± 20.4 (20–93), eight (50%) were female, and nine patients (56.25%) had a prior history of epilepsy. Seven (43.75%) of the sixteen had a stroke at presentation or a history of stroke. The most common comorbidity was hypertension, seen in eleven patients (68.8%), followed by diabetes mellitus in six (37.5%), and brain meningiomas status post resection in three patients (18.75%). Twelve patients (75.00%) had focal nonconvulsive status epilepticus on cEEG, and four patients (25%) had focal convulsive status epilepticus. Some of the RSE patients were on propofol, midazolam or ketamine infusion. Thirteen (81.25%) of the sixteen patients responded to CLB with a mean of 23.5 hours since starting clobazam and a median maintenance dose of 30 mg per day administered via nasogastric tube. On average, three other ASMs were tried prior to clobazam, with the average time of initiation being 27 hours since status epilepticus onset. mRS was 0–2 in 13 out of 16 patients (81.25%), and mortality was 3 out of 16 (18.75%).

EEG data were reviewed in all sixteen patients who had cEEG monitoring during the entire course of treatment and received CLB, and three electrographic patterns were seen localised over the frontal-central, temporal, and posterior quadrants. In the first pattern, six patients (37.5%) out of sixteen patients had focal seizures and lateralised periodic discharges (LPDs). These seizures started as an increase in LPD frequency from 1–1.5 Hz to 2–3 Hz and then evolved to rhythmic theta/delta activity with embedded LPDs. In the second pattern, eight patients (50%) out of sixteen patients had focal seizures that started as repetitive spikes that evolved to theta and delta frequencies; one patient (12.5%) out of these eight patients was less responder to CBZ treatment. Overall, thirteen patients (81.25%) out of sixteen patients had the first and second patterns and were responders with a successful response to clobazam by clear resolution of the ictal pattern and/or seizures. The third pattern was seen in two (12.5%) of sixteen patients who showed focal seizures emerging with low voltage faster frequencies and evolved to theta delta frequencies; these patients were fewer responders to Clobazam treatment.

DISCUSSION

Management of refractory status epilepticus is a clinical emergency. Clobazam is not considered a first-line benzodiazepine medication for SE. Still, clobazam is often delayed and used after failures of second-line SE treatments such as levetiracetam, valproic acid, and phenytoin. By this time, RSE becomes more complex to treat with higher mortality (Vasquez et al., 2018). Our study showed success with aborting seizures when clobazam was used within 27 hours of SE onset. In addition, focal RSE with cEEG ictal patterns that emerged from evolving LPDs or repetitive spikes at ictal onset was associated with better response and outcomes.

The mechanism of action of clobazam may play a key role in the treatment of RSE with postsynaptic phasic inhibition as well as potentiating the signalling of some extrasynaptic GABAA receptors, compared to standard benzodiazepines (α1, γ2) used in first-line treatment (Huddart et al., 2018; Hammer et al., 2015). The receptor subtypes (α2, γ2) are considered intact in the SE setting and could be a potential target for the medication (Storustovu, Ebert, 2006). We theorised that targeting these intact clobazam receptors earlier may result in the successful resolution of SE.

Several reviews have been conducted regarding the efficacy of clobazam in SE, with varying results when used as the last anti-epileptic agent. Sivakumar et al. (2015) reported that 16/17 (94.1%) of their subjects had seizure termination after clobazam was added, while Madzar et al. (2016) reported 6/24 (25%) of their patients had SE resolution. Several factors potentially influenced the differences in the results of these two studies, including physician preference, preceding history of seizures, and the availability of continuous EEG monitoring. Multiple variables during the management of

RSE vary with the institution, aetiology, physician preferences, semiology, and patient history, presenting difficulty with truly comparing the efficacy of clobazam in previous studies. These variables can also be attributed to the delay of ~27 hours before starting clobazam. Our study also presents a small sample size of patients but provides additional findings of EEG correlates that support clobazam's success in treating RSE.

The retrospective nature of this study is a limitation, including multiple confounders that might have contributed to each patient's hospital course. Additionally, a control group with RSE but without the use of clobazam would have been ideal for comparison of efficacy and is a consideration for future studies.

CONCLUSION

Clobazam has a unique mechanism of action targeting the GABA-A receptors involved in postsynaptic phasic inhibition, which in our study has shown success for patients in focal refractory status epilepticus with cEEG ictal patterns characterised by evolving LPDs or repetitive spikes with good response than cEEG ictal pattern onset with low voltage faster frequencies. These findings might be promising factors for using clobazam ASM earlier on during status epilepticus after the first-line failure of treatment of SE for better outcomes. To our knowledge, this is the first retrospective series of patients with RSE that analyses the electrographic variables associated with response to clobazam in patients with refractory status epilepticus.

CONFLICTS OF INTEREST

All authors report no conflict of interest concerning this original manuscript

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