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Short burst Clobazam dosing at discharge from VEEG evaluation reduces re-presentation with seizures

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ABSTRACT

Purpose: Recurrent seizures and status epilepticus after medication reduction for inpatient Video Electroencephalograph (VEEG) monitoring is a well-known complication of this investigation. In the literature this is reported to occur at a rate of approximately 3–7%. We review the use of short burst Clobazam dosing on discharge from the Epilepsy monitoring unit (EMU) to determine if this might reduce rates of representation with seizures.

Methods: We performed a retrospective review of all cases admitted to the EMU. Their medication reduction, number of seizures, seizure severity and demographics were collected. Representations to hospital were considered if they occurred within 14 days of discharge from the unit.

Results: 264 cases were included, and 146 patients received 5 days of Clobazam 10 mg PO BD upon discharge after VEEG and 118 did not. There were significantly fewer patients re-presenting to hospital for seizures in the 14 days following discharge in those who were administered short-burst Clobazam compared to those who were not (0% and 4.23% respectively). There was also a trend towards fewer re-admissions for non-seizure indications including mental health issues or non-epileptic seizures and AED side effects. There were no definite adverse reactions to Clobazam recorded.

Conclusion: Short burst Clobazam appears to be a safe and effective means to reduce representation with seizures after medication reduction during VEEG recording. This obviously benefits patients but it may also be a cost-effective means to reduce unnecessary health expenditure.

1. Introduction

Video electroencephalogram (VEEG) is a non-invasive investigation for patients presenting with recurrent seizures. It is a crucial tool when determining whether seizures are epileptic in nature, classifying the subtype of epilepsy and determining suitability for surgery [1]. Patients are typically admitted to an epilepsy monitoring unit (EMU) for VEEG assessment and anti-epileptic medications (AEDs) are reduced or ceased in order to increase the likelihood of recording a seizure during the observation period [1].

Admission for monitoring is not without risks. Breakthrough seizures and status epilepticus after discharge post VEEG with AED reduction is a well-known complication [2–5]. In the literature this is reported to occur at a rate of approximately 3–7% [2–5]. There is a lack of high level evidence to define best practices in the EMU, both during the admission and on discharge [6]. Furthermore, significant variation exists between institutions and practitioners [7]. There is a paucity of work assessing specific interventions to reduce the risks of adverse events occurring after discharge from VEEG monitoring. The studies that do exist show modest results [5,8]. Specific interventions which have been previously utilised include intravenous AED loading on discharge, improvement of discharge documentation or discharge checklists, post discharge nursing follow up and psychiatric follow up, all of which have demonstrated trends towards reduction in reduced re-presentation [5,8,9].

Clobazam is a GABA-A receptor agonist, which may also affect sodium channels and voltage-sensitive calcium channels. It is a medication with few side effects that has been used for many years as an antiepileptic [10,11]. Furthermore, while it remains a branded drug in some regions of the world, it may still represent a cost-effective method to prevent breakthrough seizures and unnecessary hospital expenditure caused by readmissions. It is also less sedating that other benzodiazepines and has a long half-life [12]. Clobazam has been approved for the treatment of several different types of epilepsy, however, long term administration is complicated by dependence and diminished effect [13]. This may explain why it has been associated with increased risks

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Table 1
Patient demographics.

	Clobazam on d/c	No Clobazam on d/c	t-value	p-value
Total patients	*146*	*118*		
Age	*36.8 +/− 13.9*	*37.5 +/− 14.2*	*−0.418*	*0.676*
Duration of epilepsy	*15.34 +/− 13.2*	*10.4 +/− 11.8*	*3.16*	*0.002*
Admission duration	*3.32 +/− 1.09*	*2.36 +/− 2.05*	*4.828*	*0.0001*
Mean seizure count	*8.6 +/− 12.4*	*5.1 +/− 10.6*	*2.031*	*0.043*
Number of cases with GTC	*36 (24.7%)*	*4 (3.4%)*	*4.512*	*0.0001*
Average number of AEDs prior to admission	*2.4 +/− 1.0*	*1.4 +/− 1.4*	*5.824*	*0.0001*
Rapid AED reduction	*125 (85.6%)*	*59 (50%)*	*6.681*	*0.0001*
Adverse events	*7*	*5*	*−0.971*	*0.333*

df = 262.

of adverse events during VEEG admission [14]. In our institution we administer Clobazam for a short duration, after elective admissions for Video EEG where AEDs have been withdrawn. In this analysis we review the use of short burst Clobazam dosing on discharge from the EMU to determine if this might reduce rates of representation with breakthrough seizures after discharge from VEEG evaluation.

2. Methods

A retrospective review of case data was performed for all patients admitted to the EMU for VEEG evaluation between July 2015 and June 2018. Our unit is a level 4 advanced epilepsy centre specialising in Stereoelectroencephalography (SEEG) [15].

Patients were divided into two groups, those receiving short burst Clobazam on discharge and those discharged home with only their usual AEDs. Short burst Clobazam was considered as administration of Clobazam 10 mg twice daily for a period of 5 days only. There was no protocol in place for prescribing discharge medications and the decision to discharge with Clobazam was made at the discretion of the treating epileptologist. This typically occurred based on perceived severity of the case, including total number of seizures and GTCs. AEDs were restarted after sufficient seizures had been captured for accurate diagnostic classification and Clobazam was also commenced at this time. AEDs were typically restarted at the preadmission doses or substituted for more appropriate drugs and loading doses were not administered. Patients were discharged if they remained seizure free the day after AEDs were restarted and there were no generalised seizures within the preceding 24 h. All patients admitted electively were considered in the evaluation. Patients were excluded if they were admitted acutely for uncontrolled seizures and underwent video monitoring during the admission. Only the first admission for any patient was included and all repeat elective VEEG admissions were excluded. Bedside monitoring of less than 24 h was also not considered. Only adult cases were included in the analysis. All representations for possible seizures in patients classified during their evaluation as non-epileptic, were recorded as non-seizure related representations to prevent potential bias from incorrect diagnosis in the emergency department.

2.1. Data collection

A data search was performed using the electronic medical records system at our institution (Verdi, IP Health Pty Ltd, North Melbourne, Australia), the Queensland Health electronic medical records system and the patient database held in the Advanced Epilepsy Unit, Mater Adult Hospital, Brisbane. Demographic information was collected and tabulated, including age of epilepsy onset, epilepsy duration, seizure frequency, current and prior anti-epileptic drugs (AEDs). Data was also collected on the individual AED dosages on admission and the subsequent dose reduction during the VEEG study. The number of seizures and seizure types during admission was also collected.

Re-presentations to hospital were considered if they occurred within 14 days of discharge from the unit. Re-presentations were included from our institution and all other public hospitals within the state of Queensland. No funding was obtained for the study.

Table 2
Diagnostic classification at conclusion of evaluation.

Diagnosis	No Clobazam on d/c	Clobazam on d/c
Unclassified	*15*	*10*
Focal	*15*	*120*
GGE	*4*	*4*
NES	*56*	*2*
Focal and GGE	*0*	*1*
Epilepsy and NES	*12*	*8*
Other	*16*	*1*

(GGE – Genetic generalised epilepsy, NES – non-epileptic seizures. Other: non-epileptic jerks / movement disorder, parasomnia, cardiac arrhythmia, syncope).

2.2. Statistical analysis

Continuous variables are presented as mean ± 1 SD unless otherwise stated, and categorical variables were presented as frequencies and percentages. Comparison of discrete outcomes was performed using Fisher's exact test. Differences between the groups were compared using the independent samples t-test. A critical value of < 0.05 was considered significant. Uncorrected p-values were used for group comparison to determine similarity, and where multiple comparisons were performed the Bonferroni correction was used. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 23.0 (Armonk, NY).

3. Results

A total of 338 patients underwent video monitoring between July 2015 and July 2018. 264 of these were included in this study according to the selection criteria outlined above. Of these patients 146 (55.3%) were discharged with short-burst Clobazam. There were 128 pre-surgical evaluations (48.5%) and all except 12 were given Clobazam on discharge. There were 136 (51.5%) diagnostic admissions, and a significantly lower proportion (30) were also given Clobazam on discharge (p-value 0.001). Diagnostic evaluations were typically for event classification and confirmation of epilepsy diagnosis.

A comparison of the patient characteristics, average duration of admission and average number of seizures is outlined in Table 1. There was no significant difference between patient age in the two groups ($t(262) = -0.418$; p-value = 0.676). The mean duration of admission for the Clobazam group was *3.32 +/− 1.09* days, and for the non-Clobazam group was *2.36 +/− 2.05* ($t = 4.824$; $p = 0.0001$). There were significantly more seizures recorded per admission for the Clobazam group compared to the non-Clobazam group (*8.6 +/− 12.4* and *5.1 +/− 10.6* respectively) ($t = 2.031$; $p = 0.043$). GTCs occurred in

Table 3
Re-presentations.

	Total Patients	Frequency of all-cause non-elective re-presentations	Frequency of re-presentation with seizures
Clobazam on d/c	146	6.85% (10)	0.0% (0)
No Clobazam on d/c	118	7.62% (9)	4.23% (5)
p-value*		0.077	0.017

* Critical p-value after Bonferroni correction was < 0.025.

more patients in the Clobazam group (36 vs 4 patients). The patient's receiving Clobazam were on more AEDs prior to admission (t = 5.824; p = 0.0001). Rapid reduction of AEDs (> 50% reduction per drug on day one) occurred in 187 patients (69.6%). Of these 125 received Clobazam on discharge (t = 6.681; p = 0.0001). Despite this there was a similar frequency of adverse events during admission in both groups. The patients receiving Clobazam had a longer duration of epilepsy (t = 4.828; p = 0.0001). At discharge AEDs were typically unchanged or substituted but not increased in both groups (68.4% without Clobazam were unchanged or substituted and 70.3% receiving Clobazam were unchanged or substituted). Reasons for AED substitution included side effects, indication (focal vs generalised epilepsies) and young females on valproate. Diagnostic classification of the evaluations is outlined in Table 2. There was an over-representation of non-epileptic seizures in the non-Clobazam group.

There was a statistically significant difference in the number of patients re-presenting to hospital for seizures in the 14 days following discharge in those who were administered short-burst Clobazam compared to those who were not (0 and 5 respectively) (p-value 0.012). The percentage of all-cause non-elective re-presentations to hospital was also lower amongst patients discharged with Clobazam however this did not reach significance (p-value 0.077). These results are displayed in Table 3.

The most common reason for non-seizure related re-presentation included dissociative attacks and other mental health issues (Table S1). This included one case of acute psychotic symptoms and it was unclear if this re-presented post ictal phenomena or medication side effect. There was also another patient admitted with side effects related to new anti-epileptic agent (Lacosamide). There were no definite adverse reactions to Clobazam recorded.

4. Discussion

There were significantly fewer readmissions with breakthrough seizures in the group receiving five days of Clobazam on discharge from the EMU. Readmission rates for breakthrough seizures are reported in the literature to be between 3–7% [2–5]. This is similar to the rates we found in the non-Clobazam group. There is a paucity of data assessing interventions on discharge to prevent readmission after Video EEG evaluation. Some studies have utilised discharge checklists and optimisation of documentation with trends towards improvement [8]. While others have focussed on mental health concerns and preventing readmission in patients suffering with non-epileptic seizures [5]. Both of these, while showing trends towards reduced representations, were not significant. A single study analysed the administration of IV Lacosamide on discharge from the EMU, however rates of breakthrough seizure were not assessed [9]. With the use of short burst Clobazam we have demonstrated a significant reduction in the number of re-presentations for breakthrough seizures within 14 days of discharge. This is a helpful and convenient method of reducing risk to patients on discharge after Video EEG evaluation. Furthermore, there were no definite adverse reactions caused by its administration. Clobazam appears to be a safe and effective means of improving safety on discharge from the EMU.

Much of the analysis displays clear biases which is inherent to the retrospective design of this study. The decision to administer Clobazam on conclusion of the Video EEG study was made at the discretion of the treating epileptologist. It is therefore to be expected that these patients were perceived by the epileptologist to be the more refractory cases and were deemed to be at a higher risk of breakthrough seizures after discharge. The results confirm this quite clearly. There were significantly more patients in the Clobazam group who were on more AEDs at admission. There were more seizures recorded, including more generalised seizures, in the Clobazam group and more pre-surgical evaluations indicating that these patients had more refractory epilepsy. The Clobazam patients also had a significantly longer duration of epilepsy prior to their admission. In addition to this, Clobazam was given more frequently to patients who had undergone rapid AED reduction on day one of admission, which makes them higher risk for breakthrough seizures on discharge. These biases indicate that there were significantly more severe and refractory epilepsy cases in the Clobazam group. However, despite these biases, there was still a significant reduction in seizure representation in the Clobazam group. While this is not conclusive proof, it might be expected that if this result was tested in a randomised control trial, that this reduction would be even greater as selection bias would be eliminated.

There was also a trend towards fewer non-seizure related re-presentations. The most common reason for non-seizure related re-presentation in both groups was mental health issues. This finding is not unusual, and several other studies have reported similar findings [2–4]. It is possible that the trend towards fewer re-presentations seen in our study might be due to an unintended anxiolytic effect caused by Clobazam. The anxiolytic effect of Clobazam has been known for some time, and it has been previously used to treat functional (psychosomatic) disorders [16]. This finding may indicate that there are patients admitted to the unit with either unrecognised or under-treated mental health disorders. This serves as a reminder that these are important issues that should not be neglected in the pursuit of seizure freedom and that the management of epilepsy, and prevention of readmission, requires a holistic approach. It is also important to be mindful of the potential for abuse with benzodiazepine medications, however we have chosen to use Clobazam in our institution, as the associated risk for abuse is much less [17].

5. Conclusion

Short burst Clobazam appears to be a safe, convenient and effective means to reduce re-presentation with seizures after VEEG recording. This obviously benefits patients but may also be a cost-effective means to reduce unnecessary health expenditure.

Disclosure

None of the authors report any disclosures.

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No funding was received for this trial.

Declarations of interest

None.

Ethical statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.seizure.2019.03.008.

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