Original article

Inadequate benzodiazepine dosing may result in progression to refractory and non-convulsive status epilepticus

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ABSTRACT – *Aims.* Status epilepticus (SE) is defined as ongoing seizures lasting longer than five minutes or multiple seizures without recovery. Benzodiazepines (BZDs) are first-line agents for the management of SE. Our objective was to evaluate BZD dosing in SE patients and its effects on clinical/electrographic outcomes.
Methods. A retrospective analysis was conducted from a prospective database of SE patients admitted to a university-based neurocritical care unit. The initial presentation and progression to refractory SE (RSE) and non-convulsive SE (NCSE) with coma was evaluated. Outcome measures included length of stay (LOS), rates of intubation, ventilator-dependent days, and Glasgow outcome scale (GOS). The lorazepam equivalent (LE) dosage of BZDs administered was calculated and we analysed variations in progression if 4 mg or more of LE (adequate BZDs) was administered.
Results. Among 100 patients, the median dose of LE was 3 mg (IQR: 2-5 mg). Only 31% of patients received adequate BZDs. Only 18.9% of patients with NCSE without coma received adequate BZDs (p=0.04). Among patients progressing to RSE, 75.4% had not received adequate BZDs (p=0.04) and among patients developing NCSE with coma, 80.6% did not receive adequate BZDs (p=0.07). Escalating doses of BZDs were associated with a decrease in cumulative incidences of RSE (correlation coefficient r=-0.6; p=0.04) and NCSE with coma (correlation coefficient r=-0.7; p=0.003). Outcome measures were not influenced by BZD dosing.
Conclusion. The majority of our patients were not adequately dosed with BZDs. Inadequate BZD dosing progressed to RSE and had a tendency to lead to NCSE with coma. Our study demonstrates the need to develop a hospital-wide protocol to guide first responders in the management of SE.

Key words: benzodiazepines, status epilepticus, convulsive status epilepticus, refractory status epilepticus, non-convulsive status epilepticus

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Status epilepticus (SE) was defined as 5 minutes or more of continuous seizure activity or recurrent seizure activity without recovery between seizures. SE is a neurological emergency that requires emergent treatment to reduce patient morbidity and mortality (Brophy *et al.*, 2012). Recently, the International League Against Epilepsy redefined SE as ongoing seizure activity due to failure of mechanisms responsible for seizure termination or initiation of mechanisms that provoke ongoing seizures causing prolonged seizures after timepoint T1, which can have long-term consequences after T2. T1 and T2 are defined as 5 minutes and 30 minutes for convulsive SE, 10 minutes and 60 minutes for focal SE with impaired consciousness, and 10-15 minutes and unknown for absence SE, respectively (Trinka *et al.*, 2015). Approximately 19% of patients die within 30 days of new-onset SE and many survivors develop significant morbidity (Sivakumar *et al.*, 2015).

SE is divided into four stages: early, established, refractory, and super-refractory. Multiple studies have shown that benzodiazepines (BZDs) are effective first-line antiepileptic drugs (AEDs) to stop early SE. Several recent guidelines have recommended an initial bolus dose of intravenous (IV) lorazepam (0.1 mg/kg up to a maximum dose of 4 mg) with a repeat dose after 5-10 minutes in patients without cessation of seizures (Brophy *et al.*, 2012; Glauser *et al.*, 2016).

BZDs have a high affinity for gamma-amino butyric acid (GABA)-A receptors, resulting in an increased opening frequency of GABA-A receptor chloride channels. This facilitates increase in the amplitude or decay time of GABA-mediated inhibitory post-synaptic potentials, thus resulting in cessation of seizure activity and progression (Greenfield, 2013). BZDs are highly effective for seizure control (79%) when used early in the treatment of SE (Treiman, 1990).

Ongoing seizures require administration of a second-line AED, and for SE that does not abort, IV anaesthetic agents are recommended (Au *et al.*, 2017).

Frequently, the initial prehospital and in-hospital BZD usage is found to be inadequate or not given at all, requiring repeated doses once the patient is brought to the hospital (Chin *et al.*, 2004; Tobias and Berkenbosch, 2008; Friedman, 2011). Early termination of seizures is important, as the risk of refractory SE (RSE) and super-refractory SE increases with the duration of seizures, making effective initial treatment with BZD the most important factor in terminating ongoing SE (Friedman, 2011).

The purpose of our study was to evaluate the adequacy of BZD dosing as initial management of adult patients who present with SE. We also sought to determine the sequela of inadequate BZD dosing in this patient population.

Methods

A retrospective analysis was conducted from a prospectively maintained database. The database includes all patients admitted to a neurocritical care unit at a university-based hospital. A research coordinator is assigned to enter the data which includes demographics, comorbidities, presentation, length of stay (LOS), Glasgow outcome scale (GOS) at discharge, and primary and secondary diagnoses. Additional disease-specific data is entered based on the primary diagnosis. The database was queried for all patients with an admission diagnosis of SE between November 2013 and January 2016. A chart review was performed to collect additional data including aetiology of SE and initial presentation of SE. The initial presentation of SE was categorized as convulsive SE (CSE) or non-convulsive SE (NCSE) with or without coma, based on semiology and EEG (Trinka *et al.*, 2015). CSE was described as "episodes of excessive abnormal muscle contractions, which may be sustained, or interrupted" (Blume *et al.*, 2001). The progression of initial SE to RSE and NCSE with coma was evaluated.

The use of BZDs (lorazepam, midazolam or diazepam) for the emergent management of SE in the prehospital and hospital setting prior to administration of a second-line antiepileptic medication was studied. The total dosage of BZDs administered was converted to lorazepam equivalent (LE); 1 mg of lorazepam was estimated to be equivalent to 2 mg of midazolam and 5 mg of diazepam (Chouinard, 2004). As a conservative approach and for the purpose of this study, inadequate dosing was defined as less than 4 mg LE. The association between escalating doses of BZDs and progression of SE to RSE or NCSE with coma was evaluated. Outcome measures included GOS at discharge, rates of intubation, ventilator-dependent days, and LOS. A bad outcome was defined as GOS of 1-3 and good outcome as GOS of 4 and 5. The Mann-Whitney U test was used to compare continuous data between the groups, and chi-square analysis was used for comparison of categorical data. The association between cumulative doses of BZDs and incidences of RSE or NCSE with coma was measured using the Spearman coefficient. The local institutional review board approved this study.

Results

A total of 100 patients were included in the study. The median age was 58 years (IQR: 45-65) with 53% males. African-Americans were the predominant race (84%) in our cohort. The median weight of the patients was 72 kg (IQR: 65-85). Most patients (70%) had a history

Table 1. Baseline characteristics of patients presenting with status epilepticus and outcome measures stratified by benzodiazepine dosing.

	Inadequate BZD	Adequate BZD	*p* value
Median age (IQR)	58 (45-65)	58 (49.5-66.3)	0.95
Males (%) (*n*=53)	36	17	0.81
African Americans (%) (*n*=84)	59	25	0.25
History of epilepsy (%) (*n*=70)	46.5	24.2	0.32
Non-compliance (%) (*n*=30)	19.4	12.9	0.26

Classification of SE on initial presentation (*n*=96)
    NCSE without coma (%)
    CSE (%)
    NCSE with coma (%)
	31.2
	29.2
	8.3
		7.3
		22.9
		1
			0.04

Refractory status (%) (*n*=65)	49.5	16.2	0.04
NCSE with coma (%) (*n*=31)	25.5	6.1	0.07
Mean ventilatory-dependent days (±SD)	5 (±10.2)	2.9 (±8.1)	0.31
Median ICU LOS (IQR)	3 days (2.3-10.5)	3.5 (2-5)	0.48
Median LOS (IQR)	7 days (5-18.3)	6 days (4-11.4)	0.14
Poor outcome (%) (*n*=31)	24	7	0.22

BZD: benzodiazepine; CSE: convulsive status epilepticus; IQR: interquartile range; NCSE: non-convulsive status epilepticus; SE: status epilepticus, ICU: intensive care unit; LOS: length of stay; SD: standard deviation.

of epilepsy and 30% presented with SE due to non-compliance. As the study involved patients admitted to the neurocritical care unit, 65 (65%) patients progressed to RSE and 31 (31%) were diagnosed with NCSE with coma at some point during their admission. The initial presentation of SE and other demographics stratified by adequacy of BZD dosing are detailed in *table 1*. Age, gender, ethnic group, prior history of epilepsy, and non-compliance with medications did not affect adequacy of BZD dosing.

The median intensive care unit (ICU) LOS was three days (IQR: 2-7), hospital LOS was seven days (IQR: 4-17), and the mean number of ventilator-dependent days was 4.4 (±9.6) with only 36% of patients requiring intubation. The majority of patients (69%) had a good outcome.

Patients received IV/intramuscular (IM) midazolam, IV lorazepam or IM diazepam in the prehospital or hospital setting. Lorazepam was administered in 73%, midazolam in 22%, and diazepam in 5% of patients. BZDs were not administered as first-line therapy in 7% of patients. Only 31% of our patients received adequate BZDs as initial therapy with the median LE dose of 3 mg (IQR: 3-5 mg).

Among patients presenting with NCSE without coma, only 18.9% received adequate BZDs compared to 39% of patients with other presentations (*p*=0.04). As expected, among patients receiving adequate BZDs, there was a higher incidence of CSE as the initial presentation compared to others (70% *vs.* 30%; *p*=0.01). Among patients progressing to RSE, 75.4% did not receive adequate BZDs (*p*=0.04) and among patients developing NCSE with coma, 80.6% did not receive adequate BZDs (*p*=0.07). Escalating doses of BZD, before administering a second-line AED, in the first few minutes of SE, was associated with an overall decrease in the cumulative incidences of RSE (*p*=0.04; r=-0.6) and NCSE with coma (*p*=0.003; r=-0.7) (*figure 1*).

The rates of intubation in patients receiving adequate BZDs (28.6% *vs.* 71.4%; *p*=0.70) and the mean number of ventilator-dependent days (2.9 [±8.1] *vs.* 5 [±10.2] days; *p*=0.31) were lower in patients receiving adequate BZDs, however, neither reached statistical significance. The median ICU LOS and median hospital LOS did not vary between the groups. Only 22.6% of patients who received adequate BZDs had a poor outcome compared to 77.4%
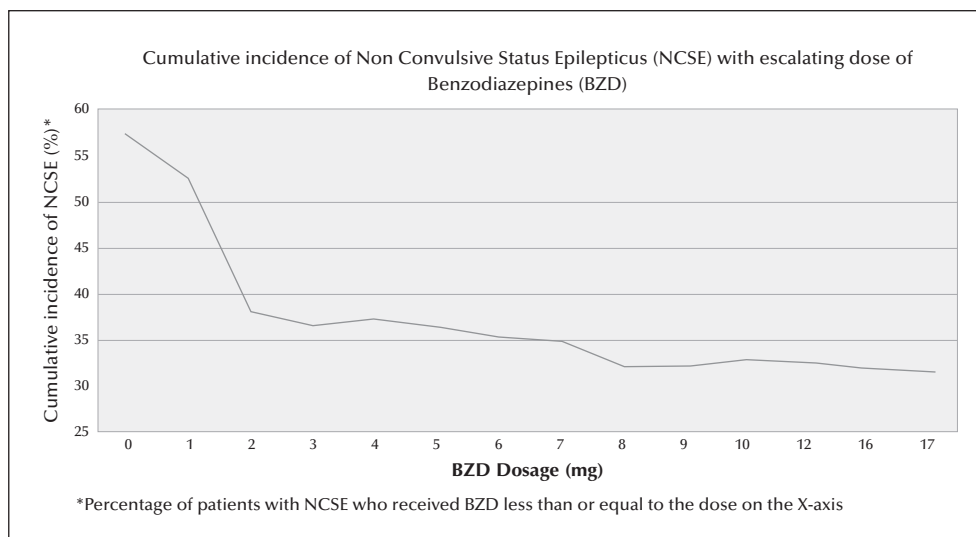
Figure 1. Cumulative incidence of non-convulsive status epilepticus (NCSE) with coma with escalating doses of benzodiazepines (BZDs).

of patients who were not adequately dosed. This again did not achieve statistical significance (*p*=0.22) (*table 1*).

Discussion

BZDs are considered the first-line treatment for SE. Adequate treatment of SE is important to stop ongoing seizures. The median cumulative LE dose, given as divided doses over several minutes in our patient population was 3 mg. The RAMPART trial reported that IM midazolam is at least as safe and effective as IV lorazepam for seizure cessation. In this trial, the effective prehospital dose of lorazepam was 4 mg in adults weighing 40 kg or more (Silbergleit *et al.*, 2012). The Neurocritical Care Society and the American Epilepsy Society recommend the same dose for in-hospital management of SE with additional recommendations to repeat the dose after 5-10 minutes in patients without seizure cessation (Brophy *et al.*, 2012; Glauser *et al.*, 2016).

Only 31% of our patients received adequate dosing. This may have been due to clinical cessation of convulsive seizures or due to concerns of airway compromise. However, the RAMPART study and other clinical trials have previously shown that endotracheal intubation is more commonly a sequela of continued seizures than an adverse effect of sedation from BZDs (Chamberlain *et al.*, 1997; Silbergleit *et al.*, 2012).

Seizures that continue for 5-10 minutes are more likely to last longer than 30 minutes (Friedman, 2011). Responsiveness to AEDs is poor, with higher mortality and morbidity in patients who continue to seize for more than an hour (Loscher, 2009). Fewer patients with NCSE without coma received adequate treatment

with BZDs suggesting a delay in diagnosis or assuming a less aggressive approach to the treatment of these patients. However, this leads to the progression of SE to RSE and NCSE with coma. A significant number of patients (72.1%) who did not receive adequate BZDs progressed to RSE, further demonstrating the need for early effective therapy. The incidence of NCSE with coma was lower with escalating doses of BZD (19.4% of patients), which shows the significance of adequate dosing of BZD in the initial management of SE (*figure 1*). Multiple previous studies have demonstrated the inadequacy of BZD administration in paediatric and adult patients presenting with SE (Chin *et al.*, 2004; Tobias and Berkenbosch, 2008; Friedman, 2011; Alvarez *et al.*, 2015). Based on our study, adult patients with SE are under-dosed, even with adequate doses defined as low as 4 mg. Our study demonstrates a system-wide need to better understand and manage patients during the early phase of the seizures. A hospital-wide policy with adherence to guidelines may facilitate this process.

In our patient population, there was a trend towards lower rates of intubation, less ventilator-dependent days, and better GOS at discharge in patients receiving adequate BZDs. However, none of these variable measures were statistically significant. This may have been due to the low number of patients in our cohort, low rates of intubation, and only 31% of patients with a poor outcome.

Our study is not without limitations. Although the patient cohort was obtained from a prospective database, the chart review was performed in a retrospective manner. The patients in our study were limited to those admitted to a neurocritical care unit, thus including only those patients with a high level of disease severity, as reflected by the high percentage of

patients with RSE and NCSE with coma. Furthermore, the patient population may not truly represent all the patients admitted to the hospital with SE. Most of the patients received less than 4 mg of LE loading dose, although the time interval for total drug administration and the initial dose of the BZD were not reviewed. We are unable to truly elucidate the under-dosing of BZDs in our patient population, which may very well have been due to cessation of clinical seizures. A prospective, controlled study to investigate initial treatment in patients with SE is required. Meanwhile, our study emphasizes the use of adequate BZDs in patients presenting with SE.

Conclusion

Our study reveals that the vast majority of adult patients presenting to the hospital with SE receive inadequate doses of BZDs. The current guidelines for administering 0.1 mg/kg up to 4 mg of lorazepam, with recommendations to repeat dosing if required, was not adhered to. Patients in whom BZDs were not adequate progressed to RSE and had a tendency to develop NCSE. Our study demonstrates the need for a gap analysis to identify deterrents to ensure adequate BZD dosing and subsequently develop a hospital-wide protocol to guide first responders in the management of SE. Further studies to evaluate the emergent management of patients with SE are warranted. □

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