ABSTRACT

Introduction:

Levetiracetam is an antiseizure medication that is commonly used in neurocritical care (NCC) patients to prevent or treat seizures. Behavioral adverse events (ADE) have been reported to occur in approximately 10% of patients taking levetiracetam; however, the incidence of these ADEs in NCC patients are unknown and may be exacerbated due to their unique CNS pathology. Therefore, the purpose of this study is to identify the incidence of levetiracetam-associated behavioral ADEs in NCC patients.

Methods:

Adult NCC patients admitted between November 1, 2014 and October 31, 2018 and diagnosed with traumatic intracranial injury, subarachnoid or intracerebral hemorrhage, or cerebral infarction were included in this study. Levetiracetam-associated behavioral ADEs were identified by documentation of: 1) diagnosis codes for delirium, agitation, irritability, hostility, violent behavior, insomnia, or anxiety; 2) administration of haloperidol, quetiapine, ziprasidone, olanzapine, or risperidone; and/or 3) implementation of physical restraints.

Results:

There were 965 patients included in this study; 52% males, and the median GCS on admission was 13. The most common neurological injuries were intracerebral hemorrhage (31%) and traumatic intracranial injury (29%). Levetiracetam-associated behavioral ADEs were identified in 415 (43%) of patients. The most common behavioral ADEs identified by diagnosis codes were delirium, agitation, and anxiety; 20% received an antipsychotic, and 6% had restraints ordered. Patients with traumatic intracranial injuries had the highest reported incidence of levetiracetam-associated behavioral ADEs (51%). Behavioral ADEs occurred a median of 1.98 (0.81-4.66) days after levetiracetam initiation.

Conclusion:

Almost half (43%) of NCC patients that received levetiracetam experienced a behavioral ADE, which occurred a median of 2 days after therapy initiation. Further studies are needed to determine the safety of levetiracetam use in NCC patients.

Introduction:

Levetiracetam is an antiseizure drug commonly utilized in the neurocritical care environment for treatment of seizures, status epilepticus, and as a prophylactic therapy in certain situations. Levetiracetam has multiple mechanisms of actions, but it is believed that its binding to the synaptic vesicle glycoprotein 2A receptor, which leads to neurotransmitter modulation, is largely responsible for its antiseizure effects(1, 2). While efficacious, levetiracetam treatment has also been associated with the risk of developing behavioral adverse events, which contribute to drug discontinuation (3, 4). Critically ill, neurologically injured patients are at a high-risk of developing behavioral adverse events for many reasons, and the addition of levetiracetam may further exacerbate this (5–7). As the use of levetiracetam in this patient population continues to grow we performed this study in order to help identify the incidence of behavioral adverse events in a critically ill, neurologically injured patient population receiving levetiracetam.

METHODS

This IRB-approved study was a single-center, retrospective analysis of patients with a neurologic injury that were admitted to an intensive care unit (ICU) between November 1, 2014 and October 31, 2018 and received levetiracetam. Patients were defined as having a neurological injury if they had a traumatic intracranial injury, a non-traumatic subarachnoid hemorrhage, a non-traumatic intracerebral hemorrhage, or a cerebral infarction. A behavioral adverse event was defined as documentation of delirium, agitation, irritability, hostility, violent behavior, insomnia, or anxiety by a diagnosis code (ICD-9 or ICD-10), receipt of an antipsychotic (haloperidol, quetiapine, ziprasidone, olanzapine, or risperidone), positive CAM-ICU, or implementation of physical restraints. Patients receiving an antipsychotic or those with a documented positive CAM-ICU were only considered to have a behavioral adverse event if it occurred while the patient was receiving levetiracetam. Patients were excluded if they were under 18 years of age or greater than 89 years of age.

Patients were identified for inclusion via an electronic medical record search process utilizing the previously noted inclusion dates and definitions, as well as documentation of levetiracetam therapy.

The primary objective was to determine the number of patients experiencing a behavioral adverse event in a critically ill, neurologically injured patient population receiving levetiracetam. Secondary objectives included time to occurrence of behavioral adverse event in those with an event, and hospital and ICU lengths of stay.

Statistical Analysis:

A multiple logistic regression model was performed to assess the associative factors of the occurrence of a behavioral event. The model included indicator variables for RASS <= -3, benzodiazepine intake, IV opioid intake, and concurrent AED intake, as well as pain score and median Keppra dosage. The odds ratios and 95% confidence intervals were reported. Two additional multiple linear regression models were performed to assess the same associative factors described above on the log-transformed hospital and ICU lengths of stay. We reported the parameter estimates, along with 95% confidence intervals. All statistical analyses were performed in R (version 3.6.1) at the 0.05 alpha level of significance.

RESULTS

965 patients were identified for the study, of which 415 (43%) were found to have a levetiracetam-associated behavioral adverse event. Baseline patient demographics were similar between patients who experienced a behavioral adverse event and those that did not (Table 1). The most common reason for a patient to have a behavioral adverse event was documentation of a diagnosis code, with the delirium diagnosis code being the most frequently documented (Table 2). 258 patients with behavioral adverse events (62.1%) were found to have a positive CAM-ICU or received an antipsychotic while concurrently receiving levetiracetam. In these patients, the median time to the first documented occurrence was 1.98 (0.81-4.66) days after levetiracetam initiation.

Patients who had a documented Richmond Agitation Sedation Scale (RASS) score of ≤ -3, those who received a benzodiazepine, or those who received another antiseizure drug, any of which occurred while the patient was concurrently receiving levetiracetam, were significantly more likely to have a behavioral adverse events (Table 3). Patients who experienced adverse events were found to have significantly longer hospital and ICU lengths of stay, and received significantly more levetiracetam doses than those who did not (Table 4). After adjusting for potential confounding variables including RASS ≤ -3, receipt of a benzodiazepine, or another antiseizure drug, patients with behavioral adverse events were still noted to have longer hospital and ICU length of stay than those that did not.

DISCUSSION

We investigated the incidence of behavioral adverse events in patients with acute neurological injuries receiving levetiracetam and identified a behavioral adverse event in nearly half of the patients sampled, a higher proportion than what has previously been reported in the epilepsy population (8). The exact mechanism of levetiracetam-associated behavioral adverse is not currently known, but there is speculation that it may be due to levetiracetam’s modulating effects on the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor (9). Perampanel, a noncompetitive antagonist of the AMPA receptor, has also been known to cause behavioral adverse events in patients, whereas brivaracetam, an SV2A modulator similar to levetiracetam, lacks action at the AMPA receptor and has been associated with fewer behavioral adverse events (10–12). Previous literature suggests that there may be increased AMPA receptor expression following acute neurological injuries, and this could help to explain why behavioral adverse events seem to be more common in this patient population (13–15). In patients who we were able to determine the time to onset of behavioral event we found that these occurred approximately 2 days after levetiracetam initiation, suggesting that people who develop behavioral events may start to show signs early in their treatment course. Previous literature has suggested that co-administration of pyridoxine may reduce the incidence of behavioral events in patients receiving levetiracetam, and while our study did not seek to analyze an effect of pyridoxine on these events, the routine use of one medication to mask the adverse effects of another should not be routinely employed in practice, particularly when the mechanism for how pyridoxine mitigates behavioral adverse events remains unknown (16, 17).

Our study question is novel and addresses a drug that has seen a steady rise in use in the neurocritical care setting, partly due to its perceived minimal adverse effect profile compared to alternative options. We selected a group of patients who may be at a higher risk of experiencing behavioral adverse events, and our sample size was fairly robust with baseline characteristics well-matched between groups experiencing behavioral events and those that did not.

Our study was retrospective in nature, and as such, data elements analyzed could have been impacted by inaccurate charting in the medical record. Additionally, the use of diagnosis codes may have impacted our construct validity as the time of entry did not reflect the time the event occurred, meaning that a patient could have experienced a behavioral event long after levetiracetam had been discontinued. However, more than half of the patients identified as having a behavioral adverse event met more than one of our specified inclusions. Finally, benzodiazepine use and over-sedation (RASS ≤ -3) have both previously been associated with the development of delirium in critically ill patients making it difficult to associate levetiracetam with the behavioral event. We did attempt to adjust for these variables during our statistical analysis with regression analysis, and still found that patients categorized as having a behavioral adverse events had longer lengths of stay.

CONCLUSION

As the use of levetiracetam continues to rise in the neurocritical care population we found that patients with acute neurological injuries receiving this agent frequently experienced behavioral adverse events. Future studies to seek to examine this association in a prospective manner, particularly in the setting of seizure prophylaxis where levetiracetam is routinely employed.

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