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Ketamine use in the treatment of refractory status epilepticus

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Summary Refractory status epilepticus (RSE) occurs when status epilepticus (SE) fails to respond to appropriate therapy with typical antiepileptic drugs (AEDs). Animal studies have shown ketamine to be a highly efficacious agent in this setting, but very few case reports describe use of ketamine in human SE or RSE. We report a retrospective review of 11 patients who were treated for RSE with ketamine infusion in addition to other standard AEDs over a nine-year period. Data collection included age, gender, history of epilepsy, etiology of RSE, daily dose of ketamine, co-therapeutic agents, duration of seizures, treatment response, and disposition. RSE was successfully terminated in all 11 patients treated with ketamine. Dosing ranged from 0.45 mg/kg/h to 2.1 mg/kg/h based upon the preference of the treating clinician and response to therapy, with maximal daily doses ranging from 1392 mg to 4200 mg. Ketamine was the last AED used prior to resolution of RSE in 7/11 (64%) cases. In the remaining four cases, one other AED was added after ketamine infusion had begun. Time from ketamine initiation to seizure cessation ranged from 4 to 28 days (mean = 9.8, SD = 8.9). In 7/11 patients, RSE was resolved within one week of starting therapy. Administration of ketamine was uniformly associated with improvement in hemodynamic stability. Six of the seven patients (85%) who required vasopressors during early treatment for RSE were able to be weaned from vasopressors during ketamine infusion. No acute adverse effects were noted. These findings suggest that ketamine may be a safe and efficacious adjunctive agent in the treatment of RSE.

Introduction

Status epilepticus (SE) is a life-threatening neurological emergency characterized by protracted continuous or intermittent seizure activity without full recovery of consciousness between seizures lasting at least 30 min, which is

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associated with significant morbidity and mortality (Abend and Dlugos, 2008). Typical first-line therapies are effective in many cases. However, in 10—40% of cases, seizures continue despite appropriate medical intervention, a condition termed refractory SE (RSE) (Lowenstein, 2006). RSE may continue in some patients for weeks or even months, a state that has been called malignant RSE (Abend and Dlugos, 2008). Various definitions of RSE have been used in the literature, including those based on time frame, persistence of seizure activity, or failure of typical first-line antiepileptic drugs (AEDs) (Kahriman et al., 2003; Perry et al., 2006). Despite the lack of a formally accepted definition, RSE is typically associated with lengthy and complicated patient hospitalizations, higher overall functional disabilities, and poor outcomes (Lowenstein, 2006; Fernandez and Claassen, 2012).

There is currently no consensus on a standardized treatment protocol for RSE. Most clinicians initially follow treatment protocols for SE, which typically outline intravenous benzodiazepine therapy followed by administration of phenytoin or fosphenytoin at weight-based loading doses. When seizures continue, phenobarbital may be considered (Lowenstein and Alldredge, 1998). When these measures fail to control seizures, continuous intravenous anesthetics are often initiated with the use of propofol, midazolam, or barbiturates as initial choices for management (Claassen et al., 2002; Holtkamp et al., 2003; Power et al., 2011).

Current therapy for SE using these typical intravenous anesthetics relies heavily on neuronal inhibition mediated via the $GABA_A$ receptor. However, after prolonged seizure activity, these receptors are rapidly internalized, and a concomitant reduction of GABA-mediated synaptic inhibition is well described (Goodkin et al., 2005). As inhibition is lost, excitatory glutamate receptors are mobilized to the cell surface, creating a self-sustaining cycle that can be difficult to control (Abend and Dlugos, 2008). Ketamine, a noncompetitive N-methyl-D-aspartate (NMDA) glutamate receptor antagonist, is an agent that has shown promise in the treatment of RSE when GABAergic agents have failed. Animal models have demonstrated the efficacy of ketamine in late SE (Borris et al., 2000) but only a limited number of case reports exist in the medical literature at the present time regarding use of ketamine in SE and RSE, with varying degrees of detail regarding dosing, duration, and outcome (Kramer, 2012). Additionally, ketamine has sympathomimetic properties, which may provide cardiovascular support, whereas other treatments for RSE may be limited by hypotension (Abend and Dlugos, 2008). We describe our experience with ketamine in treatment of RSE spanning a nine-year period.

Materials and methods

The Institutional Review Board of Allegheny General Hospital approved this study through an exemption review. A retrospective analysis was performed by reviewing the charts of adult patients identified as experiencing RSE between January 2003 and December 2011. Patient charts were screened for RSE using diagnostic billing codes assigned at the time of hospital discharge, including grand mal status, generalized nonconvulsive epilepsy with intractable epilepsy, epilepsia partialis continua, or epilepsy unspecified, and were reviewed to identify patients with RSE who were treated with ketamine. RSE was defined as either persistence of clinical or electrographic seizure activity despite appropriate medical therapy for at least 24 h, or the inability to wean from continuous IV anesthetics without seizure recurrence. Cessation of RSE was defined as no clinical or electrographic seizures for at least 24 h immediately following discontinuation of the IV anesthetic.

Thirteen patients were diagnosed with RSE and treated with ketamine during the nine-year period. These patients were initially unresponsive to a standard treatment protocol of benzodiazepines and weight-based intravenous loading doses of standard AEDs. These treatments were usually followed by continuous infusions of benzodiazepines or propofol, along with additional administration of AEDs. Two patients for whom outcome regarding seizure cessation was indeterminate were excluded from analysis. In one case, the patient was transferred to another hospital during acute treatment of SE and outcomes data were not available. In the second case, a family decision to withdraw care was made within a few hours of starting ketamine. For the remaining 11 patients, data were collected on age, gender, history of epilepsy, etiology of RSE, daily dose of ketamine, co-therapeutic agents, duration of seizures, treatment response, and disposition.

Results

In our group, the mean age was 52 (SD 18.0), 7/11 (64%) patients were male, and 6/11 (55%) had a history of epilepsy. Causes of RSE were low AED levels (3/11; 27%), infection (7/11; 64%), and metabolic disturbance (1/11; 9%). There were no identified cases of post-anoxic SE treated with ketamine. Based upon electrographic and clinical data, 6/11 (55%) were in nonconvulsive SE and 5/11 (45%) were in generalized convulsive SE.

Prior to use of ketamine, all patients were being treated with a continuous infusion of IV anesthetic. All patients were monitored with continuous EEG (cEEG) except for one patient who was intermittently monitored with EEG during titration, but did not remain on cEEG due to lack of available equipment. In all cases, clinical and/or electrographic seizures recurred when infusions of these standard intravenous anesthetics were weaned. Specifically, patients were receiving propofol (7/11; 64%), lorazepam (1/11; 9%), pentobarbital (1/11; 9%), midazolam (1/11; 9%), or a co-infusion of midazolam and propofol (1/11; 9%) (Table 1). These standard IV anesthetic infusions were titrated and informed by the EEG and clinical evaluation to achieve electroclinical seizure control.

Ketamine was the second IV anesthetic used in 8/11 (73%) cases, the third in 2/11 (18%) cases, and the fourth in 1/11 (9%) cases. The majority of patients were bolused with 1 mg/kg (3/11; 28%) or 2 mg/kg (7/11; 64%) of ketamine prior to initiation of a weight-based continuous infusion. One patient did not receive a bolus and was started immediately on a weight-based continuous infusion. Dosing ranged from 0.45 mg/kg/h to 2.1 mg/kg/h (mean = 1.3 mg/kg/h) based upon the preference of the treating clinician and response to therapy, with maximal daily doses ranging from 1392 mg to