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Ketamine to facilitate weaning from mechanical ventilation: A case report

Michelle L Malnoske[1], Caroline M Quill[1]

Abstract

Introduction: Ketamine is commonly used for procedural sedation in the Emergency Department as well as an induction agent for endotracheal intubation. It tends to have a favorable effect on both respiratory and hemodynamic parameters. Despite this, ketamine is infrequently utilized as a continuous sedative in the intensive care unit presumably due to unfamiliarity and concern regarding its side effects.

Case Report: 20 year old female presented with diabetic ketoacidosis and rapidly developed progressive respiratory failure due to aspiration pneumonia. She required treatment with venous-arterial extracorporeal membrane oxygenation and during her recovery phase, she struggled with delirium requiring high doses of sedation with propofol and midazolam; this led to hemodynamic instability and inability to perform aggressive diuresis. Ketamine was initiated with a profound change in both hemodynamics and mental status that occurred within hours.

Conclusion: This case demonstrates the benefits which ketamine can provide as a non-benzodiazepine sedative in the intensive care unit. The adverse effects associated with this drug occur rarely and most can be managed with drug dose reduction or administration of glycopyrrolate (for hyper-salivation) or benzodiazepines (for emergence psychosis). The benefits to ketamine include favorable effects on respiratory reflexes, mechanics and hemodynamics.

Keywords: Ketamine, critical illness, hypnotics and sedatives.

Introduction

Ketamine is a rapid acting, general anesthetic that produces a cataleptic-like state. It causes dissociation by direct action on the cortical & limbic system. It is a non-competitive NMDA receptor antagonist that blocks the neurotransmitter glutamate and at low doses it can produce analgesia (at μ-opioid receptors), modulate central sensitization, hyperalgesia and opioid tolerance [1]. We describe a case where ketamine changed the trajectory of a young patient's severe illness allowing for a swift recovery and avoidance of tracheostomy.

Case report

A 20 year old female with type 1 diabetes presented to the emergency department with 1-2 days of nausea and vomiting. Her vital signs demonstrated a heart rate of 120 beats/minute and respiratory rate (RR) of 24 breaths/minute. A venous blood gas on admission revealed a pH of 6.91 and pCO2 of 22 mmHg; beta-hydroxybutyrate level was elevated at 10.18 mmol/L and blood sugar was 519 mg/dL. WBC count was 38.5 thousand/μL and venous lactate was 4 mmol/L. She was diagnosed with diabetic ketoacidosis, and started on intravenous fluids and insulin. After 8 hours of resuscitation and insulin therapy, her tachypnea persisted and she had emergent hypoxemia with worsening complaints of dyspnea. Over the next four hours she developed progressive hypoxemia requiring intubation and mechanical ventilation. Her post-intubation chest X-ray showed worsening bilateral infiltrates. Her hypoxemia was refractory to escalating levels of positive end expiratory pressure (PEEP), paralysis with atracurium, inhaled epoprostenol, and positional maneuvers. In consultation with cardiothoracic surgery, the decision was made to proceed with venous-arterial extracorporeal membrane oxygenation (VA ECMO) due to right heart dysfunction noted on echocardiography. Her course was complicated by acute hemorrhage of the axillary arterial cannula site leading to compartment syndrome of the right arm. Fasciotomies were performed but led to significant bleeding from the incision sites. Massive transfusion protocol was required for treatment of her hemorrhagic shock. During the six days of VA ECMO, the patient required paralytics and high doses of analgosedation in management of her hypoxemia. Despite maintaining renal function with adequate urine output (100-200 mL/hr) and creatinine between 0.88-1.17mg/dL, she developed

[1]Division of Pulmonary and Critical Care Medicine, University of Rochester Medical Center, 601 Elmwood Avenue, Rochester, NY 14642, USA.

Address of Correspondence
Dr. Michelle L Malnoske
Division of Pulmonary and Critical Care Medicine, University of Rochester Medical Center, 601 Elmwood Avenue, Rochester, NY 14642, USA.
Email: Michelle_Malnoske@URMC.Rochester.edu

Dr. Michelle L Malnoske

profound volume overload.

Once she stabilized for VA-ECMO decannulation, attempts at diuresis were limited due to sedative drug induced hypotension. She had severe, agitated delirium with Adult Sedation Agitation Scale ratings ranging from 2 (very sedated) to 5 & 6 (agitated or very agitated); she required continuous opiate and benzodiazepine infusions to prevent ventilator dyssynchrony and to maintain her safety and comfort. Dexmedetomidine was trialed for four days and despite maximal dosing (1.5mg/kg/hr), it exacerbated hypotension and was not effective in controlling her delirium. Quetiapine, an antipyschotic was also added in escalating doses (50mg to 100mg twice a day), again without improvement in agitation/delirium scores. Propofol was successful in controlling her agitation but led to hyper-triglyceridemia (430 mg/dL) and hypotension that limited attempts at diuresis; she required 3-4 mcg/min of norepinephrine to maintain blood pressures with this medication. Ketamine was proposed as a potential alternative to her complex sedative regimen. She was given a bolus of 1mg/kg and started on a 1mg/kg/hour infusion. Within three hours, patient was calm and appropriately interactive with providers and family; Adult Sedation Agitation Scale ratings were 3 (calm and cooperative) and 4 (sedated but follows commands). Her propofol and norepinephrine infusions were discontinued and fentanyl drip was transitioned to intermittent hydromorphone over the course of a few days (Figure). Once the propofol and norepinephrine infusions were discontinued, she tolerated more aggressive diuresis and her ventilator support was weaned to minimal settings. She was successfully extubated 5 days after initiation of the ketamine.

Discussion

Ketamine was developed in 1962 by Calvin Stevens and is a phencyclidine derivative [2]. Ketamine is rarely utilized for continuous sedation in the ICU likely due to unfamiliarity and concern for adverse side effects. With more data supporting use of non-benzodiazepine sedatives in the ICU [3,4], ketamine is becoming a drug of interest when the patient cannot tolerate propofol or dexmedetomidine due to side effects. Ketamine is both water and lipid soluble [2]. When administered intravenously, the onset of action is 30 seconds and its elimination half-life is 2-3 hours with excretion primarily through the urine [5]. Despite this, there is little evidence that supports adverse effects in renal failure. Metabolism occurs mainly in the liver via the P450 system including N-dealkylation to norketamine (an active metabolite, though only 1/3 as potent as ketamine) [5]. It is important to note that ketamine crosses the placenta; therefore infants born with ketamine used in anesthesia will also be partly anesthetized [1].

Ketamine has been shown to have advantageous effects on respiratory and circulatory systems. In a systematic review by Miller et al. [6], the noted respiratory effects of ketamine on ventilated patients include decreased respiratory rates, increased chest wall compliance, decreased airway resistance and decreased peak inspiratory pressures, particularly in cases of refractory bronchospasm due to asthma or COPD. In respect to hemodynamics, this systematic review also demonstrated that patients on ketamine for continuous sedation either experienced no change or improvement in mean arterial pressure as well as decreased use of vasopressors [6]. Ketamine has been described to increase in blood pressure, stroke volume and heart rate whilst maintaining systemic vascular resistance [1]. Compared with other sedatives in the ICU, ketamine appears to have a side effect profile that is equivalent if not better than other sedating agents. Umunna and colleagues demonstrated that the rate of adverse events with ketamine was 13% compared to other studies that demonstrate adverse event rates as high as 20-40% with drugs like dexmedetomidine and benzodiazepines [7].

Despite the positive effects that can be seen with the use of ketamine, there are important considerations and cautions with its use. The evidence for the adverse effects are primarily from the usage of ketamine as an induction agent for intubation and procedural sedation, therefore, further study on its use as a continuous sedative agent would be needed to confirm their persistence in this usage. Emergence psychosis has been described to occur particularly with use in procedural sedation in roughly 10-20% of patients [8]. Emergence phenomena can be as mild as vivid dreams to severe psychosis with frank delirium and irrational behavior [5]. The frequency of this side effect can be reduced to 50% by pre-treatment with benzodiazepines [5]. Hyper-salivation is also a frequently reported adverse effect of ketamine [1] and is primarily an issue when used in induction for intubation and procedural sedation, when an airway is not secured. When using ketamine as a continuous sedative in a ventilated patient, this side effect can be more bothersome rather than lead to poor outcomes. It can also be easily treated with anti-cholinergic medications, such as glycopyrrolate [1].

Ketamine causing increased intraocular pressure was first described in a study carried out in 15 children in 1971, where it was noted that after receiving 5mg/kg intramuscular ketamine for an ophthalmologic procedure, the intraocular pressure by indentation tonometry increased by 37% at a peak time of 15 minutes [9]. More recent studies have not demonstrated this effect [10, 11], both in children and adults when more accurate intraocular pressure measurements were taken by applanation tonometry. Although the data appears to be conflicting, it is reasonable to avoid ketamine in the setting of ocular injury and active glaucoma as there may be a risk to increase intraocular pressures.

Increased intracranial pressure (ICP) has been a frequent adverse effect of ketamine based on an observational study of 11 male healthy volunteers in 1971 [12]. The proposed mechanism for ketamine leading to increased ICP, especially in a spontaneously breathing patient is increase in pCO2 leading to increased cerebral blood flow. Therefore, in ventilated patients receiving this medication for sedation, this should not be a major issue. Moreover, recent studies have not supported this finding regarding increased ICP as a major side effect of ketamine [13-15]. In fact for traumatically brain injured patients, ketamine has been found to lower ICP and have favorable effects on cerebral perfusion pressure, mean arterial blood pressures and reduction in vasopressor requirements [15].

There is one patient population which ketamine should be avoided and that is those with catecholamine dependent cardiac performance [6]. Although, ketamine is known to increase catecholamines by increased release and

reduced neuronal reuptake, it is a known negative cardiac inotrope [16]. When given to patients with normal heart function, the surge of cathecholamines appears to balance this negative inotropic effect; this does not occur in those with catecholamine dependent cardiac performance [5], Christ et al. demonstrated a 21% decrease in cardiac index in patients with left ventricular failure with the initiation of a ketamine infusion; this was not seen in the group receiving midazolam [16].

Conclusion

Overall, ketamine is a possible non-benzodiazepine alternative for sedation in the ICU. The adverse effects associated with this drug tend to occur rarely and most can be managed with cessation of the drug or administration of glycopyrrolate (for hyper-salivation) or benzodiazepines (for emergence psychosis). The benefits to ketamine include favorable effects on hemodynamics and respiratory reflexes/mechanics. The favorable effect on hemodynamics was evident in our patient as she could withstand aggressive diuresis once ketamine was initiated. This led to decreased ventilator support and successful extubation without need for tracheostomy. It is our opinion that the transition to ketamine truly altered this patient's course for the better. This further supports the fact that ketamine can safely and effectively be used as an alternative sedative drug in the ICU. More research is needed to further confirm the safety of this drug in the critically ill and to see if there are potential beneficial outcomes using ketamine as a non-benzodiazepine sedative drug.

Clinical Relevance

1. Ketamine is a non-benzodiazepine option for continuous sedation in the ICU particularly in those with side effects from commonly used sedatives.
·2. Advantageous effects of ketamine include pain and sedative effects, decreased airway resistance, and increased blood pressure.
3. Ketamine should be avoided in patients with increased intraocular pressure and those with catecholamine dependent cardiac output.

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