Case Report

Pharmacokinetics of Ketamine at Dissociative Doses in an Adult Patient With Refractory Status Asthmaticus Receiving Extracorporeal Membrane Oxygenation Therapy

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ABSTRACT

Purpose: First-line management of severe asthma exacerbations include the use of inhaled short-acting β-agonists, anticholinergics, and systemic corticosteroids. Continuous intravenous ketamine given at dissociative doses may be a pharmacologic option in patients who are intubated with life-threatening severe bronchospasm unresponsive to standard therapy. We describe the case of a 44-year-old man admitted to the intensive care unit for status asthmaticus requiring intubation and mechanical ventilation.

Methods: The patient developed severe refractory hypercapnic respiratory failure necessitating additional respiratory support with veno-venous extracorporeal membrane oxygenation (ECMO) therapy. Ketamine treatment was initiated at 0.5 mg/kg/h continuous infusion on the day of admission for pain control and required up-titration to 2 mg/kg/h by intensive care unit day 4 for bronchodilation. Whole blood samples were obtained for pharmacokinetic analysis of ketamine during ECMO.

Findings: The plasma concentration at steady state was 1018.7 ng/mL, with an estimated clearance of 1.96 L/kg/h after up-titration. The V_d was 14.18 L/kg, the k_e was 0.14 hr^{-1}, and the $t_{½}$ was 5 hours.

Implications: Compared with healthy adults, there was a 6.5-fold increase in the V_d. However, the V_d was similar compared with critically ill patients not receiving ECMO. Further studies should focus on the effect of ECMO on ketamine pharmacokinetic properties. (*Clin Ther*. 2019;41:994–999)

Key words: acute respiratory distress syndrome, anesthetic, asthma exacerbation, extracorporeal membrane oxygenation, status asthmaticus, pharmacokinetics.

INTRODUCTION

Asthma exacerbation is one of the leading primary diagnoses in the emergency department (ED), accounting for 1.7 million visits annually in the United States.[1] An estimated 25% of those patients encountered in the ED for asthma will be hospitalized, with approximately 10% of those admitted to an intensive care unit (ICU).[2] Although first-line treatments with oxygen, systemic

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corticosteroids, and bronchodilators are sufficient in reducing the symptomas and airflow obstruction in most patients, approximately 3% to 5% of those admitted to the ICU will develop respiratory failure, requiring intubation and mechanical ventilatory assistance.[3] Extracorporeal membrane oxygenation (ECMO) therapy is a salvage therapy for severe acute asthma exacerbation when ventilation cannot be maintained with maximal medical therapies, including deep sedation and neuromuscular blockade.

Ketamine is a dissociative anesthetic capable of inducing analgesia at low doses and both analgesia and anesthesia at higher doses. It exerts its effects by noncompetitively antagonizing the *N*-methyl-D-aspartate receptor within the limbic and cortex system, thereby producing a cataleptic dissociated state. In bronchial smooth muscle, ketamine reduces bronchospasm and airway resistance because of its sympathomimetic properties in the airways.[4] In patients presenting with severe status asthmaticus, case reports have described use of intravenous ketamine in children and adults as a means to avoid mechanical ventilatory support with bolus doses of 0.1 to 2 mg/kg followed by a continuous infusion of 0.15 to 2.5 mg/kg/h.[5,6]

The effects of ECMO on ketamine pharmacokinetic properties have not been described. Factors such as critical illness, varying degrees of organ dysfunction, components in the ECMO circuit, and the physicochemical properties of drugs have been implicated to contribute to the pharmacokinetic variability in this population. Importantly, interactions between the individual drug and the components of the ECMO circuitry are substantial, particularly for lipophilic protein−bound drugs.[7] Given the lipophilicity of ketamine (LogP = 2.9),[8] adsorption of drug into the ECMO circuitry may affect its systemic disposition in patients. As a result, individual drug distribution, CL, and V_d may be altered because of adsorption or sequestration into the ECMO circuit.

We describe the pharmacokinetic properties of ketamine in a critically ill patient undergoing ECMO therapy. Pharmacokinetic parameters of interest (C_{ss}, V_d, CL, and $t_{½}$) are estimated, compared with the literature, and critically discussed.

CASE REPORT

A 44-year-old African American man with a medical history of uncontrolled, moderate, persistent asthma and hypertension, who was self-reported to be nonadherent to treatment, presented to an outside hospital with increasing shortness of breath unresponsive to a recent steroid prescription from his primary physician. His height was 170 cm, and his weight was 81 kg (ideal weight, 65.9 kg). He was given bilevel noninvasive positive pressure ventilatory support for acute hypercapnic respiratory failure and quickly progressed to requiring intubation and invasive mechanical ventilatory support. A chest tube was placed for bilateral pneumothorax. Despite aggressive medical therapy, including therapeutic neuromuscular blockade and ventilator strategies to maximize expiratory time and mitigate gas trapping, ventilation could not be adequately maintained, and the patient was placed on a veno-venous (VV) ECMO via the right internal jugular vein using a 27F Avalon cannula. The ECMO circuit consisted of a Quadrox PLS oxygenator, Rotaflow pump, and tubing set all coated in Bioline (Maquet Cardiopulmonary AG, Hirrlingen, Germany). In accordance with local protocol, midazolam and fentanyl were used for primary pain control. Ketamine treatment was initiated as an adjunct for pain management as a continuous infusion on day 0 at a rate of 0.5 mg/kg/h after ECMO was started at an outside hospital. Pulmonary symptoms included reduced breath sounds and wheezing that required bronchotherapy with nebulized budesonide and ipratropium-albuterol in addition to montelukast and high-dose intravenous methylprednisolone. A respiratory pathogen polymerase chain reaction swab taken on admission produced a positive result for parainfluenza virus type 3, and sputum cultures tested negative for bacterial infection. After initiation of VV ECMO, he was given ultralow tidal volume ventilation with a tidal volume of 200 mL (4.5 mL/kg ideal weight) on volume-control ventilation. The $Paco_2$ was kept in physiologic range with a high sweep setting on the VV ECMO circuit. On ICU day 2, nebulized arformoterol was added to the regimen, and ketamine was up titrated to 1 mg/kg/h. Ketamine was subsequently titrated to 2 mg/kg/h on ICU day 4, targeting a dose for treatment of severe acute asthma exacerbation. The patient's hospital course was further complicated by *Clostridium difficile* colitis, ventilator-associated pneumonia, *Enterococcal* sepsis, and gastroduodenal bleed. During ICU days 8 through 11, the wheezing and airway resistance significantly improved, and his

tidal volume on volume control increased to 330 mL by ICU day 9 and reached 520 mL after ECMO decannulation. Figure 1 A trends lung compliance and airway resistance during ketamine infusion. Airway resistance was calculated as the difference between peak inspiratory pressure and plateau pressure divided by the flow rate. Pulmonary compliance was calculated as the ratio between the tidal volume and the difference between the peak inspiratory pressure and the positive end-expiratory pressure. All parameters were measured daily from the mechanical ventilator record and maintained by the respiratory therapist. The patient was decannulated from ECMO on ICU day 13 and underwent tracheostomy on ICU day 15. His chest tube was removed the following day on ICU day 16. The ketamine infusion was gradually weaned and discontinued on hospital day 27.

After informed consent, arterial blood sampling for ketamine analysis was obtained. A sample was taken 41 hours after the initial ketamine infusion. Additional samples were taken at 16, 100, 208, and 268 hours after ketamine up-titration on ICU day 14. Ketamine plasma concentrations during the continuous infusion are shown in Figure 1 B together with the observed decline in airway resistance. Plasma ketamine concentrations were analyzed using a validated ultra-HPLC-MS/MS spectrometry following the US Food and Drug Administration Guidance on Bioanalytical Method Validation.[9]

Table. Ketamine pharmacokinetic parameters during the continuous high-dose infusion compared with published values.

Parameter	Observed	ICU Patients[a]	Healthy Adults[b]
C_{ss} (ng/mL)[c]	1018.69	—	—
V_d (L/kg)	14.18	16	2.18
CL (L/kg/h)	1.96	2.16	0.89
k_e (hr^{-1})	0.14	0.31	0.38
$t_{1/2}$ (h)	5	4.98	3.27

ICU = intensive care unit.
[a] Mean values in 12 ICU patients after a 2-mg/kg intravenous bolus and 2-mg/kg/h infusion for 2 hours.[11]
[b] Mean values in 10 healthy adults after a 9- to 10-mg/kg/h short infusion.[10]
[c] Mean value of 3 samples obtained 20, 42, and 54 t½s after high-dose continuous infusion.

The mean (range) C_{ss} during high-dose ketamine infusion was 1018.7 (953.5–1063.6) ng/mL. This value represents the mean of the three plasma samples collected at approximately 20, 42, and 54 $t_{1/2}$s during the continuous infusion. Patient-specific pharmacokinetic parameters, including the V_d, CL, k_e, and $t_{1/2}$ were estimated during the infusion. The CL was estimated by dividing the rate of infusion by the C_{ss} (CL = dose [mg/kg/h]/C_{ss}). On the basis of a

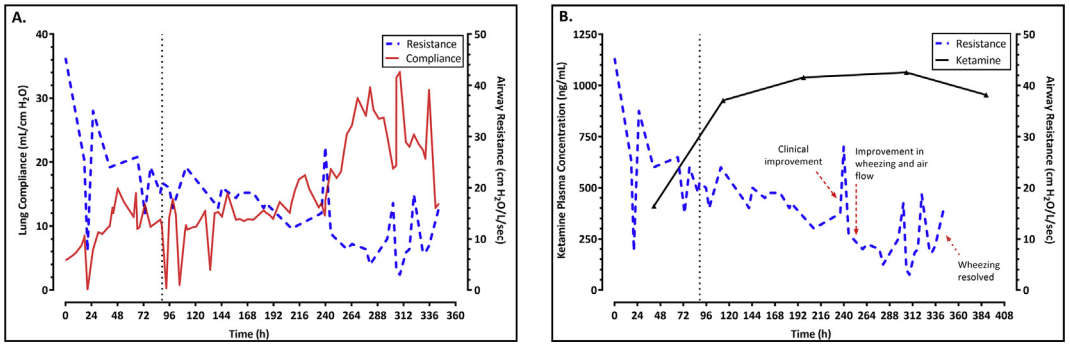

Figure 1. Airway resistance and pulmonary compliance (A) and concentration response during ketamine infusion (B) as a function of time. The vertical dashed line represents ketamine up-titration to 2 mg/kg/h (intensive care unit day 4). The red arrows represents clinical observations during the patient's hospitalization.

reported plasma $t_{1/2}$ of 4.98 hours in ICU patients, C_{ss} was presumed to have been reached approximately 24 hours after ketamine up-titration. As such, the first plasma sample collected (approximately 16 hours after up-titration) was used to calculate a patient-specific k_e constant together with the mean of the plasma concentrations obtained at steady state using the following equation:

$$k_e = -2.3/t \times \log (C_{ss} - C_p/C_{ss})$$

where C_p is the plasma concentration taken at time t (first sample, 16 hours after up-titration) and C_{ss} is the steady-state ketamine plasma concentration during the continuous infusion. The estimated k_e was then used to calculate the V_d using the relationship $(R_0/k_{el})/C_{ss}$, where R_0 is the infusion rate. The $t_{1/2}$ was estimated using $t_{1/2} = 0.693/k_{el}$. The pharmacokinetic parameters are described in the Table together with values reported in ICU patients and healthy adults.[10,11]

After clinical improvement from a severe acute asthma exacerbation, the patient was successfully decannulated off VV ECMO and discharged from the hospital 33 days after ECMO removal. His follow-up visit to the outpatient clinic after hospital discharge revealed no shortness of breath, and he reported that his condition was well controlled with aformoterol, nebulized budesonide, ipratropium-albuterol, and montelukast. There were no self-reported psychiatric behavior abnormalities reported during the follow-up visit.

DISCUSSION

Ketamine has several pharmacokinetic and pharmacodynamic advantages for initial and maintenance management of life-threatening asthma exacerbations. As an inductive agent during rapid sequence intubation, the quick onset and short duration of action make ketamine an ideal agent for emergency airway management. In addition to its sedative and analgesic properties, ketamine has sympathomimetic activity at the bronchial smooth muscle, resulting in bronchodilation. These unique pharmacokinetic and pharmacodynamic properties make ketamine a useful agent for the initial management of severe asthma exacerbations that require intubation. In cases where patients present with severe asthma exacerbations unresponsive to conventional therapy that require emergency intubation, ketamine was reported to improve clinical and laboratory values after repeated administration.[12–14] Infusion doses associated with efficacy ranged from 0.75 to 3 mg/kg/h.[13–15] These reports may suggest a dose-dependent bronchodilatory response often not seen with subanesthetic doses used in acute pain management. At dissociative doses, patients may be at risk for emergence phenomenon due to ketamine's dose-related psychomimetic effects. Enhanced airway secretion and hypersalivation are also anticipated from autonomic stimulation and may be a potential downside to using ketamine.

We observed improvement in the patient's wheezing by the fifth day after initiating treatment with high-dose ketamine, with a complete resolution of symptoms 10 days after up-titration. Reduction in airway resistance and an increase in pulmonary compliance were also observed during that period. These observations, however, should be interpreted cautiously. Symptomatic improvement may have been attributable to other concomitant medications and interventions during clinical care. These medications include therapeutic agents such as high-dose corticosteroids, anticholinergics, β_2-agonists, leukotriene receptor antagonists, and paralytics. Lastly, improvement may also have been possible with time during ECMO therapy.

Ketamine is commercially available as a racemic mixture. The pharmacokinetic properties of ketamine can be characterized by multicompartment models. In healthy adults, the estimated V_d, CL, and $t_{½}$ of racemic ketamine are 2.18 L/kg, 0.88 L/kg/h, and 3.27 hours after a short infusion, respectively.[10] These parameters are largely altered in critically ill patients in whom the V_d may increase by as much as 7.3-fold.[11]

This case is the first, to our knowledge, to report the pharmacokinetic properties of high-dose ketamine given to a patient unresponsive to standard asthma therapy during ECMO. The C_{ss} during the continuous infusion was 1018.7 ng/mL. This concentration represents the mean of 3 samples obtained approximately 20, 42, and 54 $t_{½}$ during the high-dose ketamine infusion. The concentrations achieved align with previous reports in those receiving a 2-mg/kg/h ketamine infusion administered during 2 hours.[11] Interestingly, the estimated

pharmacokinetic parameters using the C_{ss} concentration did not largely differ among ICU patients. Moreover, it was hypothesized that the V_d for ketamine during ECMO would have been increased because of its lipophilicity and potential interaction with the ECMO circuit. Aside from lipophilicity, individual protein binding may also have a higher likelihood for drug sequestration during ECMO. In an *ex vivo* study comparing drug lipophilicity and protein binding in ECMO circuits, drugs with higher protein binding were observed to have greater loss in the circuit despite having similar lipophilic profiles.[7] Drugs having similar lipophilicity, such as ciprofloxacin and thiopentone (LogP = 2.3), but have contrasting protein-binding profiles (ciprofloxacin, 20%–40%; thiopentone, 80%; with mean losses of 4% and 88% in the circuit after 24 hours, respectively). Ketamine is lipophilic (LogP = 2.9) and is 10% to 30% bound to plasma proteins. The low protein binding of ketamine may in part explain the similar V_d observed in critically ill patients not undergoing ECMO, suggesting the possibility of minimal interaction between ketamine and the ECMO circuit.

Apart from its lipophilicity, ketamine is also highly water soluble.[8] Although our patient appeared overweight (body mass index, 28 kg/m^2), the patient was muscular and likely had a higher proportion of lean body mass. In patients who are overweight or obese, the effect of weight on ketamine pharmacokinetic properties may not be significant. Despite its large V_d, ketamine is also highly soluble in aqueous medium, which may allow adequate concentrations in plasma relative to dose regardless of weight. Together, these observations should be validated in controlled *ex vivo* and clinical studies.

Although therapeutic drug monitoring is not routinely performed for sedatives in the intensive care setting, the results of this report may be of use in understanding the dose–exposure association and the effect of the ECMO circuitry on ketamine pharmacokinetic properties. Such information can optimize dosing to ensure adequate tolerability and efficacy of ketamine when used during ECMO.

CONCLUSION

A continuous infusion of 2 mg/kg/h produced a C_{ss} of 1018.7 ng/mL. There was a 6.5-fold increase in the V_d compared with healthy adults; however, this increase was similarly observed in critically ill patients administered ketamine. Other pharmacokinetic parameters remained consistent compared with patients in the ICU not receiving ECMO. Dedicated pharmacokinetic studies will be needed to determine optimal dosing and the potential effect of ECMO on ketamine disposition.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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