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Ketamine for Treatment of Acute Agitation

Introduction

1. Ketamine is a sedative that has been used for patients with extreme/refractory undifferentiated agitation
2. Indications for utilizing ketamine for emergent sedation of agitated patients include
    a. Patient poses and immediate threat to patient and healthcare provider safety (RASS +4)
    b. Failure and/or futility of alternative non-pharmacologic de-escalation strategies
    c. Absence of IV access
    d. Not a candidate for intramuscular antipsychotics and/or benzodiazepines due to unacceptable protracted onset of action

Pharmacology	
Properties	Rapid acting general anesthetic producing cataleptic-like state due to antagonism of N-methyl-D-aspartate **(NMDA) receptors in the central nervous system.** • Ketamine also has significant analgesic/dissociative properties at lower doses
Dose	**2-5 mg/kg IM to a max single dose of 500mg** 1-2 mg/kg IV
Administration	IM: Inject deep IM into large muscle (glute or vastus lateralis muscle) IV: Administer over at least 60 seconds
Formulation	10 mg/mL 50 mgmL **100 mg/mL * must use for IM administration to reduce volume**
PK/PD (for amnestic effects)	**Onset: 3-5 mins IM; <1 minutes IV** **Duration: 15-25 mins IM; 5-10 minutes IV** Bioavailability: 93% IM Metabolism: Extensively through hematic N-demethylation Elimination: Greater than 90% urine, <5% feces
Adverse Effects	• **Hypertension** • **Tachycardia** • **Hypersalivation** • Nausea and vomiting • Laryngospasm • **Emergence phenomenon during recovery phase** • Increased muscle function (hyperactivity, twitching, rigidity)
Contraindications	• Significant elevations in blood pressure may be hazardous, ACS, ADHF, and unstable dysrhythmia
Warnings and Considerations	• **Rapid IV administration may increase risk of respiratory depression/apnea** • Verify concentration of formulation • Caution in diagnosed schizophrenia • Hypotension in catecholamine depleted states • Pregnancy and lactation (crosses placenta)

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Overview of Evidence

Author, year	Design/ sample size	Intervention & Comparison	Outcome
Lin 2020	Prospective, randomized, open-label pilot study N = 93	• Ketamine 4mg/kg IM or 1mg/kg IV • Haloperidol 5-10mg IM/IV + lorazepam 1-2 mg IM/IV	**More patients of patients receiving ketamine achieved sedation within 5 and 15 minutes** vs the haloperidol + lorazepam group. • 22% vs 0% at 5 mins • 66% vs 7% at 15 mins
Mankowitz 2018	Systematic safety and efficacy review N = 650	• Ketamine for undifferentiated agitation	**Mean time to sedation was 7.21min and effective in 68.5% of patients.** **30.5% of patients required intubation**, but not all secondary to ketamine administration.
Cole 2016	Prehospital Prospective, open label, observational N =146	• Haloperidol 10mg IM • Ketamine 5mg/kg IM	**Median time to adequate sedation was faster with ketamine (5 min**) vs haloperidol (17 min) Intubation rates were higher with ketamine (39%) than haloperidol (4%), as well as more complications (49% vs 5%, respectively). • **38% hypersalivation** • **10% emergence reaction**
Isbister 2016	Subgroup analysis from DORM II study (prospective observational study of ED acute behavior disturbance) N = 49	Ketamine as rescue treatment: • Droperidol alone: n = 46 • Droperidol + DZP or MDZ n = 2 • Midazolam alone: n = 1	**Median time to sedation post-ketamine was 20 minutes (IQR 10-30**) 3 patients had adverse reactions after ketamine • Vomiting: n = 2 • Oxygen desat: n = 1 (not intubated)
Riddell 2016	Prospective observational study N = 106	• Ketamine • Lorazepam • Midazolam • Haloperidol • Benzodiazepine + haloperidol	**More patients in the ketamine group were no longer agitated at 5 minutes than those in other groups**
Scheppke 2014	Retrospective chart review N = 52	Ketamine ~4mg/kg IM *Recommended midazolam 2-2.5mg IM or IV following ketamine for emergence reaction.	**96% of patients obtained sedation with a mean time to sedation of 2 minutes** 3 patients experienced significant respiratory depression. • About ½ of patients received midazolam after ketamine administration
Trials in Progress			
Barbic Estimated completio n 12/2020	Parallel, prospective, randomized, controlled trial	Ketamine 5mg/kg IM Midazolam 5mg IM + haloperidol 5mg IM	Primary: Time to adequate sedation Secondary: safety and tolerability, requirement of rescue medication

DZP= Diazepam; MDZ= Midazolam

Conclusions

1. Ketamine has been shown to be effective with a quick time to sedation, but is not without risks including respiratory depression.
2. Ketamine should be reserved for specific indications above and as last line for patient/provider safety and should be used with caution in patients who have an underlying psychiatric disorder.

References

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