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Ketamine for Treatment of Acute Agitation

Introduction

1. Ketamine is a sedative 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 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 mg/mL, 100 mg/mL ***must use 100 mg/mL 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 hypertension 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 et al., 2020	Prospective, randomized, pilot (n=93)	Ketamine 4 mg/kg IM or 1 mg/kg IV Haloperidol 5-10 mg IM/IV + lorazepam 1-2 mg IM/IV	**Ketamine achieved greater sedation within 5 and 15 minutes** (22% vs 0% at 5 mins; 66% vs 7% at 15 mins)
Mankowitz et al., 2018	Systematic review (n=650)	Ketamine IV or IM	• **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 et al., 2016	Prehospital prospective, observational (n=146)	Haloperidol 10 mg IM Ketamine 5 mg/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 in ketamine group**
Isbister et al., 2016	Subgroup analysis from DORM II study; prospective, observational (n=49)	Ketamine as rescue treatment after • Droperidol alone • Droperidol + DZP or MDZ • Midazolam alone	• **Median time to sedation post-ketamine was 20 minutes (IQR 10-30**) • 3 patients had adverse reactions after ketamine (vomiting n=2; desaturation n=1)
Riddell et al., 2016	Prospective, observational (n=106)	Ketamine Lorazepam, midazolam, haloperidol, or benzodiazepine + haloperidol	**Ketamine resulted in a greater number of patients with no agitation at 5 minutes than other medications**
Scheppke et al., 2014	Retrospective chart review (n=52)	Ketamine ~4mg/kg IM *Recommended midazolam 2-2.5 mg IM or IV following ketamine for emergence reaction	• 96% of patients obtained sedation, mean time to sedation was 2 minutes • 3 patients experienced significant respiratory depression • About ½ of patients received midazolam
Trials in Progress			
Barbic et al., Completed March 2020, results pending	Parallel, prospective, randomized, controlled	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. Used ketamine with caution in patients who have an underlying psychiatric disorder
3. Ketamine should be reserved for specific patient populations and as last line for patient/provider safety

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