

Ketamine: Uses and Abuses

Nancy Balch, PharmD, BCCCP
nbalch@mgh.harvard.edu

Disclosure Statement

- I have no personal or financial conflicts of interest relating to this presentation

Objectives

- Explain how the mechanism of action of ketamine allows it to be used in different clinical situations
- Create protocols for use, and monitoring such use, of ketamine in emergency departments vs intensive care units vs out-patient clinics
- Analyze patient symptoms and patterns indicating potential ketamine abuse

Ketamine Timeline

1956: phencyclidine invented

1962: invented (1/10th potency)

1964: prisoner study

1966: 1st published ketamine study-anesthesia

Ketamine Timeline

1970: FDA approval

Late 1970's: abuse starts

1999: controlled substance

Mechanism of Action

- Primary: N-methyl-D-aspartate (NMDA) receptor antagonist
- Partial mu agonist (opioids bind to mu)
- Active metabolite, norketamine
- Actual action for disease states theoretical

Other Stated Mechanisms of Action

- Anticytokine effect
- Acetylcholine muscarinic, nicotinic receptor inhibitor
- L-type calcium and sodium channel inhibitor
- Adrenergic, serotonergic, dopaminergic (D₂)
- Neuronal sodium channel inhibitor
- Many others proposed

Mechanism of Action

- Lower risk of respiratory effects than other meds
 - Lower dose, administer correct = least risk
 - Higher doses, faster admin = respiratory depression
- Different actions at different doses
- Does not cure anything
- Further discussed under different treatments

Metabolism, Renal Excretion

- Hepatically metabolized
 - 4 metabolites, 1 metabolite is active
 - Ketamine T_{1/2} 10-15 min, metabolite T_{1/2} 2.5 hrs
 - Cytochrome P450: 3A4, 2B6, 2C19
- Renally excreted
- Small amount eliminated in bile
- Animal Pharmacokinetics differ from human



Concentrations

- **10 fold difference: high risk of error**
 - Store separately vs ability to prevent error
 - Ordering: safety processes to prevent error
- IV: **10 mg/mL**
- IM: **100 mg/mL**

Administration

- IV: over AT LEAST 1 minute
 - Decrease risk of respiratory depression, apnea
 - Increased hypertension with rapid administration
 - Faster onset if repeat dosing required
- IM:
 - lasts longer than IV administration
 - Higher incidence of vomiting
- Neither route considered safer than other
- Risk of aspiration



Monitoring

- Blood pressure:
 - Peaks a few min after admin
 - Baseline approximately 15 min after admin
- Respiratory rate, oxygenation
- Level and length of sedation
- Verbal + tactile stimulation during recovery
 - Minimize as much as possible
 - Potentially decrease emergency reactions
 - Adult and Pediatric
 - Benzo's no longer required for pedi's

Some Potential Adverse Reactions

- Cardiac: hypertension, cardiac depression
- CNS: reemergence syndrome, psychosis
 - hallucinogenicity: one reason for abuse
- Pulmonary:
 - Increased secretions, bronchodilation
 - mainly in elderly or critical: respiratory depression, apnea
- Hyperreflexia, clonus
- Long term: potential renal &/or hepatic toxicity, schizophrenia symptoms, cognitive impairment

Potential Med Interactions

- Theophylline, aminophylline: ↓ seizure threshold
- Vasopressor, sympathomimetics: ↑ increased blood pressure, heart rate
- CNS depressants: ↑ sedation, recovery time, respiratory depression, coma, death

Protocol Based on Location of Use

- Clinics
- Emergency Department, Intensive Care Unit
- General Care Floor

Clinic Protocols

- Must state: call 911 for any potential emergency
- Clear statement of disease state to be treated
- Screening of patients, including ability to fast
- Contain dosing
 - Recommend maximum dose
 - Include guidance on obese patients

Clinic Protocols

- Only 1 concentration or pre-drawn exact doses
- Determine training required for everyone who may be involved
- Ability to monitor patients before, during, and after administration
- Patient not driving vehicle x 24 hrs after dose

Emergency Department, ICU Protocols

- Clear dosing (including obese), potential limits
- Protocol for each disease state
- Who administers dose
- Patient not driving vehicle x 24 hrs after dose
- Pedi, Adult code carts available vs other

General Care Floor Protocols

- Same as Emergency Department, ICU, except:
- Restrictions on ordering (Pain, Palliative Care, Specialty Provider, etc)
 - Restrictions on disease state(s) allowed to treat
 - Restrict to floors able to monitor appropriately
 - ? Additional statement for times of critical nurse staffing

Severe Agitation

- Prehospital, Emergency Department, ICU
- Concurrent therapy increases risk of adverse effects
- Optimal dosing regimen not yet known
- Dissociative sedation
- IM lasts longer than IV administration
- Dosing (may repeat 10+ min after):
 - IV (10 mg/mL): 1 to 2 mg/kg x 1, then 0.5 to 1 mg/kg x 1 prn
 - IM (100 mg/mL): 4 to 6 mg/kg x 1, then 2 to 3 mg/kg x 1 prn

Procedural Sedation

- Single dose sedates
 - Additional doses only used to prolong sedation
 - Does not put patient to lower level of sedation
- Provides sedation and pain control
- Data in pediatrics greater than adults
- Monitor for recovery agitation
 - Potentially less problems if guide patient mentally
 - Potentially greater risk in adults than patients

Procedural Sedation

- Dosing, may repeat in 5 to 10 min:
 - IV (10 mg/mL): 1 to 2 mg/kg x 1, then 0.5 to 1 mg/kg x 1 prn
 - IM (100 mg/mL): 4 to 6 mg/kg x 1, then 2 to 5 mg/kg x 1 prn
- Lower dosing to be used if concomitant medications
- Action with IM dosing may take up to 5 minutes longer than with IV dosing

Intubation

- Induction agent (instead of etomidate, etc)
- May be preferred in asthma, hypotensive patients
- IV administration preferred, for more rapid onset
- Dose:
 - IV (10 mg/mL): 1 to 2 mg/kg
 - Shock (septic shock, cardiac shock, etc): 1 mg/kg

Analgesia- Acute Pain

- Substance P, mu, dopamine, serotonin, vs ?
- Should require specialized staff training
- Acute injuries, Sick cell crisis, Pre-op, etc
- Increased dose does not provide increased pain control, does increase adverse effects
- Unknown optimal dose:
 - IV (10 mg/mL): 0.25 to 0.5 mg/kg (max 35 mg), then 0.05 to 0.25 mg/kg/hr x 48-72 hrs
 - Intranasal (100 mg/mL): 0.2 to 1 mg/kg, split dose between nostrils; 0.25 to 0.5 mg/kg in 10-15 min prn. Recommended max total dose 40 mg

Analgesia- Chronic Pain

- Lower doses than other uses = less side effects
- Intermittent vs continuous infusion, oral, subcutaneous (may have subc pump)
- Palliative care cancer patients: refractory pain
 - May be run as continuous infusion (10 mg/mL)
 - Not recommended as titratable order
- Pain Clinics: refractory pain
 - Limited data for noncancer pain treatment
 - Limited data on potential long term adverse effects

Depression

- Action first noted in 1970's
- Primarily for severe depression resistant to all other treatments
- Psychiatrist to be involved
- Consent should be required
- Low dose
 - Subanesthetic dosing
 - Less adverse effects of higher dosing
 - Potentially less long term adverse effects
 - Theorized mechanism of action(s)

Depression

- Intranasal: Esketamine (ketamine derivative): FDA approved
- May take 2-3 weeks for effect
- Requires maintenance dosing
- For some patients, effect may last only 2 weeks

Depression

- Ketamine IV (10 mg/mL):
 - 0.3 mg/kg to 1 mg/kg (0.5 mg often used)
 - Weekly vs 1+ administrations during a week
 - Unclear how long may administer, studied up to 6 weeks in duration
- Esketamine, intranasal (100 mg/mL):
 - Depression, treatment resistant
 - Start: 56 mg twice weekly initially, titrate prn to 84 mg twice weekly x 4 weeks
 - Week 5 prn: Continue therapeutic dose weekly, week 9+ weekly vs decrease to every 2 weeks
 - Major Depressive Disorder (MDD), (+) suicide ideation:
 - Start: 84 mg twice weekly x 4 weeks-> reduce to 56 mg if able
 - Use not studied after 4 weeks, risk vs benefit

But there is a Dark Side to Ketamine

- Illegally obtained vs created in illegal lab
- May be sold as ketamine, or any other psychoactive agent
- May be contaminated with other substances for profit
 - Ground glass to add weight
 - Acetaminophen, caffeine, fentanyl
 - Cornstarch, talcum powder, detergent, baking soda

Some Street Names

- Ketamine, K, Vitamin K, Jet K, Jet
- Special K, Special la Coke, Special a la Coke
- Keller, Kelly's Day, K-hole, K-Hold, K-Ways
- Keta K, Kit Kat, Kate, Ket, Kaddy, Kay
- Cat valium, Cat Tranquilizer, Cat Killer
- Blind Squid, Donkey, Baby Food
- Flatliners, Bump, Tac et Tic
- Liquid E, Liquid G, Honey oil
- 1980 acid, Super acid, Super K, Super C
- Purple, Mauve and Green, Green, Green K
- Speedball (ketamine + ecstasy)

Why is it Abused?

- Poor coping mechanism
- Self-treatment
- To get high
- Pain relief
- Curiosity
- May be felt to be safe
 - Rarely deadly as sole substance of abuse
 - Contaminants increase risk of morbidity/ mortality
 - No monitoring
 - May have baseline disease states

Methods of Abuse

- Chemical properties allow it to be easily abused
 - Water soluble
 - Lipid soluble
- Any route of administration may be used
 - Orally, inhaled, rectally, smoked
 - IM, subcutaneous, IV
- Inhalation most common form of abuse
 - Evaporation down to a powder
 - Easily snorted

Symptoms of Ketamine Abuse

- Dose dependent effects
- Nystagmus, dizziness, aphasia
- Lower doses
 - Mild dissociation
 - Dysphoria
 - Hallucinations
 - Intoxication

Symptoms of Ketamine Abuse

- Higher doses
 - Psychosis, schizophrenic symptoms
 - Complete, or near complete, dissociation
 - Agitation at excessive dosing
 - Higher action at mu receptors

Overdose:

Intentional and Unintentional

- Respiratory: laryngospasm, respiratory depression
- Cardiac: tachycardia, hypertension, arrhythmias
- Neurologic: paranoia, slurred speech, ataxia, muscle rigidity, seizures, CNS depression
- Other: redness, flushing, dry skin, hyperthermia, increased secretions, abdominal pain, nausea, vomiting, aspiration, rhabdomyolysis

Immediate Treatment

- Contact local Poison Control
- No reversal agent
- Rule out other potential causes
- If able, determine co-ingestion(s), time of last ingestion
- Symptomatic treatment
- Monitor for potential need to intubate
- No dialysis: too large volume of distribution
- Full exam: trauma may have happened, main cause of mortality if sole agent abused

Immediate Treatment

- Benzodiazepines: Decrease or treat seizures, agitation, psychosis, hypertension, hyperthermia
- Catapres (clonidine): decrease blood pressure
- Robinul (glycopyrrolate): decrease secretions
- Fluid resuscitation prn
- Minimal stimulation: lights off, away from noise, minimal procedures

After Initial Treatment

- Monitor renal function
- Addiction Services
- Education on illicit ketamine
 - may not be ketamine
 - may have contaminants
- Observe
 - At least 6 hrs, or at least 2 hrs after last symptoms, whichever is longer
 - Longer observation if hepatic/renal dysfunction

Questions?

Nancy Balch, PharmD, BCCCP
nbalch@mgch.harvard.edu

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