# Ketamine: Uses and Abuses

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# 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**

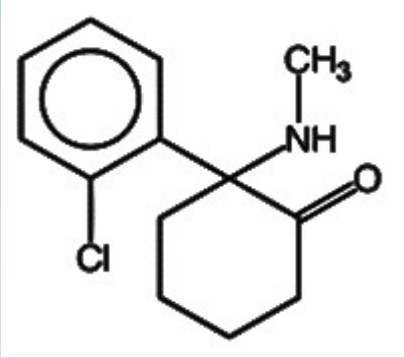
# Ketamine Timeline

**1970: FDA approval**

**Late 1970's: abuse starts**

**1999: controlled substance**

# Mechanism of Action




- Primary: N-methyl-D-asparate (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 ($D_2$)
- 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 ½ 10-15 min, metabolite T ½ 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


NDC 42023-115-10
(Ketamine HCl Inj, USP)
CONCENTRATE
500 mg/5 mL
(100 mg/mL)
For Slow Intravenous or Intramuscular Use
MUST BE DILUTED PRIOR TO IV USE
5 mL Multiple Dose Vial
NDC 67457-181-00 20 mL
Ketamine Hydrochloride
Injection, USP
200 mg/20 mL
(10 mg/mL)
For Intramuscular or Slow Intravenous Use
Rx only
Multi-Dose Vial

# 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, Sickle 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, arrythmias
- 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?*

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