Ketamine:
Uses and Abuses

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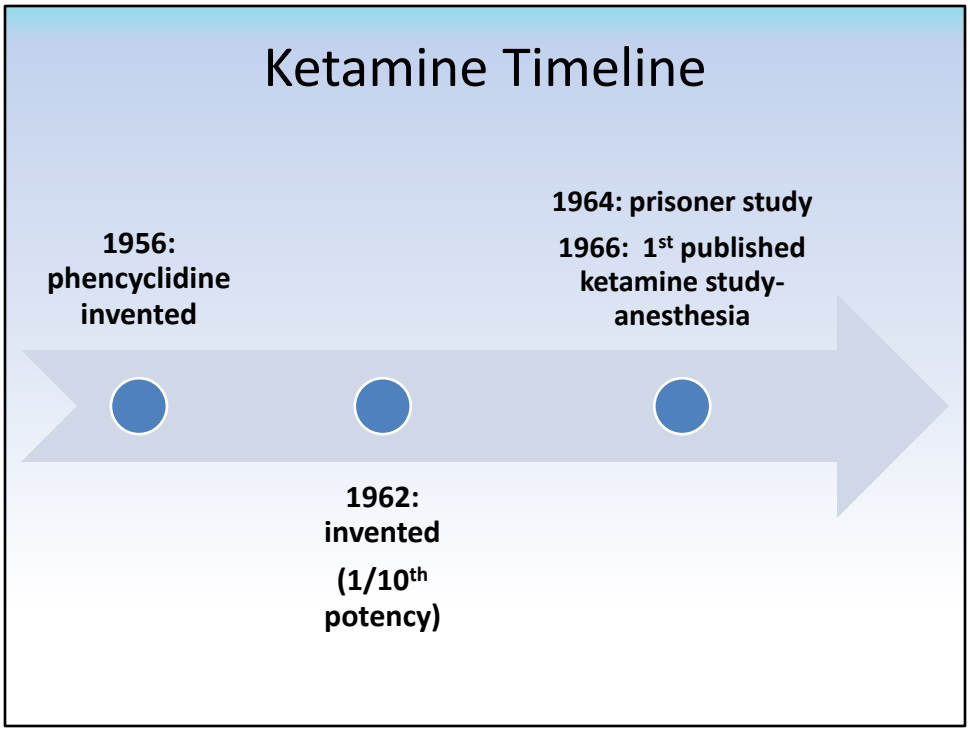
Disclosure Statement

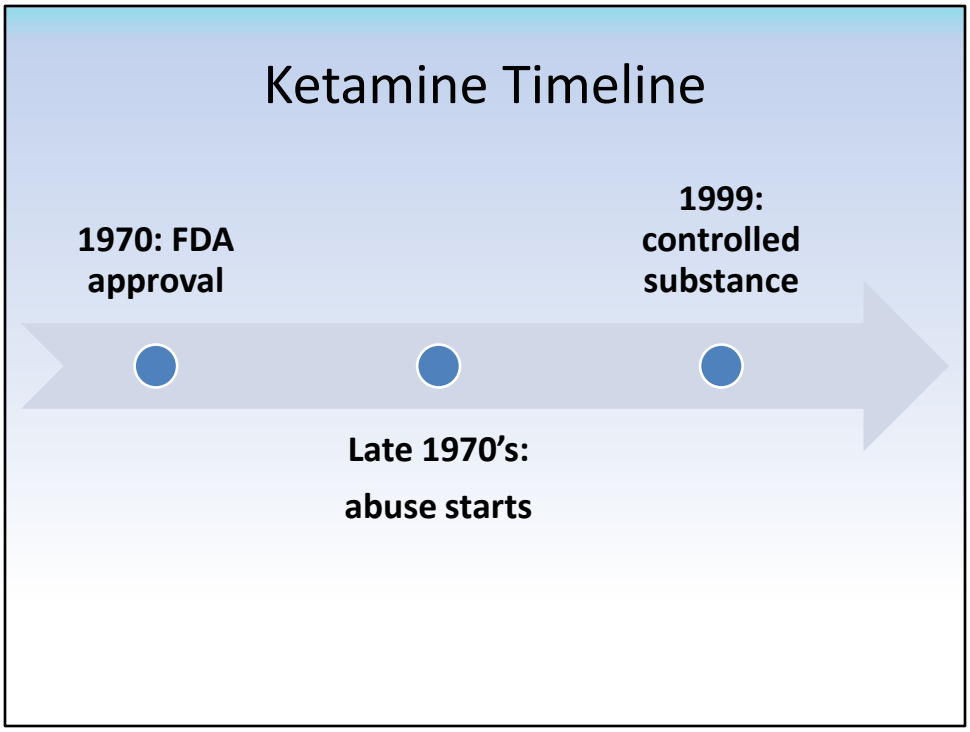
Non-Declaration Statement: I have no relevant relationships with ineligible companies to disclose within the past 24 months. (Note: Ineligible companies are defined as those whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.)

Educational Objectives

- At the conclusion of this session, participants should be able to:
  - 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

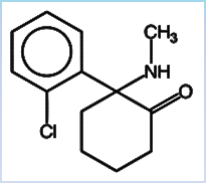


- Phencyclidine = PCP, initially created as a potential treatment
- Legal to perform studies on prisoners in 1964



- Took 29 years after abuse started, for ketamine to become a 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

- Norketamine also provides action, potentially anesthetic action

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

- Unable to determine all actions of ketamine, on the body, with current science
- More information potentially available in the future

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

- Important to note does not cure anything
- Lowest risk of adverse event by administering slowly

Metabolism, Renal Excretion

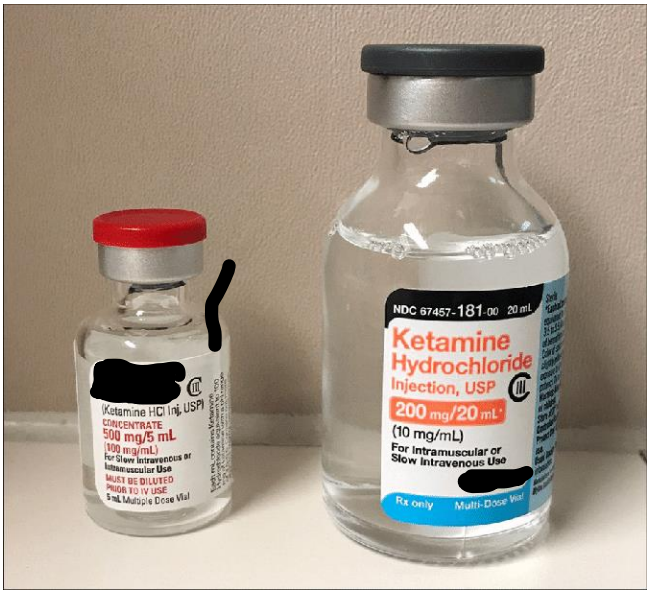
- Hepatically metabolized
  - 4 metabolites, 1 metabolite is active
  - Ketamine T ½ 10-15 min, metabolite T ½ 2.5 hrs
  - Cytochrome P450: 3A4, 2B6, 2C19
- Renally excreted
- Small amount eliminated in bile
- Animal Pharmacokinetics differ from human

- Takes 5 half lives (T 1/2) for 90% of a medication to be removed from the body
- Minimum of 50 minutes for 90% of ketamine to be removed from the body
- Minimum of 12.5 hours for 90% of ketamine's active metabolite to be removed from the body

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

- Highest risk of error is by storing together or near each other
- Deaths have occurred by using the wrong concentration (100 mg/mL instead of 10 mg/mL)
- Deaths have occurred by drawing up multiple doses in a single syringe (instead of a single dose per syringe)



- Of note, font size of the concentration is smaller than the med name

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 emergence reactions
  - Adult and Pediatric
  - Benzo's no longer required for pedi's

- Only transient increase in blood pressure
- During recovery, keep room as quiet as possible, minimal touching of patient
- Only benzo's if needed due to emergence reaction

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

- Benzo's, administered with ketamine, increase risk more than they increase benefit

Protocol Based on Location of Use

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

- Safest recommendations are for different protocols for different uses
- Usually separate clinics
- Pain clinic for ketamine use for pain, etc
- Unless multiple specialists in single clinic (Pain Specialist for pain use, Psychiatry for depression use, etc)

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

- Lack of maximum dosing increases risk of adverse events
- Over-estimation of weight increases risk of adverse events and has caused deaths

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

- Safest to have 1 dose per syringe
- If may need to redose a patient, should have the next dose in a separate syringe
- Active metabolite takes 12 ½ hrs to remove 90% of it from the body
- Some patients will take longer to clear ketamine and the active metabolite

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

- Separate protocols for each use
- Do not put all protocols together
- Increased risk of error, as someone may mix protocol information in error

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

- IM lasts longer than IV
- We have separate orders for each dose (not listed in the instructions that 'may give second dose, etc)
- Separate order prompts to draw up each dose in a different syringe
- Different dosing may be seen in future

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

- Guide patient before administration of ketamine
- Ask them their favorite or happiest place in the world
- Try to have them imagine being there before ketamine administration

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

- IM may take longer, but also lasts longer

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

- Etomidate may decrease blood pressure

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

- Unknown exact mechanism of analgesia, theoretical mechanism, due to current science

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

- Expect to see long term effects with ketamine being used longer
- Some patients have experienced psychosis with long term use

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)

- Does not cure depression

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

- Main use for depression: treatment until medications at therapeutic levels
- Not recommended as long term treatment for depression

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

- Illegal labs usually creating a chemical structure similar to ketamine
- Any psychoactive agent may be added, instead of actual ketamine

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)

- More street names than are listed here
- Street names change to evade anyone knowing is ketamine

Illicit Ketamine

- Illicit ketamine may be transported in everyday containers
- US Customs and Boarder Protection seized 34 lb illicit ketamine, in containers such as the one pictured here (estimated value > $219,000)
- Picture courtesy of US Customs and Boarder Protection

- Imagine how much ketamine is in the bottle!

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

- People may not be taking ketamine and will have no idea what they are taking

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

- Very easily abused, unfortunately

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

- Potentially for reversal agent in future, but none available at this time
- Volume of distribution: all of the organs, cells, etc, a medication distributes to, after administration. If a small volume of distribution, most is in the vasculature.

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

Take Home Points

- 10 mg/mL = IV, 100 mg/mL = IM: errors in concentration have caused deaths
- Ketamine does not cure anything
- Different doses cause different actions
- All potential uses of ketamine may not yet be known

When Does Ketamine Have Different Actions

- When given orally instead of intravenous or intramuscular
- When administered at different doses
- With different rates of administration
- If administered using 10 mg/mL concentration versus 100 mg/mL concentration

Why Should Different Treatment Areas, to Include Different Clinics, Have Different Protocols for Ketamine Use?

- Allows for maximum billing of insurance
- Every use of ketamine legally requires a different protocol
- For the safety of all Providers involved
- For the safety of all patients involved

Which are NOT Potential Symptoms of Ketamine Abuse?

- Psychosis, schizophrenic symptoms
- Agitation at excessive dosing
- Stroke like symptoms
- Complete, or near complete, dissociation

Questions?

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