Ketamine: Old Drug & New Twists

Kimberly Westra CRNA, DNP, MSN
Discussion Outline

- The History of Ketamine
- Pharmacology of Ketamine
- Anesthetic Uses of Ketamine
  - Benefits
  - Risks
  - As anesthetic or sedative
  - Dosing
  - Contraindications
- Uses in clinics for depression/PTSD
  - Patients listing ketamine as a home medication
The history of Ketamine

- Dates to 1926
  - Called CL-581
    - Derived from PCP which was used as an anesthetic drug functioning as a strong NMDA receptor antagonist (NMDAR)
    - PCP was long acting and powerful but had equally powerful hallucinogenic properties and resulted in significant psychosis
- In 1962 an American Scientist by name of Calvin Stevens synthesized the ketamine molecule from CL-581
  - Veterinarian use began in 1963
  - Human testing started in 1964
Starting in the 1970's was used worldwide for multiple purposes:

- Anesthetic
- Used in Vietnam on front lines due to its ability to alleviate pain while supporting hemodynamics and respiratory effort in injured soldiers
- Used in Argentina for mind regression
- Subculture uses for new age spiritualism and mind exploration

Ketamine was found to have a shorter duration of action:

- Less hallucinogenic side effects
- And little to no psychosis

In 1965 the first "recreational use of ketamine was documented described at the time by Professor Edward Domino as a dissociative anesthetic.

It was patented in 1966 by Parke Davis Laboratories and available by prescription in 1969 as "Ketalar".

Patented in 1970 by FDA.
History of Ketamine

- CDS began filing a control substance status in 1981
  - Hearings were delayed because actual abuse was proven insufficient to warrant control
  - It was not classified as a Schedule 3 medication until 1995
If you ever get cold, just stand in a corner for a bit. They're usually around 90 degrees.
Pharmacology of Ketamine

- Designated as dL2 (o-chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride
  - Formulated with a pKa of 7.5 (slightly basic) and greatly affected by pH gradient
  - Available in 10, 50, or 100mg/ml
  - Can be given IM, IV (subcutaneous, oral, nasal, rectal, epidural, intrathecal, inhalation) ** route effects bioavailability and action (PO)
  - Phemerol (benzethonium chloride) is added as a preservative

- Biotransformation
  - N-demethylation (forms metabolite I aka norketamine)
    - Cytochrome P450/hepatic
  - Hydroxylation of cyclohexone ring (forms metabolites III and IV)
  - Conjugation w/ glucuronic acid and dehydration of hydroxylated metabolites to for cyclohexene derivative (forms metabolite II) ** enhanced renal excretion
Pharmacology of Ketamine

- Low protein binding (not albumin dependent)
  - Both lipid and water soluble so very high volume of distribution
    - Readily crosses blood brain barrier
    - Volume of distribution means it goes everywhere blood/tissue/brain
    - When tissues tested lowest areas of high concentrations found were heart tissue, blood and skeletal muscle

- IV administration
  - Alpha phase (initial slope) of 45 min
  - Phase I corresponds to clinical effects we see
  - Anesthetic action terminated by redistribution from CNS to peripheral tissues
  - As well as by hepatic biotransformation to norketamine
    - Norketamine is 1/3-1/5 as potent as ketamine and is an active metabolite
      - This comes into play later when discussing the longer lasting effects we see
      - Norketamine is responsible for continued decreased requirements for anesthesia/pain med
Pharmacology of Ketamine

- Half-life of ketamine is 2.5 hrs (2-4 hrs depending on text)
- 85-95% of ketamine excreted in urine
  - Small amounts in bile, feces
- Ketamine not detectable in standard drug screen
- Because of large volume of distribution as well as norketamine, specialized drug screens can show a positive test for up to 14 days after
  - Single doses do not seem to test positive this long
  - Infusions or repeated doses do
  - This is important for people who get drug tested specifically
    - They may need documentation if an issue arise
  - Narcotics etc do not stay in system long – only marijuana shows such a long +
Neuroscience of Ketamine

That was sodium funny

I slapped my neon that one
Neuroscience of Ketamine

- NMDA receptor Antagonist
  - N-methyl-D-aspartate

- Sterio-selective Noncompetitive antagonist
  - Glutamate and to a weaker degree glycine are full agonists for receptor

- Abbreviated NMDAR

- NMDA allows for transmission of electric signals between brain and spinal cord
  - I.e., it allows the brain and body to talk
  - NMDA must be open for signals to pass
  - An antagonist deactivates this receptor “closing” down the signals

- Ketamine also works weakly on other receptors including mu, sigma, and kappa
  - Acts as anticytokine (pain), inhibits Ach muscarinic and nicotinic receptors (salivation, HR), inhibits L-type Ca+ and Na+ (will see importance of nerve transmission later), adrenergic receptors, serotonin receptors, dopaminergic receptors, neuronal sodium channels (local anesthetic activity)
Pharmacology of Ketamine

- Multiple binding Sites
  - NMDA-receptor
    - Non competitive NMDA receptor antagonist that blocks glutamate
    - Bind to PCP binding site and prevents neuronal Ca^{2+} influx
    - S(+)-isomer showing 4 times greater affinity than R(-)-isomer
    - Norketamine is also an NMDA-R antagonist
  - Opioid Receptors: Weak agonist (\(\mu > \kappa > \delta\))
  - GABA Receptors: Weak agonist, reduce GABA reuptake
  - Sympathomimetic agonist activity at \(\alpha1\)- and \(\beta2\)-adrenoceptors
  - Muscarinic Ach receptors: inhibitor, anticholinergic effect

Neuroscience of Ketamine

IT'LL GET BETTER....

I PROMISE.
NMDA is a glutamate receptor and ion channel protein found in nerve cells

- Glutamate is the most abundant free amino acid in the brain and is involved in multiple transmission processes
  - Glutamate is excitatory
    - Overstimulation of receptors can actually "excite" the cell to death in an excitotoxicity process
    - Highest concentration of glutamate found in synaptic (nerve terminals) vesicles
    - Glutamate is the major excitatory neurotransmitter in our CNS
      - None of this was realized until the 1980s so it is fairly new territory
  - 3 different types of glutamate receptors
    - Activated when glutamate/glycine bind
    - Allows + charged ions (Ca+, Na+, K+) to flow
      - It is nonselective in cation flow

Neuroscience of Ketamine
NMDA receptor

- Gated by ligand binding (strong)
- Flow is voltage dependent (weak)
- So it works both ways but the ligand binding is primary

Ca2+ flow is presumed key

- Recently Ca2+ has been identified as key to synaptic plasticity and memory function
- Cellular learning and memory
- Overactivity of NMDA leads to excessive Ca2+ influx and excitotoxicity
  - This is involved in neurodegenerative disorders and why NMDAR meds are used/researched to treat those disorders (amantadine etc)
Neuroscience of Ketamine

NMDA Receptor Pharmacology

CERC-301 (antagonist on the NR2B variant)

Rapastinel / NRX-1074 (partial agonist)

7-CI-KYNA (full antagonist)

AV-101 (oral prodrug)

NR2B (NR2A-D)

Glutamate binding site

Glycine binding site

K⁺

Cellular side

Cytoplasmic side

Channel blocking antagonists
Ketamine, PCP, d-methadone, memantine

N⁺

Ca²⁺

Source: VistaGen, BioNap
Synaptic plasticity

- A process (both presynaptic and post synaptic) that results in synaptic strength (or weakness) via changes and mechanisms that contribute to the expression. It is thought to contribute to learning and memory
  - When they strengthen it results in an increase in their activity
  - When they weaken a decrease
- Found in both excitatory and inhibitory synapses and dependent upon that Ca2+ release
- Without getting into too much neuronal explanation
  - Long term potentiation (LTP) is dependent on Ca2+ as well as genetic involvement. By changing the structure of dendritic spines, the spines are lengthened and the change they make synaptic contacts with axonal terminals is increased which increased LTP
  - Recall dendrites and axons within transmission of spinal nerves and brain. They send and receive signals for communication
- Stimulation of Ca2+ release essential but recall excitotoxicity (a negative feedback system is in place within our bodies)
  - “too much of a good thing”
Ketamine and dendrites
Synaptic Plasticity

- Synaptic plasticity
  - Pathologic pain
    - Increased pain perception due to sensitization
      - Allodynia
      - Hypersenstitivity
    - Ketamine binds to NMDA receptor inhibiting this excitotoxicity
      - Not only does it antagonize (block)
      - It modifies
      - Thereby not only stopping the perception of current stimuli
        - By inhibition of nociceptive pain pathways
      - But prevents the formation of pathological pain due to overstimulation
Synaptic Plasticity

Plasticity of the brain

- **Plasticity**: Refers to the brain's ability to reorganise neural pathways throughout the lifespan as a result of experience.
- Put simply: The brain's ability to change with learning.
- There is a change in the internal structure of neurons, notably the synapses &
- increase in the number of synapses
Ketamine Anesthetic Actions

- Termed a dissociative anesthetic
  - Selectively interrupts brain pathways
  - Produces a somaesthetic sensory blockade
  - Possible selective depression of thalamocortical system
  - With no obtunding of RAS or limbic system
  - Recall previous where we discussed the “brain and body” interaction
  - Often in movies/dramatic reenactments a ketamine dose produces an awake individual who could be physically harmed but not react as if their brain couldn’t receive the signal from their body**
Ketamine action

Lavand'homme et al. Anesthesiology 2005; 103: 813-820
Ketamine has a WIDE safety margin

- Several unintentional documented overdoses have been followed by delayed but complete recovery
- Studied in >12k procedures with > 10k patients in >105 separate studies as a SOLE (high dose) agent and all in all was rated as 90-93% excellent, 4-6% fair and 3-4% poor
- Toxicity only established in animals (rats) receiving >100x an adult human high dose
  - Pregnancy cat C –
  - Studies in reproducing animals showed no different outcomes as compared to placebo
- A review of over 70k anesthetics shows only 1 death attributable to ketamine and that was in a severely compromised patient
Ketamine in Anesthesia/Sedation

- Wide range of uses
  - Anesthesia, analgesia
  - General use is to induce/maintain anesthesia
  - But do not discount its synergist ability in sedation
    - As an adjunct
      - Decreases pain
      - Decreases opioid requirements in variety of settings
      - Prevention of opioid tolerance (pronocioceptive system)
      - Recall prev. discussion as it aids with hyperalgesia
- Nocioception and inflammatory signals begin with stimulation (incision, procedure start)
  - Ketamine is short acting so multiple smaller doses or infusion beneficial
  - Some studies show in anesthetic cases a preincisional dose followed by infusion can provide pain benefits up to 6 months post op
  - **ERAS protocols **Narcotic Sparing Anesthesia
  - Neuraxial anesthesia being used as well
What patients are we seeing clinically more and more

- Obese
- OSA
- Addicts
- Recovering addicts
- Pain disorders
- High med tolerance
- Fibromyalgia
- Respiratory compromise
- **for anesthesia ** shock, asthmatic, severe resp compromise

Ketamine in these patients presents a unique benefit that no other sedative/anesthetic offers

- The ability to maintain respiratory effort (as well as bronchodilation)
- The ability to make opioid work better but not add or cause increased tolerance or need
- The ability to continue such benefits for days/weeks/months after given
Knowing what receptors and actions ketamine has we can deduce patients who shouldn’t receive (benefit does not exceed risk)

- Severe CAD (primarily CHF AND beta blocked)
- Tachyarrythmia
- Malignant hypertension
  - Both increased HR and BP strongly dose dependent and it is not uncommon to see a lower BP in some cases
- Severe pulmonary hypertension
- Severe liver disease (primary route of metabolism)
- Allergy (rare)

Must watch with MAOI’s **methylene blue
Anesthesia vs sedation

**Anesthesia**
- Due to short action multiple doses required
- Because nociceptive changes/cascades begin with incision
  - Recommendation 0.5mg/kg prior to incision with infusion of 0.25mg/kg/hr running thru case
  - As with all medications titrate to effect/need slow infusion for increases in bp/hr that aren’t within acceptable parameters

**Sedation**
- Titrate to effect
- Easiest method is to dilute to 10mg/ml and give 10mg at a time to effect
- You can expect normal side effects like increased salivation
  - These are preventable with small doses of glycopyrrolate if HR is amenable
- Synergistic use with fent/versed
- Ketamine is an anesthetic – if a patient is unable to open eyes and answer you- you have crossed the line between conscious sedation and anesthesia and are therefore out of practice parameters
Although ketamine is one of our oldest medications, its use fell off in the last decade or two so there is a renewed need to educate.

- Different does not = bad
  - Ketamine will present differently post op
    - Can expect nystagmus
    - Staring
    - Giggling
    - Confusion at times
    - Disorientation
    - Nausea
    - Diplopia
    - Tonic/clonic movements
    - Headache
  - When combined with benzos/barbs/narcotics will see increased sedation
  - When given with benzo – the dissociation side effects are minimalized

Most often a patient just needs a quiet setting with verbal reassurance.

- Verbal reorientation
- Recognition that the symptomology will pass quickly
- Most effects only last 15-20 min after last dose and all symptoms are dose dependent

Post op education needed
Ketamine has ZERO physical addictive potential

- Let me reiterate that..... ZERO
  - Abuse of ketamine is done by choice – there is no withdrawal or craving

Regular long term use can lead to tolerance

- Keep in mind that those that use ketamine on the streets are averaging 3gm of ketamine a day which is 100 x the doses we are using to start with
- One small study tested ketamine found in raves – 100% were adulterated with other substances (most oft LSD and cocaine – some had Epsom salt) – and some samples contained ZERO ketamine.

The dangers of recreational ketamine related to the environment not really the medication itself

- Unsteady gait (falls)
- Balance difficulty
- Impaired vision
- Analgesia resulting in burns or nerve compression from laying on an arm

Most oft ketamine is not abused alone but with other medications which leads to overt sedation and the risks that arise from it

- Long term abuse can lead to urinary disorders and poss brain lesions (these are very questionable however) – but none of these effects are seen with normal doses/infusions of ketamine.
- Understand that abuse almost ALWAYS has a dual diagnosis (depression, bipolar, ptsd) that results in self medication (abuse)
Over the past 30 years practitioners noticed that other things occurred after ketamine administrations:

- Alleviation of depression
- Alleviation of anxiety
- Alleviation of symptoms from PTSD
- OCD, Post partum depression, eating disorders, severe anxiety, alcoholism...

In 2017, Ketamine Infusions for these and certain pain disorders was listed as a top 10 medical innovation of the year.

Some have touted this as the most important finding in psychiatric medicine in over 50 years.
Keep in mind that ketamine has been branded for a long time

- It is an off label use (but off label use is common, permitted, and prevalent in medicine)
- All studies thus far have been done by practitioners as the FDA refuses to fund
- Currently over 302 studies are ongoing in the US
- NIH currently has a study going
- In Pikesville an ongoing study has been occurring for 4 years and state FDA approval is near

- We have established the safety profile for ketamine
- We have established how it works neurologically
- We have established that it aids in synaptic plasticity and how the brain/body communicated
All studies show same results

- Approximately a 75% efficacy for treating the disorders listed
- A surprising 30% complete remission rate
  - These are individuals who have tried multiple medications, therapy, in some cases ECT and magnet therapies but their disease process is refractory to it all
- Effects are generally seen immediately or within 24 hours of 1st dose
- Specific protocols are followed
- Treatment has been available in bigger cities for 5 or more years but local centers are just now becoming available
- Immediate remediation of suicidal ideations (being used in ER’s for this)
- Certain pain disorders show promising results
  - Neurologically mediated pain
  - Trigeminal neuralgia, lymes, migraines, gastroparesis, phantom limb pain
Ketamine Mechanism of Action

Regular Mood
Synaptic stability

Depression
Synaptic destabilization

Rapid Antidepressant
Synaptic formation

Stress
decreased BDNF

Coping, exercise,
Enrichment; Synaptic
formation

Ketamine
Glutamate Burst

Depression Relapse
Failure of Synaptic
maintenance

BDNF

Depression & Anxiety: R. Duman, 2014
These disorders are debilitating

- In 2012 the WHO projected that depression would affect 121 million people by 2020 worldwide.

- Serious depressive states have a lifetime prevalence of 15-20% and are projected by 2020 to be the 2nd leading cause of disability worldwide.

- The global economic loss due to depression/anxiety/ptsd/bipolar disorder and the sales of meds to treat these is 50 billion dollars each year.

- Every year 14.8 million Americans suffer from major depression.
  - Of those who seek treatment 30-40% will not get better with standard treatment modalities.
    - This places them at much higher risk of alcohol and drug abuse as well as suicide.

- These disorders consistently carry a higher co-morbidity rate and on average someone with a diagnosis will die 20 years younger than their counterparts.
“it is acute misery. Living with my depression feels like pain. I was aware I had a problem by the time I was in 7th grade. I had a very traumatic childhood and spent it in an intense state of fear. By the time I reached adolescence I had a pretty good idea that I wasn’t able to do things like other kids were able to do. It felt like it was literally a character that I was talking to on and off and hanging in the closet at the end of the day. The character looked happy, successful and put together and confident, but it was being powered by a depressive sufferer who was wracked with anxiety. I tried every known depressive therapy, everything that doctors commonly prescribe: SSRIs, SNRIs, tricyclics, benzodiazepines. A lot of my energy in life has been spent trying to find a way to get relief from this pain. On my worst days, I lost the energy. I didn’t have the ability or the strength to inhabit that character anymore...I just didn’t see anyway around it. The way I thought about it in my own mind is – it is the reasonable humane thing to do – end my life. There is only so much untreatable suffering that one person can be expected to endure in their lifetime. The day I received by infusions my symptoms were raging. It was relatively bad – the anxiety, the anhedonia (inability to experience pleasure), the insomnia. They turned on the drip and I was in a dreamlike state, like a spectator watching my thoughts unfold in front of me. Within 15-20 minutes I was aware something was different. They started to ask me questions to monitor my mood and I had trouble pinpointing my symptoms so I could describe them. Within a couple of hours of the infusion, I had a clear awareness that something was missing. It didn’t strike me as a wave of massive relief. It didn’t feel like superpowers. I didn’t have euphoria. It was a gradual realization over a few hours that something was missing. What was missing was horrible. The biggest changes for me occurred within 24 hours after my first infusion. If you suffer from lifelong depression as I have, it is all you ever know, it becomes a part of your Identity. You feel the world is all about pain. When I got relief from my first infusion, it was like being emancipated.”
Dennis Hartman founder of Ketamine Advocacy Network
Ketamine has profound use ability both as anesthetic, sedative and treatment modality.

Do not fear using a medication with a known/long safety profile.

Educate yourself and others on what it can do and what to expect if used.

Remember different doesn’t equate to bad.

Ketamine used as anesthetic and sedative has advantages that reaches far beyond immediate use (depression, anxiety, PTSD etc).

Like any medication it has benefits and risks specific to that medication.

Do not be surprised to see ketamine listed as a medication – it is being used outpatient.
References

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