

Pharmacology of IV Ketamine for Pain

Taylor Butler, PharmD, BCOP, BCPS
Clinical Pharmacy Specialist – Cancer Pain
Nashville, TN
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	Yes, as follows:	
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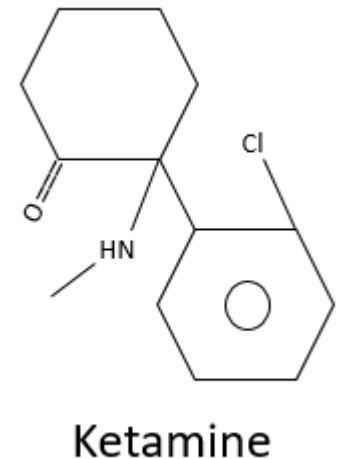
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Learning Objectives

- Discuss the pharmacokinetics of intravenous ketamine
- Recognize pharmacodynamic principles of intravenous ketamine

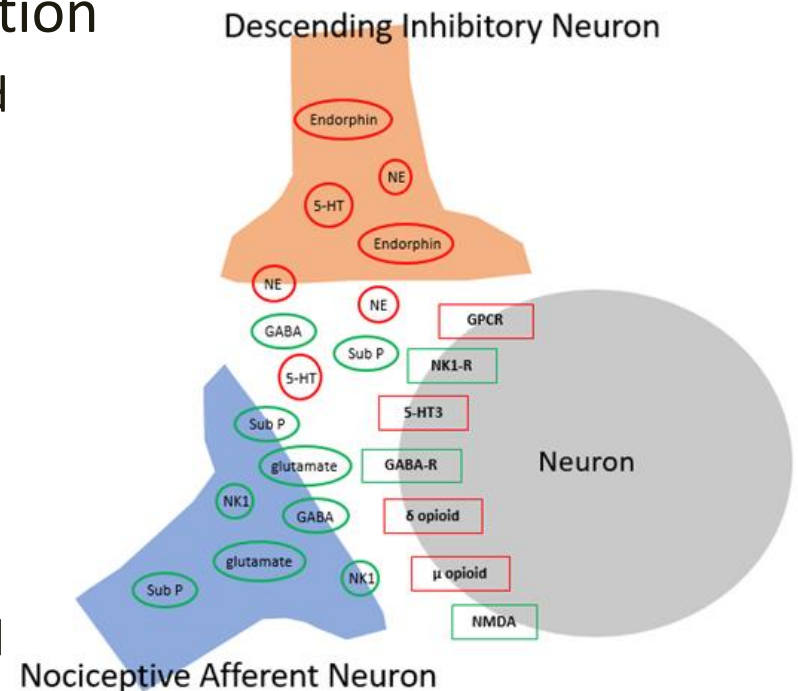
Ketamine

- Mechanism of action: blocks the N-methyl-D-aspartate receptor
- Class: NMDA antagonist
- Ketamine refers to the racemic mixture of (R,S)-ketamine
 - FDA approved esketamine is NOT interchangeable
 - This talk will specifically focus on adults and IV ketamine



MECHANISM MANIA!!!

- NMDA activation leads to the activation of long-term potentiation
 - May lead to persistent and elevated response to painful stimuli
 - Both peripherally and centrally
 - Chronic activation may alter neuroplasticity and lead to neurodegeneration in the central nervous system
 - In turn, this activation may also be critical to certain CNS functions and may lead to side effects to NMDA antagonists



Ketamine Pharmacokinetics

- Absorption
 - Rapidly achieves peak concentration ~ 1 minute
 - Oral, intramuscular, intranasal, intrathecal, epidural
- Distribution
 - Rapidly distributed to highly perfused tissues (including CNS)
 - Large volume of distribution

Ketamine PK (cont.)

■ Metabolism

- Active metabolite, norketamine, via CYP3A4 and CYP2B6
 - IV skips first pass metabolism
 - Use caution with liver dysfunction and CYP3A4 and CYP2B6 inhibitors
- Norketamine further metabolized to active and inactive metabolites

■ Elimination

- >80% eliminated thru urine as active and inactive metabolites
 - No dose adjustments with kidney dysfunction
- Half-life ~ 2-4 hours (Metabolite half-life extended)
- Amount of time ketamine is detectable prolongs with repeated infusions

Ketamine Pharmacodynamics

■ Clinical therapeutic effects

— Anesthetic

- Dissociative – not unconscious but a trance that patients don't remember

— Analgesic

- Wide variety of pain syndromes

— Antidepressant

- Active placebo-controlled studies for treatment-resistant depression

— Anti-inflammatory

- Reduce proinflammatory cytokines
- Primarily studied perioperatively

Indication	Common Dosing
Anesthetic	1-2 mg/kg IV bolus
Analgesic	0.15 mg/kg IV bolus (varies)
Antidepressant	0.5 mg/kg as IV infusion over 40 min
Anti-inflammatory	0.15-0.25 mg/kg IV bolus

Source: Zanos P, Moaddel R, Morris PJ, et al. Ketamine and Ketamine Metabolite Pharmacology: Insights into Therapeutic Mechanisms. *Pharmacol Rev* 2018; 70(3): 621-660.

Ketamine Pharmacodynamics

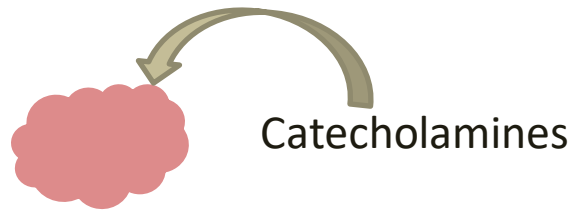
- CNS side effects
 - Psychoactive
 - Dissociative - distortions in stimuli and/or perception of self/time
 - Psychotomimetic - disorganized thinking, hallucinations, nightmares, withdrawal, motor retardation
 - Within 10 minutes of administration and up to 40 minutes after
 - Memory and cognitive impairment
 - Decreased mental sharpness, concentration, and memory recall
 - Abuse
 - Olney's lesions
 - Vestibular disturbances
 - Nausea
 - Dizziness

Source: Zanos P, Moaddel R, Morris PJ, et al. Ketamine and Ketamine Metabolite Pharmacology: Insights into Therapeutic Mechanisms. *Pharmacol Rev* 2018; 70(3): 621-660.

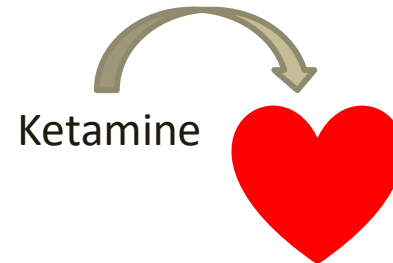
Ketamine Pharmacodynamics

- Peripheral side effects
 - Ocular effects
 - Nystagmus, diplopia, dilation
 - Urologic effects
 - Hypothesized to be impact on interstitial cells in the bladder
 - Dysuria, increased frequency, urgency, incontinence, pain, hematuria
 - Cardiovascular
 - Tachycardia, hypertension, palpitations

MECHANISM MANIA!!!



MOA: Sympathomimetic effects on the autonomic nervous system



MOA: Negative inotropic effect (and peripheral vasodilation)

↑ CO

↑ HR

↑ BP

Summary of Ordering Considerations

- Dosing widely varies
- Caution with organ dysfunction
 - No change in dosing recommendations
- Caution with CYP2B6 and CYP3A4 drug interactions
 - No dosing changes recommended
- Monitoring – see next presentations!

Summary of Patient Counseling

- Indication
 - Benefit
 - Mechanism
 - Evidence?
- Expectations
 - Length of benefit
 - Side effects
 - Reversible
 - Cost
- CNS side effects
 - Hallucinations (stimuli/time)
- Negative “trip”
- Dizziness
- Decreased mental sharpness
- Peripheral side effects
 - Blood pressure – consider increased monitoring at home
 - Report altered heart rate
 - Blood in your urine or discomfort or increased urgency when urinating
 - Eyes moving back and forth

Summary

- Ketamine has unique pharmacokinetics, including rapid absorption, extensive distribution and hepatic metabolism, and primarily renal elimination
- Ketamine pharmacodynamics appear to be dose-dependent and may be used for a variety of different indications

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