PainWeek

Ketamine: It's Not Just For Horses

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Disclosures

- Nothing to disclose

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Objectives

- Describe the pharmacokinetic mechanism of action for ketamine
- Assess a patient's pain history and previous treatments to determine appropriateness for ketamine initiation
- Identify and treat ketamine related side effects

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Case

CN, 46yo female with metastatic cervical cancer, sacral plexus involvement, severe pain that keeps her from getting out of bed and interacting with her husband and young children.

Current medications:

Methadone 30 mg TID

Morphine PCA 15 mg/hr and 15 mg Q15 min prn

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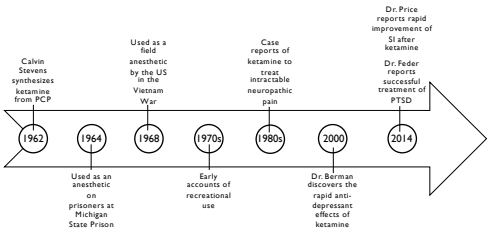

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Mechanism of Action

- Ketamine is an NMDA Antagonist
  - –Blocks NMDA receptors on neurons
  - –Result:
    - •Ketamine at high doses: state of dissociative anesthesia
    - •Ketamine at low doses: sensory loss, analgesia, amnesia
  - –Weak mu-opioid receptor agonist = potentiates the effect of opioids
  - –Potentiates the effects of GABA

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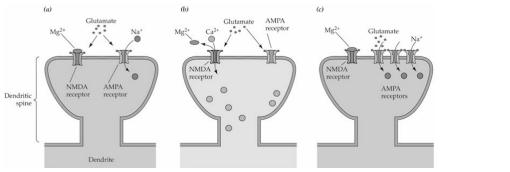
NMDA Receptor-Channel Complex



Kemp, J. A., and McKernan, R. M. (2002). NMDA receptor pathways as drug targets. Nature Neuroscience, 5(Suppl.): 1039–1042.

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Neuropathic Pain

- World Health Organization (WHO):
  - –"Agents, which block the activity of NMDA receptors, are helpful to treat poorly responsive pain syndromes, especially, neuropathic pain."
  - –"The addition of ketamine to opioid treatment has been shown to be beneficial in chronic pain."

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Pharmacokinetics

- Onset of action
  - –IV = 30 seconds
  - –IM = 5 minutes
  - –SC = 15-30 minutes
  - –PO = 30 minutes
- Duration of action
  - –IV = 5-10 minutes
  - –IM = 12 minutes-2 hours
  - –PO = 4-6 hours
- Half Life
  - IV/SC = 2-3 hours
  - IM = 1-3 hours
  - PO = 3 hours
  - Norketamine = 12 hours

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Pharmacokinetics

- Bioavailability
  - ~25% SL
  - ~20% PO
  - 93% IM
  - 100% IV
  - 100% SQ
- Excretion
  - Urine

- Metabolism
  - 80% first pass
  - Cytochrome P450 mediated N-demethylation to norketamine by CYP3A & CYP2B6
- Metabolite
  - Norketamine
    - 1/3 more potent as an anesthetic
    - Equipotent for analgesia
    - Long half-life (12 hours)

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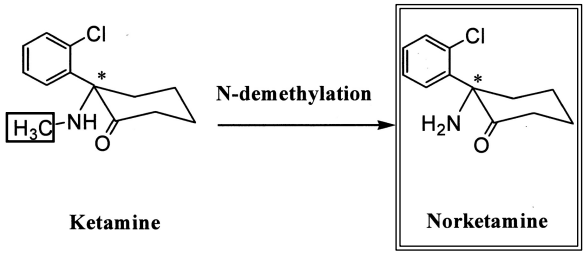

Ketamine

Norketamine

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Routes of Administration

- Intravenous
- Intramuscular
- Subcutaneous
- Oral
- Rectal
- Intranasal

- Transdermal
- Epidural
- Intrathecal
- Intra-articular
- Topical

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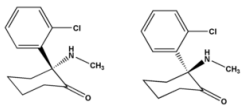
Formulations

- Racemic
  - –R(-) and S(+)
- S(+):
  - –3-4 times more potent as an analgesic
  - –Has a shorter duration of action
  - –More rapid clearance
  - –Fewer neuropsychiatric effects



(S)-Ketamine

(R)-Ketamine

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Comparison of S+ and R- Enantiomers

Comparison of the effects of *S*-(+)- and *R*-(−)-ketamine (ratios)

Ketamine	*S*(+)	*R*(−)
NMDA affinity	4	1
Plasma concentration	1	1
Cerebral concentration	1	1
Elimination rate	1	0.8–1
Anaesthetic potency	3	1
Side-effects	Similar to racemic mixture	

Pal A., Heining M. *Continuing Education in Anaesthesia Critical Care & Pain*, Volume 7, Issue 2, 1 April 2007, Pages 59–63

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Mucositis or Oral Tumors

- Following chemotherapy and radiotherapy
- Oral tumors or lesions

- Oral rinse with:
  - –Ketamine 4mg/mL in artificial saliva or flavored drink

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Opioid Induced Neurotoxicity

- Symptoms of neurotoxicity
  - –Allodynia
  - –Delirium
  - –Hallucinations
  - –Hyperalgesia
  - –Myoclonus
  - –Seizure

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Hyperalgesia

- Chronic use of opioids = chronic hyperstimulation
- Pain signaling pathways are altered

- Ketamine
  - –Delays desensitization
  - –Improves the re-sensitization of the mu receptor
  - –Prevents opioid tolerance and hyperalgesia

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Ketamine for Depression

- Unipolar
- Bipolar (not in mania)
- Suicidality
- Anxiety
- PTSD

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Side Effects

- Increased BP, intraocular pressure
- Psychomimetic
- Delirium
- Vivid dreams
- Hallucinations
- Dizziness

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Case

CN, 46yo female with metastatic cervical cancer, sacral plexus involvement, severe pain that keeps her from getting out of bed and interacting with her husband and young children.

Current medications:

Methadone 30 mg TID

Morphine PCA 15 mg/hr and 15 mg Q15 min prn

Using 3-4 prn doses/hr

Total ~ 1440 mg IV morphine/day ~ 4,320 mg PO morphine

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What else do you need to know about the patient?

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Dosing Examples

Route	Initial Dose	Max Initial Dose	Titration
PO/SL	2.5-5 mg Q6-8h	10-25 mg Q6-8h	50-100% of initial dose Q24h
SQ	2.5-5 mg Q6-8h	10-25 mg Q6-8h	Assess pain 30-45 min after dose completion. If no significant decrease in pain, increase dose by 25%-35%
IV	2.5-10 mg Q6-8h	15-30 mg Q6h	Assess pain 15 min after dose completion. If no significant decrease in pain, increase dose by 25%-35%
SQCI	0.3-0.6 mg/hr	1.25-4 mg/hr	Increase by 50-100 mg/day
IVCI	0.3-1.5 mg/hr	100 mg/24hr	Increase by 50-100 mg/day

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Dosing

- Most patients achieve pain relief at oral doses <200 mg/day
  - (divided doses)
- Maximum recommended daily dose range is 500-700 mg/day regardless of route
- Administer IV intermittent doses over ≥30 min
- IV continuous infusion also available

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- Wide therapeutic range
  - Makes overdose difficult
  - LD50 in animals is ~ 100 times the average IV dose for humans
    - Average IV dose in humans is 5-50 mg

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Side Effect Management

- Pre-medication with lorazepam or haloperidol
- Start with low doses
- Side effects are less frequent with oral administration

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Treatment Duration

- Withdraw ketamine after:
  - –Analgesia has been obtained
  - –Opioid dose have been weaned to an acceptable level
- The benefit from a short course can last several days to weeks
  - –Treatment can be repeated if necessary

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Withdrawal

- Ketamine withdrawal is not expected in short-term use
  - –If use >10 days, taper the dose over minimum 24-48 hours
  - –Maximum de-escalation with chronic use:
    - •15-20 mg (5 mg per dose) every 3 days
  - –Whole body hyperalgesia and allodynia have occurred with abrupt discontinuation of courses ≥3 weeks
- Development of tolerance is possible

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CN

- What if she had mucositis?

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Ketamine for Depression

- Currently off-label
- Inexpensive
  - –Average cost: $10 per 500 mg for ketamine solution
- Rapid onset of action
  - –2-24 hours
  - –0.2-0.5 mg/kg IV infusion over 40 minutes
  - –Duration of effect 3-17 days

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History of Organ Dysfunction

- Renal insufficiency
  - –Norketamine can accumulate
  - –Minimally removed during dialysis (lipophilic)
  - –Dosage adjustment not recommended
- Hepatic insufficiency
  - –Potential for prolonged duration of action
  - –Consider dose reduction and/or extended dosing interval
  - –Transient increase in LFTs

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Drug Interactions

- No major drug interactions
- Use caution if administering with other CNS depressants

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Monitoring of Ketamine Administration

- BP >160/95
  - Assess for anxiety
  - May need to treat with appropriate antihypertensive agents and decrease ketamine until medications take effect and BP returns to <160/95
- HR >110, assess for anxiety and treat with benzodiazepine
- RR <8, decrease opioids, add oxygen
- SaO2 <92%, add oxygen
- Pain
- Anxiety
- Dysphoria

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Relative Contraindications

- Severe cardiovascular disease
- Uncontrolled hypertension
- Recent MI or CVA
- Thyroid conditions
- Porphyria
- Elevated intracranial pressure
- Elevated intraocular pressure

Absolute contraindication

- History of psychosis (primarily schizophrenia)

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Conclusion

- When to consider ketamine for pain:
  - Opioid dose titrated to an endpoint defined by intolerable side effects
  - When other therapies have failed or not been efficacious
  - Escalating pain, hyperalgesia, allodynia, and relative nonresponsiveness to opioids
- When to consider ketamine for depression
  - Depression especially with suicidality and/or limited prognosis (4-6 weeks)
  - Depression that is refractory to other therapies

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Protocol Development

- Multidisciplinary effort
  - Pharmacy
  - Pain team
  - Palliative team
  - Emergency room?
- Review state/institutional policies for administration
  - Some states do not allow nurse administration

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Examples: Oral Protocol

- Initial PO dose: 0.5-1.5 mg/kg/day divided in 3-4 equal doses
  - Maximum initial dose = 50 mg q8h
- Decrease opioids by 25%-50% if somnolence or signs of opioid-induced neurotoxicity are present
- Increase ketamine by 50% per dose every 48 hours until effective
- Typical effective dose: 1.5-3 mg/kg/day

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Examples: IV or SQ Infusion

1. Start infusion at 5-10 mg/hr (~0.075-0.15 mg/kg) IV or SQ
2. Decrease long acting pain medications by 25%-50%
3. Decrease short acting pain medications by 0%-50%
4. Increase ketamine by 5-10 mg/hr every 1-4 hours for first 2 days
   - Maximum 35-50 mg/hour (~0.5 mg/kg)
5. As pain improves decrease short and long acting medications further
6. Continue infusion for 24-48 hours after reaching max dose
7. Taper off by 5mg/hr Q1-2h

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Take Away

- Effective for pain management at lower doses than required for anesthesia
- Can use lower doses via oral route
- Mix with cranberry juice, lemonade, or soda to mask taste
- Helpful in cases of suspected neurotoxicity
- Potential to decrease opioid utilization
- Effective for topical pain relief

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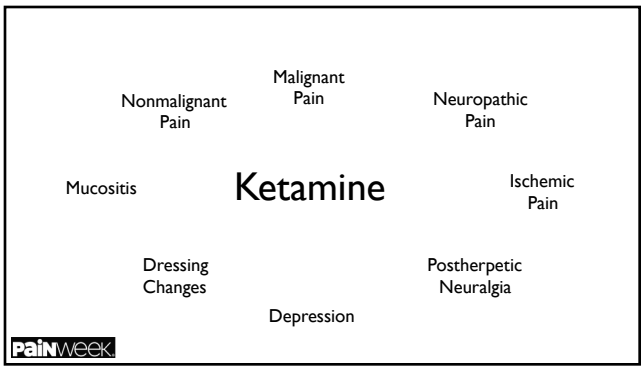

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