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Ketamine for Migraine Headaches

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Disclosure

- Nothing to disclose

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Learning Objectives

- Review the diagnostic criteria for migraine
- Describe the clinical presentation of migraine
- Explain ketamine pharmacology
- Discuss the clinical application of ketamine for migraine

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Migraine

- Affects 37 million Americans
- Estimated 13% of the US population
- Occurs most often in women (18% of women compared to 6% of men)
- Ages 35-55

http://www.ninds.nih.gov/doctors/OP129A_Clinician_fa.pdf

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Migraine Cost

- 15.5 billion dollars…
- Each year in lost revenue due to loss of work hours and use of medical facilities
- 91% miss work or can't function normally during attack
- The WHO ranks migraine as the 19th most common reason for disability
- 36 million days of bed rest due to migraine

http://www.ninds.nih.gov/doctors/OP129A_Clinician_fa.pdf

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Clinical Presentation of Migraine

- Paroxysmal episodes of headache
- Associated symptoms
  - Nausea
  - Vomiting
  - Visual changes
  - Photophobia
  - Phonophobia
- Duration: 4-72 hours
- May be precipitated by a trigger

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Clinical Presentation of Migraine (cont'd)

Phases of migraine:

1. Prodrome
2. Aura
3. Headache
4. Postdrome

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Classic Picture of Migraine

- Unilateral
- Location: fronto-temporal
- Quality: throbbing
- Intensity: moderate to severe
- Aggravating factors: routine physical activity
- Can alternate from one side to another
- Patients seek quiet, dark space

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Common Associated Features

- Sensitivity to environmental stimuli
  - Photophobia
  - Phonophobia
  - Smell
  - Motion
- Nausea and vomiting

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Migraine Without Aura Diagnostic Criteria

- At least 5 attacks fulfilling the following criteria:
  - Headache lasts 4-72 hours
  - Headache has at least 2 of the following:
    - Unilateral location
    - Pulsating quality
    - Moderate to severe pain
    - Aggravation with activity

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Cephalalgia 2018, vol. 38 (2-211)

Migraine Without Aura Diagnostic Criteria (cont'd)

- During headache:
  - Has nausea/vomiting OR photophobia/phonophobia
- Not attributed to any other disorder

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Migraine With Aura

- Can precede headache by 60 minutes, or occur at headache onset
- Typically characterized by visual, sensory, and/or speech symptoms
  - Visual scotoma
  - Sensory paresthesia
  - March of symptoms

Like migraine, but with fully reversible neurologic symptoms that develop over 5-20 minutes and resolve within 60 minutes

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Other Migraines

- Status migrainosus
  - A migraine attack that lasts over 72 hours
  - Intense pain and disability
  - Often refractory to usual outpatient treatments
- Chronic migraine
  - 15 or more headaches per month
  - Duration of least 3 months
  - Absence of medication overuse headache
  - Can transform from episodic migraine

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Common Migraine Comorbidities

- Sleep disturbance
- Depression
- Anxiety
- Panic disorder
- Bipolar disorder
- Epilepsy
- Obsessive-compulsive behavior
- Fibromyalgia
- Cognitive impairment

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US Headache Consortium Recommended Treatment of Migraine

- Specific migraine treatment
  - Triptans
  - Ergot and its derivatives
- Nonspecific pharmacological treatment
  - Antiemetics
  - NSAIDS and nonnarcotic analgesics
  - Narcotics: opiate analgesics
- Miscellaneous medications
  - Steroids
  - Intranasal lidocaine
  - Valproic acid IV
- Nonpharmacological treatment
  - Biofeedback
  - Visual imagery
  - Icepack
  - Relaxation therapy
  - Yoga
  - Medication

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Ketamine

- Introduced commercially in 1970 as a “rapidly acting, non barbiturate general anesthetic”
- IV anesthetic that causes sedation, analgesia, bronchodilation, and sympathetic nervous stimulation
- Noncompetitive N-methyl d-aspartate (NMDA) receptor antagonist
- Blocks the release of excitatory neurotransmitter glutamate and provides anesthesia, amnesia, and analgesia
- Also interacts with opioid receptors

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Ketamine (cont'd)

- Can decrease central sensitization and the "wind-up" phenomenon
- Multiple sites of action:
  - NMDA receptor antagonist
  - Serotonin and norepinephrine reuptake inhibition
  - Lipophilic, crosses blood brain barrier
- Onset of action: 1-5min IV, 15-30 SC, 30 min PO

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Ketamine (cont'd)

- Rapid-acting general anesthetic, often used in sub-anesthetic doses for pain
- Profound analgesia
- Normal pharyngeal-laryngeal reflexes
- Normal or slightly enhanced skeletal muscle tone
- Cardiovascular stimulation
- Respiratory stimulation
- Patent airway is maintained

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Ketamine and the Cardiovascular System

- Tachycardia
- Rise in cardiac output
- Fall in total peripheral resistance
- Little or no effect upon vasoconstriction responses of epinephrine
- Pressor response to ketamine is blocked by B-blockade
- Recommend cardiac evaluation prior to treatment to rule out potential contraindications

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Psychomimetic Side Effects

- NMDA receptors are important for:
  - Sensory perception
  - Proprioception
  - Cognition
  - Consciousness

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Psychomimetic Side Effects (cont'd)

- NMDA receptor antagonists commonly have psychomimetic side effects
  - One of the main disadvantages of ketamine
- Clinical experience shows that anxious and apprehensive patients are more likely to have these side effects

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Psychomimetic Side Effects (cont'd)

- Ketamine may be more likely to bind to NMDA receptors when the channel is in an open or active state
- Reduction in side effects when patient is in a quiet relaxed atmosphere could be explained by the NMDA receptor is more likely to be closed
- Pretreatment with a benzodiazepine may be preventative
  - May be less effective if administered after ketamine is bound to the NMDA receptor

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Contraindications to Ketamine

- Pregnancy (placental transfer)
- Substance abuse
- Glaucoma
- Thyrotoxicosis
- Significant psychiatric comorbidities including bipolar disorder and schizophrenia
- Active post-traumatic stress syndrome
- Uncontrolled hypertension or hypotension
- Cardiac failure

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Contraindications to Ketamine (cont'd)

- Renal failure
- Liver failure
- Prolonged QT syndrome
- Neurogenic bladder or urinary retention
- Known elevated CSF
- Methadone usage
- Daily opioid dose > a morphine equivalent of 120 mg
- History of stroke unless cleared by cardiology and neurology
- Significant cognitive dysfunction

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Ketamine for Treatment of Refractory Migraine

- When first and second-line drugs fail, ketamine may be a suitable option
- In clinical use for over 30 years
- Theory that the NMDA receptor antagonist may be useful in pathological pain states has been known for at least 20 years
- Can be given by multiple routes: IV, IM, SC, oral, rectal, nasal, transdermal, epidural, or intrathecal
- Appears to be most effective for nociceptive and/or neuropathic pain

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Hocking, Graham. Ketamine in Chronic Pain Management. Anesthesia and Analgesia. December 2003. Vol 97, pp 1730-1739

Ketamine for Treatment of Refractory Migraine (cont'd)

Can be given by multiple routes:

- IV
- IM
- SC
- Oral
- Rectal
- Nasal
- Transdermal
- Epidural
- Intrathecal

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Ketamine May Help Treat Migraine Unresponsive to Other Therapies

- In a study presented at the Anesthesiology 2017 annual meeting, 75% of patients experienced an improvement in their migraine intensity after a 3-7 day inpatient treatment with ketamine
- Dr. Schwenk at Thomas Jefferson University Hospital
- 61 patients, had intractable migraine (failed all other therapies)
- Admission VAS pain scale 7.5 compared to 3.4 on discharge
- Average length of infusion was 5.1 days

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IV Ketamine for Subacute Treatment of Refractory Chronic Migraine: A Case Series

- Journal of Headache Pain. 2016; 17(1): 106.
- Retrospective chart review study, total of 6 patients
- Prior to infusion: baseline EKG, Pregnancy test for females
- Dosing: 0.1 mg/kg/hr starting, increased by 0.1 mg/kg/hr every 3 to 4 hours as tolerated until target pain score of 3/10 was achieved and maintained for at least 8 hours
- Infusion then decreased by 0.2 mg/kg/hr every 3 to 4 hours until 0 mg/hr
- Pre-treatment pain scores ranged from 9 to 10
- All patients achieved score of 3 or less for 8 hours
- Average Ketamine infusion rate was 0.34 mg/kg/hr

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Newly Found Mechanisms of Action with Newer Clinical Applications

- NMDA receptor interaction with ketamine plays a role in the opioid induced antihyperalgesic effects of ketamine
- Subanesthetic doses of ketamine via NMDA receptor blockade potentiate opioid analgesia
- Ketamine exerts a protective anti-inflammatory effects by suppressing the induction of NO synthase activity
- The hypnotic effects of ketamine are caused by a combination of immediate channel blockade of NMDA and hyperpolarization-activated cation channels
- The antiproinflammatory effects may be responsible for its antihyperalgesic effects
- Immediate analgesic effects are mediated predominantly by a combination of opioid system sensitization and antinociception

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Anesth Essays Res. 2014 Sep-Dec; 8(3): 283–290.

Ketamine Dosing

- Anesthesia induction dose: 1 mg/kg to 4.5 mg/kg
  - Average amount required to produce 5-10 minutes of surgical anesthesia is 2 mg/kg
- Pain management dosing for CRPS:
- 0.3-0.6 mg/kg/hr
- Max rate 50 mg/hr
- Max daily dose 200 mg/day
- Outpatient for migraine: 0.4 mg/kg total infused over 90-240 minutes
- Inpatient for migraine: variable. 0.1 mg/kg/hr, increased by 0.2 mg/kg/hr as tolerated to goal effects as tolerated. Duration 3-7 days, or until pain resolves

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Patient Education

- Due to duration of ketamine, avoid the following for a minimum of 24 hours after administration:
  - Driving a car
  - Operating hazardous machinery
  - Engaging in hazardous activities

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Patient Education (cont'd)

- Contact physician if:
  - Severe confusion
  - Hallucinations
  - Unusual thoughts
  - Extreme fear

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Ketamine for Treatment of Refractory Migraine

Less serious side effects include:

- Dream-like feeling
- Double vision
- Jerky muscle movements
- Dizziness
- Drowsiness
- Nausea
- Vomiting
- Loss of appetite
- Insomnia

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