Pharmacologic Management of Migraines
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Disclosures
- No financial disclosures relevant to this talk.

Objectives
- Overview of headaches
- Brief pathophysiology of migraines
- Discuss acute medications used for migraines
- Discuss prophylactic agents used for migraines
- Discuss vitamin supplements used for headache prevention
Epidemiology

- Migraines begin earlier in males than in females.
- Migraine incidence and prevalence increases more in girls than boys during adolescence.
- Migraine with aura seems to begin earlier than migraine without aura.
- One study found that the incidence of migraine with aura peaked in females between ages 12 and 13 while migraine without aura peaked between ages 14 and 17.
- One-year prevalence rate of migraines in 12-19 year olds in the US in one large population-based study was 6.3%.

(Carmona & Bruera, 2009)

World Health Organization

Rates severe migraine as one of the most disabling chronic disorders.

Estimates that 324 million individuals worldwide have migraines.

(Pathy & et al., 2000)

Pathophysiology- Migraine

- Primary headache disorder
- Pathophysiology is not completely understood.
- Genetically influenced
Pathophysiology

Most widely accepted theory proposes that vasoactive peptides are released from the primary sensory nerve terminals that innervate the meningeal blood vessels. The peptides activate perivascular trigeminal nerves and cause dilatation of the meningeal arteries as well as perivascular inflammation.

(Loder, 2010)

Pathophysiology—continued

First order neurons terminate in the brain stem and activate second order neurons. Second order neurons ascend to the thalamus and activate third order neurons. Third order neurons enter the higher cortical centers leading to pain and allodynia.

(Loder, 2010)

Pathophysiology—continued

Abnormal brain-stem modulation of sensory information is thought to result in sensitivity to light, sound, and smells for certain migraine patients. Sympathetic nervous system activation is thought to cause the nausea and vomiting that can occur with migraines.

(Loder, 2010)
International Headache Classification of Pediatric Migraine

A. ≥ 5 attacks fulfilling features B-D
B. Headache attack lasting 1-72 hours
C. Headache has at least 2 of the following 4 features:
   1. Either bilateral or unilateral (frontal/temporal location)
   2. Pulsating quality
   3. Moderate to severe intensity
   4. Aggravated by routine physical activities
D. At least 1 of the following accompanies the headache:
   1. Nausea and/or vomiting
   2. Photophobia and phonophobia

International Headache Classification of Adult Migraine

A. ≥ 5 attacks fulfilling criteria B-D
B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
C. Headache has at least two of the following characteristics:
   1. Unilateral location
   2. Pulsating quality
   3. Moderate or severe pain intensity
   4. Aggravated by or causing avoidance of routine physical activity
D. During headache at least one of the following:
   1. Nausea and/or vomiting
   2. Photophobia and phonophobia
E. Not attributed to another disorder

Aura

- Aura can last 5-60 minutes
- Visual symptoms may be unilateral or on both sides of the visual field.
- Consists of one of the following criteria without motor weakness:
  1. Fully reversible visual symptoms, including positive features (seeing flickering lights, spots, or lines) or negative features (loss of vision) or both.
  2. Fully reversible sensory symptoms, including positive features (feeling pins and needles) or negative features (numbness) or both.
  3. Fully reversible dyaphasic speech disturbance.
AAN goals of long-term treatment

- Reduce headache frequency, severity, duration, and disability
- Reduce reliance on poorly tolerated, ineffective, or unwanted acute pharmacotherapies
- Improve patient’s quality of life
- Avoid of acute headache medication escalation
- Educate and enable patients to manage their disease
- Reduce headache-related distress and psychological symptoms

Treatment options

- Acute/episodic treatment
- Prophylactic/preventative agents
- Non-pharmacologic/biobehavioral interventions

Acute/episodic treatment

- Goals for this type of treatment-
  1. Treat the attack consistently and quickly without it reoccurring.
  2. Restore the patient’s functioning.
  3. Provide cost-effective treatment
  4. Minimize side effects.
  5. Optimize self-care so patient does not have to use additional resources- i.e. Emergency room

Lewis et al. (2004)
Treatment of acute migraines

Lewis et al. (2004).

Ibuprofen
- This has been shown to be effective [Level A] for the treatment of migraines in children.

Acetaminophen
- This medication has been shown to “probably” be effective [Level B] in the treatment of migraines in children.
Triptan Agents

- Serotonin 5-HT receptor agonists.
- 3 potential mechanisms of action
  1. Cranial vasoconstriction
  2. Peripheral neuronal inhibition
  3. Inhibition of transmission through second-order neurons of the trigeminocervical complex

Triptan Agents continued

- Potential side effects: tingling, paraesthesias, sensation of warmth, flushing, neck pain, and chest tightness.
- Contraindications: Ischemic heart disease, uncontrolled hypertension, cerebrovascular disease.

Triptan Agents - what are the choices

- Sumitriptan (Imitrex)
- Zolmitriptan (Zomig)
- Naratriptan (Amerge)
- Rizatriptan (Maxalt)
- Eletriptan (Relpax)
- Almotriptan (Axert)
Triptans commercially available in the US

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Triptan Agents- Pediatric Population
- Sumatriptan nasal spray has been shown to be effective (Level A) in treating migraines in adolescents.
- Oral and subcutaneous sumatriptans have inadequate data to make a judgment call (Level U).
- Nasal sumitriptan has been shown to benefit children as young as 5 although not FDA approved.
- Most triptans are used “off label” in the pediatric population.

FDA approval in the Pediatric Population
- Rizatriptan (Maxalt) approved down to age 6 in 2011.
- Almotriptan approved down to age 12 since 2009.
Butalbital
- Butalbital is an intermediate-acting derivative of barbituric acid.
- Barbiturates reversibly depress the activity of excitable tissue and can produce CNS depression.
- Metabolized by the liver.
- Butalbital products are often compounded with aspirin, acetaminophen and/or caffeine for the treatment of migraine and tension-type headaches.
- An example would be Fioricet (Butalbital 50 mg + acetaminophen 325 mg + caffeine 40 mg) (Silberstein & McCrory, 2001)

Butalbital continued
- Can cause rebound headaches if overused-use with caution! “Excessive” use = taking an acute agent more than 2-3 days a week.
- Dosing: 1-2 tablets at onset of headache with a maximum of 6 tablets per day.
- Patient can build up a tolerance and dependence.
- These medications “may be effective” and may be used as a back-up if other medications are ineffective or contraindicated. (Silberstein & McCrory, 2001)

Sprix (ketorolac tromethamine)
- Non-narcotic, NSAID
- Comes as a nasal spray
- FDA approved in adults for acute moderate to severe pain
- Should not be mixed with other NSAIDs (ibuprofen, naproxen) on the same day
Opiates?
- These drugs are avoided, as they mask the pain without treating the pathophysiologic mechanism underlying the migraine.
- They lead to addiction

Abortive management in the emergency room
- Typically if patient in status migrainosus-headache longer than 72 hours.
- Imaging is typically not indicated if neurological examination is normal.
- Hydrate before administering medication.
- American Academy of Neurology advises against use of opioids as first-line therapy for acute migraine.
- Some are discharged with a 7 day course of naproyn after headache has been adequately treated.

Abortive management in the Pediatric Emergency Room
- Antidopaminergic drugs such as prochlorperazine (Compazine) and metoclopramide (Reglan).
- NSAIDS- Ketorolac
- Anti-epileptic drugs: sodium valproate
- Triptans
Abortive Management in the Pediatric Inpatient Setting

- Dihydroergotamine (DHE)
- No triptan use 24 hours prior to receiving DHE.
- Pre-medicate with anti-emetics

Case study #1

- 12-year-old male with no significant past medication history and normal neurological examination complains of migraines that occur twice per month. The headaches do not respond to ibuprofen, acetaminophen, or naproxen.
- What alternatives could you consider?

Preventative Medications for Migraine- when to consider

Consider if patient is having 3-4 or more headaches per month.

Also- consider impact the headache has on an individual’s function. Evaluate using the MIDAS (migraine disability assessment) or PedMIDAS (pediatric migraine disability assessment).
PedMIDAS Score Range

Disability Grade

0 to 10: Little to none
11 to 30: Mild
31 to 50: Moderate
Greater than 50: Severe

Goal of preventative treatment

50% reduction in headache frequency and severity
Preventative treatment

FDA approval

Currently, no medications for migraine prevention are FDA approved in the United States for the pediatric population.

Highest level of evidence for headache prevention

- Topiramate
- Divalproex sodium
- Propranolol
- Metoprolol

*These were rating from the American Headache Society and the American Academy of Neurology. The rating are for adults.

(Loder, Burch & Rizzoli, 2012)
Cypheptadine
- It is a serotonin and histamine antagonist. It may also have some calcium channel blocking properties.
- The evidence is insufficient to determine the efficacy of cypheptadine for the treatment of migraine.
- Side effects include sedation and weight gain. Due to these effects, it is used more commonly in younger children.
- Dosing: 4 mg (used in study) or 0.2-0.4 mg/kg per day.
- It is not FDA approved for the treatment of migraine.

Beta Blockers
- Specifically propranolol, atenolol, and metoprolol.
- Potential side effects: drowsiness, fatigue, sleep disorders, nightmares, depression.
- Contraindicated in patients with asthma, congestive heart failure, diabetes, Raynaud’s disease.
- Not fully understood how these medications work in migraines. Thought to inhibit cortical spreading depression, thus preventing migraines.

Beta-blockers- Propranolol
- Propranolol is most commonly used for headache prevention in this class.
- It is a non-selective beta blocker
- Conflicting Class II evidence for its effectiveness.
- FDA approved in adults for treatment of migraines.
- Adult dosing: 80-240 mg/day
Anti-depressants

- Tricyclic antidepressants: amitriptyline or nortriptyline.
- Recognized in the 1970s as being effective for migraine therapy in adults.
- Most studies in children with this medication has been open-labeled.
- Side effects: sedation
- Also may need to monitor EKG due to concern of arrhythmia (particularly with nortriptyline).

Anticonvulsants

- Topiramate
- Divalproate sodium
- Gabapentin
- Zonisamide
- Levetiracetam

Topiramate

- FDA approved for prevention of migraines in adults.
- Maximum dose of 200 mg/day for prevention of headaches in children.
- Presumable mechanism of action: decreasing brain hyperexcitability and increasing the threshold for activation in the brainstem areas that initiate migraines.
- Potential side effects: weight loss, parathesias, cognitive deficits, acute closed-angle glaucoma, anhydrosis.
Divalproate sodium
- FDA approved for prevention of migraines in adults.
- Daily dose typically between 250 mg and 1,000 mg.
- Extended release version found to be well-tolerated in adolescents 12-17 in one study.
- Potential side effects: somnolence, nausea, weight gain

Gabapentin
- Decreases the release of noradrenaline, dopamine, and serotonin.
- Dosing 1200 mg to 2000 mg
- Evidence inconclusive- considered a 3rd line treatment.

Zonisamide
- A sulfonamide
- It has been used as an antiepileptic drug in Japan since 1989.
- Potential side effects: weight loss, behavioral changes (irritability), gastrointestinal discomfort
- Dosing- in 1 study used 5.7 mg/kg per day. It was started at 1 mg/kg per day and titrated up by 1 mg/kg per day every 2 weeks up to goal dose. This study found Zonisamide to have “some efficacy in headache reduction.”

(From: Pakalnis & Kring, 2006)
Zonisamide continued
- Second study initiated dose at 50 mg per day and increased up to 400 mg/day, as tolerated (increasing up every 1-2 weeks).
- Mechanism of action is unknown. Thought to block voltage-gated sodium channels, inhibit carbonic anhydrase, enhance release of GABA, facilitate serotonergic and dopaminergic neurotransmission, and inhibit potassium-mediated release of glutamate.

Levetiracetam
- An anti-epileptic drug indicated as adjunctive therapy for treatment of partial onset seizures in adults and seizures.
- It is a pyrrolidone derivative thought to have effects on the synaptic vesicle protein SV2A brain binding site.
- Potential side effects: Irritability, behavioral issues, somnolence.

Levetiracetam continued
- In one study, pediatric patients 6-17 years of age were started on 20 mg/kg per day divided twice a day. This dose was increased up to 40 mg/kg per day divided twice a day.
- This study noted that Levetiracetam had “some efficacy in reducing migraine frequency.”
- A retrospective pediatric study noted some benefit at doses ranging from 250 mg to 1,500 mg daily.
**Calcium Channel Blockers**
- Flunarizine has been shown to be effective but not available in the United States.
- Verapamil is most widely used in the United States for migraine prevention.
- Most useful in patients with prolonged aura or hemiplegia with migraines.
- Potential side effects: constipation, edema.

**Realistic expectations with preventative medications....**
- Preventative medications take time to work- sometimes weeks to months before an effective level and response is achieved.

**Prophylactic Medications**
- Topiramate, Valproate, Beta-Blockers, and Tricyclic antidepressants seem to all suppress cortical hyper-excitability. The theory is that by suppressing this hyper-excitability state, a patient will have fewer migraines.

(Mathew, 2011)
Onabotulinumtoxin A (Botox)

- Approved by the FDA in 2010 for treatment of chronic migraine in adults.

(Loder, Burch & Rizzoli, 2012)

Case Study #2

- 18-year-old female with no significant past medical history and normal neurological examination who is experiencing migraines 6 times per month.
- Would treatment options would you consider?

Nutricuticals

- Magnesium
- Riboflavin
- Coenzyme Q-10
- Vitamin D
- Butterbur
- Feverfew
Magnesium

- Essential cation
- Deficiencies have been linked to
  - vasoconstriction
  - neurotransmitter release
- Deficiency results in the generation and release of substance P which acts on sensory fibers resulting in head pain.

Magnesium continued

- Level B according to the American Academy of Neurology which means it is “probably effective”.
- Based on 2 positive Class II studies.
Riboflavin

- An essential vitamin for membrane stability and maintenance of energy-related cellular function.
- Its use is based on the hypothesis that a deficiency in mitochondrial energy reserve is a cause of migraines.

Condo et al., 2009; Sun-Edelstein & Mauskop, 2009

Riboflavin continued

- International study of 41 pediatric and adolescent patients between 2002 and 2007
- Either 200 mg or 400 mg doses of riboflavin administered for 3, 4, or 6 months
- Results of the study suggest the following:
  - Continue the supplement for 4 months to determine effectiveness.
  - Riboflavin is well-tolerated
  - 200 mg may be an adequate per day dosage
- Randomized control studies with larger sample sizes still needed
- Currently a Level B "probably effective" according to the American Academy of Neurology.

CoQ10

- It is thought that mitochondrial dysfunction may play a role in migraine pathogenesis.
- Coenzyme Q-10 is thought to improve abnormalities in mitochondrial encephalomyopathies.
CoQ10 continued
- One small Class II study showed that CoQ-10 was significantly more effective than the placebo in decreasing migraine frequency.
  Dose: 100 mg three times per day.
- The effect of CoQ-10 seems to begin after about 4 weeks and continues to optimize over 12 weeks.
- The supplement seems to help more with attack frequency and gastrointestinal symptoms and less with headache severity.
- Level C (possibly effective).

Petadolex (Butterbur)
- Perennial shrub whose roots are thought to have anti-migraine properties.
- Two Class I studies show that Petasites (50-75 mg twice a day) to be effective – adult studies
- There has been an uncontrolled study in pediatrics using doses of 50-150 mg daily.
- Level A (established efficacy)

Feverfew
- Species in the chrysanthemum family. Leaves have been used as a headache remedy.
- Available preparations have great variation in dosage.
- Potential side effects include: sore mouth, tongue ulcers, swollen lips, abdominal pain, and loss of taste.
- Level B in adults (probably effective)
Medications can be helpful but....

Must stress non-pharmacologic therapies as well including:
1. Sleep hygiene
2. Regular meals
3. Exercise
4. Avoidance of dietary triggers

Summary
- There are numerous abortive therapies for migraines. Triptans can be considered in some patients if over-the-counter medications fail to provide relief.
- Preventative medications should be considered for headaches occurring 4 or more times per month.
- Alternative therapies are available for the treatment of migraines if the patient does not want to take a medication.

Questions?

http://www.nyheadache.com
References


References Continued


