ED Pharmacotherapy of Migraine: What is the Latest?

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Why Discuss Migraines?

• About half of the global adult population has an active headache disorder
  • 10% have migraine
  • In US, 12% overall (women 18%, men 6%).
  • Years Lost to Disability: #6
• ED visits in US: #4
• Genetic component

Kelley NE, Tepper DE. Headache 2012;52:114-128
Learning Objective(s)

1. Briefly describe the mainstay of migraine therapy during the initial ED presentation

2. For treatment of resistant migraine, discuss the evidence for the use of:
   a. Valproic acid
   b. Propofol

3. Discuss the evidence for use of steroids to prevent recurrence of migraine
Out of Scope for Today’s Lecture…

- Other types of headaches
- Migraine prevention treatment
- Chronic (outpatient) therapy
- Non-medicinal therapies
- Pediatric migraine
Primary Headaches

1. Migraine
2. Tension
3. Cluster (and other trigeminal autonomic cephalgias)
4. Other Primary
# Primary Headache Types

<table>
<thead>
<tr>
<th>Pain Description</th>
<th>Migraine</th>
<th>Tension</th>
<th>Cluster</th>
</tr>
</thead>
<tbody>
<tr>
<td>Photo/phono-phobia, n/v, aura</td>
<td>Throbbing, moderate to severe, worse w/exertion</td>
<td>Pressure, tightness, waxes and wanes</td>
<td>Abrupt onset, deep, continuous, excruciating, explosive</td>
</tr>
</tbody>
</table>

| Associated Symptoms | None | Tearing, congestion, rhinorrhea, pallor, sweating |
Migraine Definition

• Headache 4-72h

• ≥ 2 of:
  • Unilateral location
  • Pulsating quality
  • Moderate-to-severe intensity

• Aggravated by routine activity
  +
  • Photophobia and phonophobia OR N/V

• At least 5 attacks, not secondary.

International Classification of Headache Disorders (ICHD-2)
Pathophysiology: It’s complex…

- Involves multiple processes
- Involves CNS and PNS
  - Neuropeptide release
  - Vasodilation
  - Nociceptor stimulation
  - Central activation
- Feedback from hyper-sensitized brain → exacerbation pain signaling
- Role
  - Causal (≥)? Result? In parallel?
- As progress → sensory disturbances and pain
Pathophysiology

- Brainstem neuronal hyperexcitability
- Cortical spreading depression w/ aura
- Abnormalities of 5-HT, CGRP, NE, DA, GABA, glutamate, NO and endorphins
- Trigeminal activation
Presymptomatic hyperexcitability increases brain stem response to triggers

Release of Neurotransmitters
(5-HT, NE, DA, GABA, Glutamate, NO, CGRP, Substance P, Estrogen)

Neurotransmitters activate the Trigeminal Nucleus

- Dilation of Meningeal blood vessels (Throbbing)
- Activation of Area Postrema (N/V)
- Activation of Hypothalamus (Hypersensitivity)
- Activation of cervical trigeminal system (Muscle spasm)

Activation of Cortex and Thalamus (Head pain)
ED Presentation - Characteristics

• Symptoms
  • Unusually severe and/or prolonged
  • Not typical of usual headache

• Treatment
  • Usual acute migraine treatment has been ineffective.
  • > 50% use over-the-counter “simple” analgesics; often ineffective.
  • Few have used migraine-specific medications (e.g. triptans, ergotamine)
  • No medications at all: Men > women (31% vs 9%, p=.003)
  • Not previously seen by a neurologist (22% vs 5%, p=.004).

Kelley NE, Tepper DE. Headache 2012;52:114-128
First Things First….. Rule Out Badness!

**Emergent**
- SAH / ICH / SDH
- CNS infection
- CO Poisoning
- Temporal Arteritis
- ↑ ICP: Mass, Idiopathic Intracranial Hypertension, Shunt Failure
- Cerebral Sinus Thrombosis
- Cervico-cranial Artery Dissection
- Acute Angle Closure Glaucoma

**Non-emergent**
- Tension
- Migraine
- Cluster
- Febrile headache
- Dental, TMJ
- Trigeminal Neuralgia
- Post-LP headache
Case

• 42 yo F to ED at 2200h c/o throbbing right frontal headache w/ N, V, photophobia, and phonophobia and pain “10”

• HPI
  • Gradual onset while at work at 2 pm
  • Rx: 2 tabs naproxen 500 mg and 2 tabs sumatriptan 100 mg without relief.
  • Similar quality vs other headaches

• PMH – migraine without aura (12 /mo)

...Case

• Comes to ED 2x/mo for migraine refractory to PO Rx

• “Allergy”: dystonic reactions and akathisia to dopamine antag during a previous ED visit

• Exam – Non-contributory
  • Neuro: normal
  • HEENT: normal visual fields & fundoscopic exam; no evidence face /head infection

• Adds: “Usually I get relief from 3 doses of hydromorphone 2 mg + diphenhydramine 50mg IM. Asks for same.

What do you do?

a. Give patient her usual ED Rx (hydromorphone IV + diphenhydramine 50mg IM)
b. IVF 1L NS @ 250ml/hr + Ketorolac 30 mg IM
c. Sumatriptan 100 mg PO

Answer: b.
Mainstay of ED Treatment of Migraine

• IVF - NaCl 0.9% 1 L to run at 250 ml/hr
• Anti-nauseant (dopamine antagonist)
• NSAID – Ketorolac 30mg IV
• Triptans
• Dihydroergotamine (DHE)
• Opioids – No!

www.acep.org ACEP Position Paper on Approach to Migraines
Role of Opioids

- Opioids are not necessary, and may be harmful.
- Chronic opioid use >9 days per month may contribute to medication-overuse headaches.
- Treating symptoms with more opioids should generally be avoided.
- Eliminated opioids at MCR for migraine presenting to the ED.

American College of Emergency Physicians (ACEP) Clinical Position Statement on Treatment of Migraines
Opioids in Patients with Migraines: Poor Outcomes

• Progression of the underlying migraine disorder from episodic to chronic migraine
• Increased frequency of return visits to ED
• Less responsiveness to subsequent treatment with triptans
• Less frequent headache relief than patients who received DHE or DA antagonists

MCR ED Migraine Headache Algorithm

ED Headache Guidelines

Headache

*See notes for red flags, medication contraindications, etcetera

- IV Hydration
- Ketorolac 30mg IV
- Anti-Emetic of choice

Red Flags

- Compazine 2.5-10mg
- Reglan 5-10mg
- Droperidol 1.875mg

Evaluate and treat accordingly (imaging, labs, etcetera)

DHE Contraindication?

- No
- Yes

DHE 0.5mg IV test dose

1g valproate in 250cc NS over 1 hour

Resolved?

- No
- Yes

If tolerated and effective, can give one more dose of 0.5mg IV 30-60 minutes later

Resolved?

- No
- Yes

Opiate naïve?

- Yes
- No

IV opiate of choice

Resolved?

- No
- Yes

Neurology Consult

- Dismiss home with outpatient follow-up
- In typical migraines, consider dexamethasone 10mg IV prior to dismissal
- Consider nasal DHE prescription
## ED Headache Protocol: Results

<table>
<thead>
<tr>
<th>Feature</th>
<th>Pre-guideline N=772</th>
<th>Post-guideline N=637</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Narcotics</strong></td>
<td>Median (IQR; Range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>212 (27)</td>
<td>88 (14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Non-narcotic analgesics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>88 (11)</td>
<td>81 (13)</td>
<td>0.45</td>
</tr>
<tr>
<td>Aspirin</td>
<td>85 (11)</td>
<td>79 (12)</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>4 (1)</td>
<td>2 (&lt;1)</td>
<td>0.70</td>
</tr>
<tr>
<td><strong>Non-narcotic NSAIDS</strong></td>
<td>407 (53)</td>
<td>354 (56)</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>Non-narcotic analgesics or NSAIDS</strong></td>
<td>457 (59)</td>
<td>401 (63)</td>
<td>0.15</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>13 (2)</td>
<td>18 (3)</td>
<td>0.15</td>
</tr>
<tr>
<td>Compazine</td>
<td>227 (29)</td>
<td>158 (25)</td>
<td>0.054</td>
</tr>
<tr>
<td>Reglan</td>
<td>105 (14)</td>
<td>31 (5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Droperidol</td>
<td>93 (12)</td>
<td>176 (28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DHE</td>
<td>13 (2)</td>
<td>4 (1)</td>
<td>0.071</td>
</tr>
<tr>
<td>Valproate</td>
<td>22 (3)</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Refractory Migraine in the ED
Valproic Acid (Valproate) - Rationale

- Valproate increases g-aminobutyric acid (GABA)
- Reduces serotonergic cell activity in the dorsal raphe nucleus
- Reduces central activation in the trigeminal nucleus caudalis
- Reduces neurogenic inflammation through GABAA receptor antagonism

Valproic Acid

Comparison of Intravenous Valproate Versus Intramuscular Dihydroergotamine and Metoclopramide for Acute Treatment of Migraine Headache

Intravenous Sodium Valproate Versus Prochlorperazine for the Emergency Department Treatment of Acute Migraine Headaches: A Prospective, Randomized, Double-Blind Trial

Randomized trial of IV valproate vs metoclopramide vs ketorolac for acute migraine

Valproic Acid - Data

• Mathew et al
  • 73% patients had substantial headache relief (mild or no pain) 30 min post valproate 300 mg IV.
  • No control group
  • N=2/ 66 mild, transient light headedness.

• Edwards et al
  • VA 500 mg IV vs DHE 1 mg IV plus metoclopramide 10 mg IV;
  • Headache relief at 4 hours was the same in both groups (60%).

...Valproic Acid - Data

- Tanen et al
  - Valproate 500 mg IV vs Prochlorperazine 10 mg IV
  - Pain reduction (VAS) at 1 hour was greater for prochlorperazine (-64.5 vs -9.0; P < .01)
  - No difference in sedation between the treatments.

### Valproic Acid (Valproate) - Evidence

<table>
<thead>
<tr>
<th>Study</th>
<th>Rx</th>
<th>Outcome</th>
<th>AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edwards et al</td>
<td>VA 500 mg IV vs (DHE 1 mg IV + metoclopramide 10 mg IV)</td>
<td>Headache relief at 4 hours was the same in both groups (60%).</td>
<td>VA: none DHE: 15% N, V, D)</td>
</tr>
<tr>
<td>Tanen et al</td>
<td>Valproate 500 mg IV vs Prochlorperazine 10 mg IV</td>
<td>Pain reduction (VAS) (1hr): Prochlorperazine &gt; VA (-64.5 vs -9.0; p &lt; .01)</td>
<td>No △</td>
</tr>
<tr>
<td>Friedman et al</td>
<td>VA 1g IV vs metoclopramide 10 mg IV vs ketorolac 30mg IV (all over 15min)</td>
<td>Pain reduction (1-10) (1hr): VA 2.8 vs Met 4.7 vs Ketor 3.9 Need for rescue Rx: VA: 69% vs Met 33% vs 52% Ketor Sustained headache free: VA 4% vs Meto 11% vs Ketor 16%</td>
<td>Meto: restless: 5%</td>
</tr>
</tbody>
</table>
Valproic Acid (Valproate) IV Protocol

- Valproic acid IV loading dose: 15 mg/kg in D5W or normal saline at 20 mg/min, followed by 5 mg/kg every 8 hours as needed
- Maximum recommended rate: 20 mg/min
- No telemetry required
- Avoid during pregnancy or with past hepatic disease

Valproic Acid (Valproate) - alternate

• Valproic acid 1 g IV in 250 cc NaCl 0.9% over 1h
• Efficacy ~ DHE 1 mg IV + metoclopramide 10 mg IM
  • DHE may result in less recurrence over 24 hours
• Benefits
  • Lack of CV side effects
  • Lack of interaction with triptans or ergotamines
  • Lack of sedation
  • Absence of potential for addiction or habituation
• Most common: Valproic acid 500 mg at 20 mg/min x 1 dose (after NaCl 1L )

….. Case

Given the data regarding Valproic Acid in migraine, would you recommend:

a. Valproic Acid 1g IV
b. Valproic Acid 500mg IV
c. Not at all
Propofol - Rationale

• Refractory migraine headaches: GABAergic receptors in a lower activity status
• GABA-A receptor agonist
  • Chloride channels in the β1-subunit
• Sodium channel blocker
• Sub-anesthetic doses
  • Low doses affect only frontal lobe (EEG)
• May also decrease
  • Central sensitization
  • Cortical spreading depression

Propofol

Intravenous Propofol: Unique Effectiveness in Treating Intractable Migraine

**RESEARCH ARTICLE**
Effectiveness of intravenous Dexamethasone versus Propofol for pain relief in the migraine headache: A prospective double blind randomized clinical trial

**ORIGINAL ARTICLE**
The Efficacy of Propofol vs. Subcutaneous Sumatriptan for Treatment of Acute Migraine Headaches in the Emergency Department: A Double-Blinded Clinical Trial

Propofol

- Improvement of patient-rated VAS (0-10)
  - HA resolution 100%: 63/77 (83%)
  - HA relief 50-90%: 14/77 (18%)
  - HA reduction (VAS) 95.4%

- Average time to maximum reduction of HA severity: 20-30 min

- Safety: No cases of ‘falling asleep’ or loss of consciousness

Propofol IV vs Sumatriptan SQ

• DB RCT in ED

• Inclusion
  • Age 18-45
  • International headache society (IHS) criteria for migraine

• Exclusion
  • Pregnancy
  • CAD/Vascular disease
  • Opiate dependence
  • DBP >105mm Hg
  • Ergotamine or 5HT-agonists in 24h

...Propofol IV vs Sumatriptan SQ

- Rx: Sumatriptan 6mg SQ vs Propofol 30-40mg IV + 10-20mg propofol IVP q 3-5min (max 120mg, sedated to Ramsey score 3-4)
- Either group: Granisetron 1mg IV if persistent N/V
- Blinded ED MD assessment @ t=0, 30, 60, 120
  - HA-severity on 11pt VAS
  - Symptoms, including N, V, photophobia and phonophobia
  - AE
  - F/U phone call at 24hrs for HA recurrence.

Propofol IV vs Sumatriptan SQ: Results

- Pain intensity lower @ 30min (p=0.034)
- Rate of pain reduction faster (p=0.002)
- Less antiemetics & rate of HA recurrence (p=0.045)
- No difference
  - Pain intensity @ 60 & 120 min
  - Photophobia and phonophobia.

- Adverse Effects
  - Prop: less chest tightness and rash (inj) (p=0.001)
  - No difference in hypotension/drowsiness

Propofol IV vs Dexamethasone IV

- **Inclusion**
  - Age > 18
  - International headache society (IHS) criteria for migraine

- **Exclusion**
  - Abortive Rx pre ED
  - DM
  - Active peptic ulcers
  - MI within last week
  - Familial hypokalemic periodic paralysis

Propofol IV vs Dexamethasone IV

- Propofol 10mg IV + 10mg q 5-10 min until VAS pain ≤ 2 (max 80mg) vs dexamethasone: 0.15mg/kg IV (max 16mg)
- Blinded assessment @ baseline (blinded)
  - HA-severity on 10pt VAS
  - Symptoms, including N/V, photophobia and phonophobia
  - HA severity @ 5, 10, 20, 30 and 45 min
  - No phone-call f/u for HA recurrence

Propofol IV vs Dexamethasone IV: Results

• Propofol
  • Pain intensity significantly lower at all time points (p=0.001).
  • Rate of pain intensity reduction faster at all times with prop (p=<0.05).

• Adverse Events
  • No significant difference in BP, HR, O2 sat
  • “Mild sedation” in 44.4%
<table>
<thead>
<tr>
<th>Study</th>
<th>Rx</th>
<th>Outcome</th>
<th>AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krusz Open label N=77</td>
<td>• Propofol 20-30mg IV bolus q 3-5 min</td>
<td>• Average total dose 110mg</td>
<td>• ‘Falling asleep’ or LOC (n=0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Patient-rated VAS (0-10)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• HA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Resolution 100% :63/77 (83%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Relief 50-90%:14/77 (18%)</td>
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<tr>
<td></td>
<td></td>
<td>• Reduction (VAS) 95.4%</td>
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<tr>
<td></td>
<td></td>
<td>• Severity: maximum reduction: Tmean: 20-30 min</td>
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<td></td>
<td>• 'Falling asleep' or LOC</td>
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<tr>
<td>Moshtaghion DB RCT in ED</td>
<td>• Sumatriptan 6mg SQ vs • Propofol 30-40mg IV + 10-20mg propofol IV</td>
<td>Pain: P &gt; S:</td>
<td>P &lt; S:</td>
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<tr>
<td>N=90</td>
<td>P q 3-5min (max 120mg, sedated to Ramsey score 3-4)</td>
<td>• Intensity lower @ 30min (p=0.034)</td>
<td>• Chest tightness and rash (inj)</td>
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<td>• Faster reduction (p=0.002)</td>
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<td></td>
<td></td>
<td>• Fewer antiemetics</td>
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<td></td>
<td>• Less HA recurrence (p=0.045)</td>
<td>• BP↓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P=S:</td>
<td>• Drowsiness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pain @ t=60 &amp; 120 min</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Photophobia &amp; phonophobia</td>
<td></td>
</tr>
<tr>
<td>Soleimanpour DB, RCT in ED</td>
<td>Propofol 10mg IV + 10mg q 5-10 min until VAS ≤ 2 (max 80mg) vs</td>
<td>Pain: P &gt; D</td>
<td>P = D: BP, HR, O2 sat</td>
</tr>
<tr>
<td>N=90</td>
<td>Dex: 0.15mg/kg IV (max 16mg)</td>
<td>• Intensity lower at all time points (p=0.001)</td>
<td>• “Mild sedation” in 44.4%</td>
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<tr>
<td></td>
<td></td>
<td>• Faster at all times with prop (p=&lt;0.05)</td>
<td></td>
</tr>
</tbody>
</table>

Propofol – Bottom Line

• Propofol is ideal for abortive treatment of migraines in ED in sub-anesthetic doses

• Rapid acting, minimal AE

• Likely more effective than triptan & dexamethasone at reducing:
  • Pain (on VAS), HA recurrence, associated HA symptoms (N/V, photophobia, phonophobia)

• Reliable monitoring and in controlled conditions
….. Case

Given the data Propofol in migraine, would you recommend:

a. Propofol 10 mg IV q 5 min IV (to max 80mg) with monitoring (procedural sedation)

b. No propofol
Propofol – Should we go all in yet?

- For now, approach as procedural sedation with all attendant monitoring
- Q. Is time commitment feasible or reasonable?
- Q. What is the ideal depth of sedation?
If all fails…. Or if not ready for Propofol

• Paraspinal or occipital nerve blocks
• Requires some expertise
• Feasibility vs propofol
Steroids upon ED Dismissal?

• Headache recurrence up to 60%

• Rationale - suppress sterile inflammation underlying migraine

• As part of rescue therapy not superior vs other Rx
…Steroids upon ED Dismissal?

- Prior to dismissal, appears to be effective:
  - Sustained pain relief
  - Prevent headache recurrence
  - Reduce ED recidivism
  - If HA duration $\geq 72h$, or high VAS score

- Baden et al.
  - Recurrence 12.9% vs 58.3%, $p<0.001$)
  - Equal incidence of side effects (19.4% vs 20.8%, $p=1.0$)

- Dexamethasone 10 mg IV x 1

- Little risk of AE with single dose
  - Burning / itching with IV injection

Baden EY. CJEM. 2006;8:393-400
<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Dexamethasone</th>
<th>Control</th>
<th>Odds Ratio (M-H, Random, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Donaldson 2008</td>
<td>21</td>
<td>57</td>
<td>18</td>
</tr>
<tr>
<td>Friedman 2007</td>
<td>64</td>
<td>102</td>
<td>69</td>
</tr>
<tr>
<td>Jones 2003</td>
<td>14</td>
<td>34</td>
<td>17</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>193</strong></td>
<td><strong>165</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

Total events: 99, 104

Heterogeneity: $I^2 = 0.00$; $I^2$ = 0%

Test for overall effect: $Z = 2.26$ ($P = 0.02$)
Questions?

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