ADVANCES IN MIGRAINE MANAGEMENT

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Outline

- Migraine throughout the decades
- Trigeminovascular theory
- Abortive treatment of migraine
- Prophylactic treatment of migraine
- Menstrual migraine
- Complicated migraine
- Medication overuse
- Rescue therapy
Early Classification of Migraine

- Common Migraine (without visual aura)
  - nausea, vomiting, photophobia
- Classical Migraine (with visual aura)
  - ex. scintillating scotoma thought to represent neuronal spreading neuronal spreading depression
- Basilar Artery Migraine- ER Bikerstaff
- Migraines in Children- Bo Bille

Early Pathophysiology of Migraine

- Aura secondary to vasoconstriction
- Pain secondary to vasodilation
- Excessively permeable blood vessels released “neurokinins” causing sterile inflammation
- Changes in serotonin metabolism noted
- HOWEVER, many migraines were felt to be psychosomatic
Early Treatments of Migraine

- Preventive Pharmacotherapies
  Methysergide (serotonin antagonist)
  Hydergine (dihydroergotamine mesylate)

- Abortive Pharmacotherapies
  Ergotamine tartrate
  Intravenous dihydroergotamine
  Oral Analgesics
  Fiorinal (aspirin, caffeine, butalbital)

1970’s and 1980’s Classification of Migraine


- 1988 International Classification of Headache Disorders (ICHD)
1970’s and 1980’s Pathophysiology of Migraine

- 1970’s Harold Wolff
  Vascular Theory of Migraine
- 1980’s Jes Olesen
  Spreading Depression of Leao
- 1980’s Michael Moskowitz
  Described Trigeminovascular Disorder with plasma extravasation from cerebral vessels with stimulation of trigeminal nerve

1970’s and 1980’s Treatment of Migraine

- Preventive Medications discovered:
  Calcium antagonists
  Valproate
  Lithium (for cluster headaches)
  Indomethacin (for indocin-responsive)

- 1984 Scientists at Glaxo synthesized, a serotonin 1B/1D agonist “sumatriptan”
1990’s---Decade of the Triptans

- 7 “triptan” medications marketed in U.S. for abortive treatment
- Valproate FDA approved for migraine prophylaxis in U.S.
- Gabapentin and Topiramate: Open-label and double blinded trials for migraine prevention—positive
- Phase-Specific Treatment of Migraines

PHASE-SPECIFIC TREATMENT OF MIGRAINE

Phase I: Prodrome
- OTCs, NSAIDs, Non-narcotic analgesics

Phase II: Aura
- Triptans

Phase III: Early Headache
- Rescue or rescue combinations

Phase IV: Late Headache

Phase V: Postdrome

Phase-Specific Treatment of Migraine (Adapted from Cady)
2000’s– Credibility and Activism

- Imaging Studies Confirm thalamic activation contralateral to headache pain in migraine and cluster headaches
- Association of Migraine with stroke, cardiovascular diseases and pre-eclampsia
- No new abortive medications but research on the development of CGRP-inhibitors
- Topiramate- FDA approved for prevention

MIGRAINE PATHOPHYSIOLOGY

Pain Syndrome

- Trigeminal nucleus activated
- Calcitonin gene – related peptide (CGRP) released by trigeminal nerve
- CGRP release causes vasodilation
- Plasma protein extravasation causes sterile inflammation in the dura mater
ABORTIVE TREATMENT OF MIGRAINE

Selective 5-HT 1B/1D, receptor agonists (“Triptans”)

- Sumatriptan (Imitrex)
- Rizatriptan (Maxalt)
- Zolmitriptan (Zomig)
- Naratriptan (Amerge)
- Almotriptan (Axert)
- Frovatriptan (Frova)
- Eletriptan (Relpax)
### SELECTED TRIPTAN COMPARISON TABLE

<table>
<thead>
<tr>
<th></th>
<th>Eletriptan (Relpax)</th>
<th>Sumatriptan (Imitrex)</th>
<th>Rizatriptan (Maxalt)</th>
<th>Frovatriptan (Frova)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bioavailability</strong></td>
<td>50%</td>
<td>15%</td>
<td>45%</td>
<td>20-30%</td>
</tr>
<tr>
<td><strong>Tmax</strong></td>
<td>1.5 hrs</td>
<td>2.5 hrs</td>
<td>1.5 hrs</td>
<td>2-4 hrs</td>
</tr>
<tr>
<td><strong>Half-Life</strong></td>
<td>4 hrs</td>
<td>2.5 hrs</td>
<td>2-3 hrs</td>
<td>26 hrs</td>
</tr>
<tr>
<td><strong>Efficacy at 2 hrs</strong></td>
<td>45-64%</td>
<td>46-62%</td>
<td>60-70%</td>
<td>37-46%</td>
</tr>
<tr>
<td><strong>Usual Dosage</strong></td>
<td>20-40 mg</td>
<td>25-50 mg</td>
<td>5-10 mg</td>
<td>2.5 mg</td>
</tr>
</tbody>
</table>

### Triptan Medication Warning

- History of Cardiovascular Disease
- Uncontrolled Hypertension
- Complicated Migraine
- Age greater than 65
- Pregnancy
- Frequent use of other serotonergic medications
ADDITIONAL ABORTIVE TREATMENTS OF MIGRAINE

Non-selective serotonin agonists
- Dihydroergotamine
- Ergotamine

Barbiturate-containing compounds
- Fiorinal/Fioricet

Non-Steroidal anti-inflammatory drugs
- Naproxen Sodium

DRUGS APPROVED BY FDA FOR MIGRAINE PROPHYLAXIS

- Methysergide maleate 1962
- Propanolol 1979
- Timolol 1990
- Divalproex sodium 1996
  - Delayed-release tablets
  - Divalproex sodium 2000
  - Extended-release tablets
  - Topiramate 2004
OTHER PROPHYLACTIC MEDICATIONS

- Tricyclic Antidepressants
  Controlled trials showing benefits of amitriptyline in migraine, tension, posttraumatic and mixed headaches
- Calcium Antagonists
  Modest benefits of verapamil and flunarizine in double-blind placebo controlled studies

MIGRAINE PREVENTION AND NEUROPATHIC AGENTS

Mechanisms of Action

Anti-epileptic medications may prevent the release of vasoactive neuropeptides from the trigeminal sensory nerve

- CGRP (Calcitonin gene-related peptide)
- Neurokinin A
- Substance P
### EFFICACY OF DIVALPROEX IN MIGRAINE PREVENTION

<table>
<thead>
<tr>
<th>End Point</th>
<th>Divalproex (n=70)</th>
<th>Placebo (n=57)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean 4-week migraine headache frequency</td>
<td>3.5</td>
<td>5.7</td>
<td>≤.001*</td>
</tr>
<tr>
<td>Responder rate (%)</td>
<td>48</td>
<td>14</td>
<td>&lt;.001*</td>
</tr>
</tbody>
</table>

*Difference between the divalproex and placebo treatment groups.

### EFFICACY OF TOPIRAMATE IN MIGRAINE PREVENTION

<table>
<thead>
<tr>
<th>End Point</th>
<th>Topiramate</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean 26-day migraine frequency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edwards et al*</td>
<td>3.0</td>
<td>3.8</td>
<td>.09</td>
</tr>
<tr>
<td>Potter et al†</td>
<td>3.3</td>
<td>3.8</td>
<td>.0015</td>
</tr>
<tr>
<td>Responder rate (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edwards et al*</td>
<td>46.7</td>
<td>6.7</td>
<td>.035</td>
</tr>
<tr>
<td>Potter et al†</td>
<td>26.3</td>
<td>9.5</td>
<td>.226</td>
</tr>
</tbody>
</table>

*Analysis of covariance with baseline migraine frequency as covariate.

†Topiramate n=15; placebo n=15.

‡Topiramate n=19; placebo n=21.

Responder rate defined as the percentage of patients who showed ≥50% reduction in migraine headache frequency from the baseline phase.
MENSTRUAL MIGRAINE

Introduction

- Link between estrogen and progesterone and migraines in women
- No gender difference with migraine in prepubertal children
- Migraine significantly more common in adult women than in men
- Peak incidence of migraine during adolescence (for women) and in second decade (for men)

MENSTRUALLY ASSOCIATED MIGRAINE

- 10% of women with any kind of migraine have onset of migraine headaches at menarche
- 33% of women with menstrual migraine have onset at menarche
- 3 Types of menstrually associated migraine:
  - Menstrual Migraine (MM)
  - True Menstrual Migraine (TMM)
  - Pre-Menstrual Migraine (PMM)
EXOGENOUS ESTRADIOL DELAYS ONSET OF MIGRAINE

Plasma estradiol levels during normal cycle and estradiol-treated cycle. In this patient, treatment with estradiol postponed migraine for 6 days. (Reprinted from Somerville BW. The influence of progesterone and estradiol upon migraine. Headache 1972;12:795-802.)
ADVANCES IN MENSTRUAL MIGRAINE MANAGEMENT

Abortive Treatments
- Zolmitriptan – first large prospective double-blind trial comparing zolmitriptan to placebo in a population of women with menstrual migraine
- Most triptans now used for hormonally mediated migraines

Preventive Treatments
- Estrogen replacement (Transdermal Estradiol)
- NSAIDS (Mefenamic acid)

COMPLICATED MIGRAINE
- Involves significant neurological deficits
- Recovery may take hours to days
- Rarely may represent a stroke
- Treatment should NOT include ergotamines or “Triptans”
- Treatments include Valproate, Verapamil and aspirin
- Oral contraceptive use contraindicated
MEDICATION OVERUSE

Analgesic-rebound headache
- Opiates
- Caffeine-containing combination analgesics

Triptan medication overuse
Treatment includes taper off offending agent(s) and placement on daily prophylaxis

THE ROLE OF RESCUE MEDICATIONS

- What are Rescue Medications?
- When are they used?
- Who needs to be “rescued”?
PATIENTS IN NEED OF RESCUE THERAPY

- The patient has used the maximum dosage of a triptan or ergot for the day
- The patient typically uses high doses of NSAIDs as an abortive agent and has used the maximum amount of an NSAID for the day (e.g., a patient who cannot use a triptan).
- The patient has already treated the maximum of two headaches this week with a triptan and is now experiencing a third headache.

PATIENTS IN NEED OF RESCUE THERAPY

- The patient has been instructed to maintain a 4 to 5 day hiatus between uses of an ergot or triptan and the last headache treated with that agent has been less than 4 days ago.
- Triptans are effective, on average, 70 percent of the time; therefore, a patient who usually gets relief from a triptan may experience occasional failures and require a rescue medication.
## COMMONLY PRESCRIBED MIGRAINE RESCUE AGENTS

<table>
<thead>
<tr>
<th>Medication</th>
<th>Schedule</th>
<th>Dose Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meperidine Hydrochloride</td>
<td>CII</td>
<td>IM, oral</td>
</tr>
<tr>
<td>Combination of butalbital, aspirin, and caffeine</td>
<td>CIII</td>
<td>Oral</td>
</tr>
<tr>
<td>Combination of doceine, butalbital, and caffeine</td>
<td>CIII</td>
<td>Oral</td>
</tr>
<tr>
<td>Butorphanol tartrate</td>
<td>CIV</td>
<td>Nasal spray</td>
</tr>
<tr>
<td>Combination of codeine and Acetaminophen</td>
<td>CIII</td>
<td>Oral</td>
</tr>
<tr>
<td>Combination of hydrocodone Bitartrate and acetaminophen</td>
<td>CIII</td>
<td>Oral</td>
</tr>
</tbody>
</table>

## CRITERIA FOR PRESCRIBING OPIOID MEDICATIONS FOR MIGRAINE SUFFERERS

- The patient reports identical previous migraine headaches, and
- During the migraine, the sufferer is in moderate to severe distress, and
- The patient has no history of substance abuse, and
- At least one of the following should apply:
  - In the past, the patient consistently has not obtained relief from the 5-HT<sub>1B/1D</sub> agents (i.e., triptans and ergots)
  - In the past, the patient has consistently not obtained relief from the non-opioid agents.
  - The patient has used the maximum amounts of his/her usual abortive agents (e.g., triptans, NSAIDs) and the headache persists or recurs (see Table 1).
  - The usual migraine abortive agents (NSAIDs or 5-HT<sub>1B/1D</sub>) are contraindicated (see Table 1).