Indomethacin - responsive headache

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Introduction

- The first primary headache disorder identified in 1976 by Sjaastad and Dale as an indomethacin responsive headache syndrome.


- In 1984 hemicrania continua (HC) was described by Sjaastad.


- As per the International Classification of Headache Disorders, 3rd edition (beta version) (ICHD-III beta), paroxysmal hemicrania (PH) and HC are now classified as trigeminal autonomic cephalalgias.


How indomethacin exerts its effect in PH and HC?

- Indomethacin inhibits two isoforms of COX (COX-1 and COX-2).

- Indomethacin inhibits the production of nitric oxide (NO).

- Indomethacin has been shown to effect NO-induced vasodilation.

- Recent studies also demonstrated a direct effect of indomethacin on trigeminal activation itself.

- Modulation of cerebral vasodilatory, prostaglandin production and direct cerebral blood vessel vasconstriction.

Indomethacin’s therapeutic effect on Valsalva-induced headaches may be due to decreases in intracranial pressure:
- after traumatic brain injury and in idiopathic intracranial hypertension.


Indomethacin Pharmacology

- Oral bioavailability is approximately 100%.

- Non-steroidal anti-inflammatory drugs (NSAID).

- Peak plasma concentrations are reached within 0.5 to 2 h.

- Indomethacin has been shown to have the highest penetration into the central nervous system when compared to other NSAID.


- Onset of action is within 30 min and the duration is about 4 to 6 h.

- It is metabolized via the liver.

- Plasma half-life averages 3 h but can range from 3 to 10 h.

- Tolerance is one of the major limitations.

- Gastrointestinal complications: from dyspepsia to gastrointestinal bleeds.

- Affects renal function, liver function, and platelet activity.

- Fatigue, dizziness, headache, and confusion.

Indomethacin-responsive headaches

... a heterogeneous group of primary headache disorders.

Absolute response to indomethacin

The epidemiology of these conditions is incompletely defined.

Traditionally, indomethacin responsive headaches include a subset of trigeminal autonomic cephalalgias.

- Paroxysmal hemicrania

- Hemicrania continua

- Cluster headache, mumps headache, and ophthalmoplegic migraine have been described as also respond to indomethacin.

Disclosure

I have no relevant financial relationships with the manufacturers of any commercial products and/or provider of commercial services discussed in this CME activity.
**Paroxysmal Hemicrania**

- Frequent
- Short-lasting
- Unilateral headache
- Orbital, supraorbital, or temporal region
- Ipsilateral autonomic features

**HISTORICALLY**

- Females : Males ratio at 2:1
- Mean age of onset of 34 years

**PRESENT STUDIES**

- Females : Males ratio at 1:1
- A slightly older mean age of onset between 37 and 42 years

Prolonged use of indomethacin has been reported to cause gastrointestinal distress and rarely renal insufficiency, making it advisable to consider alternative treatments or reduction of dosage in such cases.

**Indomethacin in Headache Therapy**

1. **Correct diagnosis of PH and HC**

2. **Treatment is usually started at a dose of 25 mg 3 times/daily**

   - median interval between drug administration and response in patients with HC and PH was 4 and 7 h


   - If patients do not obtain relief within 48 h of initiation, the dosage can be increased to 50 mg three times daily.

   - A patient as a non-responder, with dosages as high as 300 mg daily

   **Indomethacin dosages should be as small as possible**

   **Hemicrania Continua**

   - Frequent
   - Short-lasting
   - Unilateral headache
   - Orbital, supraorbital, or temporal region
   - Ipsilateral autonomic features

   2 subtypes

   **remitting** - pain-free periods lasting 1 day or longer without treatment

   **unremitting**

   Most HC patients are women
   Most patients develop HC in their third to fourth decade (mean range 35.4–49.3 years)


   Many atypical cases have been described

   - Bilateral HC
   - HC with aura
   - Seasonal HC
   - Indomethacin-nonresponsive HC

   **Autonomic symptoms in HC are less prominent than seen with PH**

   Lacrimation is the most common cranial autonomic feature (62–87%)


   **Hemicrania Continua**

   **Chronic form ≠ Episodic form**

   **Unilateral headache pain is rated as severe to very severe by 88 to 93% of patients**


   Only 35% of patients have autonomic features in all or most attacks

   **Lacrimation is the most common cranial autonomic feature (62–87%)**

   **PH attacks should last between 2 and 30 min**

   Attacks have been reported to range from seconds up to 6 h

   **Indomethacin in Headache Therapy**

   An effective dosage is maintained for several weeks

   - the dosage should be slowly reduced by 25 mg every 3 days.

   One case series of 26 patients with HC or PH showed that 42% experienced a mean decrease of 56% of their indomethacin dose required to maintain a pain-free state

   - Sjøastad has reported on three patients who have been able to reduce their indomethacin to 25 mg daily or even 25 mg every other day

   **Antonacci F, Sjaastad O. Chronic paroxysmal hemicrania (CPH): a review of the clinical manifestations.**

   **Prakash S, Golwala P. A proposal for revision of hemicrania continua diagnostic criteria based on critical analysis of 62 patients.**

   **Peres M, Stiles MA, Oshinsky M, Rozen TD. Remitting form of hemicrania continua with seasonal pattern.**

   **Southerland AM, Login IS. Rigorously defined hemicrania continua presenting bilaterally.**

   **Del Rio Sanchez M, Caminero AB, Pascual J, et al. Dose and efficacy of long-term indomethacin treatment of chronic paroxysmal hemicrania and hemicrania continua.**

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Valsalva-Induced Headaches: Cough Headache, Exercise Headache, and Headache Associated with Sexual Activity

Cough, exercise, and sex headaches
- are related to rises in intra-abdominal pressure

Cough headache usually occurs after brief rises in intra-abdominal pressure

Exercise and sex headaches often occur after more prolonged provocations
- They are rare entities
- A lifetime prevalence of 1 % for each syndrome

Each of these headache syndromes is reported to be responsive to indomethacin

Cough headache is a typically bilateral headache of sudden onset
- seconds up to 2 h

Exercise headaches are usually known as exertional headaches
is a typically bilateral headache with a throbbing or pulsatile quality
- not last longer than 48 h.
- occur at high altitude or in hot weather
- prevented by avoidance of prolonged physical exercise

Headache Associated with Sexual Activity
the preorgasmic and orgasmic subtypes as one entity

Primary Stabbing Headache

Female : Male ratio of 1.49:1.06
• Onset is usually in early adulthood (mean age 28 years)

The coexistence of primary stabbing headache
- Migraine
- Cluster headache
- Paroxysmal hemicrania
- Hemicrania continua

Primary stabbing headache
- doses of 75–150 mg daily relief pain

Hypnic Headache
sleep-related headache
Hypnic Headache

Sleep-related headache

- Occur at the same time at night (called alarm clock headaches)
- Bilateral or unilateral
- No associated autonomic features
- Patients may have nausea, photophobia, and photophobia

**Onset in usually after 50 years**
- Women are affected more than men

**At least 10 days per month and last between 15 min and 4 h after waking**

**Indomethacin, lithium, and caffeine** have been found to be effective in a number of patients

**Novel Indomethacin-Responsive Headaches**

- Typical cases of PH and HC that have been described as unresponsive to indomethacin
- Other primary headache disorders that are generally not considered indomethacin-responsive

**Vary of other medications** can be effective in patients with HC and PH

**Symptomatic Hypnic Headache**

Neuroimaging should be performed in all patients with hypnic headache

- Brain tumors
- Nocturnal hypertension

**Can produce hypnic headache-like attacks**

**Novel Indomethacin-Responsive Headaches**

Cluster Headache (CH)

Indomethacin responsive headache noted many cases of definite or possible CH in the literature

**That they felt were wrongly labeled as PH because of the patient’s response to indomethacin**

**Onset of indomethacin response in patients who met ICHD-III beta criteria for CH was more gradual compared to those of patients with other indomethacin-responsive headaches**

**Many patients with CH required larger doses of indomethacin**


**Medication overuse headache**

Indomethacin-responsive headache

**Indomethacin use > 15 days per month**

Medication overuse headache is not commonly reported patients with indomethacin-responsive headache syndromes

Indomethacin may have a disease modifying effect in the indomethacin-responsive headache syndromes

**If indomethacin is contraindicated or intolerable?**

Celecoxib and rofecoxib, melatonin and gabapentin have been reported as effective in small series of HC patients

**Cough headache**

- Acetazolamide and methysergide in open-label trials

**Exercise and sex headaches**

- Propranolol
- Celecoxib, nefedipine, melatonin, gabapentin

**Primary stabbing headaches**

- Often do not require treatment
- Celecoxib, nefedipine, melatonin, gabapentin

**Hypnic headache can be treated**

- Lithium, caffeine

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6/8/2016
CASE
A 45-year-old woman came to our clinic with a five month history of focal head pain in the right parietal region.
The affected area was perfectly circular, with a 3 cm diameter.
The pain was continuous, dull and pressing, graded 3/10.
The affected area was occasionally tender to the touch.
Neurological examination was normal.
His past medical history was unremarkable.
The patient’s CT and MRI scans of the brain, which proved normal.

INEFFECTIVE - Paracetamol and naproxen
Antipirine 50 mg/day for 1 month
Gabapentin 900 mg/day for 1 month.

With indomethacin per os (50 mg BID) provided complete pain relief.

After 3 weeks’ treatment, the indomethacin treatment was stopped, but the pain recurred with the same characteristics within few days.

Indomethacin treatment was restarted, again with a prompt response.

After 1 month, the medication was definitely discontinued.
The patient remained pain-free during 3 months follow-up (2015 March).

According to the hypothesis of a neuropathic origin of the pain in NH.

The drugs which usually work in neuropathic pain have been the most broadly used as prophylaxis.

Indomethacin responsiveness in NH has been appropriately investigated in only few cases, with contradictory results.


TAKE HOME MESSAGE
• Traditionally, indomethacin responsive headaches include a subset of trigeminal autonomic cephalalgias.
• Indomethacin, as a member of the non-steroidal anti-inflammatory drug class.
• Indomethacin completely efficacious in the treatment of the primary headache disorders: paroxysmal hemispheric and hemispheric continua.
• Neuroimaging is recommended to investigate for various organic causes that may mimic these headaches.
• Other primary headache disorders that are generally not considered indomethacin-responsive headaches have been described with good response to indomethacin (cluster headache, nummular headache, ophthalmoplegic migraine).