



Modernising Patient Pathways Programme:

Indometacin Sensitive Headache Guidance

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Indometacin is a potent Non Steroidal Anti Inflammatory Drug (NSAID). It is a strong reversible inhibitor of prostaglandin-forming cyclooxygenase (COX). It inhibits COX 1 and COX 2 but has a greater selectivity for COX 1. It has several other actions, including intracranial pressure modulation, inhibition of neurogenic inflammation and inhibition of nitric oxide.

Different mechanisms may have more importance in different indometacin sensitive headache disorders. The effect seems to be specific to indometacin. Other NSAIDs are not effective. COX 2 inhibitors can have some effect, but this is variable and they are generally less effective.

Indometacin Sensitive Headache Disorders

Trigeminal Autonomic Cephalalgias (TACs)

- Paroxysmal Hemicrania
- Hemicrania Continua

Rare Primary Headache Syndromes

- Valsalva Manoeuvres (cough headache)
- Primary Exercise Headache
- Headache Associated with Sexual Activity
- Primary Stabbing Headache
- Hypnic Headache

Indometacin is the treatment of choice for Paroxysmal Hemicrania and Hemicrania Continua, which are both classified under the Trigeminal Autonomic Cephalalgias. An absolute response to Indometacin is a diagnostic requirement for both conditions.

Hemicrania Continua is a strictly side-locked headache which is continuous from onset. There are associated exacerbations of moderate to severe headache on a background of continuous pain. Patients should have at least 1 cranial autonomic symptom with restlessness or agitation commonly present during exacerbations. This helps to differentiate it from migraine.

Paroxysmal Hemicrania is a severe unilateral headache similar to cluster headache. The main differentiators from cluster headache are more frequent attacks (more than 5 per day), shorter attacks (5-30 minutes), and Indometacin response.

	Migraine	Hemicrania Continua	Cluster Headache	Paroxysmal Hemicrania
Attack duration	4 to 72 hours	Constant	15 minutes to 3 hours	5 to 30 minutes
Attack frequency	Episodic up to 14 days per month Chronic more than 15 days headache per month of which 8 or more are migraine	Not applicable	Up to 8 a day	More than 5 a day Up to 5 an hour
Circadian features	-	-	++	+
Restlessness	-	±	++	±
Other differentiating features	Migrainous features Rarely strictly side-locked Motion sensitivity Can worsen with acute medication overuse	Typically more migrainous features than other TACs Strictly side-locked Can be restless or motion sensitive during exacerbations Can worsen with acute medication overuse	Strongest association with circadian rhythm, restlessness, attacks from sleep, alcohol triggering	Shorter and more frequent attacks than cluster
Episodic or chronic tendency	Episodic and Chronic	Chronic	Episodic and Chronic	Chronic
Acute attack treatment	See section on acute treatment of migraine	None – prone to worsen with medication overuse	Sumatriptan s/c Zolmitriptan nasal High flow oxygen	None
Preventive treatment	See section on preventative treatment of migraine	Indometacin	Verapamil	Indometacin

Indometacin is also effective for several other primary headache disorders. In contrast to Hemicrania Continua and Paroxysmal Hemicrania, the response is not absolute.

The triggered primary headache disorders (Valsalva Manoeuvre (cough headache), Primary Exercise Headache and Headache Associated with Sexual Activity) can be effectively treated with Indometacin. The Indometacin response does not differentiate primary from secondary headache and it is mandatory to appropriately investigate patients for secondary causes.

Primary stabbing headache is commonly associated with migraine and can present both on its' own or with other primary headache disorders. Single stabs occur in single or random locations spontaneously over the head. There are no associated features or cranial autonomic symptoms. The stabs can be infrequent or up to 50 a day.

Hypnic Headache exclusively occurs during sleep and causes wakening. It is very rare and needs to be differentiated from migraine and cluster headache, which can also wake patients from sleep. Conditions that may mimic Hypnic Headache include Nocturnal Hypertension, Nocturnal Hypoglycaemia and Obstructive Sleep Apnoea (OSA).

Indometacin should be considered in any strictly side locked continuous headache.

Indometacin should be considered in patients with cluster headache, where the headaches are frequent (more than 5 episodes per day), brief (less than 30 minutes) and / or chronic without remission.

Indometacin can be considered for primary stabbing headache where the stabs are frequent and disabling. If primary stabbing headache presents with concurrent migraine, patients should be warned about the risk of medication overuse headache, and may be more appropriately treated with migraine preventatives (as detailed in section 3).

Indometacin can be considered in patients with triggered primary headaches. It is mandatory to investigate these for secondary causes:

- Valsalva Manoeuvre (cough headache) – Indometacin trial if headache frequent and disabling.
- Primary Exertional Headache and Headache Associated with Sexual Activity – pre-emptive indometacin

The initial treatment of choice for hypnic headache is caffeine (e.g. strong cup of coffee) before bed or taken acutely on wakening with a headache. If this does not work, 25-150mg of Indometacin before bed can be considered.

In patients where indometacin is effective and continued:

- Use the minimum effective dose.
- Monitor regularly for side-effects.
- Regularly withhold treatment to ensure Indometacin is still required (every 3 to 6 months)
- Actively look for alternative preventative treatment and stop Indometacin if an effective alternative treatment is identified.

Investigation

Hemicrania Continua and Paroxysmal Hemicrania

It is recommended to consider Magnetic Resonance Imaging (MRI) in patients presenting with a new onset Trigeminal Autonomic Cephalalgia or in those with chronic symptoms.

Triggered Primary Headache Disorders

Imaging looking for Chiari Malformation or posterior fossa lesion is mandated in Valsalva Manoeuvre (Cough Headache). In selected patients low cerebrospinal fluid (CSF) pressure should also be considered.

On the first presentation of triggered thunderclap headache, patients should be investigated for Sub-Arachnoid Haemorrhage (SAH) and its' differential. In those without thunderclap headache, appropriate imaging looking for evidence a posterior fossa lesion or raised intracranial pressure is warranted. Rarely cardiac ischaemia can present with exertional headache. All patients with exertional headache should have an ECG and if significant concern referral for an exercise tolerance test considered. consideration should be given to the possibility

Hypnic Headache

In patients with headache that only wakens them from sleep, in addition to appropriate imaging, OSA, nocturnal hypertension and nocturnal hypoglycaemia should be considered.

Indometacin protocol

A trial of Indometacin is sufficient to confirm or exclude an Indometacin Sensitive Headache in most patients.

In Hemicrania Continua and Paroxysmal Hemicrania, Indometacin should completely stop headaches. If patients do not have an absolute response, the diagnosis should be reconsidered. A partial response may indicate an analgesic effect, these patients are at risk of developing Medication Overuse Headache.

The effect of Indometacin may be less in other Indometacin Sensitive Headaches. The lack of an absolute response does not exclude Indometacin responsiveness in these headache syndromes.

30 to 60% of patients receiving usual therapeutic doses of Indometacin experience adverse effects, with 10 to 20% discontinuing use. Most adverse effects are dose related.

Due to the high frequency of gastric side effects, adequate gastric protection (usually with a proton pump inhibitor) should be considered, especially if Indometacin is continued after a positive Indometacin trial. If using pre-emptive Indometacin, the need for gastric protection will depend on the frequency of use.

Oral trial of Indometacin

- Start indometacin 25mg 3 times a day with Proton Pump Inhibitor (PPI) cover.
- Increase to 50mg 3 times a day after 3 days to 1 week.
- Increase to 75mg 3 times a day after 3 days to 1 week.
- If there is no effect after 10 days, this should be considered a negative trial and Indometacin should be stopped.
- Once an effective dose is achieved, taper down to minimum effective dose.
- If treatment does not help, stop and reconsider diagnosis.
- Regularly stop Indometacin to ensure it is still required (a headache will usually occur within 24 hours if still needed)

Indo test

- In some patients where there remains uncertainty an Indo test can be helpful.
- Double blind 100mg intramuscular Indometacin versus saline given on different days as an outpatient.
- A headache diary will be necessary to assess response.

Pre-emptive Indometacin

- Bioavailability of orally administered Indometacin is virtually 100%, and peak concentrations are reached at between 30 minutes and 2 hours.
- Onset of action is within 30 minutes and the duration of action is 4 to 6 hours.
- Plasma half-life averages 3 hours but can range from 3 to 10 hrs.
- Treatment regimen:
 - Indometacin should be given 30 to 60 minutes before the known trigger, when the trigger cannot be avoided.
 - Start with 25mg and work up as needed (dose range 25 to 150mg).

- When the headache frequency is high or triggers cannot be anticipated, Indometacin is given 3 times daily.

Other prophylactic treatment

By definition, Indometacin is 100% effective in Paroxysmal Hemicrania and Hemicrania Continua. Evidence for other treatments is limited.

In Paroxysmal Hemicrania, COX 2 inhibitors, Topiramate and Greater Optic Nerve (GON) blocks can also be considered.

In Hemicrania Continua, COX 2 inhibitors, Topiramate, Melatonin, botulinum toxin type A and GON blocks can also be considered.

In Valsalva Manoeuvre (cough headache), Acetazolamide and Topiramate can also be considered.

References and further resources



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