Indomethacin-responsive headaches—A narrative review

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Abstract

Background: Indomethacin is a nonsteroidal anti-inflammatory drug whose mechanism of action in certain types of headache disorders remains unknown. The so-called indomethacin-responsive headache disorders consist of a group of conditions with a very different presentation that have a particularly good response to indomethacin. The response is so distinct as to be used in the definition of two: hemicrania continua and paroxysmal hemicrania.

Methods: This is a narrative literature review. PubMed and the Cochrane databases were used for the literature search.

Results: We review the main pharmacokinetic and pharmacodynamics properties of indomethacin useful for daily practice. The proposed mechanisms of action of indomethacin in the responsive headache disorders, including its effect on cerebral blood flow and intracranial pressure, with special attention to nitrergic mechanisms, are covered. The current evidence for its use in primary headache disorders, such as some trigeminal autonomic cephalalgias, cough, hypnic, exertional or sexual headache, and migraine will be covered, as well as its indication for secondary headaches, such as those of posttraumatic origin.

Conclusion: Increasing understanding of the mechanism(s) of action of indomethacin will enhance our understanding of the complex pathophysiology that might be shared by indomethacin-sensitive headache disorders.

KEYWORDS
hemicrania continua, indomethacin, paroxysmal hemicrania

BACKGROUND

Indomethacin-sensitive headache disorders are a group of rare conditions, for which understanding of the underlying neurobiology is limited. This collection of clinically heterogeneous disorders, as defined by International Classification of Headache Disorders, 3rd edition (ICHD-3), is curiously characterized by an excellent response to indomethacin for two: paroxysmal hemicrania (PH) and hemicrania

Abbreviations: CAS, cranial autonomic symptoms; CBF, cerebral blood flow; cGMP, cyclic guanosine monophosphate; CGRP, calcitonin gene-related peptide; Cmax, maximum serum concentration of the drug; CNS, central nervous system; COX, cyclooxygenase; CSD, cortical spreading depression; CSF, cerebrospinal fluid; CPH, chronic paroxysmal hemicrania; eNOS, endothelial nitric oxide synthase; FDA, food and drug administration; GABA, gamma aminobutyric acid; GTN, glyceryl trinitrate; HC, hemicrania continua; ICHD-3, international classification of headache disorders 3rd edition; ICP, intracranial pressure; IM, intramuscular; iNOS, inducible nitric oxide synthase; L-NAME, Ng-nitro-L-arginine methyl ester; L-NMMA, L-NG-monomethyl arginine; L-NNA, L-NG-monomethyl arginine; L-arginine; L-NMMA, N-methyl-D-aspartate; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; NOS, nitric oxide synthase; NSAIDs, non-steroidal anti-inflammatory drugs; nVNS, non-invasive vagal nerve stimulation; PaCO2, partial pressure of carbon dioxide; PH, paroxysmal hemicrania; REM, rapid eye movements; TACs, trigeminal autonomic cephalalgias; TCC, trigeminocervical complex; TDS, ter die sumendum, three times a day; Tmax, time at which the Cmax is observed; SSN, superior salivatory nucleus.

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HEADACHE continua (HC), and a recognized, yet not obligate response in others, such as cough headache. The reason(s) why this drug, unique among all the nonsteroidal anti-inflammatory medications, is particularly effective is unknown. Indomethacin has also been used for other diverse indications, including the treatment of hypercalcemia associated with certain neoplastic diseases, dysmenorrhea, premature labor, and patent ductus arteriosus closure. Currently, indomethacin is FDA approved only for osteoarthritis, rheumatoid and gouty arthritis, ankylosing spondylitis, or acute painful shoulder.

METHODS

We used the PubMed and Cochrane databases in September 2020 to perform a narrative literature review and searched for the following keywords: “Indomethacin-responsive headaches,” “Indomethacin-sensitive headaches,” “Indomethacin pharmacology,” “Indomethacin AND intracranial pressure,” “Indomethacin AND prostaglandins,” and “Nitric oxide AND Indomethacin.” Articles addressing pharmacology, clinical trials, and observational studies were included. The search included publications in English and Spanish. The reference lists of relevant and recent articles focusing on indomethacin-responsive headaches and potential alternatives were also reviewed and added if considered appropriate.

PHARMACOKINETICS

Indomethacin was, along with aspirin, one of the compounds used by John Vane to discover nonsteroidal anti-inflammatory drugs’ (NSAIDs) essential activity as a prostaglandin inhibitor in 1971, which subsequently led to him winning the Nobel Prize in Physiology or Medicine in 1982, shared with Bergström and Samuelsson for their work with prostaglandins.

Indomethacin (international nonproprietary name standardized by changing British spelling- th to t) is an NSAID. The chemical name of indomethacin is 1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid. It is relatively insoluble in water at neutral pH. It belongs to the group of acetic acids, as well as sulindac and tolmetin, in contrast to other usual NSAIDs, such as naproxen or ibuprofen, which are propionic acids.

There are several formulations available: capsules, extended-release capsules, suppositories, and injectables. Dose presentations range from 25 to 100 mg and vary by country. Treatment usually starts with a minimum dose of 25 mg three times per day and, if there is no response, should be increased to a daily dose of at least 150–275 mg to evaluate its efficacy properly. See Table 1 for a summary of the main pharmacological characteristics.

| Formulations | Capsules 25, 50 mg (28 units) |
|--------------|-------------------------------|
|              | Extended-release capsules 75 mg (100 units) |
|              | Suppositories 100 mg (10 units) |
| FDA approved | Not for headache |
| Dose and posology | From 25 mg TDS to at least 50 mg TDS |
|              | Posology every 8 h (half-life around 7 h) |
| Absorption   | Quick, reaches peak plasma levels in 1–2 h |
|              | 100% capsules, 80% suppositories |
|              | Slower in sustained release. Lower peak, but more maintained |
| Plasma half-life | Around 7 h (between 1.5 and 16 h) |
| Plasma protein binding | <90% |
| Excretion    | 60% renal, 40% biliary |
| Distribution | Crosses blood–brain barrier |
|              | Crosses the placenta |
|              | A low amount is excreted in human breast milk, maximum estimated infant daily dose: 0.006 mg/kg |
| Adverse events | Gastric disturbances, hemorrhage, confusion, headache |
| Main interactions (risk of hemorrhage) | Other nonsteroidal anti-inflammatory drugs |
|              | Antiaggregants or anticoagulants |
| Precautions  | Quinolones: decrease seizure threshold |
|              | Drugs with renal clearance: nephrotoxicity |
|              | Levels of digoxin, methotrexate, and lithium could increase |

Abbreviation: TDS, ter die sumendum, three times a day.

*Data of formulations obtained from BNF in December 2020. Please see text for specific references.
Absorption

Indomethacin is readily and quickly absorbed after oral administration, with peak plasma concentrations achieved after 1 or 2 h, although this rate of absorption may vary depending on particular situations, such as food ingestion. The fastest rate of absorption has been seen in fasting subjects. The bioavailability of the capsules and suppositories is 100% and 80%, respectively, relative to the equivalent intravenous dose, and there is no difference regarding effectiveness and side effects experienced between these routes of administration. The sustained-release formulation of indomethacin 75 mg contains around 300 individual pelletized particles, of which 25 mg are uncoated and available for immediate release, and the remaining 50 mg are coated with a slow-dissolving polymer that permits a gradual dissolution. Its absorption is initially slower, and peak of plasma concentration or \( C_{\text{max}} \) is around 55% lower than that of the nonsustained-release capsules, but plasma levels of indomethacin are more stable during the following 8 h, in comparison with immediate release. Interestingly, analgesic activity of indomethacin is not related to plasma or cerebrospinal fluid (CSF) concentrations.

Mean unbound free plasma concentration reaches its peak at around 2 h. Plasma half-life ranges from 1.5 to 16 h, with a mean half-life of approximately 7 h, which usually involves the necessary posology of administration twice or thrice per day. This variability in plasma concentrations may be due to enterohepatic circulation, which is highly irregular. The plasma half-life does not change when comparing the oral and rectal formulations. At therapeutic concentrations, there is at least 90% of plasma protein binding.

The pharmacokinetics of indomethacin follows a linear and dose-dependent pattern.

Distribution

The high lipid solubility permits indomethacin to cross the blood–brain barrier easily, possibly by penetrating the meninges by simple diffusion. The drug can be detected in the CSF half an hour after administration, according to a study on 52 patients with chronic lumbar pain due to radicular compression that received a single 50 mg intramuscular injection. The tight binding of indomethacin to plasma proteins, especially albumin, may play a role in the low distribution of the drug to the CSF, given the lower amount of free indomethacin available in plasma. A close relationship between the levels of indomethacin in the CSF and free plasma levels has been suggested. The slight elevation of CSF levels of indomethacin compared with plasma levels might be due to the binding of indomethacin in the CSF.

Indomethacin crosses the placenta easily and a low amount of the drug is excreted in human breast milk.

Excretion

The excretion of indomethacin is shared; about 60% corresponds to renal excretion as a glucuronidated form, and the remaining 40% has a rapid biliary secretion. This is associated with biliary recycling. Three metabolites that are pharmacologically inactive can be recovered from urine, and the proportion of unchanged recovered indomethacin increases with alkalization. The drug has a plasma clearance of 1-1.5 ml/kg/min.

PHARMACODYNAMICS

Adverse events can be present in more than 30% of patients, and the majority of them are within the gastrointestinal spectrum. Side effects such as dyspepsia, nausea, vomiting, abdominal pain, or diarrhea were frequently reported, and some patients may mitigate these effectively with gastric protection agents, such as ranitidine, proton pump inhibitors, or antacids. Gastric side effects were not different when comparing the oral and rectal administration, and there is no mucosal damage when applied intrarectally. Adverse events involving the central nervous system (CNS), such as headache or lightheadedness, have been reported and suggested in line with a possible direct central action of indomethacin. Acute pancreatitis and liver failure have been reported, as well as complications in diverse systems, including hematological, reno-urinary, ocular, or pulmonary. A thorough review of these can be found in the review by Lucas. Ophthalmic and blood examinations are advisable when administered long term.

The interactions with other anti-inflammatory drugs, either corticosteroids or NSAIDs, are especially important regarding the increased probability of gastrointestinal bleeding, and it must be used with caution when coadministered with enoxaparin, acenocoumarol, or other anticoagulants, as well as when combined with thrombolytic medication. It may also increase the concentration of salicylate or diflunisal. Interactions with certain antibiotics, such as ciprofloxacin or levofloxacin, may decrease seizure threshold. Hypotensive drugs including angiotensin converting enzyme inhibitors, diuretics, or probenecid may also interact with indomethacin, and careful attention must be paid when administered with other drugs with renal clearance, such as acyclovir or aminoglycosides, and particularly given the patient population, lithium, to avoid nephrotoxicity. Digoxin, methotrexate, and lithium levels should be monitored regularly, as these may increase.

MECHANISM OF ACTION

The unique effect of indomethacin on certain headache disorders is unknown and may not be the same for each disorder. Aside from the well-known inhibition of cyclooxygenase, in other activities, such as reduction of cerebral blood flow (CBF), the inhibition of nitric oxide (NO) pathways or attenuation of oxidative stress may be important.

Initially, described as “rabbit aorta contracting substance,” cyclooxygenase (COX) isoforms 1 and 2 participate in the synthesis of prostaglandins from arachidonic acid. COX-1 preferentially, compared to COX-2, reversibly inhibited by indomethacin, consequently
blocking the synthesis of prostaglandins. Selective COX-2 inhibitors, such as celecoxib or rofecoxib, have also proven efficacy in some patients with indomethacin-responsive headache disorders, although this can be highly variable between patients. This inhibition, which could be easily correlated with its anti-inflammatory and antipyretic action, is less likely to explain all of its analgesic activity.

**REGULATION OF INTRACRANIAL PRESSURE AND CEREBRAL BLOOD FLOW**

The regulation of intracranial pressure may play an important part in the action of indomethacin on traumatic brain injury, as well as cough, exertional, or sexual headaches, when a peak in intracranial pressure is proposed as the underlying pathophysiology.

In experimental models of intracranial hypertension, indomethacin caused a decrease of intracranial pressure, and at higher doses, also CBF, venous pH, and electrocortical activity, along with an increased difference in arteriovenous oxygen. In human studies, indomethacin was able to reduce the CSF opening pressure in patients with idiopathic and posttraumatic intracranial hypertension. Furthermore, it causes a reduction in CBF after intraventricular and rectal administration and a decreased mean flow velocity in the middle cerebral artery when measured with transcranial Doppler, without ischemic changes. Indomethacin-induced CBF decrease was restored with hypoxia and hypercapnia.

Acetazolamide, a carbonic anhydrase inhibitor, causes extracellular acidosis and an increase in CBF by vasodilation. Compared with diclofenac, another COX inhibitor, indomethacin alone was able to reverse the increment in CBF caused by acetazolamide in rats. This reduction in vessel diameter may, therefore, be mediated by other mechanisms that are not related to the inhibition of prostaglandins.

**PROSTAGLANDINS**

The role of prostaglandins has been studied in different nociceptive pathways. The intramuscular, subcutaneous, and intravenous injections of prostaglandins, used in the 1970s to induce abortion, were reported to be extremely painful. Other studies have proved nociceptive activity in humans and animals, and nociceptive behavior has been inhibited with antagonists of prostaglandin receptors, in preclinical studies.

The function of prostaglandins in headache is not clear. The levels of prostaglandins were elevated and reached a peak at 2 h after the initiation of a spontaneous migraine attack in migraineurs. Prostaglandins have been shown to be capable of triggering an attack. However, following the administration of one antagonist of prostaglandin receptors, neither the headache intensity nor the superficial temporal artery or middle cerebral artery diameter changed. Curiously, salivary levels of prostaglandins are modulated by placebo and nocebo effects, which may be related, to a certain extent, to the benefit seen in some headaches responsive to other cyclooxygenase inhibitors like ibuprofen, where a placebo effect has been seen in up to 50% of patients.

Prostaglandins are not the only substances with vasoactive activity released in the trigeminal endings that may be involved in the nociceptive activity of indomethacin. Levels of molecules including nitrates or calcitonin gene-related peptide (CGRP) were found elevated during the first hour of a spontaneous migraine attack, and a reduction in the levels of CGRP and vasoactive intestinal peptide was seen after treatment with indomethacin in a patient with chronic paroxysmal hemicrania (CPH).

**NEUROPEPTIDES**

Colocalization of nitric oxide synthase (NOS) and CGRP, which has a crucial role in the trigeminovascular system, has been shown in the trigeminal ganglion. NO may lead to the release of CGRP as shown on a rat model experiment, and in cluster headache patients, nitroglycerin, an NO donor, was able to induce headache attacks with elevated plasma CGRP. The serum levels of kininogen, an anti-inflammatory mediator and precursor of bradykinin, one of the substances known to induce the release of NO from endothelial cells, along with histamine, acetylcholine, or N-methyl-d-aspartate (NMDA), were found to be reduced in patients with CPH, which could be translated as an increased production of NO.

**NITRIC OXIDE**

NO is one of the fundamental molecules involved in the regulation of cerebral metabolic activity and blood flow. The release of NO is responsible for the formation of cyclic guanosine monophosphate (cGMP) by the enzyme guanylate cyclase, from Mg2+ and guanosine triphosphate. NO acts as a second messenger for different biological processes such as the relaxation of smooth muscle or the inhibition of platelets. Increased cGMP levels have been seen in some brain areas, and an increase in cGMP concentration in the brainstem was seen after cortical spreading depression (CSD) was evoked. The synthesis of NO in the CNS is dependent on the presence of free intracellular concentrations of Ca2+ and increased concentrations of intracellular Ca2+ may be one of the stimuli needed for the synthesis of NO and the activation of guanylate cyclase in the brain. The local release of NO has also been associated with the activation of NMDA receptors, which are usually linked to ion channels with high Ca2+ permeability and sensitivity to Mg2+ and the prolonged activation of these receptors may lead to neuronal cytotoxicity.

NO and prostaglandins may share common pathways, where they act synergistically, and the synthesis of prostanoids may play
NOS inhibitors, such as the inhibition of platelet aggregation, vascular inflammation, or leukocyte motility.\textsuperscript{72}

NO is known to induce headache in healthy subjects, and NO donors have been largely used in experimental models of headache. The intravenous infusion of nitric oxide donors triggers attacks in patients with migraine with\textsuperscript{73,74} or without aura\textsuperscript{74,76} and cluster headache.\textsuperscript{74,77} Systemic administration of nitroglycerin in preclinical models causes hyperalgesia\textsuperscript{78} and the activation of several brain areas, related to nociceptive and autonomic pathways, including spinal trigeminal nucleus caudalis, locus coeruleus, periaqueductal gray matter, or the nucleus tractus solitarius.\textsuperscript{79} The spinal expression of nNOS and eNOS was increased following the intradermal administration of capsaicin in a rat model and was appropriately inhibited by specific inhibitors.\textsuperscript{80} Likewise, NO may be implicated in neuronal sensitization in patients with migraine, which would be translated clinically as increased cutaneous allodynia.\textsuperscript{81}

In a preclinical model of trigeminovascular nociception, indomethacin proved to inhibit dural vasodilation elicited by using electrical stimulation or NO donors. However, it was unable to inhibit CGRP-induced dural vasodilation.\textsuperscript{82} Histamine, another substance with vasoactive properties and known to cause headache when infused in humans,\textsuperscript{83} was also a plausible candidate to be the target of indomethacin acting through NO. However, the infusion of methapyramine, an antagonist of the histamine H1 receptor, was unable to prevent headache induced by nitroglycerin.\textsuperscript{84} Indomethacin, as well as sumatriptan, partially blocked the dilation of meningeal blood vessels caused by NO, which was not reproducible with either the histamine receptor antagonists or flunarizine.\textsuperscript{85}

Notwithstanding, the efficacy of indomethacin may not even be related to its vasoactive properties, as has been the case with other NSAIDs,\textsuperscript{86,87} as it is not plausible that vasodilation acts as an exclusive cause of pain in primary headache disorders.\textsuperscript{88}

The direct implication of indomethacin in the CNS is supported by a recent study using an established animal model of trigeminovascular nociception. This study compared the response of postsynaptic second-order neurons in the trigeminocephalic complex (TCC) to indomethacin and naproxen at therapeutic doses, when activated by local micro-iontophoresis of L-glutamate or administration of a NO donor. While naproxen was able to inhibit dural-evoked firing and the firing evoked by L-glutamate, indomethacin was the only drug capable of inhibiting, along with the two previous triggering mechanisms, the firing induced by an NO donor.\textsuperscript{89}

The nitrergic hypothesis promoted the investigation of the inhibition of the synthesis of NO, which has been tested with general and specific NOS inhibitors. The synthesis of NO was first inhibited by Palmer and colleagues by using L-NG-monomethyl arginine (L-NMMA).\textsuperscript{62} Since then, the arginine-based inhibitors of NOS have been tried in headache.

The inhibition of the synthesis of NO in preclinical models, using the unselective NOS inhibitor Ng-nitro-L-arginine methyl ester (L-NAME) blocked the associated hyperemia during CSD, but not the neuronal firing, provoked after needle stick injury.\textsuperscript{65} When using L-NAME or another nonselective inhibitor, NG-nitro-L-arginine (L-NNA) in CSD, pial arteriolar dilation was significantly reduced.\textsuperscript{90,92} When indomethacin was administered, arterioles were dilated. When administered together with L-NNA, indomethacin abolished the effect of L-NNA on CSD-induced dilation. L-NNA inhibited topical acetylcholine-induced arteriolar dilation, and this effect was not altered by indomethacin.\textsuperscript{92}

NO synthesis blockers and headache

The first attempt to inhibit nonselectively NOS enzymes with L-NG methylarginine hydrochloride in spontaneous attacks of migraine without aura was effective in reducing headache and associated symptoms.\textsuperscript{85} The available data for the inhibition of NO-histaminergic pathways via L-NMMA in headache come from some studies that should be noted. One study used L-NMMA to assess subjective symptoms and hemodynamic effects of intravenous infusion of histamine. The infusion of L-NMMA was able to modify significantly the initial increase in the estimated local pulsatile blood flow in selected ocular vessels, caused by histamine. The authors stated that L-NMMA did not mitigate subjective symptoms. However, none of the subjects developed a "pulsating headache" after histamine. Additionally, there was a decrease in the level of "discomfort or sensation" when comparing the graphs, especially with higher dose of L-NMMA, but neither the statistics for this decrease nor the meaning of discomfort were described in the paper.\textsuperscript{94} In another study, pre-treatment with L-NMMA in patients with migraine did not prevent the headache triggered by histamine.\textsuperscript{95} However, the dose might have been insufficient, and the infusion of L-NMMA was not maintained during the histamine infusion, which may have affected the experiment, taking into account that the $T_{\text{max}}$ is achieved at 1 min after bolus finalization.\textsuperscript{96} Interestingly, L-NMMA had an analgesic effect in patients with chronic tension-type headache.\textsuperscript{97}

The specific blockade of the three NOS isoforms has also been explored in headache. Inhibition of i-NOS was not effective in reducing neurogenic and CGRP-induced dural vasodilation in preclinical studies\textsuperscript{98} has not proved to be effective in the treatment of migraine, either as an acute\textsuperscript{11} or preventive\textsuperscript{99} medication. However, the vasodilation induced by CGRP can be partially inhibited by eNOS inhibitors, although this caliber change is unresponsive to the specific inhibition of nNOS, which was nonetheless capable of inhibiting neurogenic dural vasodilation.\textsuperscript{98} When nNOS was disrupted in mutant mice after focal ischemia, depolarization manifesting as spreading depression-like waves were fewer than those compared with wild-type animals, with also lower levels of glutamate and gamma aminobutyric acid (GABA).\textsuperscript{100} A combination of one of the nNOS inhibitors with a triptan did not show a statistically significant difference in headache when taken during the aura phase, compared with placebo, in a study that may have been underpowered.\textsuperscript{101}
Indomethacin-responsive headaches

The group of primary headaches known as “indomethacin-responsive” has, paradoxically, only a moderate level of evidence, as indomethacin has not been tested in randomized, controlled trials (Table 2).

TRIGEMINAL AUTONOMIC CEPHALALGIAS

Trigeminal autonomic cephalalgias (TACs) are rare headache disorders characterized by severe unilateral headache, usually involving the first two branches of the trigeminal nerve, along with ipsilateral cranial autonomic symptoms (CAS). In accordance with the latest ICHD-3, at least one CAS should be present. These include lacrimation, conjunctival injection, nasal congestion, rhinorrhea, palpebral edema, forehead and facial sweating or flushing, ear fullness, miosis, and/or ptosis. Aside from cluster headache, the most prevalent type of TAC, there are three other types that differ in the duration and frequency of the attacks. Namely, HC, PH and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing or short-lasting unilateral neuralgiform headache attacks with CAS.

Understanding the complex pathophysiology of indomethacin-responsive TACs and their cranial autonomic pathophysiology may help us recognize some of the key structures that indomethacin may act on as a therapeutic target. As for migraine, in TACs, there is an involvement of the trigeminovascular system formed of dural and pial vessels, sensory fibers from both the first branch of the trigeminal nerve and C1-C3 dorsal ganglia, which converge in the caudal part of the spinal trigeminal nucleus or nucleus caudalis to form the TCC. Second-order neurons emerge from the TCC and ascend to reach the thalamus through the trigeminothalamic tract, which has connections with the hypothalamus, periaqueductal

| Headache type                                | Studies                  | N  | Dose                        | Efficacy                             |
|----------------------------------------------|--------------------------|----|-----------------------------|--------------------------------------|
| Hemicrania continua                          | Cittadini et al.        | 31 | 30–500 mg/day               | 100% (complete remission)            |
|                                              | Prakash et al.           | 30 | 25–100 mg TDS               | ≈100% (not specified)                |
| Paroxysmal hemicrania                        | Boes et al.              | 40 | 25–225 mg/day               | 75% (60% complete remission)         |
|                                              | Cittadini et al.         | 31 | 100–200 mg (1 IM dose vs. placebo) | 100% (100% complete remission) |
| Primary cough headache                       | Chen et al.              | 55 | 25 mg TDS                   | 72% (43.6% complete remission)       |
|                                              | Raskin et al.            | 16 | 50–200 mg/day               | 88% (4 with additional treatment)    |
|                                              | Pascual et al.           | 9  | 50–100 mg/day               | 100% (not specified)                |
|                                              | Pascual et al.           | 6  | 75 mg/day                   | 100% (not specified)                |
| Primary exercise headache                    | Diamond et al.           | 15 | 25–150 mg/day               | 80% (27% complete remission)         |
| Primary headache associated with sexual activity | Frese et al.            | 10 | 25–50 mg 30 min before sex | 90%                                  |
|                                              | Huang et al.             | 8  | 25–50 mg 30 min before sex | 88%                                  |
|                                              | Pascual et al.           | 2  | 25 mg TDS                   | 100%                                 |
| Hypnic headache                              | Silva-Néto et al.       | 70b| Heterogeneous (25–150 mg/day or ON) | 51.4% (45.7% "good response") |
| Primary stabbing headache                    | Fuh et al.               | 46 | 59 ± 16 mg/day              | 74% (=50% complete remission)        |
|                                              | Pareja et al.            | 17 | 75 mg/day for 15 days       | 65% (35% complete remission)         |
|                                              | Guerrero et al.          | 10 | 130 ± 35 mg/day             | 90% (20% complete remission)         |

Abbreviations: IM, intramuscular; TDS, ter die sumendum, three times a day.

Two patients did not tolerate oral indomethacin and received suppository formulation.

Recent review including small case series and case reports available to date. Efficacy was not measured using the same method among studies. Complete remission of headaches, which is currently part of the diagnostic criteria for HC and PC, is included when available (in parenthesis).

Table 2

Primary headache disorders responsive to indomethacin

| Headache type                                | Studies                  | N  | Dose                        | Efficacy                             |
|----------------------------------------------|--------------------------|----|-----------------------------|--------------------------------------|
| Hemicrania continua                          | Cittadini et al.        | 31 | 30–500 mg/day               | 100% (complete remission)            |
|                                              | Prakash et al.           | 30 | 25–100 mg TDS               | ≈100% (not specified)                |
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gray and locus coeruleus. From the thalamus, third-order neurons reach structures involved in the cortical pain network. The trigeminal-autonomic reflex has a paramount role in TACs. The TCC is connected with the superior salivatory nucleus (SSN). From the SSN, preganglionic parasympathetic fibers travel along with the intermedius nerve, branch of the VII cranial nerve, and then through the greater petrosal nerve. These fibers, in conjunction with sympathetic preganglionic fibers, form the nerve of the pterygoid canal. The parasympathetic fibers then synapse in the sphenopalatine ganglion. Postganglionic fibers innervate lacrimal and nasal glands as well as dural vessels, and the consecution of this reflex explains the relationship between the pain and the characteristic ipsilateral CAS.

Indomethacin was able to inhibit neuronal firing in the TCC evoked by the stimulation of the SSN. The hypothalamus has been hypothesized as a key structure in the generation of headache attacks. This is partly based on its implication in circadian rhythms and the typical periodicity of the most common TAC, cluster headache. Indeed, one of the hypotheses points to increased production of NO by the suprachiasmatic nucleus of the hypothalamus. Specifically, the firing of the A11 hypothalamic nucleus was attenuated when an NO donor was infused, and this attenuation was blocked in animals pretreated with indomethacin. Functional neuroimaging studies have shown activation of the ipsilateral hypothalamus in PH and HC, and an activation of the posterior hypothalamic and dorsal rostral pontine areas was seen in imaging studies using positron emission tomography.

Paroxysmal hemicrania and hemicrania continua

The first case of PH was described by Sjaastad and Dale in the 1970s, and the extraordinary response to indomethacin has been noted since then. The first case of HC was described by Sjaastad and Spierings in 1984 and was probably missed as an entity a few years earlier. The clinical presentation of these may overlap and can be difficult to distinguish from other primary headaches. An in-principle issue that needs to be borne in mind when considering these syndromes is how to treat partial indomethacin responders or patients who cannot be exposed for various reasons. We would argue that retaining an absolute requirement for an indomethacin effect is essential to make progress in research in this area to understand indomethacin's effect. This approach does not materially alter clinical practice.

PH is defined by ICHD-3 as severe and strictly lateralized attacks, occurring at least 5 times a day, and lasting for 2–30 min, associated with either restlessness or CAS and with an absolute response to indomethacin. In the chronic form, attacks occur for more than 1 year or with remission periods lasting less than 3 months. PH has a prevalence of 0.5 per 1000 individuals in the general population. In contrast with cluster headache, which has a male predominance, PH has been documented more frequently in women between 30 and 40 years of age.

Indomethacin can abolish spontaneous attacks of CPH and also those triggered by the NO donor glyceryl trinitrate (GTN), supporting the nitrergic hypothesis. Headache response to indomethacin has been described from 12.5 to 300 mg daily in a series of 74 patients with CPH, around 75% had a consistent response to indomethacin. The majority of patients had an average effective daily dose of 75 mg. Five patients did not respond to maximal doses of 150 mg. Two patients had an initial response to indomethacin, and this effect was lost. With cessation of the treatment, 9/13 patients could discontinue indomethacin without headache recurrence. However, in a study on PH that involved 31 patients, two thirds experienced side effects.

HC is defined as a lateralized headache that is persistent for more than 3 months and is also associated with ipsilateral CAS or restlessness, sometimes migrainous features, and responds absolutely to therapeutic doses of indomethacin. In the remitting subtype, the pain can be interrupted by remission periods that last for at least 24 h, whereas in the unremitting subtype the pain is continuous, without remissions of more than 24 h, for more than 1 year. Because of the differential diagnosis with chronic migraine, the prevalence of HC is probably underestimated. In line with this, a high incidence of HC was demonstrated when reviewing consecutive patients attending an orofacial pain clinic.

In a retrospective review of 192 cases using indomethacin 150 mg or more for 2 weeks or 225 mg for 1 week, 43 had an absolute response to indomethacin. In another retrospective analysis of 62 patients with diverse clinical presentations, daily doses of 25–300 mg were used. The response to indomethacin may be delayed up to 4 weeks for some patients and an incomplete relief of the symptoms is frequent, although a differential diagnosis with lateralized migraine in such cases remains possible.

Trials with either oral or parenteral doses of indomethacin, the so-called "Indotest," are encouraged in all patients presenting with lateralized headache. The interval between indomethacin discontinuation and pain reappearance ranges from 4 to 28 h. Long-term treatment with indomethacin is safe and generally well tolerated in most patients, with no major adverse events. With time the dose can be reduced for better longer term tolerability.

COUGH HEADACHE

Since first described by Sir Charles Symonds in 1956, primary cough headache (PCH) has not been reported upon often. Only a few studies have led to the description of the main features and the diagnostic criteria. According to the latter, it is a short-lasting (1 s to 2 h), sudden headache, brought on by and occurring only in association with coughing, straining, and/or other Valsalva maneuver. Its prevalence is thought to be around 1%, although it could affect up to 20% of patients in Cough Units. According to the currently available data, PCH occurs mainly in subjects over the age of 40 years, with the mean age of onset being 67 years. A male predominance has been described, although the male/female ratio varies among series. Interestingly, it seems to behave as a self-limited disease as the course of the symptoms normally lasts less than 2 years. Pain is usually localized...
bilaterally, with a major involvement of the occipital region. Pain quality, however, has been described as sharp, stabbing, splitting, explosive, electrical, pressing, dull, or even pulsatile. Precipitants may include not only coughing but also other Valsalva maneuvers, such as sneezing, nose blowing, laughing, crying, lifting a weight, straining at stool, and so on. However, triggers should not include sustained physical exercise, which would be typical of primary exercise headache.1

Regarding the headache-associated features, nausea, dizziness, and photophobia or phonophobia, typically associated with migraine, have been documented in a small proportion of patients.108,109,144,145 Vertigo, ataxia, and syncope have been reported as potential red flags that point to a possible secondary cause.109

The differential diagnosis with secondary or symptomatic cough headache is important. The most common reported cause of secondary cough headache is Chiari malformation type 1.145 In fact, any posterior fossa lesion could lead to similar symptoms. Other reported causes include syringomyelia, platybasia, obstructive hydrocephalus, subdural hematoma, sphenoid sinusitis, spontaneous intracranial hypotension, brain aneurysm, and even carotid artery disease.146 Overall, it is considered that almost 50% of cough headaches are symptomatic or secondary.1

The pathophysiology of cough headache is still uncertain, although different theories have been proposed. A study involving 16 patients showed that a modified Valsalva maneuver was capable of distinguishing primary from secondary headache.147 Following this result, the authors hypothesized that a transient increase in intracranial pressure during exertion due to obstruction to normal CSF dynamics may lead to secondary cough headache. Conversely, they discussed PCH may be related to congestion of the orbital venous plexus148 in the presence of jugular venous incompetence and a reduced threshold for trigeminal sensory activation.149 On the other hand, Chen and co-workers argued that a relative obstruction of CSF flow could take place given a more crowded posterior fossa in PCH patients that they described.149

PCH may respond to indomethacin, as shown in an open label trial involving 16 patients who received doses ranging from 50 to 200 mg daily.107 To what extent this is related to the fact that indomethacin may reduce CSF pressure is not known. Interestingly, other treatments such as topiramate, which is known to act as a carbonic anhydrase inhibitor and, therefore, reduce CSF pressure, have not been shown useful for the treatment of PCH.146

**PRIMARY EXERCISE HEADACHE**

The prevalence of primary exercise headache ranges from 1% to 30%150,151 without a clear gender predisposition.108,150,152–154 The highest prevalence was found in adolescents.150 Onset of head pain occurs during or within 30 min of exercise termination1,153,155 and is typically a pulsating unilateral or bilateral frontal headache.150,153,155 Headache duration is typically between 1 min and 1 day although rarely it can last up to 2 days.152,153,155 Associated features, typically associated with migraine such as nausea, vomiting, photophobia, and phonophobia, can be associated with the headache of primary exercise headache and are more frequently reported in females.150,156 Most patients undergo spontaneous resolution within 1 year of onset.152 Different hypotheses have been proposed for the pathophysiology of headache related to exertion, and the majority involve a change in intracranial pressure.33

First-line management of primary exercise headache is modification of exercise for prevention. In cases where this is not effective or ideal, indomethacin 25–150 mg daily is effective in the prevention or amelioration of primary exercise headache in over 80% of patients.109,157,158 We have recently used gepants, CGRP receptor antagonists, as an unlicensed pretreatment approach and found them useful.

**PRIMARY HEADACHE ASSOCIATED WITH SEXUAL ACTIVITY**

Despite being roughly described by Hippocrates as headache related to “immoderate venery”, it was not until the early 1970s when that the first series of patients were reported.159–162 Over time, three different types of headaches have been described,108 although the distinction is no longer in vogue.1 The so-called type 1 was characteristically defined as tension that occurred and progressed with sexual excitement.159 On the other hand, type 2 was described as sudden, explosive, and would occur close to or with orgasm, being called orgasmic headache.159 Currently, either one of the two or both types are accepted in the classification and included under the same nomenclature.1 The headache can last with severe intensity from 1 min to 24 h. The pathophysiology of “type 1” has been related to muscle tension, particularly involving the jaw muscles. Lance hypothesized type 2 was due to a hyperdynamic circulatory state, and this has not been refuted to date.159 Indeed, a relationship between this and exertional headache, currently known as primary exercise headache, was suspected, and the coexistence of both was documented in many patients.111 The coexistence has not been our experience; indeed headache associated with sexual activity in our experience almost never occurs with cough or exertional headache. Hemodynamic changes leading to stretching of certain intracranial structures were hypothesized for both headaches.163 The third type of headache, no longer considered sexual headache, appears after sexual intercourse and resembles that of spontaneous intracranial hypotension and is attributed to a CSF leak.1

Limited noncontrolled data on the best treatment exist. As a preventive therapy, beta-blockers were efficacious in 15 out of 18 patients111 and have been recommended as a first-line drug.109 Regarding indomethacin 25–50 mg, this showed efficacy as a preventive in 9 out of 10 patients, taken 30–60 min prior to intercourse. The same dose of indomethacin has also shown efficacy as an acute medication. Interestingly, this contrasts with a lack of efficacy of other NSAIDs pointing to a different mechanism of action. Triptans have also demonstrated utility as acute medications in some cases.111 Again, we have recently used gepants, CGRP receptor antagonists,
as an unlicensed pretreatment approach and found them useful. Our experience is that diltiazem can be useful for persistent headache associated with sexual activity.

**PRIMARY STABBING HEADACHE**

In comparison with the other primary indomethacin-sensitive headache disorders described herein, the prevalence of primary stabbing headache is dramatically greater in approximately one third of the general population, although this finding has not been reproduced in clinic-based studies. There is a female predominance where the female-to-male ratio in population-based studies is 1.49:1. The mean age of onset, in adult populations, ranges from 28 to 53 years of age with eldest reported age of onset at 83. The mean range of onset in pediatric cases range between 4.5 and 12 years of age with cases reported in children as young as 1.5 years of age. In our clinical experience, primary stabbing headache can be exceptionally disabling in children in a manner not often seen in adults. In approximately 70% of cases, the pain is experienced at extratrigeminal locations and can be either unilateral or bilateral. Attacks typically range from 0 to 3 s without discernable regularity although attacks lasting up to 120 s have been reported but are rare. These are usually not associated with CAS, and typical migraine features of photo sensitivity, phonosensitivity, and nausea are infrequent.

Approximately two thirds of patients with primary stabbing headache will have a partial or complete response to indomethacin with doses between 50 and 75 mg. In a smaller cohort study, up to 70% have a partial response, and 20% had complete remission with 120 mg of indomethacin daily. Indomethacin 50 mg three times daily in a small study of five patients resulted in a significant improvement.

**HYPNIC HEADACHE**

In 1988, Raskin described a headache distinct to cluster that also occurred with clockwork regularity and was responsive to lithium. Hypnic headache is a rare primary headache disorder with a prevalence between 0.07% and 0.1% of the population reviewed for headaches. Presenting patients typically present in their fifth decade of life with an average age of 58. Hypnic headache is most frequently described in the adult population with an age range between 18 and 85. However, five pediatric cases have been described. It is more common in females with a ratio of 2:1. Attacks most commonly occur between the hours of 2 and 4 a.m. and last for an average of 90 min. The pain experienced is typically dull and involves the connections between the midbrain periaqueductal gray matter, the noradrenergic locus coeruleus, and serotonergic raphe nuclei with the suprachiasmatic hypothalamic nuclei, which may influence the release of melatonin. In fact, melatonin is a molecule with a structure analogous to that of indomethacin, and a comparable clinical efficacy has been reported. Interestingly, melatonin was higher when comparing serum levels of nine hypnic headache patients and controls at different times, especially during the headache attack, although the differences did not reach statistical significance. Moreover, structural changes associated with this axis have been described. Using voxel-based morphometry in magnetic resonance images of patients with hypnic headache, a decrease in gray matter was observed in the periaqueductal area, as well as other cortical areas related to nociceptive processing. Hypnic headache does not seem to be related to the sleep stage, according to polysomnography studies, and it may be related to interrupted rapid eye movements (REM) sleep or hypoarousals due to a higher cyclic alternating pattern.

Indomethacin has been proposed as the third-line prophylactic treatment after caffeine and lithium. A number of case reports and case series have described partial to complete relief or prevention of attacks with the use of oral indomethacin, and doses between 25 and 150 mg orally before bed have been reported to be effective. In one case series, indomethacin has been proposed to be more efficacious in patients who only experience unilateral pain. Paradoxically, some patients who report resolution of nocturnal headache with indomethacin experience diurnal attacks, which resolve with cessation of indomethacin.

**MIGRAINE**

Migraine is not considered as an "indomethacin-responsive" headache. In comparison with other NSAIDs— aspirin, diclofenac, ibuprofen, and naproxen—there is a paucity of evidence to support the use of indomethacin for acute treatment of migraine. More recently, indomethacin in combination with prochlorperazine and caffeine has been compared with sumatriptan in two trials. The first study compared a combination of indomethacin 25 mg, prochlorperazine 4 mg, and caffeine 75 mg rectally to rectal sumatriptan 25 mg. The combination was superior to sumatriptan in aborting attacks. There was no difference in pain reduction between the combination and sumatriptan. In the second trial, indomethacin 25 mg, prochlorperazine 2 mg, and caffeine 75 mg orally was compared against oral 50 mg sumatriptan. In this study, there was no difference between the combination and sumatriptan in reducing pain intensity or successful abortion of a migraine attack 2 h after treatment.

**SECONDARY HEADACHES**

Within the category of secondary headaches, we find several diagnoses whose pathophysiology is related to an increase of intracranial
pressure, such as those attributed to craniotomy, idiopathic intracranial hypertension, or traumatic brain injury. Severe intracranial hypertension following a head trauma is one of the main predictors of poor outcome.

Indomethacin causes a lasting decrease in intracranial pressure, as well as in CBF when administered intravenously to patients with secondary intracranial hypertension. The effects of indomethacin 30 mg bolus followed by 30 mg/h for 7 h were compared with those of hyperventilation in patients with severe traumatic brain injury, showing a decrease in intracranial pressure (ICP) similar to that of a decrease in PaCO₂ of 6.6 mmHg, although not all the patients responded to both mechanisms, suggesting an independent action. Higher doses (50 mg bolus) reduced intracranial hypertension. This also improved cerebral perfusion pressure in patients with severe traumatic brain injury, but this change was not significant with a prolonged infusion. The perioperative infusion of indomethacin 50 mg also decreased intracranial pressure in patients intervened for supratentorial tumors.

**New approaches to indomethacin-sensitive headache disorders**

Although the possible link is ill-understood, recent evidence suggests indomethacin-responsive headaches may also respond to noninvasive vagal nerve stimulation (nVNS). The unilateral stimulation of the cervical tract of the vagal nerve inhibits trigeminal autonomic reflex bilaterally. This effect may be mediated by the hypothalamus, by the SSN, or by connections with other cerebral structures. It may also have a modulation role in the levels of extracellular neurotransmitters, such as a reduction in the increased levels of glutamate in the trigeminal nucleus caudalis when GTN was administered. nVNS was approved for the prevention of cluster headache following two randomized controlled trials. Similar studies are lacking on indomethacin-responsive headaches. However, a clinical audit in 15 patients with HC or PH showed efficacy with at least a reduction in headache intensity in 11/15. nVNS was similarly useful for both conditions, with efficacy observed in seven of nine patients with HC and four of six patients with PH. Based on this potential link, a patient with indomethacin-responsive cough headache who had a contraindication for indomethacin was effectively treated with nVNS.

**CONCLUSIONS**

The only headache disorders that include responsiveness to indomethacin as part of the diagnostic criteria are HC and PH. Yet, other headache types described herein have been effectively treated with indomethacin. The mechanism behind this distinctive response, as previously discussed, has not been fully elucidated and could be linked to a direct effect on the CNS.

Indomethacin, albeit generally well tolerated, has important side effects, particularly gastrointestinal intolerance, and CNS side effects, and remarkably can induce headache of a generalized type in patients who also have a personal or family history of migraine. A better understanding of the mechanism of action of indomethacin will lead to more specific and better tolerated treatments for rare yet highly disabling disorders.

**CONFLICT OF INTEREST**

Dr. Goadsby reports personal fees from Aeon Biopharma, personal fees from Alder Biopharmaceuticals, grants and personal fees from Amgen, personal fees from Allergan, personal fees from Biohaven Pharmaceuticals Inc., grants from Celgene, personal fees from Clexio, grants and personal fees from Eli Lilly and Company, from Electrocore LLC, personal fees from eNeura Inc, personal fees from Epalex, personal fees from GlaxoSmithKline, personal fees from Impel Neuropharma, personal fees from Lundbeck, personal fees from Mundipharma, personal fees from Novartis, personal fees from Pfizer, personal fees from Praxis, personal fees from Santara Therapeutics, personal fees from Sanofi, personal fees from Satsuma, personal fees from Teva Pharmaceuticals, other from Trigemina Inc, personal fees from WL Gore, personal fees from Dr Reddy’s, outside the submitted work; In addition, Dr. Goadsby has a patent Magnetic stimulation for headache licensed to eNeura without fee and fees for advice through Gerson Lehrman Group, LEK and Guidedpoint, and fees for educational materials from Medery, Medlink, PrimeEd, UptoDate, WebMD, and fees for publishing from Oxford University Press, Massachusetts Medical Society, and Wolters Kluwer, and for medicolegal advice in headache. The others have no disclosures.

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Drafting of the manuscript: María Dolores Villar-Martínez, David Moreno-Ajona, Calvin Chan. Revising the manuscript for intellectual content: María Dolores Villar-Martínez, David Moreno-Ajona, Calvin Chan, Peter J. Goadsby. Final approval of the completed manuscript: María Dolores Villar-Martínez, David Moreno-Ajona, Calvin Chan, Peter J. Goadsby.

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