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Review Article

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Indomethacin-Responsive Headaches in Pediatric Age: Nosographic Aspects and Limitations on the use of Indomethacin in Pediatric Population

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Abstract

Headaches are a common problem in children and adolescents. Indomethacin-responsive headaches are a poorly known and rare group of primary headaches, with few cases during childhood. These include a heterogeneous group of disorders characterized by their response to indomethacin, a non-steroidal anti-inflammatory drug which inhibits cyclooxygenase and therefore the production of prostaglandins. Indomethacin-responsive headaches include Valsalva-induced headaches (cough, exercise or sex headache), primary stabbing headache, hypnic headache and the trigeminal autonomic cephalalgias (TACs) [a group of primary headache disorders that includes cluster headache (CH), paroxysmal hemicrania (PH), hemicrania continua (HC) and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing/cranial autonomic features (SUNCT/SUNA)]. It seems useful to make a review of the literature about these disorders.

Keywords

Children, Headaches, Indomethacin, Pediatric age, Treatments

Abbreviations

ICHD-III beta: International Classification of Headache Disorders, 3rd edition (beta version); **TACs:** Trigeminal Autonomic Cephalalgias; **HC:** Hemicrania Continua; **PH:** Paroxysmal Hemicranias; **CH:** Cluster Headache; **SUNCT:** Short-Lasting Unilateral Neuralgiform Headache with Conjunctival Injection and Tearing; **RES:** Red Ear Syndrome

Introduction

Indomethacin-responsive headaches are a small group of primary headaches, exhibiting a limited number of cases in the childhood. They include a heterogeneous group of poorly known and rare headache disorders characterized by their response to indomethacin, a non-steroidal anti-inflammatory drug. The epidemiology of these conditions is not completely understood and detailed, although there is an emergence of case reports of headaches responsive to indomethacin. Indomethacin-responsive headaches include Valsalva-induced headaches (headache related with cough, exercise or sex), primary stabbing headache, hypnic headache and the TACs. These latter are primary headache disorders characterized by a common clinical phenotype consisting of unilateral pain on one side of the head in the trigeminal nerve area, occurring in association

with ipsilateral cranial autonomic symptoms, such as eye watering and redness or drooping eyelids. Another typical feature of TACs is rhythmicity (particularly in CH). TACs are rarely reported in pediatric age and include CH, PH, HC and short-lasting unilateral neuralgiform headache attacks (SUNCT and SUNA).

Something about indomethacin

Indomethacin is a non-steroidal anti-inflammatory drug (NSAID) available in oral, rectal, intramuscular, and intravenous formulations. Its chemical denomination is 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid. The first use of indomethacin in clinical practice was reported in 1963 [1], but its effectiveness in headache disorder, particularly in patients with migraine, was not proved until 1964 by Sicuteri et al. [2]. In 1974, Sjaastad described the highly-sensitive response to indomethacin in a particular type of headache: the chronic paroxysmal hemicrania (CPH) [3]. Since that year, several other headaches have been highlighted to be responsive to indomethacin. Indomethacin inhibits two isoforms of cyclooxygenase (COX), COX-1 and COX-2, with greater selectivity for COX-1. Indomethacin also inhibits the production of nitric oxide (NO) and is metabolized via the liver. Onset of action is within 30 min and the duration is about 4 to 6 h. However tolerability is one of the major limitations for using this drug. Beginning the treatment at the lowest effective dose is recommended to improve tolerability, since most adverse effects are dose-related. Because of the lack of clinical studies in pediatric age, there are not enough data describing specific side effects in this population. A risk of reduction of cerebral, mesenteric and renal blood flow has been highlighted. The most important side effects of indomethacin are gastrointestinal complications, from dyspepsia to gastrointestinal bleeds and life-threatening bowel perforation. Indomethacin can also damage liver and renal function, and platelet activity. Neurologic side effects are possible, and include fatigue, dizziness and confusion. Potential interactions are reported with beta-blockers, anticoagulants, angiotensin-converting enzyme inhibitors and thiazide diuretics. Indomethacin is not approved for use by anyone younger than 14 years old, therefore pediatric off-label use is possible only after signature of informed consent by the parents and approval of the ethics committee.

If indomethacin is contraindicated or intolerable, other treatment options need to be explored but this is a significant issue for the management of HC and PH, since no other treatments as effective as indomethacin have been reported so far.

Hypothesis of indomethacin's mechanism of action in headache

Indomethacin may exhibit an important effect on some headaches even if the mechanisms are not clear. Most non-steroidal anti-inflammatory drugs easily enter the brain, but their high protein binding levels limits the absolute total amount of entry. Indomethacin, on the other hand, exhibits the highest penetration into the central nervous system. It is a reversible inhibitor of prostaglandin forming COX like other non-steroidal anti-inflammatory drugs, but it can also involve several different mechanisms other than inhibition of the COX enzyme. It may have strong vasoconstrictive activity and unique direct neuronal or NO-dependent inhibitory pathway activity [4]. Some studies reported that indomethacin can decrease intracranial pressure [5, 6]. It also inhibits phosphodiesterase, thereby increasing intracellular cyclic adenosine monophosphate levels. Furthermore, in 2016 Lucas described a specific additional activity of indomethacin directed on parasympathetic outflow pathways to the cranial vasculature [7]. This activity appears to be completely COX-independent.

Review

Given its relationship with a variety of headache disorders, indomethacin has been the subject of various studies and reviews. In this review we focused our attention on original articles reporting the latest important evidences about indomethacin responsive headaches, in general population and mostly in pediatric age.

Cluster headache (CH)

Indomethacin is generally considered to be ineffective in patients with CH, but some cases of indomethacin-responsive CH have been reported, although some may have been misdiagnosed when the diagnosis was based exclusively on the therapeutic response (Table 1).

Table 1: Diagnostic criteria (taken from ICHD-III beta) [8].

A	At least five attacks fulfilling criteria B–D.
B	Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15 - 180 minutes (when untreated).
C	Either or both of the following:
	1. at least one of the following symptoms or signs, ipsilateral to the headache:
	a) conjunctival injection and/or lacrimation
	b) nasal congestion and/or rhinorrhoea
	c) eyelid oedema
	d) forehead and facial sweating
	e) forehead and facial flushing
	f) sensation of fullness in the ear
	g) miosis and/or ptosis
	2. a sense of restlessness or agitation
D	Attacks have a frequency between one every other day and eight per day for more than half of the time when the disorder is active.
E	Not better accounted for by another ICHD-3 diagnosis.

CH is an extremely rare disease in children (0.09 - 0.4% of the pediatric population). Moreover, this headache is often underdiagnosed probably because in children "incomplete

brain development may alter the presentation of TACs" (taken from: Appendix of the International Classification of Headache Disorders, 3rd edition, beta version). Complete and immediate effect of indomethacin was noted even in children if indomethacin was used in maximum therapeutic dosage. In pediatric age, indomethacin can be administered at 2 - 3 mg/kg/day in 2 - 4 doses, up to a maximum of 4 mg/kg/day. In 1994, D'Cruz reported responses to indomethacin in two children with history suggestive of CH [9]. After that, a few other case series of childhood CH responsive to indomethacin were also reported in the literature. In 2002, Isik and D'Cruz described four young children with CH who showed complete response to indomethacin [10]. More recently, in 2009, Majumdar et al. reported eleven children with CH [11]. In this retrospective review of case notes, they noted indomethacin sensitivity in three patients (out of seven patients who received indomethacin treatment).

The optimal management of CH is challenging and drugs considered effective for one variety of CH might be ineffective for another variety of CH. The fluctuating intensity of pain attacks and variable length of cluster cycles make the evaluation of drug efficacy challenging. Even age and gender discrepancy have been reported. Females appear to be less responsive to both abortive and preventive therapies. Therefore, when treating CH patients, it may be necessary to evaluate the use of indomethacin's dosage greater than the commonly recommended dose (2 - 3 mg/kg/day in 2 - 4 doses, up to a maximum of 4 mg/kg/day), although this may expose more to the risk of presenting the already described side effects.

Paroxysmal hemicrania (PH)

PH is extremely uncommon in pediatric age, but Gladstein in 1994 described this type of disease in a child (Table 2). Klassen in 2000 and Almeida in 2004 reported other cases in childhood. Blankenburg in 2009 found five children with PH (0.8%) and three with probable PH (0.5%) amongst 628 patients (1.3% in total) [12]. Pain characteristics, autonomic symptoms and treatment response to indomethacin were similar to adult PH patients. In 2015, Raieli et al. described a case of an 8-year-old girl showing typical features of PH, with severe headache attacks lasting for six months [13]. The attacks were unilateral, located in the right orbital region radiating to the frontal region, jaw and neck, pain was associated to ipsilateral autonomic symptoms, phonophotophobia and allodynia. The pain was not responsive to most non-steroidal anti-inflammatory drugs. When she started a cycle of indomethacin added to the topiramate, the attacks disappeared in a few days. Because of the onset of side effects correlable to the use of indomethacin, topiramate was increased and indomethacin was progressively decreased until full suspension, but painful attacks restarted. Finally, she had no attacks with indomethacin in a daily dose of 25 mg. In 2011, Tarantino et al. reported two cases of PH in pediatric age, concerning a 7-year-old boy and an 11-year-old boy with typical features of PH [14]. During the headache attack, pain intensity was not responsive to the most non-steroidal anti-inflammatory drugs. After failure of the treatments, indomethacin was chosen amongst other drugs, at an initial dose of 25 mg/day in the 7-year-old boy and 50 mg/day in the 11-year-old boy. A fast amelioration was seen, with an important reduction of the attack frequency and an improvement of the quality of life.

Table 2: Diagnostic criteria (taken from ICHD-III beta) [8].

A	At least 20 attacks fulfilling criteria B-E.
B	Severe unilateral orbital, supraorbital and/or temporal pain lasting 2 - 30 minutes.
C	At least one of the following symptoms or signs, ipsilateral to the pain:
	a) conjunctival injection and/or lacrimation
	b) nasal congestion and/or rhinorrhoea
	c) eyelid oedema
	d) forehead and facial sweating
	e) forehead and facial flushing
	f) sensation of fullness in the ear
	g) miosis and/or ptosis
D	Attacks have a frequency above five per day for more than half of the time.
E	Attacks are prevented absolutely by therapeutic doses of indomethacin1.
F	Not better accounted for by another ICHD-3 diagnosis.

Hypnic headache

Hypnic (or alarm clock) headache (HH) is an uncommon headache disorder. Approximately 250 cases, almost exclusively in adults, have been published in the literature [15]. Indomethacin is noted to be particularly useful if hypnic headache is unilateral (Table 3). There is evidence that hypnic headache is related to REM sleep. Hypnic headache primarily occurs in age groups over 50 years and is female predominant. Indomethacin has been described as a possible treatment for hypnic headaches and showed efficacy in patients with unilateral hypnic headache, especially if there were trigeminal autonomic symptoms associated. However, children with hypnic headache have also been reported. The first description was in 1998 by Raskin [16]. In 2005, Grosberg et al. reported a 9-year-old girl with typical hypnic headache [17]. Following the initial evaluation, these headaches resolved spontaneously and did not recur in the 2 months of follow-up. Neither preventive nor abortive medications were required. In 2011, Cerminara et al. reported three children between 7 and 11 years old with HH features, but their treatment choice was not indomethacin but melatonin, with good amelioration in 6-12 months [18]. In 2015 Raimundo Pereira Silva-Neto described five children ranging from 7 to 11 years old diagnosed with HH [19]. Successful treatment with melatonin in 2 out of the 5 patients was successfully achieved. In 2008, Prakash et al. [20] presented a case report of an adolescent with relapsing and remitting HH, moderate to severe, with no relief from other pharmacological treatments but with complete response to indomethacin (75 mg at bedtime). As for adult patients, we suggest that indomethacin might represent a helpful treatment option in children with HH, in case other treatments fail.

Table 3: Diagnostic criteria (taken from ICHD-III beta) [8].

A	Recurrent headache attacks fulfilling criteria B-E.
B	Developing only during sleep, and causing wakening.
C	Occurring on 10 days per month for >3 months.
D	Lasting 15 minutes and for up to 4 hours after waking.
E	No cranial autonomic symptoms or restlessness.
F	Not better accounted for by another ICHD-3 diagnosis.

Primary stabbing headache

Primary/idiopathic stabbing headache (PSH/ISH) is a short-lasting but troublesome syndrome characterized by brief, jabbing stabs predominantly felt in the orbital, temporal and parietal areas, the frequency of which may vary from one to many per day, usually responding to indomethacin (Table 4). PSH was first described by Lasche in 1964 as "ophthalmodynia periodica". PSH is considered an indomethacin responsive headache, and is more frequent in young children compared with older children and adolescents. Unfortunately, there are few important studies of ISH in children. Some remarkable studies were made by Fusco et al. [21] and Soriani et al. [22] who reported, respectively, 23 and 83 pediatric patients with PSH. Raieli et al. reported 17 patients between 2 and 14 year old with PSH [23]. Several cases showed significant improvement with indomethacin (75 mg/day). Attacks were reduced >50% in frequency. One study by Raieli et al. on headache in 105 children below 6 years of age, reported ISH in 13 (12.4%) [24]. In 2013 Montella et al. reported a study on 8 patients ranging between 11 and 67 years [25]. Seven subjects presented PSH associated with migraine without aura. Only one patient suffered of isolated PSH. Seven patients responded to indomethacin. In 2015, Mandel identified 42 patients with PSH between children and adolescents [26]. Some patients responded to indomethacin, whilst others stopped the treatment because of its side effects. More recently, some patients have responded to melatonin. In 2016, Grengs and Mack identified 26 patients with ISH from a database containing 1543 pediatric patients with Chronic Daily Headache (1.69%) [27]. Most of the patients were female. Half of the patients were treated with indomethacin and half showed remarkable improvement.

Table 4: Diagnostic criteria (taken from ICHD-III beta) [8].

A	Head pain occurring spontaneously as a single stab or series of stabs and fulfilling criteria B–D.
B	Each stab lasts for up to a few seconds.
C	Stabs recur with irregular frequency, from one to many per day.
D	No cranial autonomic symptoms.
E	Not better accounted for by another ICHD-3 diagnosis.

Hemicrania continua

In adults, oral indomethacin should be used initially in a dose of at least 150 mg daily and increased if necessary up to 225 mg daily (Table 5). Smaller maintenance doses are often employed. In pediatric age, Fragoso and Machado in 1998 described the case of an adolescent who had suffered from unilateral continuous headache since she was 8 years old [28]. Treatment with indomethacin at a dosage of 50 mg/day promptly relieved the pain which had affected her for the previous 9 years.

Table 5: Diagnostic criteria (taken from ICHD-III beta) [8].

A	Unilateral headache fulfilling criteria B-D.
B	Present for >3 months, with exacerbations of moderate or greater intensity.
C	Either or both of the following:
	1. at least one of the following symptoms or signs, ipsilateral to the headache:
	a) conjunctival injection and/or lacrimation
	b) nasal congestion and/or rhinorrhoea
	c) eyelid oedema
	d) forehead and facial sweating
	e) forehead and facial flushing
	f) sensation of fullness in the ear
	g) miosis and/or ptosis
	2. a sense of restlessness or agitation, or aggravation of the pain by movement.
D	Responds absolutely to therapeutic doses of indomethacin.
E	Not better accounted for by another ICHD-3 diagnosis.

Coughing, straining, sex and/or other Valsalva manoeuvre induced headache

Valsalva-induced headaches are not common in childhood (Table 6). This kind of disorder occurs in association with coughing, straining, sex and/or other Valsalva manoeuvre. In 2012 Gelfand and Goadsby reported 2 cases in adolescents, highly responsive to indomethacin [29].

Table 6: Diagnostic criteria (taken from ICHD-III beta) [8].

A	At least two headache episodes fulfilling criteria BD.
B	Brought on by and occurring only in association with coughing, straining, sex and/or other Valsalva manoeuvre.
C	Sudden onset.
D	Lasting between 1 second and 2 hours.
E	Not better accounted for by another ICHD-3 diagnosis.

Red ear syndrome

The red ear syndrome (RES) was described for the first time by Lance in 1994 [30]. Red ear syndrome is characterized by unilateral/bilateral episodes of burning sensation and pain in the ear, in association with ipsilateral erythema, frequently precipitated by touch, movements of head or neck, or temperature changes [31]. RES episodes can occur in association with primary headaches, including migraine in pediatric age, but they are isolated in some patients.

The prevalence and incidence are unknown, and the age of symptom onset ranges between 4 and 92 years [32]. RES is an important symptom in childhood, although it is not limited to pediatric patients. RES is slightly more frequent in females (1.25:1) [33] with inverted ratio in the pediatric age (1:2) [34].

Few clear evidences are available in literature about therapy of RES. In Lance's case series, both pharmacological and non-pharmacological treatments (prescription of a dental plate, local anesthetic block, surgical section, or an application of ice-pack to the ear) produced a partial remission of symptoms. In 2016, Raieli et al. proposed a review of the literature about RES, and reported 13 cases in which indomethacin was used [35]. The review evidenced that in 5 cases an improvement was reported.

Preadolescent indomethacin-responsive headache without autonomic symptoms Preadolescent indomethacin-responsive headache is an uncommon disease, poorly understood, and the literature shows few case reports about this phenomenon, with only 13 cases in children younger than 13 years. In 2013, Myers and Smyth described the cases of two children with similar characteristics of indomethacin-responsive headache [36]. The first patient was a 2-and-a-half-year-old girl, the second was a 5-year-old boy, and they showed a similar clinical picture, characterized by frequent episodes of paroxismal pain, in frontal or temporal head. The pain was defined to be severe, with sudden onset, with duration from seconds to minutes. Sometimes they experienced multiple events per week, sometimes multiple episodes per day, without autonomic migrainous symptoms. No possible secondary causes for headaches were discovered after global examinations. Neither clinical presentation full filled IHS criteria for TACs or for any existing and described headache syndrome, but children exhibited a dramatic amelioration with indomethacin, from 1 to 1.5 mg/kg/day, divided twice daily.

Discussion and Conclusion

Despite the previously described restrictions by the FDA on the use of indomethacin in children, which limit its use in clinical practice, there is a lack of information regarding the specific responsiveness of some types of pediatric headaches to indomethacin. Indomethacin-responsive headaches are very unusual, especially during childhood. The differential diagnosis of unusual headaches in pediatric population is extremely difficult, primarily because children often are incapable of describing important clinical features. Therefore, it requires a systematic approach. In the clinical cases evaluated in this review, we found that indomethacin can be useful to treat different kind of headaches, even in pediatric age. PH and HC, by definition, must show an absolute and dramatic amelioration and the response to indomethacin is considered an important parameter for diagnosis. Indomethacin is generally considered to be ineffective in patients with CH, but the review of the literature shows that there are cases of CH indomethacin-responsive and that some cases may be misdiagnosed when the diagnosis is based exclusively on the therapeutic response. Complete and immediate effect of indomethacin was described even in children. We suggest that indomethacin could be a helpful treatment option even in children with headache, after failure of other treatments. Treatment usually starts with a dose of 25 mg three times daily with meals, and a response is usually fast. Otherwise after 48 hours the dosage can be increased to 50 mg three times daily. There is disagreement on the maximal helpful dose, but dosages should be as small as possible because of the important side effects.

The aim of this review was to focus exclusively on the pediatric age, and we believe it may be an indication for clinicians who face some types of headaches, which, although they are rare in children, often require a specific therapeutic intervention: the use of indomethacin.

Conflict of Interest

None.

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