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# Cluster headache responsive to indomethacin: Case reports and a critical review of the literature

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## Abstract

*Introduction*: Response to indomethacin is an essential feature for the diagnosis of both paroxysmal hemicrania (PH) and hemicrania continua (HC). Cluster headache (CH) is widely considered to be a disease unresponsive to indomethacin.
*Case reports*: We report four patients with CH who responded to indomethacin. Two patients, who were refractory to the usual therapy for CH, fulfilled the criteria for chronic CH. Conversely, two patients had a history of episodic CH and showed response to both indomethacin and the usual therapy for CH.
*Literature review*: We also reviewed the literature for the presence of indomethacin response in patients with CH. We noted a large number of cases labeled as CH by the authors which showed a response to indomethacin.
*Discussion*: Many cases of definite or possible CH were wrongly labeled as PH because of patients' responding to indomethacin.
*Conclusion*: The response to indomethacin in patients with CH may not be as immediate as in other indomethacin-responsive headaches, and many patients may need larger doses.

## Keywords

Cluster headache, paroxysmal hemicrania, hemicrania continua, indomethacin

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## Introduction

Cluster headache (CH) is a primary headache syndrome characterized by strictly unilateral severe pain in or around the eye, accompanied by ipsilateral cranial autonomic features. The optimal management of CH is challenging. Many drugs are available for the treatment of CH, and a good proportion of these agents provide reasonable relief. However, no one intervention works for every patient, and some of the options are highly effective for a small percentage of patients. Because of this variability, it is incumbent on the treating physician to use all potential medical options before subjecting the patient to surgery (1).

The clinical features and pathophysiology of both paroxysmal hemicrania (PH) and hemicrania continua (HC) markedly overlap with those of CH. PH and HC both respond in an absolute way to indomethacin (2). Indomethacin is largely considered to be ineffective in patients with CH. Anecdotal evidence suggests that some CH patients may respond to indomethacin (1,3). Here we report four patients with CH who responded to indomethacin. We also critically review the literature for previous reports of indomethacin responsive CH.

## Case Reports

### *Case 1*

A 42-year-old man presented with a two-year history of recurrent right-sided headaches. The patient described episodes of excruciating burning pain in the right supraorbital, orbital and temporal regions. The frequency of this headache was one to two attacks per week during the first year of illness. After about one year, the frequency gradually increased to about five to

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seven attacks per week. The usual duration of attacks was one to two hours. They were accompanied by conjunctival injection, lacrimation and nasal discharge. The patient described the intensity of headache as 'intolerable'. Pacing activity was present during the attacks. There was no circadian rhythmicity of the attacks, which could occur at any time, including nocturnally. The patient denied the presence of aura, nausea, photophobia and phonophobia. There was no history of interictal discomfort. MRI of the brain was normal. Oral sumatriptan and rizatriptan were ineffective during the attacks. The patient had never tried oxygen inhalation or injectable triptans. He had unsuccessful trials with prednisolone, lithium, verapamil and naproxen. Indomethacin was started and the patient showed complete response at the dose of 75 mg three times a day (tid) after a week. Reduction of the dose always led to recurrence of the symptoms.

## *Case 2*

A 46-year-old man presented with a six-year history of episodic cluster headache (ECH). The cluster period lasted for about four to five months, with remission periods of one to five months. The headaches in a cluster period were stereotyped. The pain was described as very excruciating, sharp and unbearable, centered on the supraorbital and orbital areas. The pain was accompanied by autonomic manifestations such as ipsilateral conjunctival injection, tearing and rhinorrhoea. During most of the attacks the patient felt restless and had pacing activity. He had one to two attacks of headaches daily, including nocturnal attacks, with each attack lasting about one to four hours. Between attacks, he was headache free. He denied experiencing aura, nausea, photophobia or phonophobia. MRI of the brain was normal.

The patient's symptoms were relieved with oxygen inhalation and injection sumatriptan. During the cluster period he previously achieved relief with verapamil or lithium. However, in a recent the co-existence of both PH and CH in the same patient (going on for about six weeks), both the drugs were largely ineffective. Indomethacin was started at 25 mg tid. It was gradually increased to 100 mg tid, and the patient responded in about two weeks after the start of treatment. A tapering of indomethacin done after two months was successfully made to 75 mg tid. However, further tapering tried on many occasions in the next four months led to recurrence of the headaches.

## *Case 3*

A 36-year-old male presented with a 14-month history of intermittent excruciating headache. The headache always occurred on the left side, and was centered on the supraorbital, orbital and temporal areas. The cranial autonomic features were noted in most of the attacks. Restlessness or pacing activity was present in about one-tenth of the attacks. The headaches always lasted approximately one to three hours. The usual frequency of attacks was one to two attacks per day. There were occasional nocturnal exacerbations. Between attacks he was headache free. He denied experiencing aura, nausea, photophobia or phonophobia. He did not identify any triggering factors for the exacerbations. MRI of the brain, orbit, and cervical spine revealed no abnormality. Magnetic resonance angiography (MRA) was normal. Injectable sumatriptan previously provided symptomatic relief of the attacks. He had unsuccessful trials with sodium valproate, topiramate, amitryptiline and naproxen. Indomethacin was started, and the patient showed complete response at the dose of 75 mg tid after about one week. In the next five months, he had five to six headache episodes of mild-to-moderate intensity in the same areas, three of which were related to reduction of indomethacin dose.

## *Case 4*

A 26-year-old male presented with a four-month history of daily severe left-sided headaches. These headaches were excruciating, causing him to cry and run around his home. The headaches, strictly on the left side, were mainly in the orbit, with radiation to the supraorbital, infraorbital and temporal areas. He had accompanying lacrimation and conjunctival injection. The headache always lasted for more than 30 minutes (range 30 minutes to 2 hours). The frequency of attacks was variable, from one attack every alternate day to four attacks per day. Nocturnal attacks were common. Between attacks he was headache free. No precipitating or aggravating factors were noted. MRI of the brain and MRA were reported as normal. The patient was advised indomethacin as prophylactic therapy and sumatriptan for an acute attack. Oral sumatriptan did not relieve his symptoms. However, injectable sumatriptan provided marked relief within 20–30 minutes. Indomethacin was started at the dose of 25 mg tid and it was gradually titrated. The patient showed complete response in about two weeks at the dose of 100 mg tid. The patient had to omit the drug because of gastritis after two weeks. This led to recurrence of the headaches. The patient was asked to take verapamil and he showed complete response at the dose of 240 mg daily. The drug was successfully tapered off after about three months. However, the headache recurred after about two months. The headache again responded to verapamil.

## Literature review

We searched MEDLINE with the following keywords: cluster headache, paroxysmal hemicrania, hemicrania continua, cluster headache and indomethacin, and headache and indomethacin. All the case reports and case series on CH and PH were reviewed to identify the patients with CH responsive to indomethacin. We analysed each individual case in relation to current International Headache Society (IHS) criteria. We carefully reviewed the reference lists of all the papers found. The search was restricted to papers written in English.

### *CH unresponsive to indomethacin*

Most of the investigators presently regard CH as a disease unresponsive to indomethacin. This assumption is based mainly on a report published in 1974. In this report, Sjaastad and Dale made a first case report of chronic paroxysmal hemicrania (CPH) and simultaneously mentioned 10 cases of CH unresponsive to indomethacin. However, the report did not have any details of indomethacin use in the patients with CH (4).

A negative response to indomethacin was noted in the recent past in one open-label study in 18 patients with CH. From day 8 of the active period, indomethacin 100 mg was administered intramuscularly every 12 hours for two consecutive days. The mean daily attack frequency before the test was not statistically different from that on day 1 and day 2. There was no refractory period in any patient after indomethacin administration (5).

There are just a few case reports where indomethacin was used and found ineffective.

### *CH responsive to indomethacin*

CH responsive to indomethacin was first reported by Geaney (6). However, this report does not fulfill the criteria for CH. Nevertheless, in the literature, there are many case reports/series of CH where indomethacin was effective (Table 1) (7–18). Watson and Evans (8) reported 60 patients with chronic cluster headache (CCH). They treated 11 patients with indomethacin at the dose of 25 to 50 mg tid. Four had good immediate effect. The effect was sustained in three patients for a median of three months. One patient discontinued therapy because of nausea. The immediate effect of indomethacin (36%) was comparable to that of other effective drugs, lithium (43%), methysergide (37%) and prednisone (36%). The response rate for verapamil and pizotifen was markedly low in that analysis.

Gotkine et al. (16) reported a 47-year-old male with ECH since his teens. He controlled his headaches for about two decades with indomethacin.

Buzzi and Formisano (14) reported a 35-year-old male with ECH. He responded to indomethacin on at least two occasions. On the first occasion headache subsided with indomethacin (100 mg daily) within three days. However, on the second occasion, headache subsided in one week with 100 mg dose. Recently, Prakash et al. (3) reported a 42-year-old male with a 13-year history of CCH who showed complete response to a very high dose of indomethacin (150 mg tid) after about one week of the therapy. Shah and Prakash (18) reported a 22-year-old male who had CH and PH at the same time. Both types of headache responded to indomethacin. Even atypical CH has been reported as an indomethacin-responsive headache. A few case reports of valsalva-induced CH showing response to indomethacin have been reported in the literature (12,13).

Complete and immediate effect of indomethacin was noted even in children. D'Cruz (9) reported response to indomethacin in two children with history suggestive of CCH. After that, a few other case series of childhood CH responsive to indomethacin were also reported in the literature. Isik and D'Cruz (11) reported four young children with CH who showed complete response to indomethacin. Recently, Majumdar et al. (17) reported 11 children with CH. In this retrospective review of case notes, they noted indomethacin sensitivity in three patients (of seven patients, in whom indomethacin was tried).

### *Indomethacin for acute attacks of CH*

Indomethacin was never evaluated in any ongoing acute attacks. However, Anghileri et al. (15) reported a patient with CH in whom a few acute attacks were successfully treated with intravenous indomethacin (100 mg). Indomethacin injection was effective in stopping ongoing headache within a couple of minutes. D'Amico et al. (10) described three patients with CH in whom indomethacin was effective during attacks of headache. In one patient they described complete cessation of headache within about 20 minutes after administration of indomethacin. In addition, there are a few other case reports where indomethacin (in isolation or with other drugs) provided some improvement during an acute attack of headache.

## Discussion

Indomethacin was introduced in the clinical medicine in 1963 (19). Its use in a headache disorder was first demonstrated by Sicuteri et al. (20) in 1964 in patients with migraine. In 1974, Sjaastad reported a special type of headache (CPH) that was highly sensitive to indomethacin (4). Over the years, many other headache disorders were shown to have a response to indomethacin.

**Table 1.** Cluster headache responsive to indomethacin

| Reference | Year | No | Sex | Age | Types | Duration | Daily dose (mg) |
|---|---|---|---|---|---|---|---|
| Klimek (7) | 1984 | 1 | F | 50 | Episodic | 5 years | NA |
| Watson et al. (8) | 1987 | 4 | NA | NA | Chronic | NA | 75–150 |
| D'Cruz (9) | 1994 | 2 | M | 8 | ?Chronic | 6 months | 50 |
| | | | F | 10 | Chronic | 2.5 years | 50 |
| D'Amico et al. (10) | 1996 | 3 | M | 42 | Episodic | 11 years | NA |
| | | | F | 63 | Chronic | 18 years | NA |
| | | | F | 37 | Episodic | 10 years | NA |
| Isik et al. (11) | 2002 | 4 | M | 10 | NA | 4 years | 50 |
| | | | M | 2 | ?Episodic | 1 year | 20 |
| | | | F | 2.5 | NA | 6 weeks | 30 |
| | | | F | 4 | NA | NA | 50 |
| Ko et al. (12) | 2002 | 1 | M | 86 | Episodic | 10 years | 25 |
| Rozen (13) | 2002 | 1 | M | 86 | Episodic | 10 years | 25 |
| Buzzi et al. (14) | 2003 | 1 | M | 35 | Episodic | 15 years | 125 |
| Anghileri (15) | 2006 | 1 | M | 42 | Episodic | 10 years | 100 IV |
| Gotkine et al. (16) (case 2) | 2006 | 1 | M | 47 | ?Chronic | NA | NA |
| Prakash et al. (3) | 2008 | 1 | M | 42 | Chronic | 13 years | 450 |
| Majumdar et al. (cases 2,4,7) (17) | 2009 | 3 | M | 11 | Episodic | 8 years | NA |
| | | | M | 14 | Episodic | 1 year | NA |
| | | | M | 8 | Episodic | 1 year | NA |
| Shah et al. (18) | 2009 | 1 | M | 22 | Chronic | 13 months | 300 |

M = male; F = female; NA = details not available.

Our four patients fulfilled the IHS criteria for CH (2). Two patients (cases 1 and 3) fulfilled the criteria for CCH, and both were refractory to usual therapy. Cases 2 and 4 were ECH. Both ECH patients showed response to the usual therapy of CH. A response to indomethacin in patients with episodic hemicranial pain is highly suggestive of PH. Therefore, a possibility of PH or PH with CH should be considered in the differential diagnosis. There is considerable overlap in the clinical characteristics of PH and CH, and phenotypically these headache disorders cannot be differentiated from each other. Points which help to differentiate between these two types of headache are lower frequency and longer duration of the attacks in CH, and a response to indomethacin in patients with PH (2,21). None of the patients ever had attack frequency of more than five per day or duration of less than 30 minutes. Presence of nocturnal attacks and a response to injectable sumatriptan in three patients (except case 1) favor the diagnosis of CH. The presence of clustering and a response to oxygen inhalation (case 2) further support a diagnosis of CH. Case 1 never received a trial with injectable sumatriptan and oxygen inhalation. Therefore, we cannot rule out a possibility of PH. However, the frequency and duration of the attacks never fulfilled the criteria for PH, and case 1 seems more likely a case of CCH. Indomethacin showed response at the dose between 225–300 mg daily. The response was noted between one and two weeks after the initiation of indomethacin therapy.

The optimal management of CH is challenging (2,22). 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 (23). Females appear to be less responsive to both abortive and preventive therapies (24). Very large dosages, much higher than the usual recommended doses (for other disorders) may be necessary when treating CH patients (3,25). Drugs considered effective for one variety of CH might be ineffective for another variety of CH (1,23,25). Patients with CCH respond well to sumatriptan as opposed to ECH. On the other hand, zolmitriptan was found effective for ECH and ineffective for CCH (1). Because of these disparities, inconsistent results were noted with almost all the drugs that are considered efficacious for CH. For example, the beneficial effect of lithium has been demonstrated in

several open clinical trials. Nonetheless, a double blind placebo-controlled trial failed to demonstrate the superiority of lithium over placebo (26). Likewise, sodium valproate did not show any beneficial effects over placebo (27). Minimal or no effect was reported even with topiramate or methysergide in open-label studies (1).

All these findings should be considered before claiming a drug ineffective in patients with CH. In addition, a few more points should be considered in a trial with indomethacin. The shorter half-life of indomethacin (four hours), variable dose requirement (12.5–450 mg) in various headache disorders and variability in the time interval between administration and response (a few hours to 10 days) might complicate the study of indomethacin in patients with CH. The response to the drug in various indomethacin-responsive headache disorders is immediate (within 24 hours) and complete (21,28,29). The expectation of this type of immediate and total response even in patients with CH might lead to considering indomethacin as ineffective in CH. Immediate and complete response cannot be expected even with any first- or second-line preventive therapies in CH; preventive therapy usually takes one to four weeks to show a response (1,22). Two of our patients showed a response to indomethacin after one week. Another two patients took two weeks to show a response with indomethacin.

Very large dosages may be necessary when treating CH patients (25). Our four patients responded at the higher doses (225–300 mg) of indomethacin. CH patients are known to tolerate medications much better than non-cluster patients (25). Indomethacin, however, has not been evaluated systematically in CH patients. As noted above, a negative response was noted in one open-label study in 18 patients with CH. However, negative or minimal response is noted with almost all drugs which are currently deemed efficacious for CH patients. Therefore, a negative result in an open-label study in a small population is not sufficient to determine a drug to be inefficacious in these patients. The authors of that study (5) themselves suggested 'indotest' in patients with three to four attacks per 24 hours. However, the mean of frequency in that study was 1.6/24 hours (range 1–3). Therefore, this population of CH patients, with the mean frequency of attacks of 1.6/day, may not be a good subset to show the response of indotest (5). In addition, indotest itself is not 100% sensitive even in patients with other indomethacin-responsive headache disorders. Cittadini et al. (28) have reported a positive response to indotest in only 82% of patients with PH. Because CH patients usually respond with higher doses, the possibility of positive response at higher doses (>100 mg IM) cannot be ruled out completely. Response to IV injection of indomethacin (100 mg) in a couple of minutes on a few occasions in Anghileri et al.'s (15) case report again confirms a variable response to drugs in patients with CH.

A response to indomethacin is not contrary to the IHS criteria for CH. However, a physician hesitates in making a diagnosis of CH (in a patient responsive to indomethacin) even if a patient fulfills all the features of IHS criteria for CH. The frequency of more than five attacks in day (at least on more than 50% occasions) is an essential feature for the diagnosis of PH. We reviewed the case series of PH in the literature not fitting in the present diagnostic criteria for PH. Many of these cases fulfilled the criteria for CH (Table 2) (30–35). The largest such case series was published by Fuad and Jones (33), who described 11 female patients with PH. Indomethacin response was described in only eight patients. The frequency of attack was one to two per day in at least five patients (of eight indomethacin-responsive patients). The duration of attacks in these five patients was 30 minutes to a few days. These patients do not meet the criteria for PH, and Zidverc-Trajkovic et al. (36) rightly labeled them as CH.

Another important point is how to define a patient with headache duration of 15–30 minutes and headache frequency of five to eight per day. A large percentage of patients in the case series/case reports of PH had attack duration of 15–30 minutes (or more), and attack frequency of five to eight per day (or less). The periodicity, or clustering, is in important feature in CH. However, this periodicity is not observed in all patients. The clustering of attacks cannot be determined in CCH; this is why it is not included in the IHS classification system. Many authors have suggested that a response to indomethacin is the only way to differentiate PH from CH. However, as noted above, a response to indomethacin is not contrary to the IHS criteria for CH. Therefore, it is possible that the same patient may fulfill the criteria for both diseases at the same time. There are many case reports/series in the literature where a possibility of both diseases, according to IHS criteria, exists at the same time (Table 3) (33,37–42). The largest case series on PH was published by Boes and Dodick (43). They reviewed 72 patients with suspected PH. The authors used modified diagnostic criteria for CPH, and themselves considered a possibility of CH in some of these patients. We further reviewed their data for the presence of possible CH according to the present IHS diagnostic criteria (2004). The mean minimum attack duration of 20–40 minutes was noted in 20%. The usual attack duration of more than 30 minutes was reported in 44% of patients. The maximum attack frequency was between two and five per day in 37% of patients. Another 35% of patients had an attack frequency of 6–10 per day. These data indicate that a large number of these patients may

**Table 2.** Possible misdiagnosis of cluster headache (according to IHS criteria)

| Reference | Year | Age | Sex | Authors' diagnosis | Frequency (attacks/day) | Duration of attacks | Dose of indomethacin (mg/day) |
|---|---|---|---|---|---|---|---|
| Newman (case 3) (30) | 1993 | 39 | M | EPH | 5 | 15 min | 75 |
| Gladstein et al. (31) | 1994 | 8 | M | CPH | 3 | 15–30 min | NA |
| Veloso et al. (32) | 2001 | 1 | M | EPH | 3–5 | 15–30 min | 75 |
| Fuad et al. (33) (cases 3–8) | 2002 | 40 | F | PH | 1 | Hours–days | NA |
| | | 37 | F | PH | 1 | Up to 12 hours | NA |
| | | 56 | F | PH | 1 | Up to 3 days | NA |
| | | 38 | F | PH | 2 | 30 min | NA |
| | | 68 | F | PH | 2 | Up to 24 hours | NA |
| | | 59 | F | PH | 1 | Up to 3 days | NA |
| Siow (34) | 2003 | 66 | F | EPH | 3–4 | 20 min | 25 |
| Pugach (35) | 2008 | 56 | M | CPH | <3/day | 20 min–few hours | 75 |

IHS = International Headache Society; M = male; F = female; EPH = episodic paroxysmal hemicrania; CPH = chronic paroxysmal hemicrania; PH = paroxysmal hemicrania; NA = details not available; min = minutes.

**Table 3.** A possibility of both (?) PH and CH at the same time according to present IHS criteria

| Reference | Years | Age | Sex | Frequency (attacks/day) | Duration of attacks |
|---|---|---|---|---|---|
| Jotkowitz (37) | 1978 | 41 | M | 8 | 20–30 min |
| Kudrow (cases 2 and 4) (38) | 1987 | 76 | F | 3–6 | 15–20 min |
| | | 42 | M | 6 | 20–30 |
| Newman et al. (case 2) (39) | 1992 | 56 | F | 4–5 | 10–30 min |
| Leon et al. (40) | 1994 | 55 | F | 4–6 | 20 min |
| Pareja (41) | 1995 | 35 | F | 5–6 | 20–60 min |
| Mateo et al. (42) | 1999 | 42 | F | 4–6 | 15 min |
| Fuad and Jones (cases 1 and 2) (33) | 2002 | 55 | F | 6 | 30 min |
| | | 65 | F | 6 | 30 min |

PH = paroxysmal hemicrania; CH = cluster headacache; IHS = International Headache Society; M = male; F = female; min = minutes.

fulfill the present diagnostic criteria for CH. In addition, many of them may fulfill the criteria for both PH and CH at the same time. The episodic form of CH is far more common than the chronic form (in contrast to PH). Nine patients in Boes and Dodick's case series were able to withdraw the drug without headache recurrence. The authors considered their attacks as first attacks of EPH. The details of these patients are lacking in the article. However, in the presence of headache duration greater than 30 minutes and headache frequency of less than five attacks per day, a successful withdrawal of the drug may be more likely in the patients with CH (rather than PH).

Zidverc-Trajkovic et al. (36) compared the clinical features of CH headache patients with those of PH patients. Indomethacin was given only to the patients with suspected PH (as a diagnostic criterion). About 20% of the patients in both groups had attacks of 15–20 minutes and about one-half of patients in both groups had three to seven attacks daily. These data again suggest a possibility of both diseases (PH and CH) occurring at the same time, according to the present diagnostic criteria.

Recently, Cittadini et al. (28) reported 31 patients with PH. Four patients had fewer than four attacks a day. The duration of attacks in these four patients was not described. However, the mean duration of the attacks was 17 minutes and the median was 19 minutes. The possibility of fulfilling the criteria of both diseases remains open. PH is a very rare disease. The relative

frequency of PH with CH is just 1–3% (28). Therefore, a question may arise: does the response of indomethacin in a patient fulfilling the IHS criteria for CH change the diagnosis to an extremely rare disease, PH? Verapamil is the drug of choice for patients with CH. However, the response to verapamil was almost identical in both CH and PH in Zidverc-Trajkovic et al.'s study (36). This raises a few questions. Does a response to verapamil (before a trial with indomethacin) in a borderline case point to a diagnosis of CH? Should one change the diagnosis of CH to PH if the same patient shows a response to indomethacin as well?

HC is another indomethacin-responsive headache disorder. The duration and frequency of the exacerbations have not been defined in the IHS criteria for HC (2). The pain exacerbation periods usually last 20 minutes to a few days. The frequency of exacerbations is also variable, from two to three times per week to 10–20 times per day (29). In a recent study of 25 patients with HC, 32% fulfilled the diagnostic criteria for CH relating to headache exacerbations (44). Recently, a few large case series have demonstrated the presence of interictal pain in patients with CH. Donnet et al. (45) reported presence of interictal pain in 48% of patients with chronic CH. The presence of interictal pain in patients with CH (and responsiveness to indomethacin) may further complicate the effort to differentiate CH from HC, especially if frequency and duration of the exacerbations match the IHS criteria for CH. Therefore, a possibility of misdiagnosed CH (because of a response to indomethacin) exists in a few patients diagnosed as having HC (44). This possibility will be very high in the patients with the relapsing-remitting type of HC.

Why indomethacin for CH? Indomethacin is a potentially toxic drug. Various available medical options for CH are relatively less noxious than indomethacin. Therefore, we need to consider: what are the requirements to consider indomethacin as an alternative treatment for CH?

The treatment of CH (and other trigeminal autonomic cephalalgias [TACs] and HC) is based on empirical data rather than on a pathophysiological concept (22). Our review of the literature suggests that indomethacin-responsive CH exists and that a number of cases may be misdiagnosed when one relies on therapeutic responsiveness to make a diagnosis. Bogucki and Niewodniczy (46) reported a patient with recurrent (up to 30 per day) short-lasting headaches (maximum duration 20 minutes). The patient did not show a response to indomethacin (100–300 mg daily for two weeks). He responded to lithium and the authors claimed a diagnosis of CH. However, Newman et al. (47) classified this patient's disorder as episodic paroxysmal hemicrania (EPH) in a review of the literature. Later, Sjaastad (48) defended the original diagnosis of CH because the patient did not show a response to indomethacin (and did show a response to lithium). This may be a classical example of diagnostic dilemma when one relies on therapeutic responsiveness to make a diagnosis, and even headache experts may have differences of opinion. Shah and Prakash (18) recently reviewed the literature for the presence of PH and CH in the same patient. They suggested that the coexistence of both PH and CH in the same patient may be both over- and underreported, due to making a diagnosis on the basis of therapeutic responsiveness. The correct diagnosis is important for prognostic purposes.

About 10% of total CH cases may be refractory to the usual medical therapies. A trial of indomethacin may be given to these patients before subjecting the patients to a surgical procedure. On average, a cluster period (of ECH) usually lasts for 6–12 weeks. Indomethacin given for a shorter period may be less toxic as compared to long-term therapy for PH. Therefore, indomethacin may be used as an alternative to the usual therapies of CH.

## Conclusions

HC and PH are highly and specifically sensitive to indomethacin. However, a response to indomethacin may occur in CH if indomethacin is used in maximum therapeutic dosages ($\geq$300 mg daily). We hope that our review will act as catalyst for pharmacological research into the role of indomethacin in treating CH. It is also hoped that physicians will be more cautious in making a diagnosis of primary headache disorder only on the basis of a response to indomethacin.

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