

Brief Communication

Favorable Response to Analgesics Does Not Predict a Benign Etiology of Headache

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Background.—Distinguishing between primary and secondary headaches (HAs) is essential for the safe and effective management of patients with HA. A favorable response to analgesics may be observed with both classes of HAs and therefore is not a good predictor of who needs further evaluation.

Objective.—To systematically review the data that a favorable response to analgesics including triptans should not be used to exclude a serious secondary cause of HA.

Design.—PubMed search of English-language articles between 1980 and 2007 and reference lists of these articles. Two authors independently reviewed articles for study results and quality. Inclusion was based on 100% agreement between authors. We included articles that described secondary HAs as (1) having a favorable response to analgesics and/or (2) having a favorable response to sumatriptan. Of the 548 studies identified by our search strategy, 18 were included in our final analysis.

Results.—Seven of the 18 studies found that 46/103 patients (44%) described a significant or complete resolution of secondary HA from medications such as anti-emetics and nonsteroidal anti-inflammatory drugs (NSAIDs). Eleven of the 18 articles including 25/25 patients (100%) described a significant or complete resolution of secondary HA from sumatriptan, a serotonin 5HT agonist.

Conclusions.—A favorable response to analgesics including triptans should not be used to exclude a serious secondary cause of HA.

Key words: secondary headache, analgesics, misdiagnosis, sumatriptans

Abbreviations: CVST cerebral venous sinus thrombosis, HA headache, ICH intracranial hemorrhage, ICP intracranial pressure, IHH idiopathic intracranial hypertension, NSAIDs nonsteroidal anti-inflammatory drugs, SAH subarachnoid hemorrhage

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INTRODUCTION

Headaches (HA) account for 1-4% of all emergency department visits.¹⁻⁴ HA disorders are generally classified into primary and secondary. The former (migraine, tension-type, and cluster HAs) are far

more common and generally are not associated with any specific underlying pathology. Secondary HAs, which account for 4-14% of all acute severe HAs presenting emergently,^{1,3-8} are due to underlying disorders, which may be life-, brain- or vision-threatening. Distinguishing between these 2 groups is essential for the safe and effective management of patients with HA.

In addition to providing pain relief, physicians must decide which patients with HA can be treated for their pain and discharged without further testing

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beyond history and physical examination and which require further diagnostic evaluation. Sometimes, physicians use a favorable response to pain medication to determine who needs further diagnostic workup. Many articles on migraine HA state that triptans and ergot alkaloids are “specific” treatments for migraine, suggesting at least to a non-HA specialist that a favorable response to either of these drugs has diagnostic implications.⁹⁻¹¹ Furthermore, book chapters and clinical guidelines discourage this practice;^{12,13} however, the evidence base supporting this recommendation is limited to a few case reports.

The purpose of this article is to comprehensively examine the evidentiary basis for the assertion that a favorable response to analgesics including triptans should not be used to exclude a serious secondary cause of HA.

METHODS

The goal was to identify 2 groups of articles that described secondary HAs as (1) having a favorable response to analgesics and (2) having a favorable response to triptans. We performed 2 structured PubMed searches from 1980 to 2007 to identify relevant English-language articles. For group 1, the search contained (“Headache/drug therapy”[MeSH] AND (misdiagnosis[tw] OR “Diagnostic Errors”[MeSH] OR complication[tw])). For group 2, the search contained (“Headache/drug therapy”[MeSH] OR “Cluster Headache/drug therapy”[MeSH] OR “Migraine Disorders/drug therapy”[MeSH]) AND “Sumatriptan”[MeSH] AND (misdiagnosis[tw] OR “Diagnostic Errors”[MeSH] OR complication[tw]).

Based on the search details described above, 454 articles were retrieved from group 1 and 94 articles were retrieved for group 2. One author (J.P.) eliminated some articles based on the irrelevant titles. Both authors independently reviewed the remaining abstracts and retrieved potentially relevant articles. In addition, references from the bibliographies of those articles were searched to obtain other relevant data, yielding a total of 7 for group 1 and 11 for group 2 (see Fig.). Eighteen articles were included based on 100% agreement between authors. We analyzed the results of these articles to determine the medication used to treat HAs, the dosage, the degree of response to the

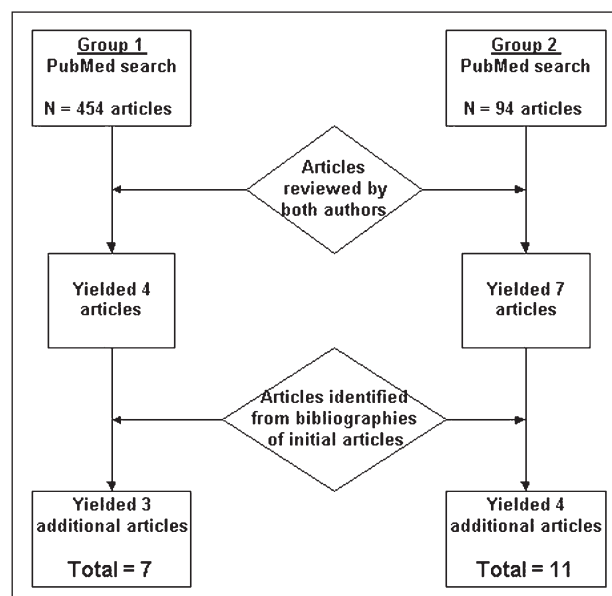


Figure.—Search method.

analgesic, and the underlying etiology of the HA, and the elapsed time until the correct diagnosis was made. For the purpose of this article, we use the word *analgesic* to describe any medication that was administered with the intention of relieving the HA pain, and not specifically to refer to any one class of medication. For example, we included anti-emetics, even though they are not analgesics, since they are commonly used by emergency physicians to treat the HA pain, especially if the patient is thought to have migraine.

RESULTS

Of the 555 articles identified by our search parameters, 18 were selected as relevant to our topic, representing a total of 128 patients.

Seven of the 18 studies found that 46/103 patients (44%) described a significant or complete resolution of HA from medications such as anti-emetics and nonsteroidal anti-inflammatory drugs (NSAIDs) (Table 1). Five were case reports.¹⁴⁻¹⁸ Two articles, one retrospective and the other prospective, described relief of HA from simple or common analgesics.^{19,20} We contacted the authors but were unable to get the data about the specific medications, which were not reported in the articles. In all the studies, the HAs had secondary causes including subarachnoid hemorrhage (SAH), subdural hematoma, intracranial hem-

Table 1.—Secondary Headaches Treated with Nontriptan Analgesics

Reference (case reports unless specified otherwise)	Medication	Response to analgesics	Etiology of HA	Time elapsed until Dx
Agostoni et al ¹⁹ Retrospective n = 23 Prospective n = 18	“Common analgesics”	“Yes” 4/23, 1/18 “Partial” 9/18	CVST	Not reported
Barclay et al ¹⁴ n = 2	Chlorpromazine IV	1. “Temporary improvement” 2. “Marked improvement”	1. Subdural hematoma 2. SAH	1. 2 weeks 2. 24 hours
Evans RW ¹⁵ n = 1	Toradol 60 mg IM	Intensity rating from 10 to 1	Hemorrhagic pituitary macroadenoma	Same day
Fernades CM ¹⁶ n = 1	Chlorpromazine 5 mg IV	Complete relief	Aseptic meningitis	15 hours
Forsyth et al ²⁰ Prospective n = 52	“Simple analgesics”	Relief in 22/52 subjects (42%)	Brain tumor	Diagnosis was known prior to Rx
Gross et al ¹⁷ n = 3	DHE and metaclopramide	Complete resolution of HA	1. Viral meningitis 2. Viral meningitis 3. Meningeal carcinomatosis	Diagnosis was known prior to Rx
Seymour et al ¹⁸ n = 3	1. Ketorolac 60 mg IM 2. Prochlorperazine 10 mg IM, lorazepam 1 mg IV, ibuprofen 800 mg PO 3. Prochlorperazine 10 mg IV	1. “Marked improvement” 2. “Improved significantly” 3. “Obtained relief”	1. SAH 2. SAH 3. ICH	1. 5 days 2. 30 hours 3. 24 hours

CVST = cerebral venous sinus thrombosis; DHE = dihydroergotamine; Dx = diagnosis; HA = headache; ICH = intracranial hemorrhage; IM = intramuscular; IV = intravenous; Rx = treatment; SAH = subarachnoid hemorrhage.

orrhage, meningitis, cerebral venous sinus thrombosis (CVST), pituitary adenoma, and brain tumor. In 4 of the studies, 7 patients had a delay in the real diagnosis by hours to weeks, at least in part, because of a misinterpretation of the favorable response to analgesics.^{14-16,18}

Eleven of the 18 articles including 25/25 patients (100%) described a significant or complete resolution of the HA from sumatriptan, a serotonin 5HT agonist (Table 2). One article was a prospective study and the remaining 10 were case reports.²¹⁻³¹ The HAs had pathologic causes including carotid artery dissection, temporal arteritis, pituitary hemorrhage, carbon monoxide exposure, tumor, idiopathic intracranial hypertension (IIH), or SAH. In 6 of the studies, 10 patients had a delay in the real diagnosis by hours to weeks because of a favorable response to analgesics.^{22,24,25,28-30}

DISCUSSION

Though it may seem intuitive that a favorable response to analgesics should suggest a benign cause of HA, there are a number of arguments to the contrary.

First, any medication may have a placebo effect; therefore, medication given to a patient with HA could have an effect on that basis alone.³² Second, many analgesics and anti-emetic medications have nonspecific sedating effects. The placebo effect and the nonspecific sedative effects both could lead to marked improvement of a patient's HA.

Third, the current paradigm for the pathophysiology of HA based on Moskowitz's work on migraines^{33,34} suggests that all head pain is mediated by a single mechanism. Various stimuli in the brain such as raised intracranial pressure (ICP), traction on intracranial vessels, or meningeal irritation all acti-

Table 2.—Secondary Headaches Treated With Triptans

Reference (case reports unless specified otherwise)	Medication	Response to analgesics	Etiology of HA	Time elapsed until Dx
Abisaab et al ²² n = 1	SMT SQ	“Immediate relief”	Bilateral CAD	1 day
Caekebeke et al ²³ n = 1	SMT 6 mg SQ	“Improved dramatically”	Temporal arteritis	Not reported
Krimsky & Weiss ²⁴ n = 1	SMT 6 mg SQ	Resolved	Pituitary hemorrhage	1 day
Leira et al ²⁵ n = 1	SMT 50 mg PO, indomethacin, and prednisone	80-90% relief	CAD	“Few days”
Lipton et al ²⁶ n = 1	SMT 6 mg SQ	Complete relief	Carbon monoxide exposure	Over 50 successfully treated HAs with SMT
Manfredi et al ²⁷ n = 2	1. SMT 50 mg PO 2. SMT 50 mg PO	1. 8 to 0 on VAS 2. “Significant improvement”	Head and neck cancer	Diagnosis was known prior to Rx
Mathew et al ²¹ Prospective n = 12	SMT, ergotamine, DHE	“Responded”	Idiopathic intracranial HTN with migraine	Diagnosis was known prior to Rx
Pfadenhauser et al ²⁸ n = 3	1. SMT 6 mg SQ 2. SMT 100 mg PO 3. SMT 6 mg SQ	1. 100 to 60 VAS 2. “Some improvement” 3. 100 to 50 VAS	SAH	1. 6 hours 2. Hours 3. 24 hours
Rosenberg et al ²⁹ n = 1	SMT 6 mg SQ and diazepam 10 mg IM	Improvement	SAH	4 days
Rothrock J ³⁰ n = 1	SMT 6 mg SQ	Severe to mild	SAH	Hours
Shah et al ³¹ n = 1	SMT 6 mg SQ	Resolved completely	Pituitary microadenoma	Not reported

CAD = carotid artery dissection; Dx = diagnosis; HTN = hypertension; PO = by mouth; SAH = subarachnoid hemorrhage; SMT = sumatriptan; SQ = subcutaneous; VAS = visual analog numeric scale.

vate the trigeminal afferent C fibers that reside on pial and dural blood vessels.^{35,36} This activation results in the transmission of pain and release of neurogenic peptides that activate an inflammatory cascade causing vasodilatation and perivascular inflammation.³⁷ Activation of serotonin 5HT receptors inhibits neuropeptide release and decreases vasodilatation, therefore blunting the meningeal nociceptive process.³⁸ Because 5HT₁ receptors are considered the most important serotonin receptor, triptans (which are 5HT₁ receptor agonists) have been used in the treatment of migraine and other nonspecific HAs.³⁹ Dihydroergotamine is another potent 5HT₁ receptor agonist. Therefore, on both theoretical and pharmacological grounds, it is logical that both triptans and ergot alkaloids would be expected to treat pain from HA of multiple etiologies.

Fourth, some patients with serious secondary causes of HA have intermittent pain, which opens the possibility of misinterpreting a response to a medication when in fact the pain would have remitted spontaneously. Numerous studies have described HAs from secondary causes as intermittent in nature.^{19-21,40-49} The fact that HAs that are life-, vision- or brain-threatening can be intermittent is yet another reason that a “response” to various pain medications should not be interpreted as meaning that a given patient’s HA is due to a primary HA disorder since it might be that the HA would have resolved without any medication. Patients with intermittent HA had a diverse list of HA etiologies including temporal arteritis, narrow-angle closure glaucoma, CVST, tumor, IHH, carotid and vertebral artery dissection, and spontaneous intracranial hypotension.^{19-21,40-49}

Lastly, there are numerous case reports of patients with HA of secondary causes who had favorable responses to analgesics. The first group of reports illustrates patients with a wide variety of underlying pathology who received 5 different commonly used nontriptan medications. Although these medications may have other mechanisms of action than the 5HT1 agonists, all 5 can relieve HA by interrupting the trigeminovascular pain pathway. Ketorolac is an NSAID and is believed to have antimigraine effects by acting directly on blood vessels or on the nerve fiber in the dura.³⁴ DHE, an ergot alkaloid, has affinity for many receptors but does excite 5HT1D receptors that inhibit neurogenic peptide release.¹⁰ Metoclopramide, a dopamine antagonist, also inhibits 5HT3 receptors that have an excitatory effect on peptide release.⁵⁰ The phenothiazines, chlorpromazine and prochlorperazine, are powerful dopamine antagonists, anti-emetic at the chemoreceptor zone, and alpha antagonists. The mechanism by which phenothiazines exert their antimigraine effects is unclear but they may act through a combination of all receptor sites to decrease nausea and vasoconstriction.^{51,52} These series of reports show that all 5 medications have the ability to relieve HAs caused by various underlying pathologic stimuli.

The second group of articles demonstrates that triptans can relieve pain from nonmigraine HAs. 5HT1 receptor agonists blunt pain transmission through the trigeminovascular system regardless of the underlying stimuli. The triptan used in almost all these reports is sumatriptan, probably because this is the one that has been available for the longest period of time and because it is available for parenteral use. Miner et al have already shown that sumatriptan is effective for the treatment of undifferentiated primary HAs.³⁹ Other triptans would be expected to have similar effects.

Collectively, this evidence demonstrates that a favorable response to triptans cannot be used to establish the diagnosis of migraine or to distinguish primary from secondary HAs. Not surprisingly, a favorable response to these medications has been found to delay the real diagnosis by hours to days. This implies that both physicians and patients feel that additional diagnostic testing such as lumbar

puncture and/or brain imaging is not necessary after initial successful treatment with analgesics.

The ability to differentiate between primary and secondary HAs remains a clinical challenge. While these data show that the response to analgesics should not be used as a predictor of a benign HA, there are findings in the history and physical examination that, when factored together, should lead to consideration of further diagnostic workup. HAs that are increasing in intensity or that patients describe as the worst of life should be evaluated for SAH.^{53,54} Abrupt onset or "thunderclap" HA can be associated with vascular causes like SAH or CVST and has been shown to be a predictor of serious pathology.^{3,55} Also patients with new focal neurological findings including third and sixth cranial nerve palsies and HA should be imaged.^{3,55} Associated symptoms like vomiting, double or blurry vision are associated with migraines but can potentially be caused by a tumor, increased ICP or masses, and aneurysms. In addition, studies have found age greater than 50 to 55 years increases the risk of harboring significant intracranial pathology.^{3,4,55} These are all important clues that can help guide the decision for further workup. It is also important to remember the International Classification of Headache Disorders criteria require 5 or more episodes of a particular type of throbbing HA to definitively diagnose migraine and 10 or more episodes to diagnose tension HA.⁵⁶ While every patient with migraine or tension HA must have their first episode at some point in time, one cannot definitively make that diagnosis at the onset.

The results of this study must be interpreted in the context of the following limitations. Our search terms were limited; therefore, all relevant communications may not have been reviewed. A formal systematic Cochrane review would be useful. In addition, due to the way we acquired the data, we cannot speculate on the frequency of a positive response to triptans in secondary HAs. Furthermore, there is likely reporting bias away from articles that report a negative response to triptans or other analgesics. However, finding additional articles would only strengthen our conclusion. Future prospective audits of treatment study outcomes would be useful to support and quantify our findings.

Although analgesics should be administered generously with the goal of maximal pain relief, physicians should use other factors like age, onset and quality of the HA, associated symptoms, and physical examination findings to decide which HA patients require further diagnostic studies to exclude secondary HA disorders. Since HAs of any etiology share a final pathophysiology treatable with various analgesics, a favorable response to analgesics should not be used to predict a benign etiology.

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