Cluster Headache Acute Therapies

Despite strong evidence for high-flow oxygen, subcutaneous sumatriptan, and zolmitriptan nasal spray, patients often receive less-than-adequate abortive treatment.

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Introduction

Cluster headache (CH) is a uniformly severe headache syndrome, characterized by strictly unilateral short-lived (20-180 minutes) pain generally located around 1 eye and typically accompanied by unilateral autonomic features, most commonly tearing. Ordinarily, 1 to 6 attacks are experienced per day when a patient is in a cycle. Much less common than migraine, CH tends to be under recognized and inadequately treated. Migraine, being a common disorder, is also found in the patients with CH population, but patients can easily separate the attacks and so should physicians.[1]

Abortive therapy aims to stop an ongoing attack and does not generally influence future attacks or cluster period cessation. Not only is CH associated with a much later diagnosis (often years), but even when a correct diagnosis is made, patients are often undertreated.

A vital part of patient education is advice and training on how to treat an acute attack. Most suggested abortive therapies have a limited evidence base, so official guidelines beyond the most popular agents are of little help and the practitioner quickly finds themselves relying on suggested therapies and anecdotes.[2] Fortunately, high-flow oxygen and subcutaneous (SC) sumatriptan work well for most patients. All too often, insurance coverage/quantity limitations heavily influence therapy and the practitioner is advised to keep this in mind. This article addresses abortive therapies for CH attacks, rather than prevention. (See *Cluster Headache Preventive Therapies* in this issue).

Routes of Administration

Attacks of CH arrive with little warning, reach a peak intensity within minutes, and need to be treated as early as possible. Such rapidity requires abortive therapy that speedily arrives in the general blood circulation. This generally precludes oral therapies, and practitioners who begin with oral abortive medications cause needless delay in proper CH treatment. Patients experiencing longer attacks sometimes do use oral therapies, with mediocre outcomes but deserve the fastest options first, unless contraindicated. In the setting of severe pain, patients will take even minimal benefit over nothing, which may account for the occasional acceptance of oral medications.

Brisk entry into the general circulation is achieved with SC administration, inhalation, and to some extent via nasal spray. The mucosal surface of the nose is rather limited in size, making transmucosal passage variable and a less optimal route for all medications to get quickly and reliably into the general circulation. In a monitored setting, intravenous therapy is also an option.

CLINICAL GEMS

Injection, inhalation, and nasal spray therapies are superior to oral treatment for acute treatment of CH.

Top Abortive Options

Oxygen

Despite good evidence from randomized controlled trials (RCTs) that high-flow oxygen via nonrebreather face mask works well, oxygen therapy is not covered by all insurance providers as a treatment for CH, although efforts are continuing to change this problem. Oxygen therapy has a level A recommendation in the American Headache Society (AHS) CH guidelines.[1] A small study with a double-blind crossover design of 19 participants who were treated with oxygen at 6 L per minute, showed this was more effective than room air at aborting CH.[3] Another randomized, controlled trial of 109 participantss with CH demonstrated relief (ie, cessation or adequate pain relief) at 15 minutes for 78%

of patients given 12 L per minute oxygen compared with 20% who had relief after being given room air.[4] A recent RCT failed to demonstrate a benefit of 12 L per minute oxygen vs 7 L per minute for aborting CH.[5] There is much anecdotal experience suggesting higher flow rates of 15 to 20 L per minute are most effective.

CLINICAL GEMS

Prescribe oxygen at 15 L/min via nonrebreather mask, not nasal cannula, to be administered for 15 to 20 minutes a soon as an attack begins.

Oxygen should be prescribed at 15 L per minute via nonrebreather mask (not a nasal cannula) to be administered for 15 to 20 minutes as soon as the attack starts. Starting 15 L per minute requires the supplier to provide a regulator that allows 15 L per minute, whereas most oxygen for cardiopulmonary disease has lower requirements. A special type of regulator called a demand valve, familiar to divers, is used less commonly and allows high-flow oxygen only with inhalation and shuts off with exhalation. Although oxygen utilization is reduced, there is no other advantage of this regulator.

Oxygen concentrators generally have a lower flow rate (1-5 L/min), with the fastest devices being approximately 10 L per minute, which may not be adequate for treatment of CH. The main disadvantage of oxygen is the bulky nature of the tanks. Given the safety and efficacy, most patients rely heavily on oxygen, sometimes as the only CH therapy.

Physicians are very familiar with the concern for respiratory depression in patients with chronic obstructive pulmonary disease receiving oxygen who may retain CO2, but it is unlikely that 15 minutes of supplemental oxygen creates a significant risk. Many patients who cannot access medical oxygen have used welding oxygen; fortunately, it is not inherently dangerous but is not as safe as medical oxygen. Welding oxygen is safer when a new tank is refilled and not swapped for another tank.

Barriers to accessing oxygen include coverage by payers and physicians' lack of familiarity and overcaution about oxygen toxicity, which is not a concern with this usage. Often patients receive less-than-adequate counsel on oxygen therapy. The patient advocacy organization Clusterbusters has excellent education material about oxygen therapy online and the organization's annual meeting provides in-person training on oxygen use.[6]

Mystery remains regarding how oxygen therapy works. Formerly, theories centered around a vascular effect, but recent work suggests a direct brain action, appropriate for this brain disorder. Oxygen has been demonstrated to have a direct inhibitory effect on the parasympathetic/facial nerve projections to the cranial vasculature.[7] Because most patients with CH have normal (near 100%) oxygenation, increases to hemoglobin oxygen saturation are limited, and the gain is mainly from dissolved oxygen. The goal of oxygen therapy is to raise the partial pressure of oxygen in the alveoli allowing gas exchange. Theoretically hyperbaric oxygen would work well as an abortive therapy, given the very high partial pressure of oxygen in hyperbaric conditions, although impractical for CH management.[8]

Subcutaneous Sumatriptan

The SC route is by far the best way to administer triptans (5-hydroxytryptamine 1B/D [5-$HT_{1B/D}$] agonists) as an abortive treatment for CH and often ends an attack in as little as 10 minutes. Subcutaneous sumatriptan has a level A recommendation in the AHS CH guidelines. In 2 RCTs, the benefit of 6 mg of SC sumatriptan as a CH abortive treatment was demonstrated.[9,10] The first showed that within 15 minutes of treatment, 74% of attacks treated with sumatriptan responded (complete or almost complete relief of headache) compared with 26% of attacks treated with placebo.[9] Oral triptans are unsuitable due to onset times and sumatriptan nasal spray is not nearly as good as the SC route. Sumatriptan nasal spray has a Level B (probably effective) recommendation in the AHS CH guidelines.[2]

Although 6 mg of SC sumatriptan tends to be the most used, many patients can respond to 3 mg or 4 mg, which is a commercially available dose. Some patients with CH obtain 6-mg vials of sumatriptan and use syringes (0.5-1.0 mL) to administer 2 mg or 3 mg at a time, which allows more injections per day than would otherwise be possible (maximum daily dose in the package insert is 2 SC 6-mg injections per day). Sumatriptan is particularly suited to self-medicating environments not appropriate for oxygen (eg, car, plane, and lecture room). Patients who experience 1 to 2 attacks per day may prefer SC sumatriptan over oxygen for convenience. It is often prudent to refill and store sumatriptan when CH is quiescent to ensure adequate supplies are available when a cycle begins.

CLINICAL GEMS

Evidence shows that 6 mg injectable sumatriptan works more quickly than zolmitriptan nasal spray.

Triptans are typically contraindicated with uncontrolled hypertension, ischemic heart disease, peripheral vascular disease, or cerebrovascular disease. As CH often affects the older population, it is common to avoid triptans due to vascular concerns.

Zolmitriptan Nasal Spray

After oxygen and SC sumatriptan, zolmitriptan nasal spray is probably the next most effective treatment for CH. Zolmitriptan nasal spray, 5 mg to 10 mg, has a Level A recommendation in the AHS CH guidelines.[2] There are 2 positive RCTs comparing 5 mg and 10 mg of zolmitriptan nasal spray with placebo.[11,12] A Cochrane review on treatment of CH attacks concluded that 6 mg of SC sumatriptan is superior to 5 mg or 10 mg of zolmitriptan nasal spray for rapid response (15 minutes).[13] In a study of 52 patients with CH, headache relief at 30 minutes was achieved by 50% of patients treated with 5 mg of zolmitriptan nasal spray and 63.3% of those treated with 10 mg, compared with 30% of those treated with placebo.[11] Zolmitriptan is available as a 5-mg nasal spray. Practitioners contemplating a 10-mg dose would be wise to explain the option of using 2 nasal sprays at the same time but refrain from writing that on the prescription, lest there be delays from a concerned pharmacist. The maximum approved single dose is 5 mg. The expense of zolmitriptan nasal spray may also limit use.

Other Less Effective Abortive Options

Lidocaine Nasal Spray

Lidocaine, 4%, has been studied, although primarily in an uncontrolled manner, for abortive relief of CH and has a modest benefit, at best; it is more suited to adjunctive therapy. Administration is ipsilateral to the pain; the head should be reclined at a 45° angle and rotated to the affected side by 30 to 40 degrees. Lidocaine, 4%, must be compounded (ie, there is no commercially available product), which adds to the expense. In a study of 30 men with CH, 27% had moderate relief using lidocaine, 4%, nasal spray.[14] Lidocaine solution, as self-administered drops into nasal passage, has also been explored as a treatment for CH and is thought to reach the sphenopalatine ganglion. Positive responses to treatment are thought to act through this ganglion, at least in part.

Ergotamine and Derivatives

Oral ergotamine has poor bioavailability and no role in the abortive management of CH. Rectal administration is also unacceptably slow for CH. Prior to sumatriptan, ergotamines were used as CH abortive agents using a variety of routes of administration such as sublingual and inhalational (commercially available ergotamine inhaler). Parenteral dihydroergotamine (DHE) can be used to induce a remission (often temporary) and has been used to abort an attack too, though intravenous administration is preferred as SC and intramuscular routes are also slow for CH. In a study of 25 patients, 137 attacks were treated with DHE nasal spray and 133 attacks were treated with placebo; although the intensity of the attack was reduced, the duration was not significantly different in the placebo group.[15] Nasal DHE is commercially available, as are vials of DHE for SC or intramuscular use. A DHE inhaler has been developed but is not commercially available. Frequent use of ergotamine/DHE is best avoided, due to accumulation and toxicity. Overall, DHE is not thought to have a role in aborting individual CH attacks (as opposed to inducing a remission). AHS guidelines state there is insufficient data from which to make a recommendation for DHE nasal spray for CH.

Any Role for Opioids?

Opioids have no role in the management of CH, with little exception. Parenteral opioids clearly relieve pain very quickly, but the problems and concerns of opioids preclude general use. Rapid-onset opioids are powerfully reinforcing with risks of overuse, abuse, and overdose. Because the effect of opioids lasts longer than a CH attack, which leaves patients under the influence of opioid without pain to balance the sedative effect, use of opioids is not advisable—including transmucosal fentanyl, despite its ability to provide quick relief of severe pain. The opioid butorphanol in a nasal spray formulation was used for quick relief of pain, including headache, but alarming rates of abuse, addiction, and even death quickly emerged.[16] Butorphanol nasal spray is best avoided.

Nasal Ketamine

Ketamine, a dissociative anesthetic and antagonist of the *N*-methyl-D-aspartate (NMDA) receptor, is being studied for treatment of depression. There are published case reports of intravenous ketamine use to treat both migraine and CH, attempting to induce a remission. Anecdotal experience suggests ketamine nasal spray may be useful in aborting CH.[17] There appears to be a dose range suitable to abort attacks before the more profound effects of amnesia, catatonia, and unresponsiveness ensue. Ketamine lacks the respiratory inhibition characteristic of opioids. Ketamine nasal spray needs a compounding pharmacy (suggested concentrations include 50 mg/mL) and is best reserved for those failing or otherwise not suitable to other abortive therapies. Although likely more effective, SC administration on an outpatient basis is impractical. Tolerance to ketamine develops rapidly and use should be accompanied by advice on breaks from the medication on a weekly and monthly basis. Users note a prophylactic effect of ketamine on CH. Cystitis, a complication among abusers of illegally obtained ketamine, has not yet been seen with medical ketamine use.

Neuromodulation Devices

In 2017, the first noninvasive vagal nerve stimulator received Food and Drug Administration (FDA) clearance for the acute treatment of pain associated with episodic CH in adult patients. (See also *Neuromodulation Therapies for Headache* in this issue.) The device is applied to the neck

and administers a brief electrical stimulation attempting to abort an ongoing CH attack. The stimulation is thought to involve the cervical branch of the vagus nerve through the skin. In 2 RCTs, the primary outcome was not achieved with use of the device for abortive relief of CH attacks; however, post hoc analysis showed a benefit in those with episodic CH, but not chronic CH.[18,19] The device requires a prescription and is rented on a monthly basis.

In an RCT of 28 participants with chronic CH, an implanted sphenopalatine ganglion stimulator provided pain relief in 67.1% of full stimulation-treated attacks compared with 7.4% of sham-treated attacks ($P < .0001$).[20] Case series using implanted sphenopalatine ganglion stimulation to treat CH have also been published. The AHS guidelines for CH classify the level of evidence for this treatment as Level B, probably effective, but it is not yet cleared by the FDA. What role stimulation devices will have in the management of CH is still undecided despite the availability of noninvasive stimulators. Patient experience in practice will be critical in judging usefulness of these treatments.

Other Agents

Rapid ingestion of caffeine at the start of an attack is advocated by some patients as an adjuvant, although there are no supportive clinical studies and outcomes are modest. Caffeine has a rapid and complete absorption from the small intestine after oral intake, easily penetrates the blood-brain barrier, and acts as a nonselective adenosine receptor antagonist. A study of octreotide, which mimics somatostatin with multiple hormonal effects, administered subcutaneously suggests a possible benefit as a CH abortive.[21] Butalbital-containing oral agents are generally not suitable because of long onset times and partial effects. Although it is difficult to control for nasal capsaicin in clinical trials, in a small RCT (n = 13) attacks were treated with capsaicin or active placebo in the ipsilateral nostril for 7 days as a CH abortive.[22] Headaches on days 8 to 15 of the study were significantly less severe in the capsaicin group vs the placebo group. There was also a significant decrease in headache severity in the capsaicin group on days 8 to 15 compared with days 1 to 7, but not in the placebo group. In contrast, capsaicin nasal spray is not thought to be particularly useful.

Interest in the use of serotonergic hallucinogens to abort a cluster cycle and maintain remission has increased in recent years, with much anecdotal success, despite their proscribed status.[23] The psychedelic agent *N,N*-dimethyltryptamine (DMT), an indole alkaloid found in nature (such as *Psychotria viridis* leaves) can be used recreationally via inhalation, and anecdotally can switch off a cluster attack in minutes at most. This short lasting (~14 minutes) psychedelic experience is profound, however, and best suited to those familiar with psychedelic agents.

Conclusions

Therapy for CH has suffered from a lack of funding for the exploration of new therapies. A limited amount of evidence exists to guide abortive treatment. The level of knowledge among neurologists for even the well accepted therapies is not where it should be, which can result in less-than-optimal counseling of patients. Practitioners are encouraged to review evidence-based guidelines (keeping in mind there is a paucity of controlled trials), keeping mindful of the level of evidence and author conflicts of interest. Specialists in headache medicine must have expertise in managing oxygen, SC sumatriptan, and zolmitriptan nasal spray, the premier abortive therapies for CH. Medical devices have recently become an option and are in development as abortive agents for CH. The position of medical devices in the abortive management of CH is still to be determined. ■

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