Headache
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ISSN 0017-8748
doi: 10.1111/j.1526-4610.2010.01830.x
Published by Wiley Periodicals, Inc.

Review Article

Cluster Headache—Acute and Prophylactic Therapy

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Cluster headache (CH) pain is the most severe of the primary headache syndromes. It is characterized by periodic attacks of strictly unilateral pain associated with ipsilateral cranial autonomic symptoms. The majority of patients have episodic CH, with cluster periods that typically occur in a circannual rhythm, while 10% suffer from the chronic form, with no significant remissions between cluster periods. Sumatriptan injection or oxygen inhalation is the first-line therapy for acute CH attacks, with the majority of patients responding to either treatment. The calcium channel blocker verapamil is the drug of choice for CH prevention. Other drugs that may be used for this purpose include lithium carbonate, topiramate, valproic acid, gabapentin, and baclofen. Transitional prophylaxis, most commonly using corticosteroids, helps to control the attacks at the beginning of a cluster period. Peripheral neural blockade is effective for short-term pain control. Recently, the therapeutic options for refractory CH patients have expanded with the emergence of both peripheral (mostly occipital nerve) and central (hypothalamic) neurostimulation. With the emergence of these novel treatments, the role of ablative surgery in CH has declined.

Key words: cluster headache, acute therapy, prophylactic therapy

Abbreviations: AEs adverse effects, CCH chronic cluster headache, CH cluster headache, DHE Dihydroergotamine, ECH episodic cluster headache, GON greater occipital nerve, HBO hyperbaric oxygen, HS hypothalamic stimulation, NBO normobaric oxygen, ONS occipital nerve stimulation, SPG sphenopalatine ganglion

(*Headache* 2011;51:272-286)

Cluster headache (CH) pain is considered the most severe of the primary headache syndromes and is arguably one of the most severe pain syndromes that afflict humans.[1] The disorder is characterized by attacks of severe, strictly unilateral pain, typically in the retro-orbital and fronto-temporal areas, associated with symptoms and signs of cranial autonomic dysfunction (tearing, conjunctival injection, rhinorrhea/nasal congestion, and Horner's syndrome) ipsilateral to the pain. Patients typically pace restlessly during an acute attack. The hallmark of CH is the circadian periodicity of the attacks. Also, in episodic CH (ECH), the cluster periods often occur at predictable times of the year (circannual periodicity). Recent imaging studies confirm activation of the hypothalamus during CH attacks.[2] These findings may explain the characteristic periodicity of CH. Activation of the trigeminovascular system has also been shown during acute attacks.

The management of CH includes: (1) patient education about the nature of the disorder; (2) advice on lifestyle changes (eg, avoiding alcohol during an active cluster period); (3) prompt treatment of the acute attack; and (4) prophylactic treatment. Most patients can be managed with medical therapy.

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Accepted for publication November 13, 2010.

Conflict of Interest: None

Rarely, surgical treatment is indicated. Recently, neurostimulation has emerged as a therapeutic option for select patients.

We performed a PubMed search of the English literature to find studies on the acute and prophylactic treatment of CH. Search terms were CH and each of the following: acute treatment, prophylactic (or preventive) treatment, triptans, oxygen, ergotamine, dihydroergotamine, lidocaine, somatostatin, octreotide, verapamil, lithium, topiramate, valproic acid, methysergide, gabapentin, baclofen, melatonin, botulinum toxin, corticosteroids, neurostimulation, occipital nerve block/stimulation, sphenopalatine ganglion block/stimulation, hypothalamic stimulation, radiofrequency, trigeminal rhizotomy, gamma knife surgery, microvascular decompression. We did not limit our search to a specific time period. We focused on clinical efficacy and tolerability of the various drugs and procedures based on data from human studies. We included the best available studies for each discussed drug or procedure. These ranged from randomized controlled trials for some treatments, to small case series for others.

TREATMENT OF THE ACUTE ATTACK (TABLE 1)

Because the pain of acute CH attacks evolves rapidly, oral medications are usually not as effective for this purpose as they are for migraine attacks. For rapid and effective pain control, the therapeutic agent needs to be given parenterally.[1]

Table 1.—Drugs for the Acute Treatment of Cluster Headache

Therapy	Level of Evidence (EFNS Guidelines)[42,87]*	Dose	More Common AEs	Comments
Oxygen	A	7-10 L/min (higher flow rates may be needed)	None	Inhaled via a non-rebreathable mask for 15-20 minutes
Sumatriptan SC	A	6 mg	Nausea, fatigue, paresthesias, chest/throat tightness	May be taken up to twice daily during a cluster period; contraindicated in patients with CV diseases
Sumatriptan IN	A	20 mg	Nausea, fatigue, paresthesias, chest/throat tightness, unpleasant taste	Slower onset of action then sumatriptan SC; contraindicated in patients with CV diseases
Zolmitriptan IN	A	5-10 mg	Nausea, fatigue, paresthesias, chest/throat tightness, unpleasant taste	Comparable in efficacy to sumatriptan IN; contraindicated in patients with CV diseases
Octreotide SC	B	100 μg	Injection site pain, abdominal pain, nausea, hyperglycemia	Can be used in patients with CV diseases
Lidocaine IN	B	1 mL (4-10%)	none	Only moderate effect on head pain
Dihydroergotamine IV, IM, SC, or IN	Not rated	1 mg	Nausea, diarrhea, muscle cramps, chest tightness, unpleasant taste (IN)	IV probably the most effective route; contraindicated in patients with CV diseases; cannot be used with triptans

*See Appendix for detailed guidelines.
AEs = adverse effects; CV = cardiovascular; EFNS = European Federation of Neurological Societies; IM = intramuscular; IN = intranasal; IV = intravenous; L/min = liters per minute; SC = subcutaneous.

TRIPTANS

The 5-$HT_{1B/1D}$ agonists (known as triptans), in an injectable or intranasal preparation, are a mainstay of acute CH treatment.[1-3]

Sumatriptan.—Sumatriptan, injected subcutaneously, is the drug of choice for acute CH attacks.[1] The efficacy of the drug for this indication was examined in a number of well-designed studies.[4-7] In 1 randomized, placebo-controlled study the efficacy of subcutaneous sumatriptan (6 mg) for acute CH treatment was examined.[4] Data from 39 patients were evaluated. Headache severity decreased within 15 minutes in a significantly higher proportion of sumatriptan-treated, as compared with placebo-treated, attacks (74% vs 26 %). Also, a significantly higher proportion of sumatriptan-treated patients were pain free 15 minutes after injection, as compared with those who received placebo (46% vs 10%). Sumatriptan was well tolerated. In another controlled study, subcutaneous sumatriptan at a dose of either 6 mg or 12 mg, or placebo, was given to 134 CH patients.[5] Fifteen minutes after injection, the proportion of patients who experienced headache relief was 80%, 75% and 35% for sumatriptan 12 mg, sumatriptan 6 mg, and placebo, respectively. The higher dose of sumatriptan was not significantly superior to the lower dose, and was associated with more adverse effects (AEs). In an open-label study from the same group, the long-term safety and efficacy of subcutaneous sumatriptan was examined in 138 CH patients.[6] Each patient treated a maximum of 2 attacks per day with a single injection per attack. A total of 6353 attacks, that occurred over 3 months, were evaluated. Headache relief was obtained in 96% of attacks. There was no evidence for decreased efficacy of the drug with continued use. Sumatriptan was well tolerated, and there was no increase in AEs with higher frequency of using the drug. In another open-label study, the efficacy and tolerability of sumatriptan in CH treatment were evaluated over a period of up to 1 year.[7] The maximum daily dose of sumatriptan was 12 mg. A total of 2031 attacks, experienced by 52 patients, were evaluated. In 88% of the attacks, treatment was effective within 15 minutes after injection, and 57% of patients were pain free at that time point. There was no significant change in the efficacy of the drug with repeated use. The response to treatment of patients who had chronic CH (CCH) was somewhat less robust, and slower to occur, as compared with that of ECH patients. Adverse effects were reported by 62% of patients. Withdrawal rate was 33%, with 4 (8%) patients withdrawing because of AEs.

The efficacy of intranasal sumatriptan in the treatment of acute CH attacks was examined in 1 placebo controlled study.[8] Patients with ECH or CCH, whose attacks lasted at least 45 minutes, were given intranasal sumatriptan 20 mg, or placebo. Data from 154 attacks, experienced by 118 patients, were analyzed. At 30 minutes after treatment, headache response rates were significantly higher for sumatriptan- compared with placebo-treated attacks (57% vs 26%). The corresponding pain-free rates at that time were 47% and 18%. The drug was well tolerated. Another study, that was open label, reported on lower efficacy of intranasal, as compared with subcutaneous sumatriptan, in acute CH treatment.[9] A limitation of that study, in addition to its open-label design, was the fact that treatment outcomes were evaluated at a relatively early time point (15 minutes post treatment).

In summary, injectable sumatriptan is effective and well tolerated for the majority of CH patients. The drug has a rapid onset of action. It remains well tolerated and effective even when taken frequently (up to twice daily) during a cluster period. The recommended dose is 6 mg, although lower doses (2-3 mg) may be effective in some patients.[10] Intranasal sumatriptan appears to be less effective, and to have a slower onset of action than the injectable preparation. Sumatriptan is contraindicated in patients with coronary artery disease or cerebrovascular disease. Because CH typically afflicts middle aged men, many of whom smoke, a clinical evaluation, oriented toward the risk of vascular diseases, needs to be done before prescribing the drug.

Zolmitriptan.—The efficacy of intranasal zolmitriptan for acute CH attacks has been studied in 2 controlled trials.[11,12] In 1 study, 92 patients received either intranasal zolmitriptan (5 mg or 10 mg) or placebo, for acute attacks.[11] Thirty minutes after treatment, headache relief rates were significantly higher for zolmitriptan compared with placebo (62%, 40%,

and 21% for zolmitriptan 10 mg, zolmitriptan 5 mg, and placebo, respectively). Patients with ECH had higher response rates to zolmitriptan (and to placebo) compared with those who had CCH. Zolmitriptan was well tolerated. In a similarly designed study, 52 CH patients treated 151 attacks with intranasal zolmitriptan (10 mg or 5 mg) or placebo.[12] Zolmitriptan, at both doses, was superior to placebo with regards to headache relief at 30 minutes (63%, 50% and 30% for zolmitriptan 10 mg, zolmitriptan 5 mg, and placebo, respectively). The corresponding pain-free rates at that time point were 47%, 39%, and 20%. Zolmitriptan, at both doses, was well tolerated.

Oral zolmitriptan was evaluated as an acute treatment for CH attacks in a randomized controlled study.[13] The drug was found to be superior to placebo in ECH, but not CCH, patients. Thirty minutes after treatment, headache response rates in ECH patients were 47% and 29%, for zolmitriptan 10 mg and placebo, respectively.

In summary, intranasal zolmitriptan may be used for the acute treatment of CH, with comparable efficacy to that of intranasal sumatriptan. Oral zolmitriptan has only limited efficacy for this purpose. As with sumatriptan, zolmitriptan is contraindicated in patients with a history of cardiovascular or cerebrovascular disease.

OXYGEN

Oxygen inhalation has been used for the treatment of acute CH attacks for decades.[1] The major advantage of oxygen is the virtual lack of AEs. As opposed to triptans, oxygen can be given to patients with a history of cardiovascular or cerebrovascular disease. The mechanism of action of oxygen on CH has long been related to its vasoconstrictive effect.[14] More recently, however, it has been shown that oxygen inhibits neuronal activation in the trigeminal nucleus caudalis when this activation is initiated by stimulation of the parasympathetic outflow through the facial nerve.[15] Oxygen has been evaluated as an acute treatment of CH in a number of studies.[16] In an open study, Kudrow examined the efficacy of oxygen for acute CH attacks in 52 patients.[17] Oxygen 100% was inhaled via a facial mask at a rate of 7 liters/minute (L/min) for 15 minutes. Thirty-nine (75%) patients experienced significant pain relief within 15 minutes. The best response was observed in younger (<50 years old) patients who had ECH. Fogan examined the efficacy of oxygen for acute CH in a double blind crossover study.[18] Nineteen men were treated with either oxygen, or air inhalation, at a rate of 6 L/min. After treatment, average pain relief score was significantly higher for oxygen, as compared with air. Rozen examined the effect of high flow oxygen on CH pain in 3 patients who had been refractory to oxygen given at the standard flow rate of 7-10 L/min.[19] All 3 patients (2 with CCH and 1 with ECH) had complete or near-complete headache response after inhaling 100% oxygen at a rate of 14-15 L/min. Two of the patients were heavy smokers. The author suggested that patients who fail to respond to oxygen at the standard flow rate should be tried on higher flow. In a recent large controlled trial, Cohen et al examined the efficacy of high flow oxygen in the treatment of acute CH attacks.[20] A total of 109 patients treated 4 CH attacks with either oxygen (12 L/min) or inhaled air, given via a facial mask for 15 minutes. Oxygen was significantly superior to placebo with regards to the primary end point (elimination of pain or "adequate pain relief" at 15 minutes—78% vs 20%, with oxygen and air, respectively).

Hyperbaric oxygen (HBO) has also been studied as a treatment for acute CH attacks.[21,22] Weiss et al treated a CH patient with hyperbaric (2 atmospheres) 100% oxygen, after she had been refractory to conventional oxygen therapy.[21] Two attacks were treated with HBO, with prompt and complete pain relief. Di Sabato et al treated 7 ECH patients with HBO in a placebo controlled study.[22] Six patients responded well to treatment, with interruption of their attack. Moreover, in 3 of the responders the CH period ended after HBO treatment. Placebo treatment had no effect on pain.

In summary, normobaric oxygen is an effective treatment of acute CH attacks in the majority of patients. It is well tolerated and has virtually no AEs. As opposed to triptans, there is no limitation to the number of times per day it can be used. A proper technique of use is crucial for good results with oxygen therapy. The patient should be instructed to use the oxygen via a non-rebreathable mask, at a rate

of 7-10 L/min, in a sitting position, for at least 15-20 minutes. Patients may increase the flow rate up to 15 L/min if needed. The optimal flow rate should be determined individually for each patient. The major disadvantage of oxygen therapy is its inconvenience of use, particularly when the patient is out of home. Portable oxygen tanks are available for patients who wish to use it in these circumstances. Oxygen therapy for CH should be used with caution, or even avoided, in patients with chronic obstructive pulmonary disease, because of the risk of respiratory depression. HBO may be considered for refractory CH patients. However, because this is not a readily available therapy, and there is no evidence for a sustained effect of it on CH,[23] the majority of patients are not likely to benefit from it.

ERGOTAMINE AND DIHYDROERGOTAMINE

Ergot derivatives were among the first agents to be used in CH treatment. Reports on the efficacy of ergotamine for this indication date back to the 1940s and 1950s.[1] These data, however, were based on small, open-label studies and on case reports. The drug has not been evaluated in controlled studies for this indication. Kudrow compared the efficacy of sublingual ergotamine with that of oxygen in 50 patients with CH.[17] The response rate to ergotamine was 70%, as compared with 82% for oxygen (with no significant between-group difference). Oxygen was better tolerated than ergotamine; however, the latter was more convenient to use. Because of limited availability and potentially serious AEs, most notably those related to the drug's vasoconstrictive effect, ergotamine is currently rarely used for acute CH.

Dihydroergotamine (DHE) is available in injectable (intravenous, intramuscular, or subcutaneous) and intranasal formulations. Although no data from controlled trials are available, clinical experience suggests efficacy of intravenous DHE for acute CH. This treatment, however, is not practical for the majority of patients because of the difficulty in receiving it promptly with attack onset. Based on our clinical experience, intramuscular and subcutaneous DHE injections are not as effective as the intravenous route, although, to our knowledge there are no studies that compared the various routes of administration of the drug for CH. The efficacy and tolerability of intranasal DHE (1 mg) in the treatment of acute CH was examined in a controlled study of 25 patients.[24] Intranasal DHE decreased the intensity, but not the duration, of the attacks, and was well tolerated. The authors suggested that the moderate efficacy of the drug in their study may have been related to the dose they used. They recommended that the drug be examined at a higher dose in future trials (the maximal recommended dose of intranasal DHE for acute headache treatment in adults is 2 mg).

In summary, because of the moderate efficacy of most ergot preparations and the difficulty of receiving intravenous DHE (probably the most effective preparation for this purpose) in a timely manner, the role of ergots in the acute treatment of CH is limited.

LIDOCAINE

Data on the efficacy of locally applied lidocaine on acute CH attacks are derived from several non-controlled studies and 1 randomized controlled trial.[25-28] Kittrelle et al examined the effect of lidocaine, applied topically to the sphenopalatine fossa, on acute CH attacks.[25] Four of the 5 treated patients experienced rapid relief from pain and associated symptoms of nitrate-induced CH attacks. The treatment was also effective for spontaneous attacks. In another study, Hardebo and Elner examined the effect of lidocaine 4%, self-applied using a nasal dropper through the nostril ipsilateral to the pain, on CH pain and associated symptoms.[26] Twenty-four patients were studied, with moderately positive results. Robbins examined the effect of intranasal lidocaine, administered through a spray bottle, on pain in 30 men with ECH.[27] Patients treated 2 consecutive CH attacks. Results were modest, with 27% reporting on "moderate relief," 27% on "mild relief," and 46% on no relief. In a placebo-controlled study, Costa et al examined the efficacy of lidocaine 10%, applied bilaterally to the sphenopalatine fossa via a cotton swab using anterior rhinoscopy, on nitroglycerin-induced CH attacks.[28] Lidocaine application resulted in elimination of pain in all (15) patients. However, there was a considerable delay (of 37 minutes on average) between the time of lidocaine

application and pain relief (the corresponding time interval for placebo was 59 minutes).

In summary, intranasal lidocaine is at best moderately effective in the treatment of acute CH attacks. It should not be used as a first-line therapy for this indication. This treatment may be used as adjunctive therapy in some patients whose attacks do not completely respond to other, more effective, therapies.

SOMATOSTATIN AND OCTREOTIDE

Sicuteri et al conducted a controlled study to examine the efficacy of intravenous somatostatin for acute CH attacks.[29] Seventy-two attacks, experienced by 8 men, were studied. Somatostatin infusion was superior to placebo, and comparable to intramuscular ergotamine, in relieving CH pain. Matharu et al evaluated the efficacy of octreotide, a somatostatin analog that can be given subcutaneously, for acute CH.[30] Octreotide 100 μg was significantly superior to placebo with regard to headache response rates (52% vs 36%).

An important advantage of these drugs is their lack of vasoconstrictive effect, making them a viable treatment option for patients who cannot use triptans because of vascular diseases.

SUMMARY—TREATMENT OF THE ACUTE ATTACK

In summary, injectable sumatriptan and inhaled oxygen are both a first-line therapy for acute CH. The decision on which of these options to use should be made after considering the patient's medical comorbidities and personal preference. In patients who do not respond well to these treatments (or in those who cannot use triptans), somatostatin or its analogs appear to be a promising therapeutic option. Intranasal lidocaine may be tried as adjunctive therapy in refractory patients.

There are little data with regard to clinical parameters that may predict response to the various acute CH treatments. In a prospective study of 246 CH patients, older age was a predictor for decreased response to triptans, whereas nausea, vomiting, and restlessness predicted decreased response to oxygen.[31] As opposed to migraine, there are few known triggers to the acute CH attack, most notable of which is alcohol. Patients should be advised to avoid alcoholic beverages during a cluster period (or, in the case of CCH, to avoid it altogether).

PROPHYLACTIC THERAPY

Prophylactic therapy for CH is divided into *maintenance prophylaxis* and *transitional prophylaxis*. Maintenance prophylactic therapies are used throughout the entire course of the cluster period with the intent of reducing the frequency and severity of cluster attacks. When treating ECH, maintenance prophylactics are generally discontinued after resolution of the cluster period and then restarted at the onset of the next cluster period. Although maintenance prophylaxis monotherapy is optimal, some patients will require a combination of maintenance medications for adequate control of CH. However, care must be taken to avoid potentially negative drug interactions. Transitional prophylactics are administered for short durations as adjunctive therapies to maintenance prophylactics in an attempt to abort the cluster period or to further reduce the frequency and severity of cluster attacks. They are often begun simultaneously with initiation of maintenance prophylaxis because they tend to work more quickly and thus provide control of CH until the maintenance therapy has time to take effect.

MAINTENANCE PROPHYLAXIS (TABLE 2)

First-Line Therapy.—Verapamil, a calcium-channel blocker, is the first-line maintenance prophylactic medication for CH. Verapamil is considered first-line therapy because of its efficacy, relative safety, and the ability to coadminister symptomatic and transitional therapies with less concern about drug interactions compared with some of the other maintenance prophylactic medications (eg, lithium carbonate). In open-label studies, approximately 70% of ECH and CCH patients have substantial improvement with verapamil therapy.[32] In a double-blind placebo-controlled trial of verapamil for maintenance prophylaxis of ECH, 15 patients were randomized to 120 mg of verapamil 3 times daily while 15 subjects were randomized to placebo.[33] During 2 weeks of treatment, 80% of patients receiving verapamil had a greater than 50% reduction in headache frequency,

Table 2.—Maintenance Prophylactic Therapy for Cluster Headache

Therapy	Level of Evidence (EFNS Guidelines)[42,87]*	Target Dose per Day	Monitoring	More Common AEs
Verapamil	A	200-900 mg	EKG	Hypotension, constipation, peripheral edema
Lithium carbonate	B	600-900 mg	Lithium levels, renal function, thyroid function	Diarrhea, tremor, polyuria
Topiramate	B	50-200 mg	Serum bicarbonate	Paresthesias, weight loss, cognitive dysfunction, fatigue, dizziness, taste alteration
Valproic acid	C	500-2000 mg	CBC, liver function	Weight gain, fatigue, tremor, hair loss, nausea
Melatonin	C	10 mg	None	Fatigue, sedation
Baclofen	C	15-30 mg	None	Drowsiness, dizziness, ataxia, muscle weakness
Botulinum toxin	Not rated	50 units	None	Muscle weakness, injection site pain
Gabapentin	Not rated	800-3600 mg	CBC	Somnolence, fatigue, dizziness, weight gain, peripheral edema, ataxia
Clonidine	Not rated	0.2-0.3 mg	None	Fatigue, hypotension

*See Appendix for detailed guidelines.
AEs = adverse effects; CBC = complete blood count; EFNS = European Federation of Neurological Societies; EKG = electrocardiogram.

including 4 patients who became attack free. Verapamil took effect quickly, with one-half of responders having substantial improvement within the first week and the other one-half responding during the second week. Meanwhile, zero patients receiving placebo had a greater than 50% reduction in headache frequency. Adverse effects due to verapamil were mild, with constipation being the most common and most bothersome. A double-blind, crossover study of verapamil vs lithium carbonate for CCH suggests that verapamil is a superior treatment.[34] In this randomized trial, each of the 24 subjects received verapamil 360 mg per day or lithium carbonate 300 mg 3 times daily for 8 weeks, and then following a 2 week washout period was switched to the other therapy for an additional 8 weeks. Verapamil and lithium both provided similar reductions in both headache index and analgesic consumption. However, verapamil worked more quickly, with over 50% of patients having significant improvement in headache index within the first week compared with 37% of those taking lithium. Furthermore, only 12% of those taking verapamil reported AEs compared with 29% of those taking lithium.

Target dosages of verapamil ranging from 200 mg to 960 mg per day in divided doses are typically used for cluster prophylaxis.[35] Most patients will respond to doses of 200 mg to 480 mg per day.[36] Immediate or extended release formulations may be used. Slow titrations up to the target dose may reduce AEs including hypotension, constipation, and peripheral edema. A method of titrating and tapering verapamil dosage in 40 mg intervals is described in a paper by Blau and Engel.[36] EKG monitoring is necessary during verapamil therapy because of the risk of heart block and bradycardia, AEs that can develop with initiation of therapy, increases in dose, and even during continued stable dose therapy.[37] In our practice, we obtain a baseline EKG before initiating verapamil therapy, repeat EKG with each increase in dose of at least 80 mg, and an EKG each 3 months if the dose has been unchanged. Patients should be informed of the possibility of developing gingival hyperplasia because of long-term use of verapamil.

Second-Line Therapy.—Lithium carbonate is a second-line therapy for maintenance prophylaxis of CH. We consider lithium as a second-line therapy

because of its potential for causing numerous AEs, the need for blood test monitoring during therapy, and its potential for causing several drug interactions. Nonetheless, lithium carbonate has been demonstrated to provide significant benefit in the treatment of CCH. Its efficacy for treating CCH has been demonstrated in the investigation discussed in "First-Line Therapy" and in a study of 8 additional CCH patients.[34,38] In the latter study, all 8 patients had at least a 75% improvement within the first 2 weeks of therapy. However, only 1 of 3 who were followed long-term had continued improvement after 18 months of therapy. The evidence for the utility of lithium carbonate for the treatment of ECH is less clear, with generally small studies providing contradictory results.[34,38,39] Lithium carbonate doses of 600 mg to 900 mg per day are typically needed to obtain target therapeutic serum lithium levels of 0.4 to 0.8 mEq/L. Lithium serum levels, renal function, and thyroid function should be monitored during lithium therapy. Common AEs to lithium include diarrhea, tremor and polyuria. Symptoms and signs of toxicity include nausea, vomiting, diarrhea, confusion, nystagmus, extrapyramidal signs, ataxia, and seizures.

Topiramate, in doses ranging from 50 mg to 200 mg per day, is considered second-line therapy for CH prophylaxis. Although we have designated topiramate as second-line therapy, consistent with the Grade B recommendation in the European Federation of Neurological Societies guidelines, topiramate use for CH prophylaxis has been investigated in open-label studies only.[40-42] Common AEs to topiramate include cognitive dysfunction, paresthesias, alteration in taste, weight loss, fatigue, and dizziness. Patients with a history of nephrolithiasis should not receive topiramate because of an increased risk of recurrent stones while taking this medication.

Third-Line Therapy.—Other therapies that may be effective for maintenance cluster prophylaxis include methysergide, valproic acid, melatonin, gabapentin, baclofen, clonidine, and botulinum toxin. Although methysergide is likely effective for preventing CH, it is not available in the USA and long-term use is associated with fibrotic complications. Thus, we cannot recommend its use. Valproic acid has been shown to provide benefit in open-label and retrospective studies only.[43,44] A double-blind placebo-controlled study of sodium valproate did not support its efficacy; however, this may have been due to an exceedingly high response rate of 62% in the placebo group.[45] Effective doses range from 500 mg to 2000 mg daily in divided doses. Common AEs include weight gain, fatigue, tremor, hair loss, and nausea. Monitoring with complete blood counts and liver function tests are necessary during valproic acid therapy. Limited evidence supports the use of melatonin for cluster prophylaxis. In a double-blind, placebo-controlled trial of 10 mg melatonin, 5 of 10 subjects randomized to melatonin had cluster remission within 5 days while none of the 10 subjects taking placebo went into remission.[46] Open-label studies of gabapentin suggest its value in maintenance prophylaxis of CH in doses ranging from 800 mg to 3600 mg per day.[47,48] Gabapentin is typically a well-tolerated medication but more common AEs include somnolence and fatigue, dizziness, weight gain, peripheral edema, and ataxia. In a small open-label study of baclofen 10 mg 3 times daily, 6 of 9 subjects went into remission within 1 week and an additional 1 subject had improvement followed by remission at week 2.[49] Although adverse events were not reported by subjects in this study, more common AEs to baclofen include drowsiness, dizziness, ataxia, and muscle weakness. Clonidine, given as a 5 mg to 7.5 mg transdermal patch (that delivers the drug at a rate of 0.2-0.3 mg daily for 1 week), has been studied in 2 small open-label studies.[50,51] In the first, which included 8 ECH and 5 CCH patients, there were significant reductions in mean attack frequency, pain intensity, and attack duration.[50] However, a second study including 16 ECH patients failed to confirm these positive results.[51] Tiredness and reduction in blood pressure were AEs noted in these studies. An open-label study of botulinum toxin type A as add-on therapy in 3 ECH and 9 CCH patients had mixed results.[52] Fifty units injected ipsilateral to the headache resulted in headache remission in 1 CCH patient, improvement in attack frequency and severity in an additional 2 CCH patients, improvement in a continuous baseline headache with no change in superimposed cluster attacks in an additional 1 CCH patient, and no benefit in the remaining 8 patients. More common AEs to

botulinum toxin therapy include weakness of injected muscles and pain at injection sites.

TRANSITIONAL PROPHYLAXIS

Corticosteroids are often prescribed concurrent with initiation of maintenance prophylaxis in order to quickly obtain cluster control. Oral and intravenous corticosteroids may both provide benefit. Varying doses of oral prednisone, ranging from 10 mg/day to 80 mg/day, were evaluated in a study of 9 episodic and 10 chronic cluster patients.[53] Peak prednisone dose was given for 3 to 10 days and tapered over 10 to 30 days. Complete relief from CH was seen in 11 patients, 3 had 50-99% relief, 3 had 25-50% relief, and 2 patients had no benefit. The ECH and CCH patients had similar responses. Investigators observed that prednisone doses of 40 mg or higher were needed for benefit. Headache recurrence was common during the prednisone taper. Other studies of oral prednisone have had similar results.[54,55] Intravenous corticosteroids, sometimes followed by oral steroids, may also provide benefit for transitional cluster therapy.[56,57] A single high dose of intravenous methylprednisolone (30 mg/kg body weight over 3 hours) delivered on the eighth day of an active cluster period provided 10 of 13 treated patients with 2 or more days of attack cessation.[56] The mean interval between steroid treatment and attack recurrence was 3.8 days. Three patients had complete cluster remission.

Although adequate trials supporting their use are lacking, ergotamine tartrate and DHE may be used for transitional prophylaxis.[58,59] In an open-label study, 23 ECH and 31 CCH patients were admitted to the hospital for treatment with repetitive intravenous DHE.[60] All patients became headache free while being treated with IV DHE: 10 patients (16%) after the first dose, an additional 12 (19%) during the first day of hospitalization, and 22 (34%) more became headache free by the second day of hospitalization. By day 3, greater than 90% of patients were headache free and by day 5 all were headache free. At 3 months after discharge, >90% of ECH patients and 44% of CCH patients remained headache free. Approximately 83% of patients reported no AEs from IV DHE. Reported AEs included nausea, non-cardiac chest tightness, and a metallic taste. Ergotamine tartrate, 3-4 mg per day in divided doses, may be administered for 2 to 3 weeks for transitional prophylaxis.[58,61] Administration just before bedtime may help to prevent nighttime attacks.

INVASIVE PROCEDURES FOR CLUSTER HEADACHE TREATMENT

With an individually tailored pharmacologic treatment plan, the majority of CH patients will achieve satisfactory results. For those who remain refractory to medical treatment, a number of invasive procedures are available. These include peripheral nerve blocks, peripheral or central neurostimulation and, as a last resort, ablative surgery. Peripheral nerve block, mostly targeting the greater occipital nerve (GON), may also be used in less refractory patients, as an adjunct to pharmacologic therapy.

PERIPHERAL NERVE AND SPHENOPALATINE GANGLION BLOCK

Efficacy of GON block in CH treatment was suggested by Anthony in the 1980s.[62] More recently, the procedure was investigated as CH treatment in a number of studies, with the majority showing positive results.[63-66] Peres et al evaluated the effect of GON block in 14 patients with CH.[63] Patients received GON block ipsilateral to the head pain using lidocaine 1% and triamcinolone 40 mg. Patients were evaluated before and 1 week after the block. Nine (64%) patients had good or moderate response. The procedure was well tolerated. Ambrosini et al evaluated the effect of suboccipital injection of lidocaine 2% with betamethasone, compared with lidocaine and saline, in 23 CH patients in a randomized, controlled study.[64] The CH attacks disappeared within 72 hours in 85% of the lidocaine + betamethasone group (with 61% remaining attack free for 4 weeks) compared with none in the lidocaine + saline group. Injections were well tolerated. Afridi et al examined the efficacy of GON block, using lidocaine 2% and methylprednisolone, in patients with refractory chronic daily headache.[65] Their sample included 19 patients with CH who received 22 injections. Thirteen of the injections (59%) resulted in a complete or partial response, with a median duration of 12 and 21 days, for complete and partial response, respectively. In

contrast to these results, Busch et al reported on only minor headache improvement in 60% of 15 CH patients who received GON block using prilocaine.[66]

Endoscopically guided sphenopalatine ganglion (SPG) blockade has been evaluated by Felisati et al for CH treatment.[67] Of 20 refractory CCH patients who underwent the procedure, 11 experienced significant, albeit temporary, symptom relief.

PERIPHERAL NERVE AND SPHENOPALATINE GANGLION STIMULATION

Peripheral nerve stimulation may be effective and indicated for the prophylactic therapy of CCH patients who are refractory or intolerant to medication therapy. Several small studies have now shown occipital nerve stimulation (ONS) to be a promising therapy for such patients. Eight patients with drug-resistant CCH, treated with unilateral ONS, were followed for an average of 15.1 months.[68] At the time of last follow-up, 2 of 8 patients were pain free, 3 had a ~90% reduction in headache frequency, 2 had ~40% reduction, and 1 patient derived no benefit. Two patients had side-shift of their cluster attacks requiring treatment with suboccipital steroid injection. Complications included electrode migration (n = 1), lead displacement after a fall (n = 1), and thoracic discomfort or tingling (n = 2). Bilateral ONS was investigated in 8 patients with medically intractable CH.[69] At median follow-up of 20 months, subjective self-assessment of benefit was graded as substantial (≥90%) in 2 patients, moderate (≥40%) in 3, mild (≥25%) in 1, and nil in 2 patients. Six patients reported that they would recommend the use of ONS to other similar cluster patients. Complications, affecting 4 of the patients, included: excessive pain at incision site (n = 1), electrode migration (n = 3), electrode fracture (n = 1), and shock-like sensation because of kinking of wires (n = 1). In 2009, results from extended follow-up of these 8 patients and an additional 6 patients treated with bilateral ONS were reported.[70] At a median follow-up of 17.5 months, 10 of 14 patients reported improvement, including 3 with >90% improvement, 3 with 40–60% improvement, and 4 with 20–30% improvement. Nine patients stated that they would recommend ONS to other patients. Complications/AEs included lead migration, painful paresthesias, muscle recruitment, neck stiffness, skin pain, and infection. Mean battery life was 15.1 months.

The SPG stimulation may also be an effective treatment for refractory CH. Five patients with CCH, refractory to more conventional therapies, were treated with SPG stimulation during 18 acute cluster attacks.[71] Stimulation resulted in complete attack resolution for 11 of the attacks, greater than 50% reduction in pain severity without complete resolution for 3 attacks, and minimal to no relief for 4 attacks. Benefits from stimulation were noted within 1 minute to 3 minutes of treatment initiation. Stimulation was well tolerated with only mild AEs from stimulator placement, including transient epistaxis and transient mild facial pain. Further investigations of SPG stimulation for the acute and prophylactic therapy of CH are needed.

DEEP BRAIN (HYPOTHALAMIC) STIMULATION

Leone et al reported in 2001 on a 39-year-old man with intractable CH whose attacks improved significantly after implantation of a stimulating electrode to the posterior hypothalamus, ipsilateral to the pain.[72] Since this first report, several studies have been published on the efficacy and tolerability of hypothalamic stimulation (HS) for CH.[73-75] Schoenen et al examined the effect of unilateral HS in 6 refractory CCH patients.[73] Three patients had "excellent" results, while another had only a transient remission. In 1 patient treatment had to be stopped because of AEs (autonomic disturbances and panic attacks), and 1 died of intracerebral hemorrhage shortly after the procedure. Leone et al reported on the long-term results of 16 previously refractory CCH patients who had HS.[74] At a mean follow-up of 23 months, major improvement in pain, or complete pain elimination, was obtained in 13 (81%) patients. The mean time to headache benefit was 42 days. Overall, the procedure was well tolerated. No hormonal, affective or sleep-related abnormalities were observed. One patient had an asymptomatic intracerebral hemorrhage that subsequently resolved. Transient diplopia was a common AE with high amplitude stimulation.

Bartsch et al reported on 6 CCH patients who underwent HS.[75] At a mean follow-up of 17 months, 3 patients responded well to treatment, being almost attack free, while 3 patients failed to respond. The procedure was well tolerated. The authors concluded that HS is effective in a subset of refractory CCH patients. Interestingly, in another study, HS was not effective in the majority of patients when used as an acute CH treatment, suggesting that this treatment affects CH through more complex pain modulating mechanisms.[76,77]

In summary, HS is an emerging viable treatment for refractory CCH. It appears to be effective in some, but not all, patients. Although the treatment is generally well tolerated, the risk of intraceberal hemorrhage, and even death, should be kept in mind when considering this treatment option.

ABLATIVE SURGICAL PROCEDURES

With the emergence of a variety of pharmacologic and non-pharmacologic therapies for CH, the role of ablative surgery in this disease has declined.[1] Candidates for surgery should have strictly unilateral, side-locked, CH attacks. A number of procedures have been used with some success for this indication, including radiofrequency ablation of the trigeminal ganglion, trigeminal sensory rhizotomy, gamma knife surgery, and microvascular trigeminal nerve decompression.[1] Radiofrequency trigeminal gangliorhizolysis has been shown as effective in up to 75% of refractory CCH patients.[78,79] In a case series of 27 patients who underwent this procedure, 2 developed anesthesia dolorosa.[79] Other complications included corneal anesthesia, keratitis, and diplopia. Trigeminal root section has been reported to be effective in 88% of 17 patients with refractory CCH, with 76% experiencing long-term pain relief.[80] Complications included corneal abrasion, masticatory muscle weakness, anesthesia dolorosa and the development of CH on the other side. One patient, who underwent the procedure twice, died after the second surgery. The authors concluded that trigeminal nerve section is a viable therapeutic option for selected refractory CCH patients. Microvascular decompression of the trigeminal nerve, with or without section of the nervus intermedius, has shown some efficacy in refractory CCH; however, response rate decreased over time.[81] Gamma knife radiosurgery is a relatively recent therapeutic approach for CH.[82,83] Despite early encouraging results,[82] more recent data showed only modest long-term pain relief and high rate of AEs, including deafferentation pain.[83]

Another surgical approach for CH targets the parasympathetic component of the disease, typically by blocking or ablating the SPG.[67,84,85] In 1 study, radiofrequency blockade of the SPG was performed in 66 CH patients.[84] Complete pain relief was achieved in 61% and 30% of ECH and CCH patients, respectively. In a more recent study, 15 refractory CCH patients were treated with radiofrequency ablation of the SPG.[85] The treatment decreased significantly the mean attack frequency, mean pain intensity and pain-related disability, and these effects lasted for 12-18 months.

In summary, ablative surgical procedures should be reserved as the last resort for refractory CH patients. The procedures that appear to be more effective in the long-term management of the disease are radiofrequency trigeminal ganglion ablation and trigeminal rhizotomy. It should be noted, however, that CH attacks have been shown to persist after trigeminal root section in a case report of man with CH, supporting the hypothesis of a central pain generator in this disease.[86]

APPENDIX

European Federation of Neurological Societies (EFNS) guidelines—evidence classification scheme for a therapeutic intervention

Class I: An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required:

(a) Randomization concealment.
(b) Primary outcome(s) is/are clearly defined.
(c) Exclusion/inclusion criteria are clearly defined.

(d) Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias.
(e) Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class II: Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a-e or a randomized, controlled trial in a representative population that lacks 1 criteria a-e.

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment.

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.

Rating of recommendations:

Level A rating (established as effective, ineffective, or harmful) requires at least 1 convincing class I study or at least 2 consistent, convincing class II studies.

Level B rating (probably effective, ineffective, or harmful) requires at least 1 convincing class II study or overwhelming class III evidence.

Level C (possibly effective, ineffective, or harmful) rating requires at least 2 convincing class III studies.

Adapted with permission from Brainin et al. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces—revised recommendations 2004. Eur J Neurol 2004;11:577-581.

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