Chapter 96

Preventive and Surgical Management of Cluster Headaches

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GENERAL MEASURES AND PATIENT EDUCATION

Patients with cluster headache learn quickly what to avoid because it triggers or worsens a headache. But some patients need to be taught that alcohol intake and napping during cluster periods usually trigger attacks and should be avoided. Certain medications that vasodilate, such as nitroglycerin, and various antihypertensive preparations can trigger a cluster headache. Prolonged exposure to volatile substances, such as solvents and oil-based paints, should also be avoided. Dietary factors other than alcohol do not seem to trigger attacks. A small percentage of cluster patients do much better when they cease smoking.

CLUSTER PREVENTIVE MEDICATIONS

The aim of prevention is to stop all attacks if possible or at least to bring the attacks under control and maintain relief with minimal side effects for as long as possible (in patients with chronic cluster headache) or until the cluster period has passed. Much preventive therapy is based on clinical experience; few randomized clinical trials have been conducted. Preventive drugs commonly advocated are verapamil, lithium, methysergide (methergine in the United States, where methysergide has been removed from the market), ergotamine, pizotifen, corticosteroids, and valproic acid. Several new drugs may also be effective (see Table 96-1).

Verapamil

Verapamil is the preventive medication of choice for both prolonged episodic and chronic cluster headache (6,22,38). Doses in the range of 240 to 360 mg twice daily are common, with an occasionally higher dose used in refractory cases. These larger doses are considerably higher than those for cardiac disease or hypertension. Verapamil may cause heart block by slowing atrioventricular node conduction. PR interval prolongation on the electrocardiogram (ECG) may serve as a coarse indicator of impending heart block. Although formal guidelines for verapamil use are not available, it is reasonable to start with 240 to 480 mg per day (depending on body surface area) after a normal ECG is demonstrated. The daily dose may be increased by 80 to 120 mg each week or two, but it is suggested that an ECG be performed prior to each increase and remains normal. Dose escalation may continue until the attacks disappear, side effects occur, or the maximum daily dose of 960 mg is reached. Standard shorter-acting verapamil preparations seem to be more effective than extended-release formulations (32). The most common side effect is constipation, but dizziness, distal edema, nausea, fatigue, hypotension, and bradycardia also occur. β-Blockers must not be given concurrently.

Lithium

Lithium is generally an effective cluster headache preventive medication but less reliably so for episodic cluster headache than chronic cluster headache (6,14,33). Most patients benefit from 600 to 1,200 mg per day. Tolerability is assessed after 3 to 4 days at 300 mg twice a day, and additional 300 mg per day administrations added until the headaches disappear. Lithium serum levels have to be checked to prevent side effects and should be measured 12 hours after the last dose. In the chronic forms of the disease, lithium should be slowly tapered off at 6- to 12-month intervals to detect those patients who have become episodic. Among the first side effects to appear are agitation, postural tremor of the hands, insomnia, weakness, nausea, thirst, slurred speech, and blurred vision. Toxicity is signaled by nausea, vomiting, anorexia, diarrhea, confusion, nystagmus, ataxia, extrapyramidal signs, and

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TABLE 96-1 Preventive Management of Cluster Headache

Short-Term Prevention (for Episodic Cluster Headache)	*Long-Term Prevention (For Prolonged Bouts of Episodic Cluster Headache and Chronic Cluster Headache)*
Prednisone or prednisolone (possibly as transitional therapy only)	Verapamil
Verapamil	Lithium
Lithium	Methysergide
Methysergide	Valproic acid[b]
GON injection[b]	Pizotifen[b]
Valproic acid (valproate semisodium)[b]	Topiramate[c]
Pizotifen[b]	Gabapentin[c]
Melatonin[b]	Melatonin[b]
Topiramate[c]	Prednisone[d]
Daily (nocturnal) ergotamine[a]	

[a] Patients with predictable nocturnal headaches only.
[b] Limited data, such as pizotifen or negative data, such as valproic acid.
[c] Unproven but promising.
[d] To be administered when all other preventatives have been without effect.

seizures. Hypothyroidism and polyuria (nephrogenic diabetes insipidus) can occur with long-term use. Polymorphonuclear leukocytosis may occur and be mistaken for occult infection. Renal and thyroid function tests are performed prior to and during treatment. Because of the narrow therapeutic window, side effects have to be carefully looked for. In warmer weather, patients should be warned not to become dehydrated, which increases the chance of toxicity.

Methysergide

Methysergide is not available in the United States. Clinical experience demonstrates that methysergide is an effective preventive for cluster headache, although efficacy findings derive only from open trials (9,34). Starting dose is 1 mg per day to minimize side effects and increments should be by 1 mg (in a thrice daily regimen) every 3 to 5 days. If tolerated, methysergide can be raised up to 12 mg/d. Common short-term side effects are nausea, vomiting, dizziness, muscle cramps, abdominal pain, and peripheral edema. Because of its vasoconstrictive properties, coronary or peripheral arterial insufficiency are both contraindications and troublesome side effects (but uncommon) and require drug discontinuation. Prolonged treatment may rarely cause retroperitoneal, pulmonary, pleural, or cardiac fibrosis (25). As a consequence, methysergide is most appropriate for patients with short cluster periods (less than 4 months). When used for prolonged periods, this risk can be minimized by 1-month drug holidays every 6 months, gradually tapering off the drug.

In cases of continuous administration, careful monitoring including yearly echocardiogram, chest x-ray, and abdominal magnetic resonance imaging (MRI) are recommended (62). To reduce the risks of vasoconstrictive effects, it is recommended to administer injectable sumatriptan a few hours apart from methysergide intake and sparingly. In the United States, methysergide is no longer available and methylergonovine, an active metabolite, is a good alternative. It is started at 0.2 mg/d and raised to three times a day rapidly. The maximum dose is usually 0.4 mg three times a day. The same cautions apply. In the United States, it is contraindicated to use any triptan when a patient is taking an ergot.

Ergotamine

A dose of 2 to 4 mg per day may be tried for 2 or 3 weeks (66) when verapamil, lithium, and methysergide are ineffective. If the attacks are predictable, the drug should be taken 30 to 60 minutes beforehand; for attacks awakening the patient during the night, 1 to 2 mg (tablets or suppositories), may be prescribed before retiring. Dr. Lee Kudrow frequently prescribed it twice daily for extended periods with no problem.

Dihydroergotamine

In an open-label study of 54 patients with intractable cluster headache (23 episodic, 31 chronic) repetitive intravenous dihydroergotamine rendered all patients headache free (50). Twelve months later, 83% of episodic cluster headache and 39% of chronic cluster headache patients remained headache free. This strategy is often effective in chronic cluster headache patients who do not respond to other preventives.

Pizotifen

Pizotifen is not available in the United States. An open-label study (65) and one controlled trial (13) reported pizotifen to be moderately effective.

Corticosteroids

Corticosteroids (prednisolone, prednisone, and dexamethasone) are the most rapidly effective preventive agents for cluster headache (2,8). Both oral prednisone and prednisolone are given to a maximum of 60 mg once daily for 5 to 10 days and thereafter the dose is decreased by 5 to 10 mg every 3 days. In long-lasting cluster periods and chronic forms, relapse is almost invariable as the dose is tapered.

Transitional Therapy

To expedite a pain-free condition at the start of a cluster period, corticosteroids (dexamethasone 8 mg

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intramuscularly or orally daily for 5 to 7 days) are useful together with other preventives until the latter begin their effects.

Corticosteroids carry a risk of potentially serious side effects: osteonecrosis is among the most feared (57).

Valproic Acid

Open-label studies with sodium valproate or divalproex sodium report effectiveness in 54 to 73% of cluster headache patients (19,23,28). The use of this drug in cluster was first reported by Arieh Kuritsky in the 1980s. A double-blind, placebo-controlled, parallel group study of sodium valproate (1,000 to 2,000 mg/d) in cluster headache prevention found no significant difference between the 50 patients in the treatment group (37 episodic, 11 chronic, 2 unspecified) and the 46 in the placebo group (36 episodic, 6 chronic, 3 unspecified) (15) . Other studies are needed to further explore usefulness of valproate in cluster headache prevention.

Topiramate

In the first four open-label studies on cluster headache prevention with topiramate, it was administered in the range 25 to 200 mg per day in a total of 30 episodic and 22 chronic cluster headache patients (17,35,52,72). The drug was moderately or markedly effective in 37 patients (70%). Two of the studies reported that topiramate was associated with rapid improvement (within 1 to 4 weeks) (35,72). In these studies, some patients were given topiramate with corticosteroids and others entered the study at the end of their cluster period (72). These observations could explain, at least in part, the observed rapid improvement. In an open-label study of 33 cluster headache patients (23 episodic cluster headache, 10 chronic cluster headache), 21% had a reduction of more than 50% in headache frequency during the 20-day study period. The response was not dose related (40).

Side effects are reported in about 40% of studied cases: less than 50% of these are reported as moderate or severe. Paresthesia at the extremities, somnolence, dizziness, cognitive symptoms, disturbances of balance, and ataxia are common. Mood changes, psychosis, and weight loss may also occur; glaucoma and nephrolithiasis are much less common. To minimize side effects, the starting dose should be 25 mg/d, which can be increased by 25 mg every week.

Gabapentin

Two case reports first indicated that gabapentin could be used in cluster headache prophylaxis (1,67). Subsequently, in an open-label trial gabapentin at 900 mg per day was administered in eight patients with episodic cluster headache and four with chronic cluster headache (36). All became pain free within 8 days. The episodic cluster headache patients discontinued gabapentin after 60 days without attack recurrence. The chronic cluster headache patients were still pain free 4 months later. The only side effect reported was drowsiness in two patients. This high response rate requires confirmation by controlled trials.

Melatonin

In view of the circadian periodicity of cluster headache, the importance of the hypothalamus in its pathogenesis (24), and the fact that serum melatonin is reduced in cluster headache patients, particularly during a cluster bout (45,69), melatonin has been evaluated as a preventive agent in cluster headache.

In a double-blind pilot study of melatonin versus placebo (39), 20 patients (18 episodic, 2 chronic) were randomized to either 10 mg melatonin or placebo for 2 weeks. A reduction in the mean number of daily attacks and a strong trend toward reduced analgesic consumption was reported in the melatonin group. Five patients in the melatonin group responded to the treatment, with cessation of cluster headaches after 5 days of treatment. No patient in the placebo group responded. Melatonin has also been reported to be effective as add-on therapy in sporadic cases (60).

Intranasal Capsaicin and Civamide

Intranasal capsaicin has been examined in open-label (20,21,64) and controlled (48) studies. The two main limitations in its use were that (a) the benefit was often transient, especially in chronic cluster headache, and (b) a significant proportion of patients were refractory to repeated treatment because of its local effects (burning sensation, lacrimation, and rhinorrhea).

In a controlled multicenter study, 18 episodic cluster headache patients received intranasal civamide (a better tolerated z isomer of capsaicin) 0.025% (25 μg) and 10 patients received placebo for 7 days. They were evaluated in a 20-day posttreatment period (63). In the treated group, there was a significant reduction in the headache frequency in the first 7 days compared to vehicle alone (-60% versus -26%), but the overall effect at day 20 was not significant. Nasal burning was rather common in the treated group. Further studies are needed to validate this treatment.

Greater Occipital Nerve Blockade

Injection of local anesthetic plus corticosteroid around the greater occipital nerve (GON) ipsilateral to the pain has been widely used but not subjected to systematic evaluation (2). A report on 14 patients treated with GON injection noted good response in 4, moderate response in 5, and no response in 5 (61). In absence of controlled studies, it is difficult to know if effectiveness of this method

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is attributable to a pure effect of corticosteroid on occipital muscles or if the effect is related to a specific effect on GON.

Other Drugs

Various other drugs, including naratriptan (58), eletriptan (73), baclofen (29), botulinum toxin (16), chlorpromazine (7), and transdermal clonidine (10,37) have been tried in open-label studies. Controlled trials are required to verify the efficacy of these agents (11).

Hyperbaric Oxygen

In a double-blind, placebo-controlled, crossover study on 12 episodic and 4 chronic cluster headache patients hyperbaric oxygen (2.5 ATA) produced no significant effect (59). The evidence for a preventive effect of hyperbaric oxygen is very weak in cluster headache; the treatment has also considerable practical limitations and lacks general availability.

Surgery

Surgery is a last-resort measure in treatment-resistant cluster patients and should only be considered when all pharmacologic options have been exhausted. Patients must be carefully selected.

Destructive Surgical Procedures

Candidates for destructive surgery are chronically intractable cluster (27) patients whose headaches are unilateral with no history of side shift. In patients whose attacks alternate sides, the risk of a contralateral recurrence after surgery is rather high. Various procedures that interrupt either the trigeminal sensory or autonomic (cranial parasympathetic) pathways can be performed, although few are associated with long-lasting benefit; in addition, side effects can be severely debilitating. Procedures sometimes reported to be successful include trigeminal sensory rhizotomy via a posterior fossa approach (31), percutaneous radiofrequency trigeminal gangliorhizolysis (51) and microvascular decompression of the trigeminal nerve (47). Complete trigeminal analgesia is necessary to obtain good results. Complications include diplopia, hyperacusia, jaw deviation, corneal anesthesia, and anesthesia dolorosa (30). To avoid corneal ulcers, long-term ophthalmic follow-up is highly recommended.

Neuromodulatory Procedures

Hypothalamic Stimulation

Lack of understanding of the causes of cluster headache has been the main limitation in the development of new therapeutic options (24). In recent years neuroimaging has expanded our understanding of the pathophysiology of the condition. Positron emission tomography has revealed activation of the ipsilateral posterior inferior hypothalamic gray matter during cluster headache attacks (56) and voxel-based morphometric MRI has documented alteration of the same area (53). Activation of posterior hypothalamus is specific to cluster headache (3,55,70,74) and this strongly suggests that the cluster headache generator is located there (56). By analogy with the use of electrode stimulation for intractable movement disorders (4), it was reasoned that stereotactic stimulation of this area might interfere with this generator and relieve intractable forms of cluster headache (42). The first patient who received hypothalamic stimulation was suffering from severe chronic bilateral intractable cluster headaches; destructive surgery to the left trigeminal was absolutely contraindicated.

Electrode implantation and continuous stimulation of the left posterior inferior hypothalamus resolved the left attacks (42). After four destructive operations on the right trigeminal, right side attacks recurred. Electrode implantation (with continuous stimulation) to the right resulted in immediate resolution of the right-sided pain (41). On several occasions, both known and unknown to the patient, the stimulators were turned off; in all cases, crises reappeared and all instances disappeared relatively quickly after turning stimulation back on. The only side effects were observed during long-term bilateral stimulation, consisting of transient vertigo and bradycardia. After 42 months (left) and 31 months (right) of follow-up, the patient remains crisis free without the need for pharmacologic prophylaxis (41). Following this success, 13 patients with intractable chronic cluster headache (46) have been successfully treated by hypothalamic stimulation (18,44). Two patients require additional preventive treatments. The procedures were well tolerated with no significant adverse events. However, a report on six other intractable chronic cluster headache patients who underwent hypothalamic electrode implantation showed that the approach is not without dangers: one of the patients died postoperatively following intracerebral hemorrhage (68) and the operation on another patient had to be stopped intraoperatively because of respiratory distress (intraoperative panic attack). All deep brain electrode implantation procedures are associated with a small risk of mortality from intracerebral hemorrhage. This kind of procedure can be performed only by a highly experienced neurosurgical group.

Activation of ipsilateral hypothalamus has been reported also in short-lasting unilateral neuralgiform pain with conjunctival injection and tearing (SUNCT) (54). Because of inconsistent results of destructive surgery in drug-resistant SUNCT patients (5,26), hypothalamic stimulation has been tried in one chronic intractable SUNCT patient. The 11-month follow-up shows deep brain stimulation is effective and safe also for SUNCT (43).

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Occipital Nerve Stimulation

The successes of GON stimulation in other headache forms (49,71) and GON injection in cluster headache prompted the use of cutaneous neurostimulation of the occipital nerve in two patients with intractable chronic cluster headache (12). In both cases continuous neurostimulation produced a pain-free state. The method is reversible and associated with relatively minor adverse events; this procedure should be investigated further.

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