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Advances in cluster headache management

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SUMMARY Cluster headache, an uncommon, excruciating headache distinct from migraine, is often misdiagnosed. Until recently, therapy was difficult, but verapamil has revolutionized treatment.

KEY POINTS Organic causes must be excluded in the differential diagnosis. ■ Treatment comprises three parts: induction, maintenance, and symptomatic therapy. ■ For induction therapy, a three-week course of prednisone will suppress attacks long enough for a maintenance drug to take effect. ■ Maintenance therapy is started at the same time as induction therapy. The most commonly used drugs are verapamil or alternatively, lithium carbonate. ■ Oxygen inhalation is the safest and most effective means of aborting individual attacks, but is inconvenient. Sumatriptan also aborts attacks. ■ The use of various therapies must be tailored to the individual patient.

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CLUSTER HEADACHE is considered the most severe of the primary headache syndromes, yet the typical cluster headache patient suffers many years and has many consultations before an appropriate diagnosis is made.¹ The suffering of these patients is compounded by the predictability of pain recurrence. Cluster headache is the most uncommon of the primary headache disorders, having a prevalence of approximately one per thousand (migraine is at least 20 times more common).² Nevertheless, the presentation and treatment of cluster headache are sufficiently distinct to consider it as a diagnosis, especially in men with severe, unilateral pain.

DIAGNOSIS

Criteria proposed by the International Headache Society (IHS) provide a systematic approach to diagnosis (*Table 1*).³ Sjaastad⁴ summarized the clinical presentation of cluster headache as unilateral, of excruciating severity, ac-

TABLE 1
DIAGNOSTIC CRITERIA FOR CLUSTER HEADACHE***Cluster headache** (all of the following must be present)

At least 10 attacks of unilateral orbital or supraorbital pain or both

Severe or very severe pain

Untreated attacks last from 15 to 180 minutes

At least one of the following signs, on the same side as the headache:

Conjunctival injection

Lacrimation

Nasal congestion

Rhinorrhea

Forehead and facial sweating

Miosis

Ptosis

Frequency of attacks from one every other day to eight per day

Attacks recur on same side of head during an individual cluster period

One of the following:

Typical history and normal examination

Suspected organic lesions on examination but normal neuroimaging results

Chronic cluster headache

Criteria for cluster headache (above)

Absence of remission for 1 year or longer, or remissions lasting less than 14 days

*From the International Headache Society, reference 3

changes in symptoms. Typical recurrences of the cluster syndrome would not generally warrant repeated imaging.

TREATING CLUSTER HEADACHE

Treatment for cluster headache has traditionally been thought of in two ways: abortive therapy and prophylaxis. But these terms are less than ideal, as some abortive therapies merely shorten individual attacks, while some prophylactic therapies can actually abort a cluster cycle. Instead of this conventional system, we propose a three-part treatment approach: induction therapy

(given for the first few days or weeks to induce cessation of cluster headaches), maintenance therapy (started at the same time as induction therapy and continued for at least several months to prevent recurrences), and symptomatic therapy (which the patient takes as needed to abort attacks that may occur despite induction and maintenance therapy).

INDUCTION THERAPY

Induction drugs are needed because the most commonly used drugs for maintenance therapy (lithium and verapamil) may not begin to take effect for 1 or more weeks. As the maintenance drug begins to work, the induction drug can be discontinued.

Glucocorticoids

Since 1952, when Horton⁸ first reported using glucocorticoids in cluster headaches, glucocorticoids have become the preferred agents for induction therapy, often providing relief within 1 or 2 days.^{9,10} These drugs have several advantages over the alternative treatment: repeated intravenous doses of dihydroergotamine (see below). They are inexpensive and relatively easy to use on an outpatient basis and rarely cause significant side effects when used for only 2 to 4 weeks.^{1,11-13}

accompanied by certain autonomic phenomena, much more common in men, and strikingly periodic in occurrence. Attacks occur in clusters lasting from days to up to 16 weeks, followed by long pain-free intervals. These attacks occur suddenly and last from 15 minutes to 3 hours. The pain, described as stabbing or burning, is located in the eye, orbit, and cheek. The pain usually occurs on the same side of the head in all attacks in one cluster. Patients may become agitated during an attack and pace up and down.

Excluding an organic basis for the symptoms is often difficult, requiring not only a meticulous history and physical examination, but often radiographic and laboratory studies. Formal studies have not addressed the utility of neuroimaging in the routine evaluation of patients with cluster headache, although such procedures have had an extremely low yield in patients with migraine.^{1,5} In some case reports, structural lesions near the trigeminal nerve presented with cluster-like symptoms (Table 2). Although few of these patients actually met the IHS criteria for cluster headache, all presented certain "danger signals" that should have suggested the possibility of an organic cause.^{6,7} Therefore, neuroimaging may be appropriate for the first bout of cluster headache, or for significant

Without maintenance therapy, cluster headaches return when the glucocorticoid dosage is tapered or discontinued. Glucocorticoids are less effective in chronic cluster headache.

Dosage and administration. Prednisone is the preferred induction agent because it is inexpensive and many physicians have experience with it. The dosage is 40 to 60 mg/day in a single morning dose, slowly reduced over approximately 3 weeks. Some investigators have reported that triamcinolone produced responses when prednisone was ineffective.¹⁴

Dihydroergotamine

Dihydroergotamine (DHE), a synthetic derivative of ergotamine, causes less vasoconstriction and emesis than does its parent compound.¹⁵

Mather et al,¹⁶ in a case series, reported giving repeated intravenous doses of DHE to 54 patients with cluster headache; their report contains a complete description of their protocol. All patients became headache-free during this therapy. The response rate averaged approximately 30% per day of treatment, and fewer than 20% of patients experienced side effects. This therapy is inconvenient, as it must be given in the hospital, in a physician's office three times per day, or at home by a home infusion nurse. It is also expensive, costing \$3000 at our institution. Thus, its role is not yet well defined. Potential candidates might be patients who cannot tolerate steroids or for whom a glucocorticoid fails. Whether intravenous DHE therapy in some way restores susceptibility to glucocorticoids is a subject of further study.

We have noted that symptoms frequently recur within a few days after repetitive intravenous DHE therapy. This problem must be addressed on an individual basis; early institution of maintenance therapy is paramount.

TABLE 2
STRUCTURAL LESIONS THAT CAN CAUSE 'CLUSTER-LIKE' SYNDROMES,
AND CLUES TO THEIR PRESENCE

Lesion	Warning sign or symptom
Sinusitis	Fever Prolonged symptoms
Arteriovenous malformations	Decreased vision Prolonged symptoms Papilledema Female patient Lack of full spectrum of autonomic dysfunction
Mycotic aneurysm of intracavernous carotid artery	Continuous headache
Vertebral artery aneurysm	Constant background headache
Nasopharyngeal cancer	Nausea and vomiting Previous treatment for nasopharyngeal carcinoma
Pituitary adenoma	Seizure Progression in frequency Impotence Testicular atrophy Optic atrophy
Chronic subdural hematoma	Progressive frequency History of trauma
Trigeminal neurinoma	Continuous headache
Sphenoidal aspergilloma	Prolonged headache Female patient

MAINTENANCE THERAPY

Cluster headache therapy requires an agent that not only prevents the characteristic volley of attacks but also can be tolerated for months or, in chronic cases, indefinitely. Most commonly used are verapamil or, alternatively, lithium carbonate. Ergotamine is reserved for resistant cases or attacks that occur only at night. Patients who continue to suffer despite these interventions may be candidates for therapy with methysergide.

Verapamil

Verapamil was first reported effective in cluster headache in 1983¹⁷ and has revolutionized treatment. Other calcium channel blockers have also been shown beneficial; however, efficacy, clinical experience, and cost strongly favor verapamil.^{1,2,6,11}

Verapamil does not begin to prevent cluster headaches until after 1 or more weeks of therapy; therefore, its rapid effects on calcium channels probably do not account for its effects on cluster headache (or on migraine).¹³ Rather, it has been sug-

TABLE 3
CLINICAL MANIFESTATIONS
OF LITHIUM INTOXICATION**Central nervous system**

Altered state of consciousness (confusion to coma)
Cerebellar symptoms
Dysarthria
Ataxia
Nystagmus
Tremors
Basal ganglia symptoms
Choreiform movements
Parkinsonian movements
Seizures
Death

Gastrointestinal

Nausea, vomiting
Bloating

Cardiac

Syncope

Renal

Polyuria
Polydipsia
Renal insufficiency

Neuromuscular

Peripheral neuropathy
Myopathy

Endocrine

Hypothermia
Hyperthermia

TABLE 4
FACTORS PREDISPOSING
TO LITHIUM INTOXICATION

Infections
Volume depletion
Gastroenteritis
Overdose
Renal insufficiency
Surgery
Decreased effective arterial volume
Congestive heart failure
Cirrhosis
Nephrosis
Drugs
Nonsteroidal anti-inflammatory drugs
Diuretics
Tetracycline
Cyclosporine
Decreased dietary sodium intake
Anorexia

gested that verapamil's affinity for serotonin receptors explains its utility in treating migraine and cluster headaches. During the latency period, one can safely use other induction therapy and symptomatic therapy agents.

Verapamil is effective in approximately 70% of cluster headache sufferers^{1,2,6,11} and has been demonstrated effective in both episodic and chronic cluster headaches. Bussone and colleagues¹⁸ compared verapamil with lithium carbonate in a double-blind crossover study in 30 patients with chronic cluster headache. Verapamil caused fewer side effects and had a shorter latency period; more than half the patients noted an onset of beneficial effects (a reduction in the headache index) by 1 week.

Adverse effects. Verapamil is generally well tolerated and causes few serious adverse reactions,^{1,2,11,15} particularly compared with other maintenance agents. The most common side effect is constipation, which warrants fiber supplementation and judicious use of cathartics when it occurs.

More serious untoward reactions result from excessive calcium channel blockade in the heart and

peripheral vasculature, leading to cardiac conduction abnormalities, myocardial depression, and hypotension.¹⁵ These effects are unlikely in patients not predisposed by either illness (cardiac, hepatic, or renal failure) or interactions with other drugs (beta blockers, digoxin, quinidine, nondepolarizing neuromuscular blocking agents, prazosin, theophylline, imipramine, carbamazepine, cyclosporine).

Of note, verapamil and lithium carbonate interact in a rather complex way.¹⁷ Verapamil can decrease lithium's effects, but lithium may have calcium-channel blocking properties and therefore enhance the effects of verapamil.¹⁹

Dosage and administration. In episodic cluster headache, a reasonable starting dosage is 240 to 360 mg/day of a long-acting verapamil preparation, given in one or two doses. Dosages required to control chronic cluster headache are higher, often approaching 480 or 600 mg/day.¹³ Careful monitoring of blood pressure and heart rate is paramount, particularly with higher doses. A systolic blood pressure less than 100 mm Hg or a heart rate less than 50 beats per minute indicates the dosage is too high.

Episodic cluster often recurs at the same time each year, and one can often plan treatment accordingly. Mathew¹ suggests starting medication early in the cluster period and tapering it slowly once the patient is free of headache for at least 2 weeks.

Recommendations for the use of verapamil in managing chronic cluster headaches are more difficult to support by either controlled study or anecdote. An individualized approach is used, with an attempt to slowly taper off verapamil after the patient has been cluster-free for several months. However, patients with chronic cluster headaches who cannot tolerate discontinuing verapamil can safely use it indefinitely.

Lithium carbonate

Studies indicate that 70% of cluster headache patients respond favorably to lithium.^{1,11-13,20,21} Lithium is particularly effective in chronic cluster headache, as its effects may persist after the drug is discontinued.^{13,22}

Adverse effects. However, lithium has many toxic effects (Table 3) and interactions (Table 4) that make it less attractive than verapamil.^{23,24} Bussone et al¹⁸ found that lithium was much slower-acting than verapamil, and more toxic. Tachyphylaxis to lithium has been reported, although its frequency is not clear.¹¹

Dosage and monitoring. The usual dosage of lithium carbonate for cluster headache is 600 to 900 mg/day in divided doses.^{1,11,12} Table 5 summarizes the guidelines for monitoring lithium levels and watching for potential adverse reactions.²⁵ Serum lithium levels average 0.5 to 1.0 mEq/L in cluster therapy, somewhat lower than in treating mood disorders.¹¹ Adverse reactions generally occur with lithium levels greater than 1.5 mEq/L. However, some reactions, including nausea, fatigue, thirst, edema, weight gain, and polyuria, may occur even with "nontoxic" levels. Tremor is quite common but tends to respond to either lowering the dose or adding a beta blocker.^{13,23,25} Because of the highly variable interactions between lithium and verapamil (see above), it is important to closely monitor the patient's clinical status for side effects, rather than simply relying on the results of serum lithium determinations when this combination is used.

TABLE 5
LABORATORY EVALUATION FOR PATIENTS RECEIVING LITHIUM*

Before treatment

Complete blood count
Serum creatinine and electrolytes
Serum thyroxine, free thyroxine, and thyrotropin
Urinalysis
Electrocardiogram[†]
Optional: 24-hour urine volume, creatinine clearance, urine osmolality[‡]

During treatment

Plasma lithium levels every 5 to 7 days after initiation of treatment and after any change in the dose; every 1 to 2 months during maintenance treatment
Serum creatinine every 6 to 12 months
Serum thyroxine, free thyroxine, and thyrotropin every 6 to 12 months
Urinalysis every 12 months
Electrocardiogram
Optional: serum electrolytes, complete blood count, 24-hour urine volume, creatinine clearance, urine osmolality[§]

*From Price and Heninger, reference 25

[†]Indicated in patients older than 50 years

[‡]If clinically indicated

[§]Should be measured more frequently during periods when other factors may alter plasma concentrations; may be measured less frequently (every 6 to 12 months) in stable patients receiving maintenance treatment

Ergotamine

Although controlled trials of ergotamine in cluster headache are lacking, clinical experience suggests it has a role in two specific circumstances: attacks that happen only at night (in which a bedtime dose of 2 mg orally may be quite effective), and for cluster headaches refractory to verapamil or lithium carbonate.^{1,20,25} Kudrow¹² found that adding a nighttime dose of ergotamine increased the efficacy of a daily verapamil regimen by 15%. He also found that adding lithium to this combination boosted efficacy by an additional 5% to 10%.

Adverse effects. Vascular reactivity explains much of the toxicity of ergotamine²⁶ and tends to limit its use to the specific circumstances stated above. Adverse reactions are fairly common but may not mandate stopping therapy. Up to 10% of patients may experience nausea and vomiting. Other common side effects include itching, local edema, changes in heart rate, weakness, numbness, paresthesia, and pain in the extremities.

In toxic ingestion, central nervous system disturbances such as depression, confusion, and seizures often coexist with vasoconstriction and ischemia in a variety of locations. Interaction with beta blockers or macrolide antibiotics may precipitate such a toxic syndrome even at therapeutic doses.¹⁵

Contraindications. Contraindications to ergotamine include peripheral vascular disease, coronary

TABLE 6
GUIDELINES FOR OXYGEN USE
IN CLUSTER HEADACHE

1. Start oxygen inhalation at the very onset of the attack
2. Have the patient assume a sitting position, upright or leaning forward (supine or nearly supine positions may increase cavernous sinus congestion, which may aggravate rather than abate the attack)
3. Use a facial mask rather than a nasal cannula, because associated nasal stuffiness may impede airway flow
4. Set the oxygen flow at 7 L/min
5. Warn the patient against hyperventilating, which may limit oxyhemoglobin saturation—a high level of oxygen saturation (98%–99%) needs to be sustained for several minutes to achieve relief of the attack

artery disease, hypertension, hepatic or renal impairment, pregnancy, and sepsis.¹⁵

Dosage and administration. As noted above, 2 mg orally is often quite effective in treating cluster attacks that happen only at night or that are refractory to verapamil and lithium. Overdosage is generally seen with dosages greater than 15 mg/day, though it has been reported with dosages less than 5 mg.

Methysergide

Patients who continue to have headaches despite therapy with verapamil, lithium, or ergotamine may be candidates for methysergide therapy. Tachyphylaxis to methysergide and this agent's toxicity and interactions restrict its use.^{1,15,24,26}

Formal studies and clinical experience agree that methysergide has efficacy in cluster headache treatment comparable to that of verapamil^{11,12} or lithium.^{24,26}

Adverse effects. Fibrotic reactions about the viscera are an unusual and controversial toxic effect.¹⁵ These include retroperitoneal fibrosis, pulmonary fibrosis, and endomyocardial fibroelastosis. Whether this effect is dose-related or idiosyncratic is not clear. Patients with lung disease or connective-tissue diseases are thought to be more susceptible to these complications.¹³ Typical adverse reactions include leg pain, edema, paresthesia, nausea, and chest pain.^{1,15} Discontinuation of methysergide therapy for 2 or more months each year is recommended,^{1,11,12} although this is not usually necessary when methysergide is used for brief periods in epi-

sodic cluster.

Contraindications. Methysergide may increase gastric acid secretion; therefore, peptic ulcer disease is a relative contraindication to its use. Other contraindications include those for ergotamine.¹⁵

Dosage. The recommended dose of methysergide is 8 mg/day. Starting at lower doses and gradually increasing them may limit the typical adverse reactions.

SYMPTOMATIC THERAPY

Cluster headaches may occur in spite of appropriate induction and maintenance therapy. Symptomatic therapies shorten or abort the active cluster headache and provide relief within several minutes. However, these therapies do not prevent future attacks. Clinical response is the strongest indication to continue or abandon a symptomatic therapy.

Oxygen inhalation

High-flow oxygen inhalation by mask is the safest and most effective method of aborting attacks (Table 6).^{1,11,12}

Adverse reactions. This therapy causes almost no adverse reactions, but requires an apparatus that is not portable. (Because of the high flow rate needed, portable oxygen tanks hold enough for only a few attacks.) Tolerance does not appear to be common, but individual attacks tend to recur shortly after "successful" treatment, and in many cases oxygen merely postpones the attack.¹

Ergotamine as an alternative to oxygen. Sublingual doses of ergotamine are an alternative to oxygen therapy when attacks occur away from home. However, the response is less than ideal, even by this rapidly absorbed route, and this therapy causes the well-known side effects of the ergot alkaloids.

Sumatriptan

Sumatriptan injections have shown promise in managing cluster attacks; however, as in migraine, its cost (\$30 to \$35 per injection) limits its general utility, as does its restriction to two injections per day. Sumatriptan tablets are not used as symptomatic therapy because the time to onset of action (about 1 hour) is too long.

Large trials have compared the efficacy of sumatriptan injection with that of placebo in cluster headache.^{27,28} The Sumatriptan Cluster Headache Study Group included 39 patients, of whom half

obtained complete relief within 15 minutes of sumatriptan injection.²⁷

Adverse effects. The common adverse effects were local injection-site reactions (7%), nausea and vomiting (5%), a pressure sensation (5%), and a feeling of heaviness (5%). (A variety of neurological symptoms such as transient dizziness, tiredness, and paresthesia may also occur.²⁸) There were no changes in either heart rate or blood pressure and no electrocardiographic, biochemical, or hematological anomalies identified.²⁷

Contraindications. Contraindications to sumatriptan include ischemic heart disease and uncontrolled hypertension. A great deal of caution must be used in patients with peripheral vascular disease or known cerebrovascular disease.²⁸

Dosage and administration. The recommended dose is 6 mg subcutaneously. This dose may be repeated once during a given 24-hour period.²⁸ A dose of sumatriptan will not prevent future cluster headaches, even on the same day. We recommend that the first dose of sumatriptan be given in a supervised setting so that the patient can be reassured about any transient sensations, such as chest pain, that may develop.

The advantages of sumatriptan in treating cluster attacks include a high efficacy rate, a rapid onset of action, and, compared with oxygen, the relatively small size of the apparatus necessary for its administration. It is therefore useful for patients who suffer frequent attacks away from home.

Cost is the major disadvantage of this product. Although tachyphylaxis has not been reported, use of sumatriptan should be limited to patients suffering no more than one cluster headache per day, to avoid exceeding the dosing guidelines.

Local anesthetics

Instilling topical anesthetics into the nose, perhaps anesthetizing the sphenopalatine ganglion, is an alternative to the above agents. This treatment is not commonly used, as administration is cumbersome at best.

Reports have been published since 1913 regarding using cocaine intranasally in acute pain syndromes thought to be cluster headache. Kittrelle and colleagues²⁹ suggest this may be impractical: a typical patient would need more than 3 g of pure cocaine per cluster period.

The same investigators reported giving lidocaine intranasally to a small number of cluster headache

patients. Postulating a local anesthetic action on the sphenopalatine ganglion, they carefully positioned the patients to permit the agent to reach this structure. Favorable responses were obtained, and further study is warranted. Although this therapy is uncommonly used, it offers the benefit of a local treatment with little noxious potential.

INVESTIGATIONAL THERAPIES FOR REFRACTORY CLUSTER HEADACHE

Patients who continue to suffer from cluster headaches despite standard therapy deserve a trial with any appropriate agent known to have value in treating migraine. Two particular drugs merit consideration before resorting to surgery: sodium valproate³⁰ and transdermal clonidine.

Sodium valproate. Kuritzky and Hering³¹ published encouraging results of an open trial of sodium valproate (also known as divalproex sodium) in 15 cluster patients. Side effects of this agent include drowsiness, tremor, nausea, vomiting, hair loss, and weight gain. The dosage of sodium valproate generally is 600 mg to 2000 mg/day in divided doses. Periodic assessment of serum levels is necessary; the target range is 50 to 100 µg/mL. Periodic monitoring of liver function and of the complete blood count is also recommended. This drug is contraindicated in patients with liver disease.¹⁵

Clonidine. A recent pilot study suggests that transdermal clonidine may prove effective in maintenance therapy of cluster headache, although further study is necessary.³²

Intranasal capsaicin. In preliminary reports, intranasal application of capsaicin (hot pepper extract) has had some benefit in some cluster patients.³³ The optimal dosage schedule has not been elaborated.

Surgery. Cluster headache should be treated by medical means, unless the headaches remain chronic, unilateral, and resistant to the therapies discussed above. In this desperate circumstance, neurosurgical intervention may provide some relief and improve quality of life. Several investigators consider radio-frequency trigeminal gangliorhizolysis the procedure of choice, even though it abolishes the corneal reflexes.^{1,12,34}

Glycerol injections. Recently, we evaluated the percutaneous injection of glycerol into the trigeminal cistern in eight patients at the Cleveland Clinic. Three patients became headache-free, and five were able to discontinue medication. The safety was no-

table: none of the patients experienced facial or corneal anesthesia.³⁵ This procedure may deserve consideration before resorting to the more destructive procedure in a patient desperate for relief.

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